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CASE REPORT

Surgical Treatment for Benign Lymphangioendothelioma After Two Incomplete Excisions: A Case Report and Literature Review

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Abstract: Benign lymphangioendothelioma (BL) is a rare, poorly identified, slow-growing benign vascular lesion characterized by asymptomatic, solitary, well-demarcated macules, or by mildly infiltrated plaque. We report a case of an atypical BL that arose as a tender, protuberant, flesh-colored mass with cyanotic vesicles, and then progressed to a persistent exudative wound after two incomplete excisions. The patient was also diagnosed with thoracic duct narrowing. Although the stenosis was removed by surgery, the right lower extremity ulceration and exudation did not improve. Thus, we performed a thorough excision and split-thickness skin graft transplant following vacuum sealing drainage, and eventually the patient had a favorable functional and cosmetic outcome. A biopsy revealed irregular, dilated vascular spaces lined with a single layer of flat endothelial cells extending from the superficial dermis to the subcutis that did not reach the striated muscles. Additionally, by reviewing the literature on BL, in this paper we summarize the diverse pathogenic, morphological, and immunohistochemical presentations for this rare disease, as well as the histopathological differential diagnosis of lymphangiomatosis, Kaposi's sarcoma, and angiosarcoma.

Keywords: acquired progressive lymphangioma, angiosarcoma, benign lymphangioendothelioma, Kaposi's sarcoma, lymphangioma, lymphangiomatosis

Introduction

Benign lymphangioendothelioma (BL) is a rare, slow-growing vascular lesion that is poorly understood. It was first reported by Wilson Jones[1] as malignant angioendothelioma in a 10-year-old girl and was later recognized as a benign condition and formally named "acquired progressive lymphangioma" (APL) in 1976.[2] BL is characterized histologically as an uncommon lymphatic vascular proliferation with infiltrating lymphatic channels dissecting collagen.[3,4] Clinically, BL lesions typically present as asymptomatic, solitary, well-demarcated macules or mildly infiltrated plaques that are pink to red-brown in color.[5] According to the PubMed, Web of Science, and Scopus databases, only 83 cases of BL (in 40 reports) have been described in English from 1963 to the present, with only a minority of cases experiencing relapse.[6–8] Although BL is considered a rare presentation of lymphatic malformation rather than a true neoplasm, complete excision is necessary due to the infiltrating character of the entity.[9]

In this report, we describe a patient with BL on the lower leg who presented with multiple ulcers and exudation, and was successfully treated with a skin graft following debridement and vacuum sealing drainage. This case report has been reported in line with the SCARE 2020 Criteria.[10] The patient provided consent for the publication of case details and images. Furthermore, we conducted a review of the literature to discuss the pathogenesis, diagnosis, differential diagnosis, and treatment options for BL.

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Case Report

Patient Information

A 25-year-old female with no history of radiation exposure presented with persistent ulceration and exudation on her right lower extremity. The condition had developed three years prior following a cutaneous lesion that had been gradually growing for seven years. At age 16, the patient sustained an injury to her right calf in a bicycle accident, resulting in the development of a 3 cm x 3 cm bruise. Over time, the bruise grew into a flesh-colored, slightly tender, protuberant mass measuring 20 cm x 35 cm with cyanotic vesicles (Figure 1). Magnetic resonance imaging showed increased signal density corresponding to the vascular lesion, extending to the superficial layer of the deep fascia. In 2018, the lesion was excised and histopathological examination revealed the presence of many irregularly shaped and anastomosing channels lined by flattened endothelial cells that had infiltrated between collagen bundles through the dermis and subcutaneous tissue. Atypical endothelial cells were absent. The endothelial cells expressed podoplanin (D2-40), CD31, and CD34, indicating the lymphatic nature of the lesion. Based on these findings, a diagnosis of BL or lymphangiomatosis was considered. In 2019, the patient's wound was seeping and steadily worsening. An ultrasound revealed that the posterior lateral region of the left cervicothoracic duct was restricted. Lymphoscintigraphy showed activity in the left jugular venous angle and increased radiopharmaceutical kinetics in the right lower limb, suggesting thoracic duct outlet obstruction and lower limb lymphangioma. In May 2021, the patient underwent debridement of the lower leg, as well as recanalization and anastomosis of the chest catheter. Pathological examination suggested the possibility of hemangioendothelioma or a generalized lymphangioma. Despite the treatment, the wound on the right calf did not heal, and the patient visited our clinic for further treatment. She had been unable to walk for a year due to severe pain. The timeline of the reported incident is depicted in Table 1.

Clinical Findings

On physical examination, a hyperpigmented, slightly indurated, 14 cm × 21 cm mass with a strong odor was observed. There were also blisters, ulcerations, continuous seeping of lymph-like clear liquid, and some bleeding (Figure 2). The ulcerations were 3 cm × 4 cm and 3 cm × 5 cm.

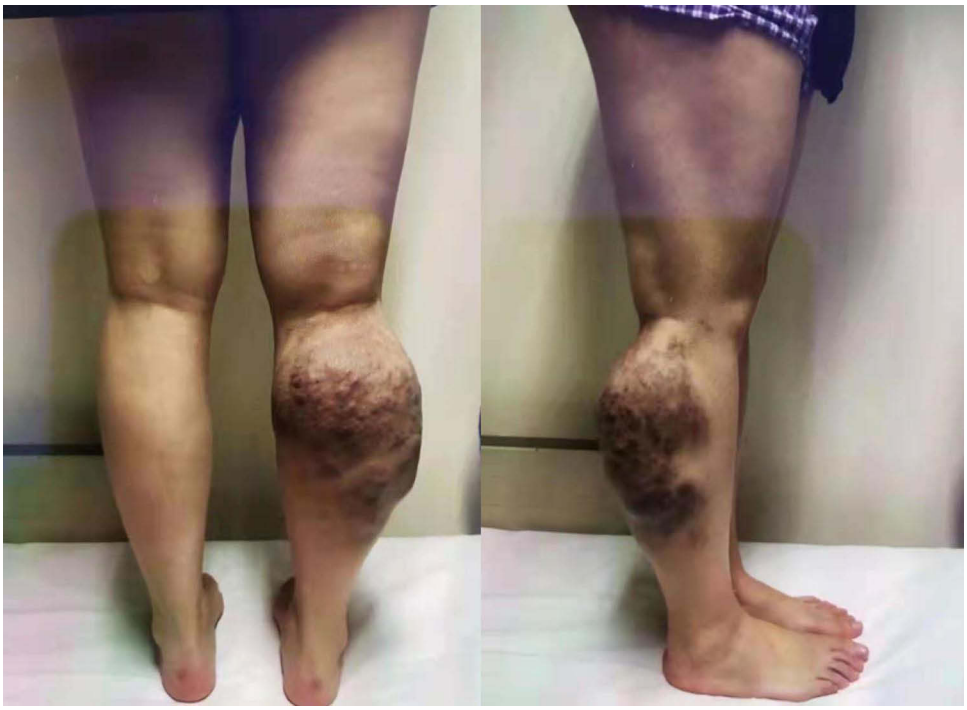

Figure 1 The condition of the patient's lower limb before the first debridement.

Table 1 Timeline of Events

Date	Information
2014	Patient sustained an injury to the right calf in a bicycle accident, leading to the formation of a bruise.
2018	The initial bruise evolved into a 20 cm x 35 cm mass with cyanotic vesicles.
2018.9	First excision surgery was performed on the protuberant mass.
2019	Persistent ulceration and exudation were observed in the bruised area. There was a restriction in the posterior lateral region of the left cervicothoracic duct.
2021.5	Second excision surgery was performed, along with recanalization and anastomosis of the chest catheter.
2021.6	The surgical wound on the right calf remained unhealed. The patient was unable to walk for a year due to severe pain.

Diagnostic Approach

A wound secretion and drug sensitivity test revealed an Enterobacter cloacae infection, which was found to be sensitive to gentamicin. No abnormalities were observed upon general examination. T2-weighted magnetic resonance imaging showed scattered lesions with increased signal density.

Therapeutic Intervention

After two weeks of dressing changes for preoperative preparation, the patient was admitted to the hospital. On the first day of hospitalization, the patient underwent debridement of the right lower leg under general anesthesia to remove the lesion by excising the skin and subcutaneous tissue. During the operation, lymph-like fluid was observed oozing from the unhealthy subcutaneous adipose tissue surrounding the wound. Therefore, the excision of unhealthy adipose tissue was extended to 2 cm around the lesion until healthy fat was exposed. The 18 cm × 28 cm incision was then cleaned (Figure 3A), two vacuum sealing drainage (VSD) sponges were placed on the wound, and two semipermeable

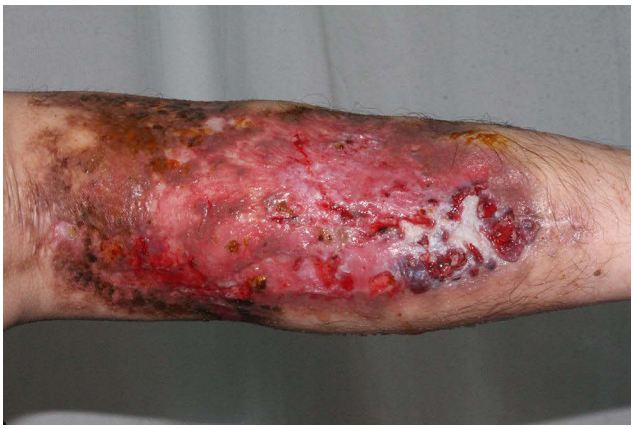

Figure 2 The lesion of the right lower leg after two debridements at admission. Multiple ulcers and a superficial scar were visible on the dorsal area of the right calf.

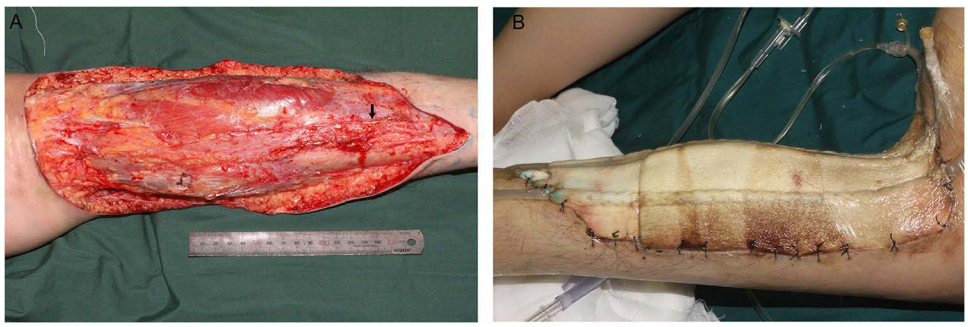

Figure 3 Surgery on the first day after admission. (**A**) The clearly necrotic tissue was entirely removed. Arrows indicate the sural nerve. (**B**) Two vacuum sealing drainage devices were installed after the debridement.

Table 2 The Intake and Output Volume of Closed Irrigation During Two VSD Treatment

Day	Intake Volume (mL)	Output Volume (mL)	Δ Value (mL)[a]	Δ/Intake Ratio[b]
2	580	720	140	0.24
3	800	950	150	0.19
4	700	840	140	0.20
5	530	550	20	0.04
6	1300	1400	100	0.08
7	900	980	80	0.09
8	400	500	100	0.25
Average1[c]			104	0.16
11	1000	1050	50	0.05
13	925	950	25	0.03
14	850	870	20	0.02
15	600	650	50	0.08
Average2[d]			36	0.05

Notes: [a]ΔDifference volume (mL) = output volume- input volume; [b]Δ/intake ratio = (output volume - input volume)/input volume×100%; [c]Average 1, average volume after the first debridement; [d]Average 2, average volume after the second debridement.

membranes were used to seal the wound before applying negative pressure (Figure 3B). Continuous negative pressure of approximately 20 kPa was applied to the wound on the right lower limb after the first debridement. Closed irrigation with sterile normal saline was then performed, and the amounts of irrigation and extraction were carefully recorded (Table 2). One week after admission, the patient underwent a second procedure in which the VSD sponges were replaced under intravenous anesthesia. During this procedure, any unhealthy subcutaneous adipose tissue and exudation surrounding the wound were also removed. The VSD was left in place for an additional week. Initially, the extraction volume was greater than the rinsing volume, exceeding it by approximately 15% (104 mL) during the first ten days after the second procedure. Over time, however, the excess volume decreased to about 5% (36 mL), and the appearance of the extracted fluid gradually changed from cloudy to transparent. Two weeks after admission, the patient received an 18 cm × 28 cm split-thickness skin graft (STSG), harvested from the right thigh, to cover the wound on the right calf (Figure 4).

The histopathological examination of the lesions, in conjunction with the patient's medical history, confirmed the diagnosis of BL. Microscopic analysis revealed irregular, dilated vascular spaces lined with a single layer of flat endothelial cells, which showed no signs of nuclear atypia or mitotic activity (Figure 5). The narrow vascular spaces within the dermis were separated by reticular dermal collagen bundles (Figure 6). The lesions extended from the superficial dermis to the subcutis but did not involve the striated muscles. There were no signs of extravasated red cells, hemosiderin, or inflammatory infiltrate.

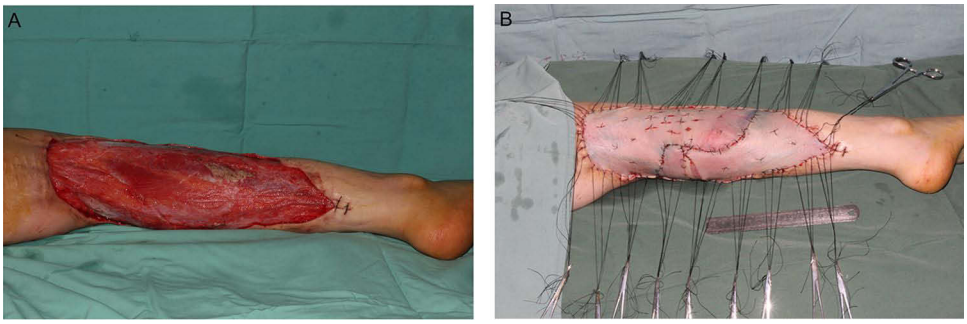

Figure 4 Skin grafting two weeks after debridement. (**A**) The necrotic tissue was completely removed, with a promising amount of fresh granulation tissue covering the wound before the skin graft operation. (**B**) The split-thickness skin graft was sutured to the wound.

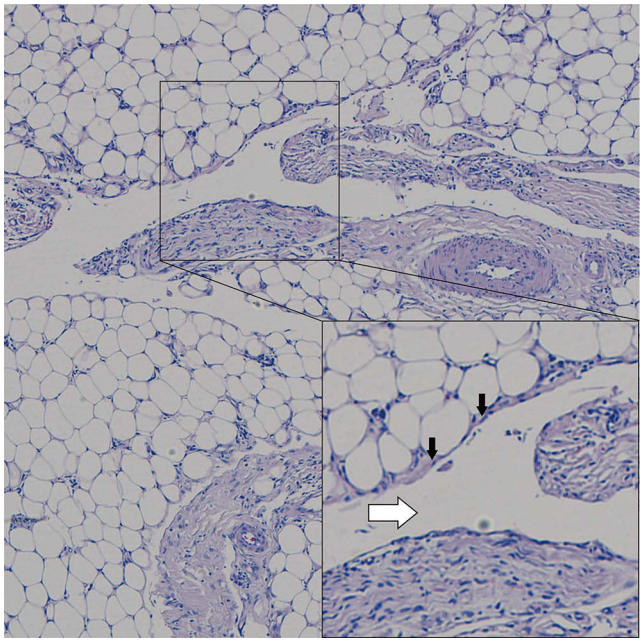

Figure 5 Pathological examination showing ectatic vascular spaces (white arrow) lined by flattened, cytologically bland endothelial cells (black arrow) dissecting through subcutaneous fat (Hematoxylin-eosin stain; original magnifications: B, × 4).

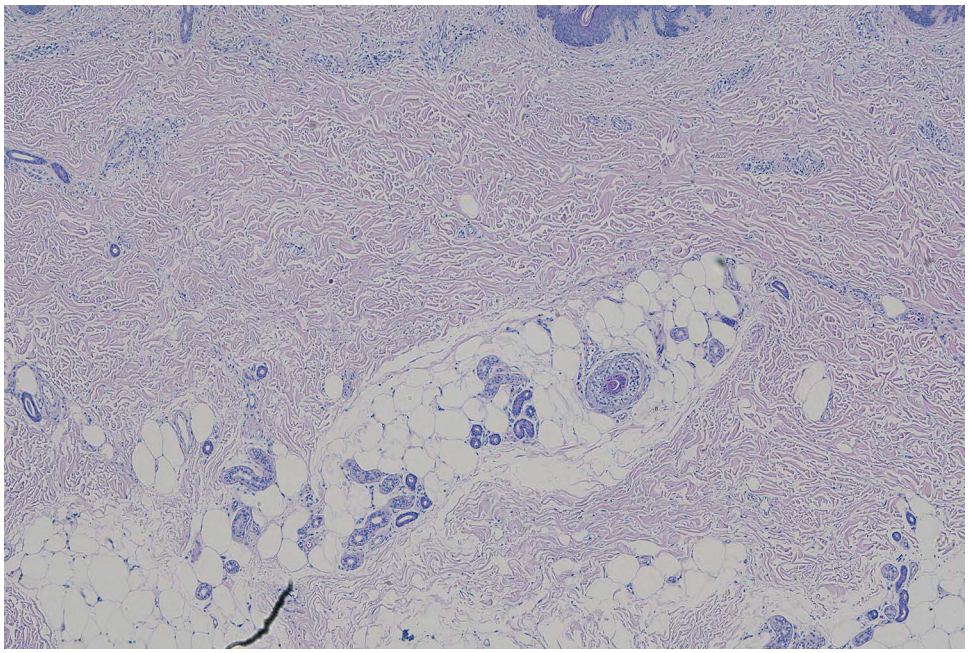

Figure 6 The narrow vascular spaces separated by reticular dermal collagen bundles in the dermis. (Hematoxylin-eosin stain; original magnifications: B, × 4).

Follow-Up and Outcome

The patient showed excellent postoperative recovery, and during the 1-year follow-up conducted remotely via video, complete wound healing was observed with no associated complications or recurrence. The patient expressed satisfaction with the functional and cosmetic outcome.

Discussion

The authors conducted a comprehensive search of the published literature in three databases, PubMed, Web of Science, and Scopus, using restricted language to English and a specific time period up to October 1, 2022. We used appropriate search keys to identify papers related to the subject of "acquired progressive lymphangioma" and "lymphangioendothelioma". After reviewing the titles and abstracts of 86 relevant papers, the authors found 37 articles reporting 80 cases. We also searched cited cases prior to the official recognition of the terms "APL" and "BL" and identified a total of 83 patients in 40 reports (Table 3), including 27 cases diagnosed with BL after radiotherapy for breast carcinoma.[6,7,11,12] Recurrences were observed only in cases with incomplete excision,[6,8,12] with only one lesion progressing to an angiosarcoma eight years later.[12]

The etiology of this benign lymphatic malformation remains unclear, but various triggering factors have been reported, including trauma,[9,13,14] tick bites,[15] surgery,[16–18] femoral arteriography,[19] cardiac catheter examination,[20] radiation therapy[6,7,11,12] and recurrent cellulitis.[21] Our case adds to the evidence that trauma may be a predisposing factor for the development of BL. Additionally, there have been reports of BL developing from preexisting congenital vascular lesions.[8,13,20–23] Kato et al[19] proposed that traumatic obstruction of lymphatic circulation, if not sufficient to induce lymphedema, could lead to lymphatic proliferation and the formation of BL lesions. Inflammatory stimuli played a critical part in the genesis and rapid growth of BL, as demonstrated by the fact that the tumor may regress gradually with topical[24] or systemic[9,13] corticosteroid therapy. However, the role of inflammatory stimuli is controversial, with some studies suggesting that corticosteroid therapy is ineffective,[21] and spontaneous recovery of the lesion has been reported in some cases.[5,25] The role of immunity in the pathogenesis of BL is crucial, as Hunt et al[26] reported that the plaque grew significantly under an immunosuppressive regimen of tacrolimus, mycophenolate mofetil, and prednisone. However, the response of different lesions to imiquimod, an immune response modifier, is perplexing.[27,28] Another hypothesis regarding BL's pathogenesis suggests that it may be a hamartoma of intermediately differentiated lymphatic vessels, blood vessels, and smooth muscle, given that lymphatic endothelial markers, various blood endothelial markers, type IV collagen, and desmin have been found to surround the vascular channels in many BL cases.[29] In terms of the nature of BL, it is widely accepted that BL is a lymphatic vascular malformation rather than a true neoplasm, as demonstrated by the absence of WT-1[23,30,31] and D2-40 expression[18,23,32–34] in endothelial cells. In the present case, positive D2-40 expression in endothelial cells further supports this view. Since the majority of evidence indicates that BL is a lymphatic malformation, sirolimus, which inhibits the incidence and progression of BL by targeting VEGFR-3, has been used to treat BL and has achieved satisfactory outcomes.[26] However, some cases of BL with lesions larger than 60 cm have shown positive WT-1 expression,[34,35] a marker of proliferation and neoplasia rather than a malformation, indicating that BL may develop a proliferative capacity in the slow enlargement process.

Jones[3] summarized five features of BL that distinguish it from malignant angioendothelioma: (1) its development primarily in young individuals; (2) its sites of predilection are not limited to the face and scalp; (3) its lesion is usually localized and flat; (4) it has a slow growth and favorable prognosis; and (5) its so-called dissection of collagen appearance, channeled with a row of endothelial cells showing no obvious cellular atypicality. Of the 83 cases we found reported in the literature, most fulfill all but the first criterion. BL has been identified in virtually every age group, with the reported age of presentation ranging between 1 and 90 years, with a median age of 46.07 (the average time to diagnosis is around 6 years). It displays no sex predilection. The most commonly affected sites are the limbs (30% of cases), followed by the breast (24% of cases), head and neck (12% of cases), and other areas such as the abdominal wall, chest, back, shoulder, buttock, axilla, and groin. In contrast to most previous cases with localized, flat lesions, our patient had a slightly tender, protuberant, flesh-colored mass with cyanotic vesicles. BL criteria should allow for morphological variability, with some cases presenting as nodular mass,[30] actinic keratosis-like lesion,[36] condyloma acuminatum,[14] and even without a visible mass or rash.[25] BL can grow to a large size, with a maximum diameter of 65 cm reported in one case.[35] Patients are generally asymptomatic, but occasionally, pain (sometimes extreme[13]), pruritus, swelling, and tenderness have been reported. Our patient experienced consistent watery clear liquid exudation after debridement, which is a symptom that has been observed in several other cases.[14,18,23,30] The lymph-like fluid in our case may have seeped from ulceration, potentially exacerbating the infection. On a histological level, BL is characterized by the

Table 3 Characteristics and Treatments of Patients with Lymphangioendothelioma Reported from 1963 to 2022

Case	Age (yr)	Duration (yr)	Sex	Location	Clinical Symptom	Physical Examination	Size	Pathological Findings	Nuclear Atypia or Mitotic Figures	Immunohistochemical Results	Follow-Up	Treatment
Jones 1963[1]	15	5	F	Right wrist	Asymptomatic	A round, flat, erythematous plaque	2cm	Multiple, slitlike, bloodless channels throughout the dermis with a dissection-of-collagen appearance	Little or no cellular atypia or nuclear hyperchromatism	NA	Without recurrence at 3 years	Wide excision
Gold 1970[4]	23	10	M	Right thigh	Tenderness	A discolored patch	>30cm	Abnormal, narrow, endothelium-lined vessels involving dermis and subcutaneous tissue	No significant cellular atypia	NA	Without recurrence at 13 years	Wide excision
Watanabe 1983[9]	5	1	M	Left temporal, retroauricular areas, forehead, neck, shoulder; left arm	Tenderness	Dark brown erythematous lesions with slight atrophy	3.5 x 6.5 cm	Left retroauricular area: dilated channels lined by a single layer of endothelial cells throughout the dermis and extending to the subcutaneous fat left upper arm: the appearance of "dissection of collagen"	Minimal or no cellular atypia	NA	Gradual regression	10 mg oral prednisolone for 3 months
Tadaki 1988[37]	8	4	M	Abdominal wall	Asymptomatic	An erythematous patch	3.7 × 7.0 cm	Tortuous vascular channels	Some cellular atypia	F-VIII-RA (-)	Without recurrence at 3 years	Excision
Jones 1990[46]	55	2	F	Forearm	NA	NA	3 cm	Delicate, thin-walled, endothelium-lined spaces and clefts throughout the dermis	None gross nuclear atypia, none multinucleate tumor cells	F-VIII-RA (-), UEA I (+)	Without recurrence at 1 year	Excision
Jones 1990[46]	28	1	F	Shoulder	NA	NA	NA	Delicate, thin-walled, endothelium-lined spaces and clefts throughout the dermis	None gross nuclear atypia, none multinucleate tumor cells	F-VIII-RA (-), UEA I (+)	NA	Incisional biopsy
Jones 1990[46]	69	0.3	F	Both forearms	NA	NA	>30cm	Delicate, thin-walled, endothelium-lined spaces and clefts confined to the subpapillary region and upper dermis	None gross nuclear atypia, none multinucleate tumor cells	F-VIII-RA (-), UEA I (+)	Died of unrelated cancers	Incisional biopsy

(*Continued*)

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Table 3 (Continued).

Case	Age (yr)	Duration (yr)	Sex	Location	Clinical Symptom	Physical Examination	Size	Pathological Findings	Nuclear Atypia or Mitotic Figures	Immunohistochemical Results	Follow-Up	Treatment
Jones 1990[46]	52	3	M	Left shoulder	NA	NA	NA	Delicate, thin-walled, endothelium-lined spaces and clefts confined to the subpapillary region and upper dermis	None gross nuclear atypia, none multinucleate tumor cells	F-VIII-RA (-), UEA I (+)	Without recurrence at 1 year	Excision
Jones 1990[46]	68	0.3	M	Forearm	NA	NA	NA	Delicate, thin-walled, endothelium-lined spaces and clefts confined to the subpapillary region and upper dermis	None gross nuclear atypia, none multinucleate tumor cells	F-VIII-RA (-), UEA I (+)	Without recurrence at 0.5 year, died of unrelated cancers at 1 year	Excision
Jones 1990[46]	59	0.3	M	Left side of back	NA	NA	NA	Delicate, thin-walled, endothelium-lined spaces and clefts confined to the subpapillary region and upper dermis	None gross nuclear atypia, none multinucleate tumor cells	F-VIII-RA (-), UEA I (+)	Without recurrence at 1 year	Excision
Zhu 1991[29]	9	3	M	Right calf	Swelling, warmth, itching, and pain; profuse lymphatic drainage at skin biopsy	A hyperpigmented, slightly indurated, irregular patch	8×9 cm	Many irregularly shaped and dilated channels, lined by a single layer of endothelium within the dermis	Minimal cellular atypia, none multinucleate cells or mitotic activity	ColIV (+), desmin (+)	NA	Incisional biopsy
Mehregan 1992[5]	58	NA	F	Left thigh	Asymptomatic	A large linear, angiomatous and tender plaque	NA	Vascular channels lined by a single row of endothelial cells that infiltrated between collagen bundles throughout the dermis	Lack of nuclear atypia and mitoses	F-VIII-RA (±), VIM (±), UEA I (+)	Resolved spontaneously after 5 months	Incisional biopsy
Mehregan 1992[5]	52	3	M	NA	Asymptomatic	A soft, deep dermal growth cyst	3.5 cm	A deep dermal and partially subcutaneous tumor composed of a proliferation of elongated endothelial cells lining collagen bundles and forming dilated vascular spaces	None abnormally large cells, mitotic figures, or nuclear atypia	F-VIII-RA (±), AAT (±), VIM (-)	NA	Excision

Renshaw 1993[47]	60	NA	F	Upper lip	NA	NA	NA	Freely anastomosing vessels beneath the epidermis, with a pattern of dissection of collagen fibers	None nuclear atypia, mitoses or prominent nucleoli	NA	NA	Incisional biopsy
Herron 1994[21]	40	40	M	Right thigh	NA	A nontender, wellmarginated, red-brown, slightly raised plaque, with the surface lichenified with scattered flat-topped papules	10 × 15 cm	Flattened, endothelium-lined channels and spaces permeated both papillary and reticular dermis	None cellular atypia	VIII (+), UEA I (+), CD34 (+), HLA-DR (+), CollV (+), laminin (+), actin (+), ICAM-I (±), XIII (-), desmin (-), Ki-67 (-)	NA	Incisional biopsy
Meunier 1994[48]	30	16	F	Right breast	Asymptomatic	Scattered yellowish papules with an 'apple jelly' appearance	Involve almost the entire breast	Many dilated, tortuous vascular channels lined by an hyperplastic endothelium; a 'dissection of collagen' appearance	Without cellular atypia	NA	Without any benefit	1 mg/kg·d oral prednisolone for 4 months
Rosso 1995[11]	49	1	F	Left breast	Asymptomatic	A slightly raised, faintly red papular lesion; a lesion surrounded by several smaller papules; a pinkish papule	0.5–1cm	An anastomosing network of thin-walled, bloodless vascular channels extended from papillary to reticular dermis dissecting collagen bundles	None atypical cells with pleoniorphic nuclei	F-VIII-RA (+), CD34 (±), UEA I (±), cyclin (-), Ki-67 (-)	Without recurrence at 23 months	Wide skin excision
Soohoo 1995[49]	9	1	M	Right knee	Asymptomatic	A violaceous macule with a central, slightly indurated brown papule	2×1 cm	Anastomosing and discrete lymphatic channels lined with flattened endothelial cells; in areas had a "dissection of collagen" appearance	NA	F-VIII-RA (-), UEA I (+)	NA	Incisional biopsy
Kato 1996[19]	52	NA	M	Right thigh	Itch and pain	A reddish purple, slightly raised, well-demarcated plaque	9.5 × 6.5 cm	Many irregularly shaped and dilated channels lined by a single layer of endothelium; some of the endothelial cells protruded into the vascular lumina; the vascular proliferation dissecting between collagen bundles	None cellular atypia and mitotic activity	vWF (-)	NA	Incisional biopsy

(Contir

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Table 3 (Continued).

Case	Age (yr)	Duration (yr)	Sex	Location	Clinical Symptom	Physical Examination	Size	Pathological Findings	Nuclear Atypia or Mitotic Figures	Immunohistochemical Results	Follow-Up	Treatment
Grunwald 1997[16]	68	5	F	Right buttock	Asymptomatic	A well-demarcated, indurated, erythematous plaque	NA	Numerous vascular channels throughout the dermis; the channels becoming narrow in the reticular dermis, giving the appearance of "dissecting the collagen bundles"	None atypical cells	F-VIII-RA (+), UEA I (+), ColIV (±), desmin (±)	Marked improved	Intensive oral antibiotic therapy (ciprofloxacin and clindamycin)
Wilmer 1998[15]	64	3	M	Back (the lumbar area)	Asymptomatic	A solitary, irregular, oval shaped plaque with a well-defined border and scaly crusts	2×4 cm	Subepithelial thin-walled vascular clefts, lined by a flat endothelium	Without cellular atypia or increased mitotic activity	CD31 (+), F-VIII-RA (+), SMA (+)	No recurrence after 18 months	Excision
Guillou 2000[8]	17	8	F	Chin	Asymptomatic	Slowly enlarging, fluctuant lump	Small	Anastomosing, angulated, and often widely dilated vascular spaces in the superficial dermis; vascular spaces dissecting the dermal collagen in an angiosarcoma-like fashion	None	F-VIII-RA (+), CD31 (+), CD34 (+), actin (+), desmin (+)	Recurrence at 7 months and 2 years; lost to follow up then on	Excisional biopsy
Guillou 2000[8]	78	>2	F	Posterior auricular area	Concomitant hair loss	Large, scaly, macular bruise-like lesion on back of head, occiput, and above and behind right ear	10cm	The same as the above	None	F-VIII-RA (-), CD31 (-), CD34 (-)	Persistent lichen planus; dead of congestive heart failure at 7 months	Incisional biopsies (x2)
Guillou 2000[8]	37	NA	M	Mouth	Painful swelling	Hemorrhagic clinical appearance	1.5cm	The same as the above	None	CD31 (+), EMA (-)	No evidence of disease at 40 months	Incisional biopsy in Nov'93; incomplete excisional biopsy in March'94
Guillou 2000[8]	71	15	M	Left foot	Asymptomatic	Discolored, 1.4×3 cm hemangiomatous lesion	2.6cm	The same as the above	None	F-VIII-RA (+), CD31 (+), CD34 (+), actin (+)	NA	Incomplete excisional biopsy
Guillou 2000[8]	52	5~6	F	Back of neck	Asymptomatic	Solitary asymptomatic bluish nodule with smooth surface	1cm	The same as the above	None	F-VIII-RA (+), CD31 (+), CD34 (+), actin (+)	No evidence of disease at 27 months	Excisional biopsy
Guillou 2000[8]	53	1.5	F	Right forearm	Asymptomatic	Fluctuant, asymptomatic, irregular and smooth reddish-brown patch	2cm	The same as the above	None	F-VIII-RA (-), CD31 (-), CD34 (-)	No evidence of disease at 12 months; keloid at the site of surgery at 6 months	Incisional biopsy, complete excision

Guillou 2000[8]	30	Childhood	M	Left breast	Asymptomatic	Small, nonitching, fluctuant, erythematous macule	0.5cm	The same as the above	None	F-VIII-RA (-), CD31 (-), CD34 (-)	NA	Excisional biopsy
Guillou 2000[8]	65	0.16	F	Left shoulder	Asymptomatic	Well-defined, slowly growing papule on shoulder with pigmentary incontinence	0.3cm	The same as the above	None	F-VIII-RA (-), CD31 (-), CD34 (-)	No evidence of disease at 10 months	Excisional biopsy with free margins
Guillou 2000[8]	56	2	F	Face	Asymptomatic	Skin lesion	1.5cm	The same as the above	None	F-VIII-RA (-), CD31 (-), CD34 (-)	No evidence of disease at 9 months	Excisional biopsy
Guillou 2000[8]	90	5	M	Scalp	Profuse bleeding while combing hair	Smooth, brown, nonulcerated, slowly enlarging nodule of the scalp	NA	The same as the above	None atypical endothelial cells	F-VIII-RA (-), CD31 (-), CD34 (-)	No evidence of disease at 4 months	Excisional biopsy
Guillou 2000[8]	27	27	M	Back	Asymptomatic	Two faintly blue-brown, pigmented areas, of which one contained a 0.5-cm nodule	7cm	The same as the above	None	F-VIII-RA (-), CD31 (-), CD34 (-)	No evidence of disease at 36 months	Wide excision (8 x 4 cm)
Guillou 2000[8]	75	Recent	F	Left foot	Asymptomatic	Small macular lesions	0.5cm	The same as the above	None	F-VIII-RA (+), CD31 (+), CD34 (+), actin (+), desmin (+)	NA	Excisional biopsy of one lesion
Sevila 2000[13]	49	49	M	Right thigh	Extreme pain; marked hyperesthesia resulting in functional limitation of the knee joint	Tender, indurated, and warm plaque, the surface of which was smooth with an erythemato-violaceous center and a bruiselike contusiform periphery	17×12cm	Thin-walled vascular channels dissecting the collagen bundles extending from the mid dermis to subcutaneous fat; large and horizontally arranged vascular spaces at superficial levels and smaller at deeper ones	None evident nuclear atypia	F-VIII-RA (+), UEA I (+), VIM (+), CD31 (+), CD34 (+), ColIV (+)	Temporary improvement using predisone; no recurrence at 1 year	Prednisone 60 mg/day for 4 weeks; complete excision and split skin graft transplantation
Yiannias 2001[36]	68	NA	F	Right forearm	Asymptomatic	A light brown patch with a slightly rough texture, resembling pigmented actinic keratosis or lentigo	2.4×1.0cm	Delicate, thin-walled, endothelium-lined spaces and clefts in the upper dermis, with an overlying pigmented actinic keratosis	NA	UEA-I (+), vWF (-)	Without recurrence at 1 month	Excision

(*Continued*)

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Table 3 (Continued).

Case	Age (yr)	Duration (yr)	Sex	Location	Clinical Symptom	Physical Examination	Size	Pathological Findings	Nuclear Atypia or Mitotic Figures	Immunohistochemical Results	Follow-Up	Treatment
Hwang 2003[50]	15	10	M	Right foot	Slightly tender to palpation	Multiple erythematous, indurated coalescing plaques	6cm	Numerous dilated, anastomosing vascular spaces dissecting between collagen bundles in the mid to reticular dermis	None cellular atypia or mitotic figures	NA	NA	Incisional biopsy
Gengler 2007[6]	44	0.6	F	Chest wall	Asymptomatic	An erythematous plaque	0.5cm	Lymphangioendothelioma-like	None nuclear/ architectural atypia	NA	Alive without disease at 36 months	Complete excision with negative margins
Gengler 2007[6]	48	1.5	F	Axilla	Asymptomatic	One nodule	0.5cm	Lymphangioendothelioma-like	None nuclear/ architectural atypia	NA	Alive without disease at 120 months	Complete excision with negative margins
Gengler 2007[6]	40	NA	F	Axilla	Asymptomatic	One papule	0.7cm	Lymphangioendothelioma-like	With nuclear/ architectural atypia	NA	Alive without disease at 48 months, metastatic breast carcinoma	Complete excision with negative margins
Gengler 2007[6]	61	1	F	Breast	Asymptomatic	One nodule	0.6cm	Lymphangioendothelioma-like	None nuclear/ architectural atypia	NA	Alive without disease at 81 months	Complete excision with negative margins
Gengler 2007[6]	44	NA	F	Breast	Asymptomatic	One nodule	0.3cm	Lymphangioendothelioma-like	None nuclear/ architectural atypia	NA	Dead of ovarian carcinoma at 152 months	Complete excision with negative margins
Gengler 2007[6]	51	NA	F	Breast	Asymptomatic	One nodule	0.6cm	Lymphangioendothelioma-like	With nuclear/ architectural atypia	NA	Alive without disease at 54 months	Complete excision with negative margins
Gengler 2007[6]	67	0.25	F	Breast	Asymptomatic	Multiple papules regressing spontaneously 3 months before development of a 6-mm nodule	0.6cm	Lymphangioendothelioma-like	With nuclear/ architectural atypia	NA	Spontaneous regression 12 months after biopsy; alive without disease at 28 months	Incisional biopsy (with positive margins)
Gengler 2007[6]	53	3.5	F	Breast	Asymptomatic	One stable nodule	0.8cm	Lymphangioendothelioma-like	None nuclear/ architectural atypia	NA	Alive without disease at 14 months	Complete excision with negative margins
Gengler 2007[6]	46	NA	F	Breast	Asymptomatic	One nodule	0.5cm	Lymphangioendothelioma-like	None nuclear/ architectural atypia	NA	Lost to follow up	Incisional biopsy (with positive margins)

Gengler 2007[6]	53	NA	F	Chest wall	Asymptomatic	One papule	0.6cm	Lymphangioendothelioma-like	None nuclear/ architectural atypia	NA	Alive without disease at 24 months	Complete excision with negative margins
Gengler 2007[6]	48	NA	F	Breast	Asymptomatic	One nodule	0.4cm	Lymphangioendothelioma-like	None nuclear/ architectural atypia	NA	Alive with disease at 65 months, no additional cutaneous lesions	Incomplete excision (R1)
Gengler 2007[6]	75	NA	F	Breast	Asymptomatic	One nodule	0.4cm	Lymphangioendothelioma-like	None nuclear/ architectural atypia	NA	Alive with disease at 61 months, no additional cutaneous lesions	Incisional biopsy (with positive margins)
Gengler 2007[6]	42	NA	F	Chest wall	Asymptomatic	One cyst	0.5cm	Lymphangioendothelioma-like	None nuclear/ architectural atypia	NA	Alive with disease at 36 months, no additional cutaneous lesions	Incisional biopsy (with positive margins)
Gengler 2007[6]	52	NA	F	Breast	Asymptomatic	One nodule	0.4cm	Lymphangioendothelioma-like	None nuclear/ architectural atypia	NA	Alive without disease at 7 months	Complete excision with negative margins
Gengler 2007[6]	53	NA	F	Breast	Asymptomatic	One papule	0.6cm	Lymphangioendothelioma-like	With nuclear/ architectural atypia	NA	Lost to follow up	Complete excision with negative margins
Gengler 2007[6]	64	0.5	F	Breast	Asymptomatic	One nodule	0.4cm	Lymphangioendothelioma-like	None nuclear/ architectural atypia	NA	Alive without disease at 40 months	Complete excision with negative margins
Gengler 2007[6]	63	5	F	Breast	Asymptomatic	Six papules present for 5 y; development of an additional 6-mm nodule	0.6cm	Lymphangioendothelioma-like	None nuclear/ architectural atypia	NA	Alive without disease at 92 months	Incisional biopsy (with positive margins) (6-mm nodule)
Gengler 2007[6]	52	NA	F	Breast	Asymptomatic	Two nodules	0.8cm	Lymphangioendothelioma-like	With nuclear/ architectural atypia	NA	Lost to follow up	Present on mastectomy specimen (recurrent breast carcinoma)
Gengler 2007[6]	56	NA	F	Breast	Asymptomatic	Two nodules	0.4cm	Lymphangioendothelioma-like	With nuclear/ architectural atypia (1 nodule)	NA	Alive without disease at 67 months	Complete excision with negative margins
Gengler 2007[6]	57	2	F	Chest wall	Asymptomatic	Six papules	0.4cm	Lymphangioendothelioma-like	None nuclear/ architectural atypia	NA	Alive without disease at 3 months	Complete excision with negative margins
Gengler 2007[6]	51	3.5	F	Chest wall	Asymptomatic	Several papules	0.7–1cm	Lymphangioendothelioma-like	None nuclear/ architectural atypia	NA	Alive without disease at 64 months	Complete excision with negative margins

(*Continued*)

Table 3 (Continued).

Case	Age (yr)	Duration (yr)	Sex	Location	Clinical Symptom	Physical Examination	Size	Pathological Findings	Nuclear Atypia or Mitotic Figures	Immunohistochemical Results	Follow-Up	Treatment
Gengler 2007[6]	50	NA	F	Breast	Asymptomatic	Several papules	0.3–0.6cm	Lymphangioendothelioma-like	None nuclear/ architectural atypia	NA	Alive without disease at 8 months	Complete excision with negative margins
Gengler 2007[6]	61	NA	F	Axilla	Asymptomatic	Several papules	0.3–0.5cm	Lymphangioendothelioma-like	None nuclear/ architectural atypia	NA	Alive without disease at 6 months	Complete excision with negative margins
Gengler 2007[6]	57	NA	F	Chest wall	Asymptomatic	Multiple nodules	0.2–0.3cm	Lymphangioendothelioma-like	None nuclear/ architectural atypia	NA	Alive with persistent telangectasis at 88 months	Complete excision with negative margins
Kim 2007[22]	7	7	F	Left little toe	Asymptomatic	A slightly tender, flesh coloured mass	NA	Irregular, dilated vascular spaces lined by a single layer of bland, flat endothelial cells in the dermis	None cellular atypia	NA	No sign of local recurrence at 2 months	Complete excision with advancement flap for closure
Paik 2007[32]	56	5	M	Left cheek	Rare bleeding with minor trauma and occasional pruritus	A blanchable, violaceous, non-tender, soft plaque containing a few compressible papules	2×7 cm	A proliferation of vascular spaces in the superficial and reticular dermis; more compressed vascular spaces with a pattern of dissection through the collagen in the deeper dermis	None mitotic figures	HHV-8 (-), CD31 (+), D2-40 (+)	NA	Incisional biopsy, close observation
Ando 2009[17]	31	2	F	Left lower leg; left abdomen; left knee	Left inguinal node swelling	An arborizing, reticulate reddish brown lesion along the postoperative scar of the left femur	25 cm (left lower leg), 5 cm (left abdomen), 16cm (left knee)	Compressed vascular spaces in the deeper dermis, the appearance of "dissection of collagen bundles"	None atypia or mitotic changes	NA	NA	Skin biopsy
Lin 2009[33]	33	>1	M	Right groin area	Frequent drainage of clear fluid sufficient to wet clothing	A soft, fluctuant subcutaneous nodule	1 × 0.2 cm	Many irregularly dilated vascular channels throughout the dermis and dissecting the collagen bundles	None cellular atypia or mitotic figures	VIII (+), CD31 (+), CD34 (+), D2-40 (+), HHV-8 (-)	Symptom-free after 9 months	Wide excision

Tong 2011[18]	75	NA	M	Right upper chest	Pruritus and occasional serous fluid discharge from minute breaks	An ill-defined scaly, slightly indurated, erythematous lesion	large	Multiple dilated, thin-walled, endothelial-lined channels in the superficial dermis	None endothelial atypia or mitotic activity	CD31 (+), CD34 (+), D2-40 (+)	Remained unchanged at 12 months	Incisional biopsy, no surgery
Revelles 2012[35]	75	1	M	Left back, left abdomen, pubic area	Asymptomatic	A large erythematoviolaceous, ill-defined, not indurated, multifocal bruise-like patches and violaceous areas	> 60 cm	Both papillary and reticular dermis permeated by irregular empty channels and spaces which were lined by a single layer of flat endothelial cells	None nuclear atypia or mitotic figures	CD31 (+), CD34 (+), D2-40 (+), Lyve-1 (+), Prox-1 (+), WT1 (+), HHV-8 (-), c-Myc (-), Ki-67 (-)	Died of disseminated aspergillosis at 8 months; no visceral vascular proliferation in autopsy	Incisional biopsy
Wang 2013[23]	19	19	F	Right thigh	Asymptomatic	A dull red patch	20 cm	Prominent proliferation of anastomotic or retiform vessels dissecting the dermal collagen in the entire dermis	None pleomorphic cells and mitoses	D2-40 (+), Prox1 (+), Ki67 (-), WT-1 (-), HHV-8 (-)	NA	Incisional biopsy
Wang 2013[23]	27	7	M	Left thigh	Exudation of watery clear liquid that looked like lymph at biopsy	A large brown plaque with no clear margin	30 cm	The same as the above	None pleomorphic cells and mitoses	D2-40 (+), Prox1 (+), Ki67 (-), WT-1 (-), HHV-8 (-)	NA	Incisional biopsy
Wang 2013[23]	36	8	F	Left thigh	Asymptomatic	A large red patch with unclear margin	10 cm	The same as the above	None pleomorphic cells and mitoses	D2-40 (+), Prox1 (+), Ki67 (-), WT-1 (-), HHV-8 (-)	NA	Incisional biopsy
Wang 2013[23]	7	3	M	Neck	Asymptomatic	A large red patch	8 cm	The same as the above	None pleomorphic cells and mitoses	D2-40 (+), Prox1 (+), low Ki67, WT-1 (-), HHV-8 (-)	NA	Incisional biopsy
Alkhalili 2014[25]	47	0.5	F	Left nipple	Itch and discomfort	A 7 mm asymmetrical outgrowth of the left nipple, without palpable masses and skin rash	0.7cm	Ectatic vascular spaces lined by flattened, cytologically bland endothelial cells dissecting through the dermis	NA	NA	Resolved spontaneously	Incisional biopsy
Flores 2014[27]	17	High school	F	Right shoulder	Asymptomatic	A blanchable, light pink to slightly beige, nonindurated patch with reticulated borders	16 × 11 cm	Interconnecting vessels lined with thin endothelium arranged horizontally and dissecting between dermal collagen bundles	None atypical cells or mitotic figures	D2-40 (+), CD31 (+)	Complete resolution after four PDL treatments; no appreciable change in the area treated with imiquimod	585-nm pulsed dye laser; imiquimod

(*Continued*)

Table 3 (Continued).

Case	Age (yr)	Duration (yr)	Sex	Location	Clinical Symptom	Physical Examination	Size	Pathological Findings	Nuclear Atypia or Mitotic Figures	Immunohistochemical Results	Follow-Up	Treatment
Hunt 2014[26]	48	Childhood	M	Left thigh	Asymptomatic	Dusky brown to bluish-red dermal papules	10 × 10 cm	Thin, irregular vascular spaces with a lobular arrangement superficially and a more slit-like appearance deeper in the dermis	None endothelial cell atypia	HHV-8 (-)	The lesion decreased in size, lightened in color, and flattened after 7.5 months	Sirolimus
Yamada 2014[7]	45	4	F	Left arm	Chronic lymphedema of left arm	Multiple small and yellowish to reddish soft nodules	Nodules < 0.6 cm	Irregular, anastomosing vascular structures in the middle to lower layer of dermis; proliferating vascular channels dissecting dermal collagenous bundles in deeper dermis	Modestly atypical endothelial cells, but no apparent mitotic figures	CD31 (+), DAKO (+), CD34 (+), D2-40 (+), LYVE-1 (+), low Ki67, HHV-8 (-)	Partial remission and neogenesis for 7 years	Incisional biopsy
Zhu 2014[14]	38	1	M	Inguinal region	Asymptomatic	A neoplasm with a smooth lustrous surface and slight oozing	2 × 2×5 cm	Epidermal hyperplasia; substantially dilated, thin-walled lymphatic vessels containing lymph fluid	Without koilocytes or atypical cells	D2-40 (+), HHV-8 (-), HPV-6 (-), HPV-11 (-)	Without recurrence at 5 years	Wide excision of the primary neoplasm, with the smaller surrounding lesions treated with cryotherapy
Mizuno 2015[20]	42	42	M	Inguinal region	Pain at night being sufficient to interrupt sleep	A indurated reddish-brown plaque with 3–5 mm diameter nodules	12 × 7 cm	Irregular, horizontal slit-like spaces dissecting the collagen bundles in the dermis	None nuclear atypia	CD31 (+), CD34 (+), D2-40 (+)	Improved induration and color, and disappearance of pain and subcutaneous nodules under electron radiotherapy	Electron radiotherapy (total 20 Gy) for two weeks

Schnebelen 2015[30]	73	NA	M	Right flank	Drainage of clear to milky white fluid at punch biopsy	A large, soft, tuberous, supple, flesh-colored mass, with irregular and wrinkled surface contours	Occupying most of the right flank	Numerous anastomosing vascular channels dissecting through the dermal collagen from the superficial dermis to the subcutis, with vascular channels becoming less dilated and more slit-like as they delved deeper into the dermis	Free of cytologic atypia; no hobnailing, hyperchromasia and increased mitotic activity	HHV-8 (-), D2-40 (+), WT1 (-)	NA	Incisional biopsy
Vittal 2016[24]	24	2	F	Left leg	Asymptomatic	An ill-defined hyperpigmented, atrophic plaque, round to oval in shape	3 × 3 cm	Horizontal, thin-walled vascular channels lined by single layer of bland endothelial cells at the dermo-epidermal junction	NA	NA	Mild improvement and exacerbation on stopping the treatment; no recurrence	Topical steroids for 6 months; excision
McKay 2017[12]	83	NA	F	Left back	NA	A small patch of thickening and scaliness	NA	Lymphangioendothelioma with no suggestion of malignancy	With no suggestion of malignancy	NA	Progressing to an angiosarcoma approximately 8 years later	Serial excision biopsies
Rudra 2017[51]	8	1.5	M	Left leg	Asymptomatic	An ill-defined, bluish, oblong-shaped plaque, studded with a few dark-blue and reddish papules	4 × 3 cm	Compact hyperkeratosis with irregular acanthosis; dilated thin-walled spaces lined by intermittent flat endothelial cells resembling lymphatic channels in the upper and mid-dermis	NA	NA	No recurrence for 1 year	Completely excision
Salman 2017[28]	5	0.16	F	Right ankle	Asymptomatic	A slightly hyperkeratotic, brown to violaceous plaque with irregular borders	5 cm	Delicate, thin-walled, endothelium-lined empty vascular spaces involving the superficial dermis and extending deep into the dermis	NA	D2-40 (+), CD31 (+), HHV-8 (-), low Ki-67 proliferation index (<1%)	A moderate response at 1 month; maintaining the initial response without any progression at 5 months	Imiquimod 5% cream three times per week
Larkin 2018[31]	1	0.6	M	Abdomen, penis, right scrotum, lower extremity	Episodic pain	A plaque with ecchymotic discoloration along the borders	12 × 15 cm	Characteristic, ectatic, irregularly shaped vascular channels lined by flattened endothelial cells infiltrating the superficial and deep reticular dermis	NA	FLI-1 (+), CD34 (+), D2-40 (+), WT1 (-), HHV-8 (-), CD3 (-), CD20 (-). CD68 (-)	Lost to follow-up after 9 months	Incisional biopsy

(*Continued*)

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Table 3 (Continued).

Case	Age (yr)	Duration (yr)	Sex	Location	Clinical Symptom	Physical Examination	Size	Pathological Findings	Nuclear Atypia or Mitotic Figures	Immunohistochemical Results	Follow-Up	Treatment
Teixeira 2022[34]	70	1	F	Bilateral breasts	Asymptomatic	A yellow-brownish infiltrated plaque with superimposed flat papules	60 cm	Slight acanthosis and irregular vascular spaces dissecting the collagen bundles lined by swollen endothelial cells	Without cellular atypia	D2-40 (+), CD31 (+), WT1 (+)	Remaining in follow-up	Incisional biopsy; wait-and-see approach

Abbreviations: NA, not available; no evidence of disease, no evidence of disease.

irregular proliferation of thin-walled vascular channels dissecting between bundles of dermal collagen. These findings can be limited to the papillary dermis but may extend into deeper subcutaneous tissue. Vascular channels are lined by a monolayer of endothelial cells, with no mitotic figures and nuclear pleomorphism. As shown in Table 3, significant quantities of endothelial cells were only observed in eight of the 83 cases.[6,7,37] Usually, extravasated red cells and hemosiderin deposition, as well as marked inflammation, are rarely observed, indicating a predominant involvement of lymphatic channels. This is further supported by positive immunohistochemistry for lymphatic-specific markers such as D2-40. Results of immunohistochemistry for other lymphatic or vascular endothelium markers such as Factor VIII (F-VIII-RA), *Ulex europaeus* agglutinin I (UEA-I), CD 31, CD 34, LYVE-1, and PROX-1 were inconsistent (Table 3), although some studies suggest that BL may be differentiated from other lymphatic skin tumors by negative staining for F-VIII-RA and strong staining for UEA-I.[21] All evidence suggests that BL is a heterogeneous disease. It is more of a pathological diagnosis than a clinical one, and we should allow for more etiological, morphological, and immunohistochemical diversity in the identification of BL.

BL is a rare lymphatic vascular proliferation that can be mistaken for various benign and malignant conditions arising from vessels. In this case report, the patient had previously been diagnosed with hemangioendothelioma, lymphangiomatosis, and BL. Upon the review of histopathology slides, the differential diagnoses included well-differentiated cutaneous angiosarcoma, hemangioendothelioma, lymphangiomatosis, and Kaposi's sarcoma in the patch stage. Lymphangiomatosis is a rare disorder that is characterized by multifocal lymphangioma involving multiple organs such as the skin, superficial soft tissue, and abdominal and thoracic viscera in 75% of cases. In the remaining 25% of cases, it presents as diffused pulmonary lymphangioma (DPL).[38] Compared to BL, lymphangiomatosis is mainly observed in children and is rarely diagnosed in patients over the age of 20, with over 75% of cases presenting with multiple bone lesions. In the case discussed in this report, the patient, who was 25 years old, experienced a progressive lower extremity lesion after previous trauma that did not reach the bone, indicating a diagnosis of BL rather than lymphangiomatosis. A definitive diagnosis of lymphangioendothelioma requires histopathological examination to distinguish it from other forms of lymphangioma, which usually show superficially dilated vascular spaces that become progressively smaller with deep extension.[5,31,39] Lymphangiomatosis shares similar histological features with the deep portions of BL, characterized by a single layer of flattened endothelium that ramifies in the soft tissue.[40] Considering portions of BL are virtually indistinguishable from lymphangiomatosis, Guillou et al[8] believed that BL may be considered a localized form of lymphangiomatosis, and the distinction between the two is best made based on presentation and pathological extent. In lymphangiomatosis, as opposed to BL, the dilated lymphatic spaces involve not only the dermis but also the subcutaneous tissue and, occasionally, the underlying fascia and skeletal muscle.[40] In the present case, the mass spread beneath the dermis and invaded subcutaneous fat but did not reach the striated muscles. Based on the clinical manifestations and infiltration depth of the lesion, a diagnosis of BL was preferred over lymphangiomatosis, even though it might be a multifocal disease.

Kaposi's sarcoma in patch stage, which shares a red-violaceous macular appearance and lymphangioma-like cell dissection of collagen with BL, can be identified histologically by the presence of erythrocytes and spindle cells, hemosiderin deposits, plasma cells, and positive anti-HHV8 immunostaining.[15,41] Differential diagnosis from well-differentiated angiosarcoma is particularly important as BL shares the histopathological presence of extensive dissection of collagen bundles with angiosarcoma. Angiosarcoma may clinically manifest as red-blue nodules or plaques that can ulcerate in the face or scalp of elderly individuals or lymphedematous extremities. BL differs from angiosarcoma in its lack of anastomosing and infiltrating vascular structures, mitosis, prominent nuclear pleomorphism or mitotic figures, and Ki-67 amplification in less-differentiated areas.[7,13,42] Yamada et al[7] demonstrated that the MIB-1 labeling index could be helpful as a supplement to the diagnosis of cutaneous BL, particularly when specimens are inadequate. However, differentiating lymphangioendothelioma from angiosarcoma remains challenging. Sevila[13] suggested that some previously reported cases of angiosarcoma may actually be benign tumors similar to BL, as they were curable in children and young adults. Therefore, the diagnosis of BL should be used with caution, especially in cases of post-irradiation lesions in adults, as this condition is known to be a precursor to the development of angiosarcoma and Kaposi's sarcoma.[12,43] Audard et al[43] even questioned the existence of BL. Hence, careful sampling of such lesions, close correlation of pathological findings with clinical characteristics, and close follow-up care are necessary.

The radiological findings in the present case were typical and quite helpful for the diagnosis and assessment of giant BL before surgery. Lymphoscintigraphy, with subcutaneously injected 99mTc-DX, effectively imaged the lymphatic malformations, enabling a good differential diagnosis from hemangioma or benign hemangioendothelioma and a good assessment of lymphatic uptake, distribution, and retention. The MRI findings were similar to those of hemangiomas, but no signal voids caused by high-flow vessels were observed.[40] MRI also helped assess tumor extent, making a valuable contribution to surgery. In the present case, scattered lesions with increased signal density superior to the deep fascia were found on MRI, corresponding to the final pathological result. Ultrasonography can also be useful for localizing and determining the cystic nature of some types of lymphangioma. The imaging examinations allowed for a comprehensive understanding of the nature and extent of the lesion.

Regarding the treatment, the differentiation between lymphangiomatosis and lymphangioendothelioma was not necessary. The main concern was whether the lesion was benign and had the potential for malignant transformation, which would determine if lymph node dissection was required. Due to the patient's history of clear fluid drainage and the tendency for the mass to infiltrate peripheral subcutis, a type of infiltrating lymphatic malformation with a risk of recurrence was suspected. Despite its penchant for infiltrating peripheral subcutis, the mass showed no signs of invading deeper tissue planes or metastasizing, indicating that the lesion was benign. Given that the lesion had reached the subcutaneous fat and that the patient had undergone two incomplete debridements before admission, thorough surgical excision was the preferred treatment. According to MRI results, the lesion had spread into subcutaneous fat but did not reach the deep fascia, so a complete excision from the skin to the superficial fascia was necessary. The wound boundary was visible to the naked eye, and the scope of the surgery was expanded to ensure a negative margin. Because of the numerous lymphatic fistulas and infections, the temporary coverage by VSD was an important part of the treatment protocols through the application of a controlled and localized negative pressure on porous polyurethane absorbent foams. By controlling infection, calculating the volume lymph fluid, improving lymphorrhea, accelerating tissue granulation, minimizing exposure of deep tissues, and increasing the survival rate of graft transplants for soft-tissue defects, the negative pressure technique played an important role in the protection of a large wound in the lower leg.[44] The volume of lymph-like fluid decreased significantly after two surgeries, and the wound no longer exhibited signs of potential sepsis, indicating that skin grafting was possible. Split-thickness skin grafting was chosen after the wound was covered with fresh granulation tissue and showed no evidence of infection. Compared to skin flap, STSG was preferred as it was more effective in preventing recurrent lymphatic malformations since it had less reticular dermis and thus fewer lymphatics. In addition, the patient's overweight (with a BMI of 28.34) and the wound size made skin flap transplantation risky. Furthermore, the transplantation of the flap from the thigh to the calf might generate morphological issues in the lower leg if microscopic anastomosis was performed. Given the above points, we eventually chose split-thickness skin graft, and we managed to achieve a good functional and cosmetic result. Moreover, medications such as sirolimus, imiquimod, glucocorticoids, and methotrexate have been reported to be effective when surgical excision is not possible due to the size and location of the lesion.[9,26,28,45] Positive WT-1 immunostaining indicates a proliferative vascular lesion that requires appropriate therapy such as systemic steroids or interferon, whereas negative results indicate a vascular malformation that does not require unnecessary systemic therapy.[35] Interestingly, antibiotic therapy was also effective.[16] Since partial or complete spontaneous remission has been documented in some cases,[5] therapeutic abstention and pharmaceutic treatment could be reserved for patients when surgery is contraindicated due to the size or location of the lesion.

Conclusion

We have discussed a case of benign lymphangioendothelioma that progressed to a persistent exudative wound after two incomplete excisions. Clinicopathological correlation, imaging examination, and pathological examination are essential for diagnosing BL and excluding lymphangiomatosis, Kaposi's sarcoma, and angiosarcoma. This case also demonstrates that complete excision and split-thickness skin graft transplant following vacuum-seal drainage is an effective course of treatment for recurrent BL. Additionally, by reviewing the literature on BL, we concluded that BL is more of a pathological diagnosis than a clinical one, and we should allow for more etiological, morphological, and immunohistochemical diversity in the identification of BL.

Data Sharing Statement

All data generated during this study are included in this published article.

Ethics Approval and Informed Consent

The Ethics Committee of the hospital approved the use of the clinical data of the patient. Consent had been obtained from the patient to use pictures, notes and lab investigations for publication on the condition that the personal information was kept confidential.

Consent for Publication

The consent for publication has been obtained from the patient.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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