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CASE REPORT

Intralymphatic Histiocytosis and Cancer of the Colon

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KEYWORDS

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PALABRAS CLAVE

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Vasos linfáticos;
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reactiva;
Linfoma intravascular

Abstract

Intralymphatic histiocytosis is a condition with nonspecific clinical features but with characteristic histopathological and immunohistochemical findings. It presents as a poorly demarcated erythematous plaque or a lesion similar to livedo reticularis, usually located on the limbs. Histologically, dilated vessels containing mononuclear cells are observed in the reticular dermis.

In the past, the majority of these cases were thought to be cases of reactive angioendotheliomatosis or intravascular lymphoma, but the development of more specific immunohistochemical markers showed that these were dilated lymph vessels containing histiocytes, and so were considered as a separate condition.

We present the case of a man with a past history of left axillary lymphadenectomy for lymphatic tuberculosis, leukocytoclastic vasculitis, and cancer of the colon. The patient developed an erythematous plaque in the left pectoral region. Histology and immunohistochemical stains of the lesion revealed histiocytes within dilated lymph vessels in the reticular dermis, but no neoplastic cells.

We present a new case of intralymphatic histiocytosis in a patient with autoimmune and neoplastic diseases.

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Histiocitosis intralinfática y neoplasia de colon

Resumen

La histiocitosis intralinfática es una entidad de clínica inespecífica, pero con una histología y una inmunohistoquímica características. Se manifiesta como una placa eritematosa mal delimitada o una lesión livedoide que normalmente afecta a las extremidades. Histológicamente muestra vasos dilatados en la dermis reticular ocupados por células mononucleares.

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Los casos descritos anteriormente se diagnosticaron de angioendoteliomatosis reactiva y de linfoma intravascular, pero el desarrollo de marcadores inmunohistoquímicos más específicos demostró que eran vasos linfáticos ocupados por histiocitos y se caracterizaron, por tanto, como una entidad propia y diferenciada.

Se presenta el caso de un varón con antecedentes de linfadenectomía axilar izquierda por una tuberculosis ganglionar, una vasculitis leucocitoclástica y una neoplasia de colon, que desarrolló una placa eritematosa en la región pectoral izquierda. En la histología y las tinciones inmunohistoquímicas se observaron histiocitos en el interior de los vasos linfáticos dilatados en la dermis reticular sin células neoplásicas.

Se presenta un nuevo caso de histiocitosis intralinfática en un paciente con enfermedad autoinmunitaria y neoplásica.

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Introduction

Intralymphatic histiocytosis is defined by histological findings, as the clinical presentation is very nonspecific. Its pathogenesis is still unclear, but an association with chronic inflammatory disorders (in patients with rheumatoid arthritis or joint prostheses) has led to the suggestion that its origin may lie in the lymph stasis that develops in these situations, with the consequent accumulation of antigens that attracts histiocytes to the affected area.¹

Before immunohistochemical techniques allowed the specific identification of lymph vessels (eg, with anti-podoplanin [D2-40]) and histiocytes (eg, with anti-CD68 [PGM1]), it was thought that the dilated vessels were blood vessels and that the cells they contained were lymphocytes or endothelial cells. For this reason, the cases were diagnosed as reactive angioendoteliomatosis or as intravascular lymphomas.

Case Report

A 67-year-old man came to the dermatology department for evaluation of an erythematous plaque in the left pectoral region; it had poorly defined borders and the lateral part had a livedoid appearance. The lesion did not affect the axilla, and there was a small periareolar halo. Physical examination revealed a nontender, noninfiltrated plaque that was of the same temperature as the surrounding skin (Figure 1A and B). The patient stated that the lesion had been present for 1½ months.

In his past history, the patient reported that 5 years earlier he had undergone lymph node clearance of the left axilla—the same side as the current lesion—for lymph node tuberculosis. He also developed leukocytoclastic vasculitis at that time, with a decrease in the C4 fraction of complement and an elevation of rheumatoid factor; since that time he had therefore been on oral corticosteroid treatment.

In view of the presentation, the initial diagnostic impression was of lymphangitis, and a 6 mm punch biopsy was therefore performed in order to determine the etiology. Hematoxylin-eosin stain revealed dilated vessels containing mononuclear cells in the deep dermis. The vessels had thin walls formed of endothelial cells

of normal appearance, with no thickening or protrusion into the lumen. There were 2 cell populations within the vessels: one formed of larger cells with finely granular, pale eosinophilic cytoplasm, accounting for the majority of cells, and the other formed of monomorphic cells with dense nuclei (Figure 2). The skin adnexa, the epidermis, and the other layers of the skin were unaltered.

Immunohistochemical staining was performed with podoplanin, cytokeratins AE1 and AE3, CD68, and CD45. The vascular walls stained intensely with the lymphatic marker D2-40 (Figure 3A). Immunohistochemistry for cytokeratins AE1 and AE3 was negative (Figure 3B), thus excluding the possibility of vascular invasion by carcinomatous cells. The larger intraluminal cells stained with CD68, which is specific for histiocytes (Figure 3C and D), and the accompanying cells with CD45, which is characteristic of lymphocytes.

A diagnosis of intralymphocytic histiocytosis was made based on these histological and immunohistochemical findings and the compatible clinical picture.

Four weeks later, the patient returned to the clinic to report that he had been diagnosed with a tumor of the colon and that the staging study had revealed splenic involvement associated with intraperitoneal and retroperitoneal lymph nodes. During this second physical examination, the skin lesions were found to have increased in size and had crossed the midline (Figure 1C and D). In view of this new situation, a new biopsy was taken from the lesion on each side of the chest; the histological and immunohistochemical results were identical to those of the first biopsy.

After surgical excision of the colon tumor and of the intraperitoneal and retroperitoneal lymph nodes, the skin lesion improved progressively until it disappeared completely (Figure 4).

Discussion

The histological presence of dilated dermal vessels containing mononuclear cells is a feature of 3 conditions: reactive angioendoteliomatosis, intravascular lymphoma, and the recently described intralymphocytic histiocytosis (Table).

Reactive angioendoteliomatosis is a benign proliferation of endothelial cells that can obliterate the affected blood

vessel. It has been associated with various disorders, such as infectious diseases (including tuberculosis), micro-occlusive vascular disturbances, rheumatoid arthritis, hematological tumors, and leukocytoclastic vasculitis.² In contrast to intralymphatic histiocytosis, the dilated vessels are blood vessels and therefore do not stand out after staining with lymphatic markers, such as podoplanin, lymphatic vessel endothelial hyaluronan receptor (Lyve) 1, or Prox-1.

Intravascular lymphoma is a neoplastic disease that, unlike intralymphatic histiocytosis, presents an aggressive course and mainly affects the vessels of the skin and central nervous system. A variant has been reported in Asian patients that also affects the reticuloendothelial system and bone marrow and clinically can give rise to a hemophagocytic syndrome. It has been demonstrated histologically and immunohistochemically that the affected vessels are blood vessels and that the cells they contain are lymphocytes, particularly B lymphocytes.³

The first case of the disease we now know by the name intralymphatic histiocytosis was published in 1994 by O'Grady et al.⁴ Those authors reported the case of a patient who presented an erythematous rash on the left knee that persisted despite treatment. Histology of the lesion showed

histiocytes that stained immunohistochemically with factor XIII within dilated dermal vessels. Based on those findings and on the benign nature of the condition, the authors named it intravascular histiocytosis, aiming to differentiate it from the aggressive intravascular lymphoma.

Subsequently, given its benign nature and its histological appearance, some authors believed the disease to be related to the final stages of the above-mentioned reactive angioendotheliomatosis, produced by organization of the thrombi that had formed.^{2,5}

Since the year 2000, the morphology of the dilated vessels (thin walls and irregular outline) has led some authors to consider the condition to be a disease of lymph vessels rather than blood vessels, giving it the name histiocytic lymphangitis.⁶ This belief was later confirmed after the development of more specific immunohistochemical stains for lymph vessels, such as podoplanin initially, and Lyve-1 and Prox-1 thereafter; these stains selectively mark the dilated vessels in the reticular dermis of these patients.

Since its acceptance as a lymphatic disease, 35 cases of intralymphatic histiocytosis have been reported in the medical literature. Clinically, all the cases described presented very subtle, asymptomatic lesions, in the form



Figure 1 A and B, Subtle early lesion in the left pectoral region that did not affect the axilla and with a small periareolar halo. C and D, Progression of the plaque to both pectoral regions 2 weeks after diagnosis.

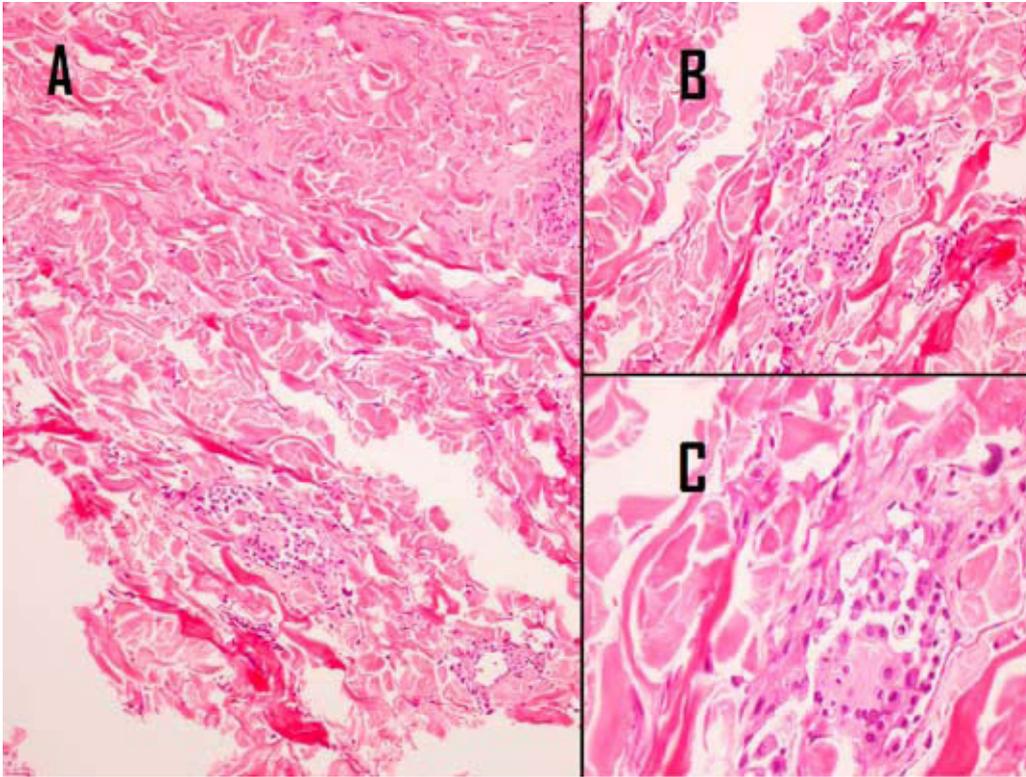


Figure 2 A, Dilated vessels in the deep dermis. B and C, Large mononuclear cells with granular eosinophilic cytoplasm within the vessels, which have thin, irregular walls, with endothelial cells of normal appearance.

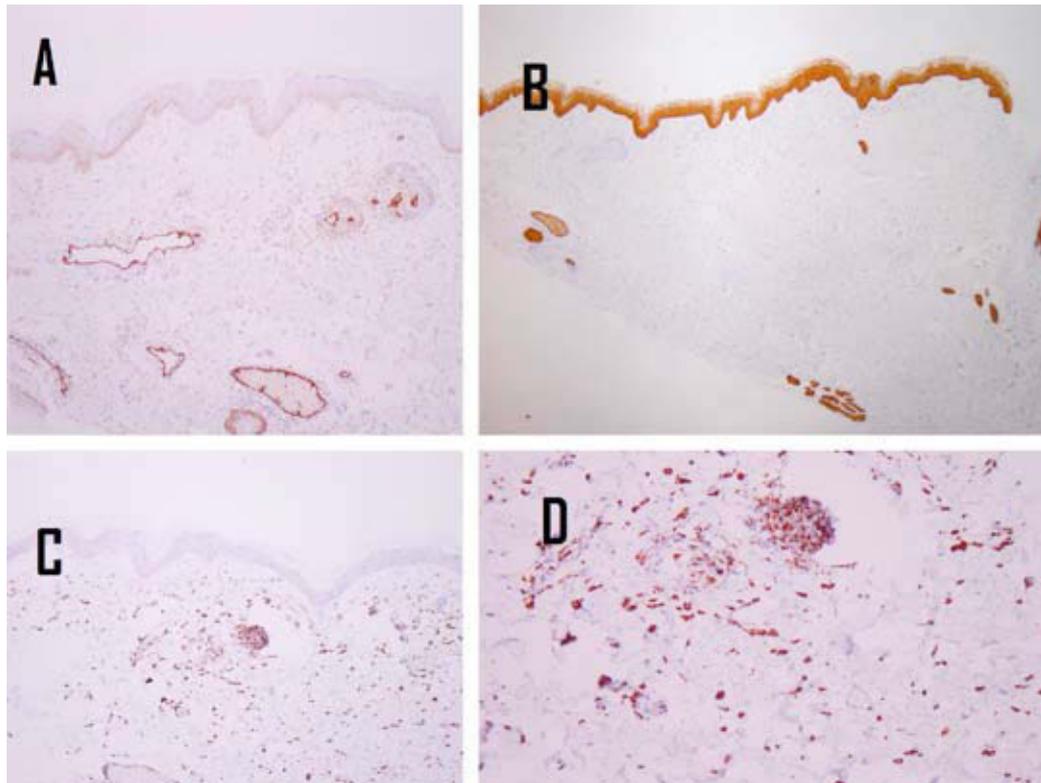


Figure 3 A, Positive immunohistochemical staining of the dilated vessels in the dermis with anti-D2-40 antibodies. B, Negative immunohistochemical staining of the intravascular cells with AE1 and AE3 anticytokeratin antibodies. C and D, Positive immunohistochemical staining of the intravascular cells with anti-CD68 antibodies.

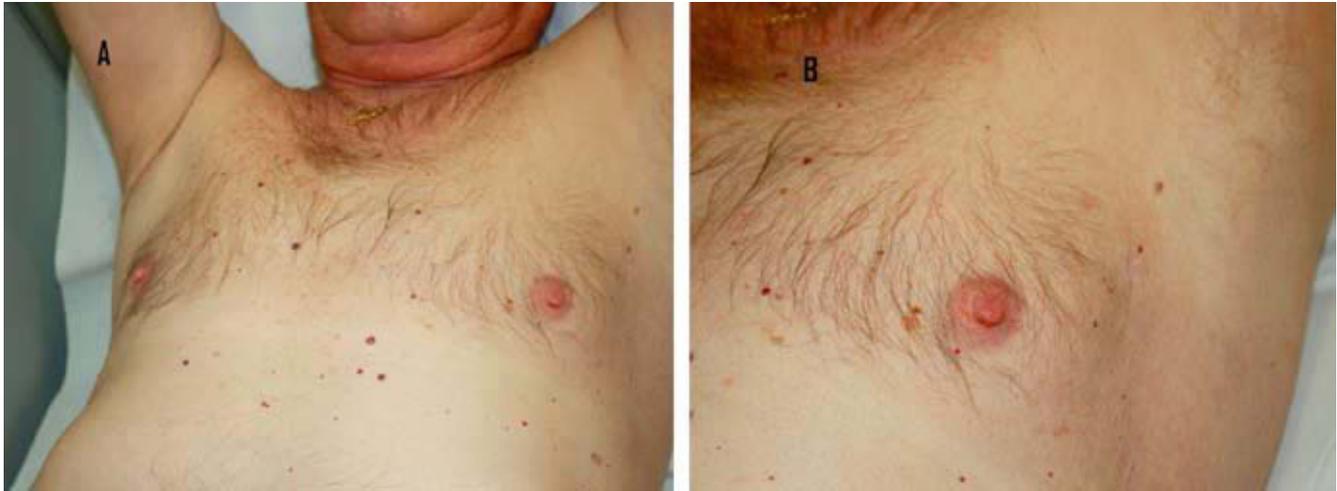


Figure 4 A, Complete resolution of the plaque on the chest after surgical excision of the colon cancer. B, Detail of the left pectoral and axillary region.

Table Differential Diagnosis of Diseases in Which Dilated Dermal Vessels Containing Mononuclear Cells Are Seen

Disease	Intralymphatic Histiocytosis	Intravascular Lymphoma	Reactive Angioendotheliomatosis
Origin of the dilated vessels	Lymph	Blood	Blood
Intravascular cell populations	Histiocytes (also lymphocytes)	Lymphocytes (particularly B cells)	Endothelial cells
Immunohistochemistry	CD68+, CD45+, D2-40+, Lyve-1+, and Prox-1+	CD20+, CD19+, CD22+, CD79a+, Factor VIII+, D2-40-, Prox-1-, and Lyve-1-	CD31+, CD34+, Factor VIII+, CD68-, CD45-, CD20-, D2-40-, Lyve-1-, and Prox-1-

of erythematous or livedoid plaques with poorly defined borders on the upper or lower limbs. Of the 35 patients reported, 19 had a past history of rheumatoid arthritis and 2 had an elevated rheumatoid factor. The areas affected were close to joints damaged by the rheumatoid arthritis. These findings have led many authors to link intralymphatic histiocytosis closely with rheumatoid arthritis.⁷⁻¹⁰ It has also been described in patients with joint prostheses,^{1,11} and a case has even been reported of resolution of a diagnosed lesion of intralymphatic histiocytosis on the knee after joint replacement.¹ With regard to a past history of cancer, 2 cases have been reported of patients who developed this condition on mastectomy scars from breast cancer and one in whom intralymphatic histiocytosis was diagnosed as a chance finding on histological examination of the surgical specimen after excision of a Merkel cell carcinoma.¹ There have been no case reports of an association between intralymphatic histiocytosis and cancer of the colon.

Our patient presented a history of conditions that have been associated both with reactive angioendotheliomatosis (tuberculosis and leukocytoclastic vasculitis) and with intralymphatic histiocytosis (positive rheumatoid factor and alteration of lymph drainage on the side of the lesion

due to axillary lymph node clearance for lymph node tuberculosis), and clinically he presented a lesion that could correspond to either disease. In addition, almost simultaneously with the appearance of the lesion, the patient was diagnosed with adenocarcinoma of the colon with involvement of intraperitoneal and retroperitoneal lymph nodes. The definitive diagnosis was based on the histological and immunohistochemical findings, which confirmed the presence of histiocytes and smaller numbers of lymphocytes within the dilated lymph vessels. This is therefore a new case of intralymphatic histiocytosis in a patient who, as in other cases reported in the literature,^{1,9} presented alterations of lymph drainage due, in this case, to axillary clearance on the same side as the lesion for an infectious disease 5 years earlier. No cases of this disease associated with colon adenocarcinoma have been reported, and we cannot therefore state that the malignant lymph node disease in this patient also contributed to the obstruction of lymph drainage and thus to the appearance of the lesion; however, the lesion developed at almost exactly the time the tumor was diagnosed and then improved progressively to become almost undetectable after excision of the tumor with associated lymph node dissection.

Conflicts of Interest

The authors declare no conflicts of interest.

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