Lymphedema is a rare manifestation of lymphoma: A case series and literature review

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Received February 6, 2025; Accepted July 15, 2025

DOI: 10.3892/ol.2025.15262

Abstract. Lymphedema, which is characterized by impaired lymphatic drainage leading to tissue swelling, represents a relatively uncommon clinical entity, with an estimated prevalence of <1% being observed in the general population. Although most cases arise from postsurgical complications or filariasis, lymphoma-associated lymphedema remains an exceedingly rare manifestation, with only 19 cases documented in the medical literature prior to the present study. The current study presented a case series of 11 patients with histologically confirmed lymphoma manifesting with lymphedema, which represents the largest single-center report to date. In the present cohort spanning a time period from 2007-2024, patients who initially presented with refractory lymphedema (9 lower extremity cases, 1 upper extremity case and 1 systemic case) subsequently received a diagnosis of lymphoma via comprehensive evaluation, including imaging (100% detection rate on CT/MRI) and histopathology examinations. The median latency from edema onset to lymphoma diagnosis was 7 months (range, 1-24 months), with 72.7% (8 out of 11) of the patients demonstrating B-cell lineage predominance. The present case series underscored the notion that although lymphedema secondary to lymphoma constitutes <0.5% of all secondary lymphedema cases, it warrants consideration in patients with atypical presentations, such as rapid progression (54.5%), systemic symptoms (81.8%) or abnormal tumor markers (66.7%). The present case report findings emphasized the idea that lymphoma should be included in the differential diagnosis of unexplained lymphedema, particularly when accompanied by warning signs such as lymphadenopathy (100% imaging positivity) or hematologic abnormalities (45.5% anemia prevalence).

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Key words: lymphedema, lymphoma, malignant lymphedema, case report, diagnosis

Introduction

The lymphatic system serves dual roles in fluid homeostasis and immune surveillance, which functions as a key component of both the circulatory and immune systems. As part of the circulatory network, it maintains tissue fluid balance by draining ~2-4 l of protein-rich interstitial fluid on a daily basis through specialized vessels equipped with intrinsic contractility and unidirectional valves. Concurrently, its immune functions facilitate antigen presentation and lymphocyte trafficking via lymph node filtration (1). Lymphedema, which is pathologically defined as the abnormal accumulation of high-protein interstitial fluid (2), arises from either primary developmental abnormalities or secondary acquired damage. Primary lymphedema typically manifests through genetic mutations affecting lymphatic morphogenesis (2) and is diagnosed via combined lymphoscintigraphy findings and molecular testing (3). Secondary forms are identified via clinical history (including histories of surgery, radiation or filariasis) and imaging evidence of lymphatic obstruction, with CT/MRI indicating characteristic dermal backflow patterns (4-6).

Although the proportion of lymphoma-associated lymphedema in secondary lymphedema is relatively low (7), the association between lymphedema and lymphoma exhibits distinctive clinical features, including rapid unilateral progression, disproportionate truncal involvement and concurrent B symptoms. For the present study, the accumulation of 11 cases over 17 years reflects both the specialization in lymphatic disorders at Beijing Shijitan Hospital (managing >1,200 patients with lymphedema on an annual basis) and improved diagnostic sensitivity via advanced imaging protocols. The present case series addresses a key literature gap, as previous reports lacked standardized diagnostic criteria, of which only 4 out of 19 previous cases documented imaging correlates (Table I) (8-26). These findings establish essential clinical benchmarks to distinguish malignancy-related edema from benign edema.

Case report

From May 2007 to December 2024, a cohort of 11 patients suffering from lymphedema (either induced or exacerbated by lymphoma) received treatment at Beijing Shijitan Hospital (Beijing, China). Following the acquisition of approval from the institutional review board [approval no. sjtkyll-lx-2022(058)], a retrospective analysis of these 11 patients was conducted. In the present case report, a cohort of 11 patients diagnosed with lymphedema underwent a series of diagnostic evaluations, including laboratory tests (blood routine examination, blood tumor marker examination), ultrasonography, MRI, CT and radionuclide imaging. The imaging findings involved characterizations of ultrasound-assessed lymph node size (short-axis diameter >10 mm defined as being abnormal), vascularity and soft-tissue edema. CT was used to evaluate lymphadenopathy (axial diameter >15 mm), visceral/organ involvement and tumor masses. MRI was used to characterize soft-tissue infiltration and lymphatic obstruction patterns, as well as to differentiate between edema and neoplastic infiltration. Additionally, bone marrow aspiration and biopsy were performed to corroborate the diagnosis of malignancy (27).

The cohort of 11 patients included 8 men and 3 women. The distribution of lymphedema types included 1 patient with upper extremity lymphedema, 9 patients with lower extremity lymphedema (Fig. 1) and 1 patient with systemic edema. The ages of the patients with lymphoma ranged from 41 to 79 years, with a mean age of 61.0±12.5 years. The interval between the onset of lymphedema and the subsequent diagnosis of lymphoma varied from 1 to 24 months, with a median duration of 7 months. Additionally, these patients presented with various clinical symptoms, including weakness, weight loss, pain, the presence of a mass and lymphadenopathy. A detailed summary of the clinical features of each patient is provided in Table I.

In the present cohort, tumor markers were assessed in 6 patients, with 66.7% (4 out of 6) of the patients exhibiting abnormalities in at least one marker. The distribution of abnormal markers included CA125 (1 patient), urinary Igκ light chain (3 patients), serum β2-microglobulin (1 patient), urinary Igλ light chain (2 patients), serum Igκ light chain (2 patients) and urinary β2-microglobulin (1 patient). Individual patients often presented with multiple marker abnormalities (Table II). Additionally, the prevalence of anemia among patients diagnosed with malignant lymphedema was 45.5% (5 out of 11 patients). Several suspicious lesions were further evaluated via imaging modalities, which yielded positive detection rates of 100.0% for ultrasonography (7 out of 7 lesions), 100.0% for CT (8 out of 8 lesions) and 100.0% for MRI (2 out of 2 lesions). Representative imaging and pathology findings from Case 4 are shown in Fig. 2. Axial chest CT demonstrated a mass adjacent to the mediastinum involving the right lung hilum and upper lobe. Contrast-enhanced CT revealed this mass exhibited heterogeneous enhancement and was contiguous with a larger mediastinal mass, confirming their connection. Whole-body lymphoscintigraphy following foot injection showed mild left lower limb thickening, significant tracer retention at the left foot injection site suggesting impaired lymphatic drainage, and non-visualization (absence of uptake) in the left inguinal, iliac and para-aortic/lumbar nodal basins, indicating lymphatic obstruction in these regions. Histopathological examination of the dissected left supraclavicular lymph node (H&E stain) revealed effacement of nodal architecture with fibrosis, scattered lymph follicles, large cells and histiocyte-like cells. The morphology led to the diagnosis of 'B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma'.

A total of 11 cases of lymphedema associated with malignant tumors were pathologically verified to have originated from the lymphatic tissue. The present cohort included 8 cases of mature B-cell lymphoma and 3 cases of mature T-cell lymphoma, as detailed in Table I and Fig. 2.

Furthermore, 11 patients underwent tumor and enlarged lymph node resection biopsies. A total of 6 patients were followed up until December 2024. Of note, 2 patients with vascular immune T-cell lymphoma died within 1 year after diagnosis. A total of 3 patients with diffuse large B-cell lymphoma were diagnosed and received chemotherapy (the specific details are unknown). These patients have survived for 7, 10 and 11 years. In addition, 1 patient with lymphoplasmacytic lymphoma has been receiving long-term oral treatment with traditional Chinese medicine (the specific details are unknown) and has survived for 14 years (Table I).

Discussion

The clinical presentations of lymphoma can vary and a notable number of cases are identified at an advanced stage, which is primarily due to the constraints of existing diagnostic methodologies (28). In certain patients, lymphedema may be the initial manifestation of lymphoma, with lymphedema representing the sole clinical manifestation of lymphoma in certain cases. While no specific molecular biomarkers are universally established for the diagnosis of lymphedema, advancements in imaging and bioimpedance technologies have provided indirect markers for the assessment of lymphatic dysfunction (29,30). For instance, bioimpedance spectroscopy and the tissue dielectric constant are non-invasive tools that quantify extracellular fluid volume and detect subclinical lymphedema with high sensitivity (31). Additionally, serum biomarkers such as β2-microglobulin and urinary immunoglobulins (e.g., Igκ/λ light chains) have been observed in patients with malignancy-associated lymphedema, although these are non-specific and often linked to underlying conditions such as lymphoma (32). Emerging research also highlights the role of inflammatory cytokines (e.g., IL-6 and TNF-α) and lymphangiogenic factors (such as VEGF-C/D) in lymphatic remodeling, which may serve as potential molecular indicators in the future (33). The current study presented a series of lymphoma cases characterized by the presence of lymphedema. The analysis of the present study, in conjunction with previous studies, indicated that lymphedema could represent a potential manifestation of lymphoma, which potentially resulted from lymphatic or venous obstruction.

Previous studies have revealed a notable association between lymphedema and lymphoma, with lymphomas being the most prevalent neoplasms associated with immunodysregulation. It is posited that abnormal lymphoid proliferation may be causally linked to lymphatic stasis (11). Insufficient lymphatic drainage can disrupt the normal trafficking of

Table I. Previous case reports of lymphoma-associated lymphedema.

First author, year	Cases, n	Patient age, years/sex	Duration of edema	Localization of edema	Accompanied symptoms	Past history	Diagnostic findings	Histological types	(Refs.)
Present study	Case 1	72/M	2 months	Lower extremity	None	None	CT enhancement: Multiple enlarged lymph nodes in the groin, pelvic cavity and retroperitoneum	Angioimmunoblastic T-cell lymphoma	-
Present study	Case 2	74/M	1 month	Upper extremity	Axillary mass	None	CT enhancement: Multiple enlarged lymph nodes in the left axilla, with notable delayed enhancement, splenic space-occupying lesions and multiple lymph nodes of varying sizes in the mediastinum	Lymphoplasmacytic lymphoma	-
Present study	Case 3	53/M	7 months	Lower extremity	Groin mass	None	CT: Multiple enlarged lymph nodes in the retroperitoneum	Follicular lymphoma	-
Present study	Case 4	41/F	10 months	Lower extremity	Enlargement of the supraclavicular lymph nodes	History of accessory breast surgery >20 years, history of hysteromyoma >2 years, history of hysteroscopic surgery >1 year	CT: Multiple lymph nodes on the lesser curvature of the stomach. Malignant mass in the upper lobe of the right lung, lymph node metastasis in the right hilum and mediastinum and multiple metastatic nodules under the anterior chest wall	B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin's lymphoma	-
Present study	Case 5	62/F	3 months	Lower extremity	Abdominal pain and enlargement of cervical and inguinal lymph nodes	None	CT: The root of the mesentery, retroperitoneum to bilateral iliac masses, multiple enlarged lymph nodes in both inguinal regions and local compression and narrowing of the inferior vena cava. The lower end of the left ureter is compressed and narrowed and the upper ureter and left renal pelvis and calyx are dilated with hydronephrosis. Multiple nodules in the spleen, considering metastatic lesions. Multiple enlarged lymph	Follicular lymphoma	-

Table I. Continued.

First author, year	Cases, n	Patient age, years/sex	Duration of edema	Localization of edema	Accompanied symptoms	Past history	Diagnostic findings	Histological types	(Refs.)
							node shadows in the upper and lower regions of both clavicles, mediastinum and axilla, with metastatic lesions not excluded		
Present study	Case 6	79/M	8 months	Lower extremity	Enlargement of cervical lymph node	None	Ultrasound: Bilateral cervical lymph nodes visible	Diffuse large B-cell lymphoma	-
Present study	Case 7	52/M	2 years	Generalized edema	Enlargement of lymph nodes in neck, armpit and groin and recurrent fever	None	Ultrasound: Multiple lymph node enlargement in both inguinal regions. Bilateral cervical lymph nodes are visible	Angioimmunoblastic T-cell lymphoma	-
Present study	Case 8	46/M	2 months	Lower extremity and perineal region	Enlargement of inguinal lymph node	None	Ultrasound: Bilateral inguinal lymph node enlargement	Follicular lymphoma	-
Present study	Case 9	73/F	2 years	Lower extremity	None	History of endometrial cancer	CT enhancement: Multiple small nodules in the right lung. Multiple swollen lymph nodes in both armpits	Angioimmunoblastic T-cell lymphoma	-
Present study	Case 10	64/M	9 months	Lower extremity	Enlargement of inguinal lymph node and loss of weight	None	Null	Diffuse large B-cell lymphoma	-
Present study	Case 11	55/M	1 month	Lower extremity	Enlargement of inguinal lymph node	None	CT: A small amount of hydrocele is present in both testicles and there is swelling in both inguinal regions and left external iliac lymph nodes. It is recommended to rule out tumor lesions	Diffuse large B-cell lymphoma	-
Sun, 2022	Case 12	69/F	40 years	Lower extremity	Multiple nodules of varying sizes, the surface of some of the lesions demonstrated erosion and	None	Null	Diffuse large B-cell lymphoma	(8)

Table I. Continued.

First author, year	Cases, n	Patient age, years/sex	Duration of edema	Localization of edema	Accompanied symptoms	Past history	Diagnostic findings	Histological types	(Refs.)
					exudation, with pain.				
Vijaya, 2019	Case 13	47/F	47 years	Lower extremity	Multiple ulcers and nodules	Null	Null	Diffuse large B-cell lymphoma	(9)
Sanna, 1997	Case 14	84/F	7 months	Lower extremity	None	History of coxarthrosis	Null	Angiotropic large B-cell lymphoma	(10)
González-Vela, 2008	Case 15	89/M	7 years	Lower extremity	Multiple violaceous, firm, slightly infiltrated nodules	History of a right femoropopliteal bypass	None	Diffuse large B-cell lymphoma	(11)
Hills, 1993	Case 16	55/M	47 years	Lower extremity and the right hand	Multiple firm purplish-blue cutaneous nodules	History of a deep-vein thrombosis of the left leg and pulmonary embolus	None	Follicular centre cell lymphoma	(12)
Dargent, 2005	Case 17	79/F	28 years	Upper extremity	A cutaneous tumor of ~2 cm width	History of chronic arterial hypertension, ischemic cardiomyopathy, hepatitis, cholecystectomy, left ovariectomy, hysteropexy for cystocele repair, varicose vein stripping and depression	None	Diffuse large B-cell lymphoma	(13)
Shabbir, 2022	Case 18	71/M	Several weeks	Upper extremity	None	An extensive history of tobacco and substance use in remission and	A CT scan of the RUE demonstrated cortical destruction Of the humeral head and proximal shaft, along	Diffuse large B-cell lymphoma	(14)

Table I. Continued.

First author, year	Cases, n	Patient age, years/sex	Duration of edema	Localization of edema	Accompanied symptoms	Past history	Diagnostic findings	Histological types	(Refs.)
						untreated HCV infection	with infiltrative enlargement of the muscles of the proximal RUE and marked soft tissue edema. There were also a few enlarged axillary lymph nodes, the largest Measuring 2 cm in short-axis. A PET scan demonstrated striking 18-FDG avidity in the humerus and surrounding musculature (msuv 10-15), as well as two FDG-avid axillary lymph nodes with msuv 5 and 14		
Massini, 2013	Case 19	45/F	Null	Upper extremity	Purplish cutaneous nodules, in part ulcerated and infected	Null	None	Mantle cell lymphoma	(15)
Wan and Jiao, 2013	Case 20	33/M	3 years	Lower extremity	Leg pain, flank pain, oliguria and dark urine	Smoking history	Vascular ultrasound revealed segmental occlusion of inferior vena cava and hypoechogenic lesion around abdominal aorta, bilateral sacral arteries and right renal artery. Inguinal ultrasound found bilateral inguinal lymphadenopathy and a hypoechoic mass in the left inguinal region. Abdominal CT scan with contrast revealed a retroperitoneal soft-tissue mass, which invaded the right kidney and surrounded the abdominal aorta, inferior vena cava, superior mesenteric	Non-Hodgkin's lymphoma of B-cell type	(16)

Table I. Continued.

First author, year	Cases, n	Patient age, years/sex	Duration of edema	Localization of edema	Accompanied symptoms	Past history	Diagnostic findings	Histological types	(Refs.)
							artery and bilateral renal vessels (Fig. 2). Left renal pelvic and bilateral psoas major muscles were also involved. CT urography revealed hydronephrosis, with occlusion of right renal pelvis and right ureter. A renal scan indicated the glomerular filtration rate to be 9.46 (left) and 65.39 ml/min (right)		
Tatnall and Mann, 1985	Case 21	76/M	3 years	Lower extremity	Leg skin nodules	History of prostate cancer	Null	Non-Hodgkin's lymphoma	(17)
Barki, 2020	Case 22	60/M	Null	Penile scrotum	Fever, weight loss	Null	Ultrasound imaging indicated a thickening of the scrotum with normal scrotal contents. CT: Bilateral upper and centrilobular pulmonary emphysema, large lateral aortic, common iliac and left external iliac lymphadenopathies	Hodgkin's lymphoma	(18)
Paydas, 2000	Case 23	63/F	Null	Upper extremity	Skin induration and ulceration ranging from 0.5 to 1 cm on the dorsum of her left hand and arm	Null	Null	Diffuse large cell lymphoma	(19)
Fan, 2017	Case 24	56/M	10 years	Lower extremity	Erythema on the right leg, multiple nodular ulcerative lesions	Null	Null	Primary cutaneous anaplastic large cell lymphoma	(20)
Torres-Paoli Sánchez, 2000,	Case 25	87/F	67 years	Lower extremity	Painful nodules	History of filariasis	None	Primary cutaneous B-cell lymphoma	(21)
Waxman, 1984	Case 26	76/M	1.5 years	Upper extremity	Null	Null	Null	Primary B-cell lymphoma (?)	(22)
d'Amore, 1990	Case 27	55/F	30 years	Upper extremity	Severe pain in the left arm, a	Null	Radiographic studies demonstrated a large mass involving the left	Primary B-cell lymphoma	(23)

Table I. Continued.

First author, year	Cases, n	Patient age, years/sex	Duration of edema	Localization of edema	Accompanied symptoms	Past history	Diagnostic findings	Histological types	(Refs.)
					lesion of the soft tissue surrounding the upper humerus		biceps and triceps muscles; the underlying cortical bone was also focally involved in this process		
d'Amore, 1990	Case 28	70/F	11 years	Upper extremity	A slowly growing, violaceous soft-tissue nodule in the right deltoid region	Null	Null	Primary B-cell lymphoma	(23)
Binjawhar, 2021	Case 29	27/M	3 years	Scrotum	None	Null	Null	Hodgkin's lymphoma	(24)
Hawkins, 1980	Case 30	49/M	6 months	Lower extremity	Null	Null	Null	Lymphoma	(25)
Hawkins, 1980	Case 31	63/M	6 weeks	Lower extremity	Null	Null	Null	Lymphoma	(25)
Hawkins, 1980	Case 32	57/F	Null	Lower extremity	Null	Null	Null	Lymphoma	(25)
Hawkins, 1980	Case 33	57/F	1 month	Lower extremity	Null	Null	Null	Lymphoma	(25)
Hawkins, 1980	Case 34	75/F	3 months	Lower extremity	Null	Null	Null	Lymphoma	(25)
Hawkins, 1980	Case 35	68/F	1 day	Lower extremity	Null	Null	Null	Lymphoma	(25)
Hawkins, 1980	Case 36	56/F	Several weeks	Lower extremity	Null	Null	Null	Lymphoma	(25)
Hawkins, 1980	Case 37	64/M	5 months	Lower extremity	Null	Null	Null	Lymphoma	(25)
Hawkins, 1980	Case 38	59/F	3 years	Lower extremity	Null	Null	Null	Lymphoma	(25)
Hawkins, 1980	Case 39	16/F	1 year	Lower extremity	Null	Null	Null	Lymphoma	(25)

Table I. Continued.

First author, year	Cases, n	Patient age, years/sex	Duration of edema	Localization of edema	Accompanied symptoms	Past history	Diagnostic findings	Histological types	(Refs.)
Elgendy, 2014	Case 40	60/M	Several weeks	Lower extremity	Mild erythema, increased warmth and moderate tenderness of the left leg	Hyperlipidaemia and hypertension	A CT scan of the abdomen and pelvis demonstrated left aortic lymphadenopathy and bulky lymphadenopathies alongside the left iliac vessels, extending to the left inguinal region with compression of the left iliac vein	Non-Hodgkin's lymphoma	(26)

M, male; F, female; FDG, fluorodeoxyglucose; msuv, maximum standardized uptake value; HCV, hepatitis C virus.

lymphocytes and Langerhans cells, which are essential for the maintenance of immunocompetence, which leads to an immunologically susceptible state in the lymphedematous region and increases the risks of infection and oncogenesis (34). Several theories have been proposed to elucidate the underlying mechanisms involved in the aforementioned process. Futrell and Myers (35) emphasized the role of the immunological status in determining the response of animal hosts to tumors implanted in the skin, regardless of the integrity of the lymphatic system. Their findings revealed that, although tumor solutions did not induce malignancy when injected into areas with intact lymphatic vessels, malignant tumors developed when injections occurred in regions with compromised lymphatics (35). Furthermore, deficiencies in the lymphatic drainage system may hinder the early detection of tumor-specific antigens (36). Chronic stasis can lead to alterations in the local lymphatic protein composition, which are characterized by a decrease in the α-2 globulin fraction and an increase in the albumin-globulin ratio (37). This delay in protein transport from the interstitial space to the lymphatic space may modify the antigenic composition and/or regional immunological competence of the tissue. The relationship between elevated lymphocyte counts and lymphatic stasis remains complex and context-dependent. While chronic lymphatic stasis can lead to localized immune dysregulation, specific thresholds for lymphocyte proliferation in lymphedema are not well-defined in the literature. However, previous studies have suggested that persistent $CD4^+$ T-cell infiltration in lymphedematous tissues contributes to chronic inflammation and fibrosis, which exacerbates lymphatic dysfunction (38). For instance, in cases of malignancy-related lymphedema, tumor-associated lymphocytes may infiltrate obstructed lymphatic pathways, although quantitative percentages are rarely reported. Further research is warranted to establish standardized values that associate lymphocyte counts with stasis severity. Additionally, systemic immunodeficiency or external factors, such as potential carcinogenic viral infections (e.g., HPV infection), may be evaluated and utilized to further elucidate the etiology of tumors (5,39).

In a study of 10 cases of lymphedema associated with lymphoma, Hawkins *et al* (25) demonstrated that unilateral leg edema was the sole presenting symptom in 7 cases. Similarly, Smith *et al* (7) reported that among 35 cases of lymphedema attributed to neoplasms, all 8 lymphoma cases presented with palpable inguinal lymph nodes, with 3 cases presenting with edema as the initial manifestation of the condition. Upon the diagnosis of lymphedema, clinicians should maintain a heightened clinical suspicion of lymphoma as a potential underlying cause.

In the present cohort of 11 patients, lymphedema predominantly affected the lower extremities (9 out of 11 patients), with a mean age of 61.0±12.5 years and a median delay of 7 months between lymphedema onset and lymphoma diagnosis. The key clinical manifestations of these patients included limb swelling, weakness, weight loss, lymphadenopathy and pain. These findings align with those of previous studies, such as that by Hawkins *et al* (25), which reported unilateral leg edema as the sole presenting symptom in 70% of patients with lymphoma-associated lymphedema. Similarly, Smith *et al* (7) noted that lymphedema secondary to malignancy often

Table II. Tumor marker profiles in patients with abnormal results.

Patient no.	CA125, U/ml (normal, <35)	Serum β2-MG, mg/l (normal, 1.09-2.53)	Urinary β2-MG, mg/l (normal, <0.20)	Serum Igκ, g/l (normal, 1.70-3.70)	Serum Igλ, g/l (normal, 0.90-2.10)	Urinary Igκ, mg/l (normal, <7.91)	Urinary Igλ, mg/l (normal, <4.09)
3	-	4.05[a]	1.40[a]	-	-	22.40[a]	4.34[a]
4	53.60[a]	-	-	-	-	-	-
9	-	-	-	1.68[a]	-	20.60[a]	4.18[a]
11	-	-	-	3.75[a]	-	8.26[a]	-

[a]Abnormal values. -, values within normal limits; MG, microglobulin.

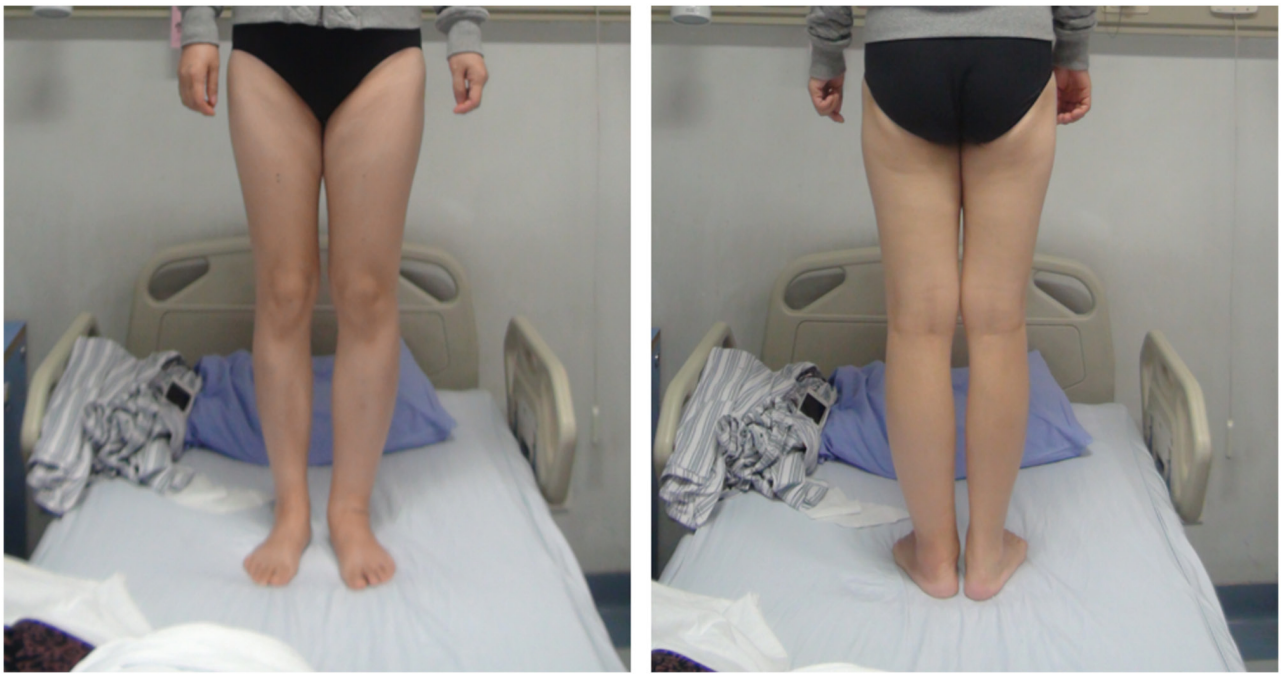

Figure 1. Case 4, a 41-year-old woman whose left lower limb swelling had persisted for 10 months and worsened for 4 months.

manifests acutely and asymmetrically, along with accompanying systemic symptoms such as fatigue and weight loss. Notably, the present case report revealed a greater proportion of lower extremity involvement (81.8%) compared with upper limb involvement (9.1%), which is consistent with a report by Tatnall and Mann (17), which described chronic limb lymphedema as a predisposing factor for non-Hodgkin's lymphoma. The present scenario contrasts with secondary lymphedema caused by breast cancer surgery, where upper limb involvement is predominant.

Lymphoma-induced lymphedema is frequently misdiagnosed initially because of its nonspecific presentation. In the present cohort, 66.7% of patients exhibited abnormal changes in tumor markers (including alterations in CA125 and β2-microglobulin) and 45.5% had anemia, which suggested systemic involvement. Furthermore, imaging modalities (such as CT, MRI and ultrasonography) achieved 100% detection rates for suspicious lesions, which thereby underscores their diagnostic utility. However, the case reported by González-Vela *et al* (11) was extremely prone to misdiagnosis: an 89-year-old male presented with multiple cutaneous lesions on his right limb, manifesting as chronic lymphedema. Upon skin examination, multiple purplish red, firm, slightly infiltrated nodules were found on his legs and instep of his foot. Biopsy of one of the nodules revealed a diffuse large B-cell lymphoma of the leg. CT scans of the patient's chest, abdomen, and pelvis did not show signs of lymph node enlargement. Bone marrow aspiration and biopsy results were normal. The patient underwent local radiotherapy and achieved significant clinical remission. The differentiation of lymphoma-associated lymphedema from lymphedema of other etiologies requires a comprehensive evaluation of the clinical presentation, imaging findings, biomarkers, pathological mechanisms and therapeutic responses. In our research, we found that lymphoma-induced lymphedema typically manifests with insidious, asymmetric lower extremity swelling (81.8% of cases) occurring over weeks to months, which is often accompanied by systemic symptoms such as weight loss,

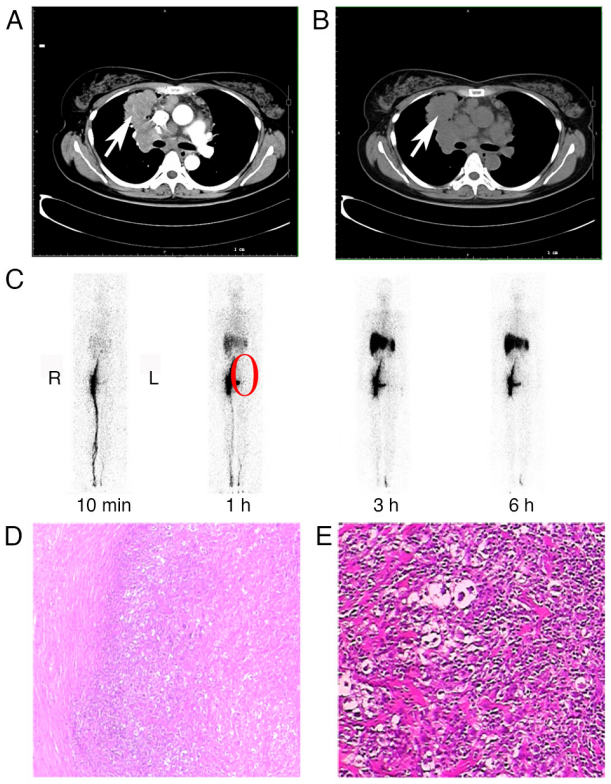

Figure 2. Case 4. (A) Chest CT scan. This axial CT image demonstrates a mass lesion (indicated by the white arrow) located adjacent to the mediastinum, specifically involving the right lung hilum and upper lobe (each mark on the scale bar corresponds to one centimeter). (B) The contrast-enhanced axial CT image (same level as 2A) reveals that the right hilar/upper lobe mass (white arrow) exhibits heterogeneous ('uneven') enhancement and is contiguous with a larger mediastinal mass, confirming their connection. (Each mark on the scale bar corresponds to one centimeter). (C) Whole-body lymphoscintigraphy image showing tracer distribution following injection in the feet. Key findings include the following: i) Mild thickening of the left lower limb, ii) significant retention of the radiotracer ('imaging agent') at the injection site in the left foot (suggesting impaired lymphatic drainage), and iii) non-visualization (absence of tracer uptake) in the left inguinal, iliac and para-aortic/lumbar lymph node basins (highlighted by the red circle), indicating lymphatic obstruction or dysfunction in these regions. (D and E) Pathology-left supraclavicular lymph node: Photomicrographs of histopathological sections from the dissected left supraclavicular lymph node (D) magnification, x200; (E) magnification, x400 (H&E stain). The morphology is diagnostic of 'B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma'. The lymph node structure is unclear, with no subcapsular sinus observed. Fibrosis is evident and scattered lymph follicles and nodular lymphoid tissue are visible. In E, large cells and dry corpse-like cells are scattered within, with some presenting as histiocyte-like.

fever or lymphadenopathy. In addition, patients may exhibit acute-onset skin pigmentation changes or localized neuropathic symptoms, which represent features that are distinct from acute unilateral swelling with tenderness/cyanosis (which occurs in venous edema) or bilateral symmetry (which occurs in systemic causes such as heart failure). Additionally, imaging serves a key role. Specifically, the use of CT/MRI in lymphoma can reveal tumor-obstructed lymphatic pathways or malignant lymphadenopathy, whereas the use of positron emission tomography-CT can identify hypermetabolic lesions, which contrasts the venous duplex findings of thrombosis observed in venous edema or the hypoalbuminemia-driven fluid shifts observed with systemic causes. Furthermore, elevated serum biomarkers (such as β2-microglobulin and CA125) are observed in 66.7% of patients with lymphoma, which further distinguishes lymphoma from hypoproteinemia (low albumin levels) or a venous etiology (elevated D-dimer levels). Pathologically, lymphoma disrupts lymphatic integrity via direct tumor infiltration or cytokine-mediated dysfunction, which thus creates an immunocompromised microenvironment, whereas primary lymphedema stems from congenital lymphatic malformations. Therapeutically, lymphoma-associated edema responds poorly to conventional compression therapy and requires tumor-directed interventions (such as chemotherapy or radiotherapy), unlike venous edema (which is anticoagulation-responsive) or primary lymphedema (which is partially improved by using decongestive therapy). Notably, lymphoma rarely induces systemic edema, which is a feature that is absent in postoperative or primary lymphedema and thereby underscores the importance of screening for malignancy in atypical presentations (40,41).

In conclusion, based on the retrospective analysis of 11 patients with lymphoma presenting with lymphedema at our institution, this case series establishes that lymphedema frequently serves as an early and occasionally isolated manifestation of lymphoma, particularly affecting the lower extremities with asymmetric progression. Key findings include a median diagnostic delay of 7 months, frequent systemic biomarkers and universal detection of malignant lesions by cross-sectional imaging (CT/MRI/ultrasonography). Critically, lymphoma-induced lymphedema demonstrates poor response to conventional decongestive therapy but shows significant improvement with tumor-directed interventions (chemotherapy/radiotherapy). These observations underscore that unilateral lower limb edema-particularly when acute, therapy-refractory or accompanied by unexplained serologic abnormalities-warrants rigorous screening for occult lymphoma. Integrating targeted imaging and biomarker assessment into the diagnostic workflow is essential to reduce delays in lymphoma diagnosis and initiate timely oncologic management, thereby altering the natural history of this potentially misdiagnosed condition.

Acknowledgements

Not applicable.

Funding

Funding for the present case report was provided by the Talent Development Program of Beijing Shijitan Hospital Affiliated to Capital Medical University during the 14th Five-Year Plan (grant no. 2023LJRCSWB); the Youth Fund of Beijing Shijitan Hospital Affiliated to Capital Medical University (grant no. 2022-q16); the Key Project of Beijing Shijitan Hospital Affiliated to Capital Medical University (grant no. 2024-C04); and the Haidian District Health Development Research and Cultivation Plan of Beijing (grant no. HP2025-04-506002).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

KH, RW, WS and YS conceptualized and designed the present case report. WS, RW and YS provided administrative support. KH, XL, JR, CY, LZ, BL, RW, YS and WS provided the study materials and recruited patients. KH, XL, JR, CY, LZ, BL, RW and YS collected and assembled the data. KH, XL, JR, RW and YS performed the data analysis and interpreted the data. KH and YS confirmed the authenticity of all the raw data. All authors wrote the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The Ethics Committee of Beijing Shijitan Hospital, Capital Medical University, approved the present study [approval no. sjtkyll-lx-2022(058)], which adhered to the ethical guidelines set forth in the Declaration of Helsinki.

Patient consent for publication

Written informed consent was obtained from the participating patients for the publication of the anonymized medical images (including radiological data) and associated case details.

Competing interests

The authors declare that they have no competing interests.

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