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CASE REPORT

Acquired Progressive Lymphangioma (Benign Lymphangioendothelioma)

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PALABRAS CLAVE

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Linfangioendoteliooma;
Tumores vasculares;
Linfangioma

Abstract

Acquired progressive lymphangioma is a rare vascular tumor with a locally aggressive behavior. Histologically it is characterized by a proliferation of numerous, dilated, thin-walled vessels lined by flat endothelial cells with no nuclear atypia. The vessels appear to dissect between the collagen fibers. It usually presents as an asymptomatic, slow-growing, reddish-brown plaque. We present the case of a 32-year-old man with acquired progressive lymphangioma. The tumor was in the hypogastric region and had arisen on a congenital vascular lesion previously diagnosed as multifocal cutaneous angiomatosis. It was very painful and impeded walking, for which reason it was decided to perform excision. Dermatologists and pathologists must be aware of acquired progressive lymphangioma as early surgical treatment, while the lesion is still small, is curative and prevents subsequent complications due to growth.

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Linfangioma progresivo adquirido (linfangioendoteliooma benigno)

Resumen

El linfangioma progresivo adquirido es una neoplasia vascular poco frecuente, de comportamiento localmente agresivo. Histológicamente se caracteriza por la proliferación de múltiples vasos dilatados de paredes finas, revestidos con un endotelio plano sin atipias y que aparentemente disecan las fibras de colágeno. Esta entidad suele debutar de forma asintomática como una placa marrón-eritematosa que presenta un crecimiento gradual. Se presenta un caso de linfangioma progresivo adquirido en un varón de 32 años. La tumoración se localizaba en el hipogastrio sobre una lesión vascular congénita diag-

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nosticada previamente de angiomatosis cutánea multifocal. Clínicamente cursaba con intenso dolor e imposibilidad para la deambulación por lo que fue resecada. El linfangioma progresivo adquirido debe ser considerado por dermatólogos y patólogos dado que su tratamiento quirúrgico precoz, cuando la lesión tiene un tamaño limitado, es siempre curativo y evita posteriores complicaciones derivadas de su crecimiento.

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Introduction

Acquired progressive lymphangioma (APL) is a rare, locally aggressive vascular proliferation first described by Wilson Jones¹ in 1964 and Gold² in 1970. In 1990, Wilson Jones et al³ proposed the term *benign lymphangioendothelioma*, which is the term generally used by other authors. There are fewer than 40 published cases of APL.⁴ APL poses a diagnostic challenge, given the histologic similarities with malignant vascular tumors such as low-grade angiosarcoma, Kaposi sarcoma, and well-differentiated angioendothelioma. Clinically it can be confused with proliferative lesions such as Kaposi sarcoma, or inflammatory disorders such as morphea, most especially the deep variant.^{4,5} We describe a case of APL and compare its clinical and pathologic characteristics with previous cases described in the literature.

Case Description

The patient was a 32-year man, who consulted for a lesion in the hypogastrium that had developed slowly but gradually over the previous 2 years. The lesion was characterized by nonspecific local discomfort and intense pain, and was accompanied by mild edema of the scrotum and top of the right thigh that made walking difficult. The patient had been born with a vascular lesion situated in the right lower quadrant of the abdomen that was biopsied in 1975



Figure 1 Brownish-erythematous macule in the hypogastrium, spreading to both flanks.

and diagnosed as multifocal cutaneous angiomatosis. There was no follow-up by any specialist. The lesion remained stable as an erythematous plaque measuring 6 cm by 4 cm, clinically compatible with a circumscribed lymphangioma. Two years prior to the consultation, the patient had noticed that the lesion was growing and had become intensely painful. There was no other past medical or surgical history of relevance.

Physical examination revealed a poorly delimited, brownish erythematous macule in the hypogastrium that extended to both flanks. The vertical diameter of the lesion at its highest point was 15 cm (Figure 1). Palpation revealed a slightly tender mass with a rubbery consistency, deep to the macule and not adherent to the deep layers.

Full laboratory tests were performed, including complete blood count, biochemistry, and serology (antinuclear antibodies, extractable nuclear antigens, anti-DNA, Borrelia, and Scl-70). Test results were within normal limits. Contrast-enhanced magnetic resonance of the abdominal wall revealed a thickening of the skin measuring 0.7 mm to 0.9 mm, with subcutaneous edema in the entire area of the hypogastric macule. There was no apparent involvement of the underlying muscles and no intraperitoneal or retroperitoneal lesions.

Histopathology revealed preservation of the epidermis, with a proliferation of irregular vascular spaces in the papillary dermis and reticular dermis (Figure 2A). The superficial vessels were distorted and dilated. As the lesion penetrated the dermis, the vessel lumens narrowed and passed between the collagen fibers, dissecting them and acquiring a pseudomalignant appearance. A close-up view (Figure 2B) revealed the thin vascular walls to be lined by a single layer of flattened epithelial cells. No nuclear atypia was observed in the endothelial cells. Immunohistochemical staining showed the neoplastic proliferation to be positive for the endothelial markers CD31 and CD34, and for the lymphatic marker D2-40, a monoclonal antibody directed against podoplanin (Figure 3).

The case was diagnosed as APL and the lesion was completely excised with a surgical margin of 1 cm of healthy tissue. The defect was repaired using a fascia lata flap harvested from the right thigh. After 18 months of follow-up there has been no evidence of recurrence.

Discussion

Acquired progressive lymphangioma, also called benign lymphangioendothelioma, is a vascular proliferation showing evidence of lymph and blood vessel differentiation.

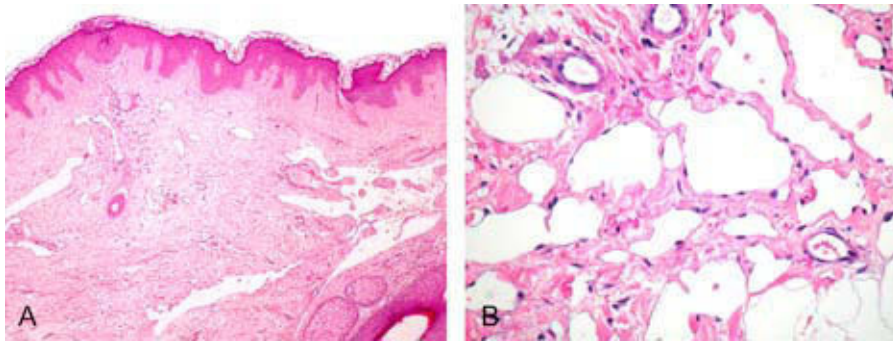


Figure 2 A, Vascular proliferation in the dermis. The vessels tend to be horizontal and to become narrower in deeper parts of the tumor, adopting a collagen dissection pattern (hematoxylin-eosin, original magnification $\times 100$). B, Thin-walled vessels with a single layer of flat endothelial cells with no atypia or mitoses (hematoxylin-eosin, original magnification $\times 250$).

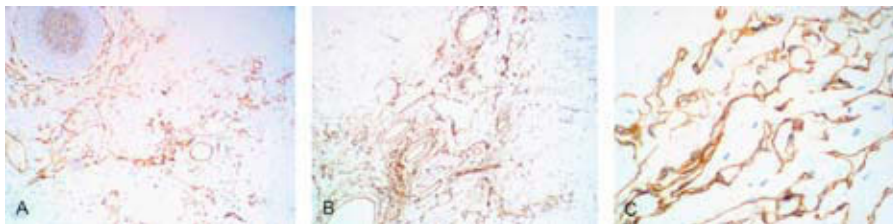


Figure 3 Endothelial cells expressing blood and lymph vessel markers. A) CD31, original magnification $\times 100$. B) CD34, original magnification $\times 100$. C) D2-40, original magnification $\times 250$.

The disorder is rare, with only 39 cases reported in the literature. The main clinical and pathologic characteristics of 37 of the 39 cases are summarized in Table 1.

The etiology and pathogenesis of APL are not well understood. Trauma as a possible trigger and the good response to treatment with oral corticosteroids in 1 case described by Watanabe et al⁶ have led to the suggestion that APL is a response to inflammatory stimuli rather than a true neoplasm; other authors, however, consider that the case described by Watanabe et al⁶ may well have been one of lymphangiomas rather than APL, given that the lesions developed in 2 different locations, and that the vascular channels showed more diffuse proliferation and greater dilation of the lumens than in other descriptions of APL.⁷ Other patients treated with systemic corticosteroids have presented a slight improvement but subsequent progression of the lesions.^{8,9} Other triggers have been described, namely, radiotherapy,¹⁰ arteriography, tick bites,⁷ and hip inflammation,¹¹ and also its appearance in relation to a congenital vascular lesion, as in our case.^{8,12} Tadaki et al¹³ postulated the possible existence of a hormonal stimulus as an explanation for the many cases of APL encountered in pubescent and prepubescent children and for the rapid growth of lesions in some cases.

It has also been suggested that APL could be a complex hamartoma composed of a smooth muscle and a vascular component in an intermediate stage of differentiation between blood and lymph vessels.¹⁴ This hypothesis is supported by the finding of desmin and type IV collagen

surrounding the abnormal vessels.^{7,11,12,14} Nonetheless, the characteristic progressive growth of APL contradicts the hamartoma hypothesis. In our opinion, the intermediate differentiation of blood and lymph vessels in APL appears to be demonstrated by positivity for typical blood vessel endothelial markers, such as factor VIII-related antigen (FVIII-RA)^{8,10-12,15,16} and CD34,^{8,12,15} and for expression of the specific lymphatic endothelial marker D2-40.^{4,5} The lesion presents clinically as a macule or slightly elevated plaque that is erythematous, violaceous, or brown in color, with well-defined borders, and a rough surface. Texture may be soft or slightly firm, and the lesion may be hypersensitive. Reviewing the cases described in the literature, we found only 17% to be symptomatic at the time of diagnosis (Table 1). APL can present anywhere on the body (Table 1), but the most frequent locations are the legs followed by the head and neck. Lesion growth tends to occur slowly over several years, explaining the large diameter of the lesion at the time of diagnosis (Table 1). Lymphatic or hematogenous spread has not been described, and the disorder is widely considered to be benign and to have a favorable prognosis. However, since growth may eventually interfere with the patient's mobility, as happened in our case, it would seem more appropriate to refer to APL behavior as locally aggressive rather than benign.^{8,9,14} APL has been described as occurring mainly in young people;⁶ however, it has been described for all age groups, although there does tend to be a bimodal distribution of cases, with the greatest incidence occurring in the 5-to-15 year and 45-to-55 year

Table 1 Summary of Acquired Progressive Lymphangioma Characteristics for 37 Cases Described in the Literature

Clinical Characteristics		Histological Characteristics	
<i>Mean age on diagnosis</i>	43 y	<i>Constant findings with H&E</i>	
<i>Sex ratio</i>	1:1	Single layer of flattened endothelial cells	
<i>Possible triggers</i>		Collagen dissection appearance	
Minor surgery, radiotherapy, arteriography, trauma		No atypia	
<i>Location</i>		No mitotic activity	
Head and neck	20%	No inflammatory infiltrate	
Oral mucosa	2%	Perilesional	
Back	8%	<i>Occasional findings with H&E</i>	
Pectoral region	8%	Focal layer of smooth muscle in the vascular wall	
Abdomen	5%	Intraluminal papillary endothelial proliferation	
Shoulders	11%	Minimal atypia and few multinuclear cells	
Upper limbs	11%	Intraluminal and/or extraluminal red-cell extravasation	
Lower limbs	33%	<i>Immunohistochemical findings</i>	
<i>Signs and symptoms on presentation</i>		CD31	10 of 11 cases
Flat lesion	46%	CD34	11 of 12 cases
Raised lesion	53%	D2-40	2 of 2 cases
Well-defined borders	59%	UEA-I lectin	13 of 15 cases
Pigmentation/erythema	86%	FVIII-RA	13 of 18 cases
Hard on palpation	59%	Peritumoral vessels positive for:	
Soft on palpation	41%	UEA-I lectin	9 of 10 cases
Local symptoms	17%	FVIII-RA	10 of 10 cases
Pain	13%	Desmin	6 of 11 cases
Pruritus	13%	Vimentin	2 of 3 cases
Soreness	3%	Actin	17 of 20 cases
Asymptomatic	83%	Type IV collagen	5 of 6 cases
Mean time to diagnosis	5.42 y	Laminin	1 of 2 cases
Mean maximum diameter	6.46 cm	<i>Treatment options</i>	
		<i>Complete resection</i>	
		Treatment of choice in localized cases; no recurrences reported	
		<i>Systemic corticosteroids</i>	
		Partial improvement in symptoms; complete remission in 1 case	
		<i>Therapeutic abstention</i>	
		For extensive cases for which surgery is not an option; spontaneous remission in 2 cases	

Abbreviations: FVIII-RA: factor VIII-related antigen; H&E: hematoxylin-eosin; APL: acquired progressive lymphangioma; UEA-I: *Ulex europaeus* agglutinin I.

age bands (46% of patients). Men and women are equally likely to be affected.

The most significant histologic finding is the presence of thin-walled vascular spaces in the subpapillary dermis and extending down to the subcutaneous cell tissue. These endothelium-lined channels tend to be horizontal, especially in the superficial dermis. The overlying epidermis is usually normal although there may be areas of acanthosis or atrophy. The vascular lumens tend to be irregular, with a dilated appearance in the superficial dermis. In the deeper parts of the lesion, the vascular spaces narrow and dissect between the collagen fibers in a pattern similar to that encountered in angiosarcoma. The vascular spaces are usually empty, although in some cases, the vessels contain a foamy proteinaceous material or hematic collections. The

presence of a mild inflammatory mononuclear infiltrate has also been described.³ The flat endothelial lining is formed of a single layer of cells, with no atypia or mitoses, and with a single hyperchromatic ovoid nucleus. Also frequently encountered are foci of endothelial proliferation that form protruding papillae within the lumen.

Analysis of the immunohistochemical studies performed in the 37 cases reviewed reveals a lack of specificity with respect to other vascular proliferations of the different markers described above (Tables 2 and 3).

In regard to their series, Wilson Jones et al³ reported that tumoral and nontumoral vessels were positive for *Ulex europaeus* agglutinin I (UEA-I) lectin, in contrast with the normal blood vessels, which were positive for FVIII-RA. Other authors have described cases of APL positive

Table 2 Differential Diagnosis for Acquired Progressive Lymphangioma

	KS	LGA	APL	PILA	RH	HH
<i>Histologic characteristics</i>						
Collagen dissection pattern	++	++	++	±	–	++
Multiple endothelial cell layers	–	+	–	–	–	–
Flat endothelial cells	+	+	++	±	–	+
Spindle-cell component	++	+	–	–	+	–
Hobnail endothelial cells	–	–	–	++	++	++
Intraluminal papillary endothelial proliferation	+	++	±	++	+	±
Nuclear atypia	+	++	–	–	–	–
Mitotic activity	+	++	–	+	–	–
Inflammatory infiltrate	++	+	–	+	++	–
Red-cell extravasation	++	±	–	±	–	+
Hemosiderin deposits	++	±	–	–	–	+
<i>Immunohistochemical characteristics</i>						
CD34	+	+	++	±	±	–
CD31	±	++	++	+	+	+
D2-40	+	±	++			
UEA-I lectin	±	+	+			
FVIII-RA	+	+	±	+	+	+
Type IV collagen			+	+		
Smooth muscle	+		+			
LNA	+	–	–	–	–	–
VEGFR-3	+	±		+	++	++

Abbreviations: ++, characteristic/constant; +, habitual/mild; ±, occasional/variable depending on series; –, absent; APL, acquired progressive lymphangioma; HH, hobnail hemangioma; KS, Kaposi sarcoma; LGA, low-grade angiosarcoma; LNA, latent nuclear antigen for human herpesvirus-8; PILA, papillary intralymphatic angioendothelioma (Dabska tumor); RH, retiform hemangioendothelioma (hobnail hemangioendothelioma); UEA-I, *Ulex europaeus* agglutinin I; VEGFR-3, vascular endothelial growth factor receptor 3.

Table 3 Immunohistochemical Stains Used for Vascular Tumors

<i>Ulex europaeus</i> agglutinin I lectin	Low-specificity marker of lymph and blood vessel endothelial cells
CD31	Marker of hematopoietic cells, platelets, and lymph and blood vessel endothelial cells
Factor VIII-related antigen (von Willebrand factor antigen)	Low-sensitivity marker of blood vessel endothelial cells
CD34	Marker of hematologic hematopoietic and exclusively blood vessel endothelial cells; limited specificity, positive for other nonvascular tissues and tumors
D2-40 (podoplanin) and vascular endothelial growth factor receptor 3	Highly specific and sensitive markers of lymphatic endothelial cells
Type IV collagen	A basement membrane component, present in blood vessels and capillaries, but not normally present in lymph vessels
Latent nuclear antigen for human herpesvirus-8	Positive in Kaposi sarcoma, especially in forms associated with human immunodeficiency virus, and negative in other vascular proliferations

for FVIII-RA^{4,5,7,8,10-12,16} and negative for UEA-I.^{10,13} Of the published reports of APL (Table 1), 87% of cases showed UEA-I expression and 72% were positive for FVIII-RA. Tests performed for other vascular markers including CD31,^{4,5,7,8,15} CD34,^{4,8,12,15} and D2-40^{4,5} (nearly all the cases reviewed, and also ours) were positive.

The differential diagnosis of APL should include malignant vascular tumors such as low-grade angiosarcoma and Kaposi sarcoma (Table 2). The existence of cords of cells with minimal atypia projecting into the lumen is the only constant histologic finding that enables low-grade angiosarcoma to be distinguished from APL.

Kaposi sarcoma, especially in the early patch and plaque stages, can be confused clinically and histologically with APL. However, unlike Kaposi sarcoma, APL is characterized by the fact that there is no atypia and no spindle-cell component.

Immunohistochemical markers are not very useful to differentiate between angiosarcoma, Kaposi sarcoma, and APL. Of note is the usefulness of human herpesvirus-8 latent nuclear antigen (LNA-1), positive both in human immunodeficiency virus-associated Kaposi sarcoma and in other Kaposi sarcoma variants. LNA-1 is typically negative in the other vascular proliferations considered in the differential diagnosis of Kaposi sarcoma (Table 2). Series with characterization of D2-40 expression in the low-grade angiosarcoma subtype would be necessary to establish whether or not the LNA-1 marker can help to differentiate Kaposi sarcoma from APL.

Complete surgical excision seems to be the treatment of choice, and recurrence has not been reported during the follow-up of cases treated by margin-control surgery or wide excision.^{3,4,8,10,13,15} Watanabe et al⁶ reported complete resolution of APL lesions after treatment with systemic corticosteroids. Other cases treated with corticosteroids showed no improvement or only mild and transient improvement, however.^{8,9} Patients have also been reported to improve in response to systemic antibiotic treatment.^{11,14}

Some authors prefer therapeutic abstention,^{3,11,16} as partial or total spontaneous remission has been observed in 2 cases.^{11,16} In the untreated patients in another study, the lesion slowly and steadily spread to cover extensive parts of the body.⁹ Growth in the lesion was accompanied by an increase in patient-reported symptoms, ranging from local discomfort and hyperesthesia to great pain and significant functional disability.^{8,9,14}

To our knowledge, we report the third case of APL positive for D2-40 expression; this finding supports our hypothesis of lymphatic differentiation in APL. The remaining histologic findings in our case corresponded to findings already described in the literature.

With the case presented here, we would like to draw attention to the locally aggressive nature of APL, a disorder widely considered to be benign, but whose symptoms can affect the patient's quality of life. We are of the opinion that suspected APL should be assessed by dermatologists and pathologists to ensure an early diagnosis leading to resection and the avoidance of complications derived from subsequent growth. Wide excision appears to be the treatment of choice, as there was no recurrence in any of the cases treated in this way.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Wilson Jones E. Malignant angioendothelioma of the skin. *Br J Dermatol.* 1964;76:21-39.
2. Gold SC. Angioendothelioma (lymphathic type). *Br J Dermatol.* 1970;82:92-3.
3. Wilson Jones E, Winkelmann RK, Zachary CB, Reda AM. Benign lymphangioendothelioma. *J Am Acad Dermatol.* 1990;23:229-34.
4. Lin SS, Wang KH, Lin YH, Chang SP. Acquired progressive lymphangioma in the groin area successfully treated with surgery. *Clin Exp Dermatol.* 2009;34:341-2.
5. Paik AS, Lee PH, O'Grady TC. Acquired progressive lymphangioma in an HIV-positive patient. *J Cutan Pathol.* 2007;34:882-5.
6. Watanabe M, Kishiyama K, Ohkawara A. Acquired progressive lymphangioma. *J Am Acad Dermatol.* 1983;8:663-7.
7. Wilmer A, Kaatz M, Mentzel T, Wollina U. Lymphangioendothelioma after a tick bite. *J Am Acad Dermatol.* 1998;39:126-8.
8. Sevila A, Botella-Estrada R, Sanmartín O, Serra V, Cabadas P, Aliaga A, et al. Benign lymphangioendothelioma of the thigh simulating a low-grade angiosarcoma. *Am J Dermatopathol.* 2000;22:151-4.
9. Meunier L, Barneon G, Meynadier J. Acquired progressive lymphangioma. *Br J Dermatol.* 1994;131:706-8.
10. Rosso R, Gianelli U, Carnevali L. Acquired progressive lymphangioma of the skin following radiotherapy for breast carcinoma. *J Cutan Pathol.* 1995;22:164-7.
11. Grunwald MH, Amichai B, Avinoach I. Acquired progressive lymphangioma. *J Am Acad Dermatol.* 1997;37:656-7.
12. Herron GS, Rouse RV, Kosek JC, Smoller BR, Egbert BM. Benign lymphangioendothelioma. *J Am Acad Dermatol.* 1994;31:362-8.
13. Tadaki T, Aiba S, Masu S, Tagami H. Acquired progressive lymphangioma as a flat erythematous patch on the abdominal wall of a child. *Arch Dermatol.* 1988;124:699-701.
14. Zhu WY, Penneys NS, Reyes B, Khatib Z, Schachner L. Acquired progressive lymphangioma. *J Am Acad Dermatol.* 1991;24:813-5.
15. Guillou L, Fletcher CD. Benign lymphangioendothelioma (acquired progressive lymphangioma): a lesion not to be confused with well-differentiated angiosarcoma and patch stage Kaposi's sarcoma: clinicopathologic analysis of a series. *Am J Surg Pathol.* 2000;24:1047-57.
16. Mehregan DR, Mehregan AH, Mehregan DA. Benign lymphangioendothelioma: report of two cases. *J Cutan Pathol.* 1992;19:502-5.