CASE REPORT

Acquired Progressive Lymphangioma
(Benign Lymphangioendothelioma)

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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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PALABRAS CLAVE
Linfangioma progresivo adquirido (linfangioendothelioma 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 tumoralción se localizaba en el hipogastrio sobre una lesión vascular congénita diag-
Introduction

Acquired progressive lymphangioma (APL) is a rare, locally aggressive vascular proliferation first described by Wilson Jones in 1964 and Gold in 1970. In 1990, Wilson Jones et al proposed the term benign lymphangioendothelioma, which is the term generally used by other authors. There are fewer than 40 published cases of APL. 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. 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 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 (antineuclear 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.
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 al. 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 al. may well have been one of lymphangiomatosis 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. Other patients treated with systemic corticosteroids have presented a slight improvement but subsequent progression of the lesions. Other triggers have been described, namely, radiotherapy, arteriography, tick bites, and hip inflammation, and also its appearance in relation to a congenital vascular lesion, as in our case. Tadaki et al. 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. This hypothesis is supported by the finding of desmin and type IV collagen surrounding the abnormal vessels. 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) and CD34, and for expression of the specific lymphatic endothelial marker D2-40. 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. APL has been described as occurring mainly in young people; 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.
Acquired progressive Lymphangioma (Benign Lymphangioendothelioma)

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. The flat endothelial lining is formed of a single layer of cells, with no atypia or mitoses, and with a single hyperchromatic 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 al. 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 1: Summary of Acquired Progressive Lymphangioma Characteristics for 37 Cases Described in the Literature

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Histological Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age on diagnosis</td>
<td>43 y</td>
</tr>
<tr>
<td>Sex ratio</td>
<td>1:1</td>
</tr>
<tr>
<td>Possible triggers</td>
<td></td>
</tr>
<tr>
<td>Minor surgery, radiotherapy,</td>
<td></td>
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<tr>
<td>arteriography, trauma</td>
<td></td>
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<tr>
<td>Location</td>
<td></td>
</tr>
<tr>
<td>Head and neck</td>
<td>20%</td>
</tr>
<tr>
<td>Oral mucosa</td>
<td>2%</td>
</tr>
<tr>
<td>Back</td>
<td>8%</td>
</tr>
<tr>
<td>Pectoral region</td>
<td>8%</td>
</tr>
<tr>
<td>Abdomen</td>
<td>5%</td>
</tr>
<tr>
<td>Shoulders</td>
<td>11%</td>
</tr>
<tr>
<td>Upper limbs</td>
<td>11%</td>
</tr>
<tr>
<td>Lower limbs</td>
<td>33%</td>
</tr>
<tr>
<td>Signs and symptoms on presentation</td>
<td></td>
</tr>
<tr>
<td>Flat lesion</td>
<td>46%</td>
</tr>
<tr>
<td>Raised lesion</td>
<td>53%</td>
</tr>
<tr>
<td>Well-defined borders</td>
<td>59%</td>
</tr>
<tr>
<td>Pigmentation/erythema</td>
<td>86%</td>
</tr>
<tr>
<td>Hard on palpation</td>
<td>59%</td>
</tr>
<tr>
<td>Soft on palpation</td>
<td>41%</td>
</tr>
<tr>
<td>Local symptoms</td>
<td>17%</td>
</tr>
<tr>
<td>Pain</td>
<td>13%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>13%</td>
</tr>
<tr>
<td>Soreness</td>
<td>3%</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>83%</td>
</tr>
<tr>
<td>Mean time to diagnosis</td>
<td>5.42 y</td>
</tr>
<tr>
<td>Mean maximum diameter</td>
<td>6.46 cm</td>
</tr>
</tbody>
</table>

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

**Abbreviations:**
- FVIII-RA: factor VIII-related antigen
- H&E: hematoxylin-eosin
- ApL: acquired progressive lymphangioma
- UEA-I: *Ulex europaeus* agglutinin I.
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.\cite{1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16} Watanabe et al\cite{6} 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.\cite{8,9} Patients have also been reported to improve in response to systemic antibiotic treatment.\cite{11,14}

Some authors prefer therapeutic abstention,\cite{3,11,16} as partial or total spontaneous remission has been observed in 2 cases.\cite{11,14} In the untreated patients in another study, the lesion slowly and steadily spread to cover extensive parts of the body.\cite{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.\cite{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.

Conflict of Interest

The authors declare that they have no conflict of interest.

References