Intralymphatic Histiocytosis. A Clinicopathologic Study of 16 Cases

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Abstract: Intralymphatic histiocytosis is a rare condition characterized by the presence of dilated lymphatic vessels containing aggregates of mononuclear histiocytes (macrophages) within their lumina. The phenomenon seems to occur almost exclusively within the reticular dermis. Although its pathogenesis remains uncertain, there has been speculation about the possible relationship between intralymphatic histiocytosis and intravascular reactive angioendotheliomatosis. In addition, several examples historically have been associated with rheumatoid arthritis. We describe our experience with 16 cases of intralymphatic histiocytosis. Clinically, the lesions were located predominantly on the upper and lower limbs, and they consisted of asymptomatic and poorly demarcated erythematous plaques and livedo reticularis–like lesions. They were characterized histopathologically by dilated vascular structures involving the reticular dermis. Some of these dilated vessels had empty lumina, whereas others contained variable number of mononuclear histiocytes. An inflammatory response of variable intensity from case to case was also present in the adjacent dermis. The dilated vessels exhibited thin walls with irregular shapes, and a single discontinuous layer of flat endothelial cells lined their lumina. Immunohistochemically, the endothelial cells lining the dilated lumina expressed immunoreactivity for CD31, CD34, podoplanin, D2-40, Lyve-1, and Prox-1, which confirmed their nature as lymphatic endothelial cells. Intralymphatic mononuclear histiocytes expressed CD68 (PGM1), although some cases also had variable immunoexpression for myeloperoxidase, CD31, and podoplanin. In the 4 cases that employed double immunohistochemistry, with podoplanin + CD68 (PGM1) or with Lyve-1 + CD68 (PGM1), each marker highlighted their specific target cells unequivocally; the endothelial cells expressed podoplanin or Lyve-1 immunoreactivity, and intralymphatic histiocytes showed CD68 (PGM1) immunoexpression. Our findings expand on the previously described morphologic and immunohistochemical features of intravascular histiocytosis. We also discuss the possible relationship between intralymphatic histiocytosis and the so-called reactive intravascular angioendotheliomatosis.

Key Words: intralymphatic histiocytosis, intralymphatic macrophages, reactive intravascular angioendotheliomatosis, intravascular lymphoma, lymphatic endothelial cell markers, immunohistochemistry, rheumatoid arthritis, breast carcinoma, joint prosthesis inflammatory reaction, CD31, CD34, D2-40, podoplanin, Lyve-1, Prox-1, CD68

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The condition known as intravascular histiocytosis was first documented in 1994 by O'Grady et al.[1] They described an otherwise healthy 77-year-old woman with a nontender erythematous rash below the left knee, which was histopathologically characterized by dilated dermal vessels, some of them containing collections of mononuclear histiocytes (macrophages) within their lumina. The intravascular cells expressed immunohistochemical markers for macrophagic histiocytes (Mac 387 and Kp1), whereas the endothelial cells of the dilated vessels stained positively with antibodies to factor VIII–related antigen. Thus, those authors named the condition "intravascular histiocytosis" and discussed the histopathologic differential diagnosis with intravascular lymphoma.

Five years later, in 1999, Rieger et al[2] described 2 similar patients, one of them with history of rheumatoid arthritis, and speculated about the possible relationship between intravascular histiocytosis and intravascular reactive angioendotheliomatosis. They hypothesized that intravascular histiocytosis might be an early stage of intravascular reactive angioendotheliomatosis whereby histiocytes are associated with organization of microthrombi followed by endothelial cell proliferation.

In 2000, Pruim et al[3] reported on 2 additional patients with long-standing rheumatoid arthritis who showed erythematous plaques on the upper limbs histopathologically characterized by intravascular collections of mononuclear histiocytes. Because the dilated vessels containing histiocytes exhibited thin walls of irregular profile and were lined by a single discontinuous layer of flat endothelial cells, they

believed that "these vessels were more suggestive of lymphatics than blood vessels," and hence, they were the first authors coining the term "histiocytic lymphangitis" to name the condition.

In an article describing the spectrum of histopathologic observations in patients with rheumatoid arthritis,[4] Magro and Crowson, in 2003, elucidated the findings of 3 patients with infiltrative erythema that were characterized histopathologically by intravascular collections of histiocytes.

Takiwaki et al,[5] in 2004, described 4 patients with irregularly shaped erythematous plaques in the vicinity of the joints involved by rheumatoid arthritis. Microscopically, they identified collections of histiocytes within dilated, thin-walled vessels. Because they were unsure about the nature of those vessels, they used the expression "intravascular or intra-lymphatic histiocytosis" to name the condition.

In 2005, Okazaki et al[6] reported an additional patient with rheumatoid arthritis and intralymphatic histiocytosis. They were the first authors to unequivocally prove the lymphatic nature of the involved dermal vessels because they showed that podoplanin (D2-40), a lymphatic endothelial cell marker, was expressed in the endothelial cells lining the dilated vessels containing histiocytes. Since then, the name "intralymphatic histiocytosis" has been preferred to describe additional examples of this disorder.[7–11]

Herein, we describe our experience with 16 cases of intralymphatic histiocytosis and expand on the previously described morphologic and immunohistochemical features of this disorder. We also discuss the histopathologic differential diagnosis with intravascular lymphoma and the possible relationship between intralymphatic histiocytosis and the so-called reactive intravascular angioendotheliomatosis.

MATERIALS AND METHODS

Sixteen patients with cutaneous lesions histopathologically characterized by intralymphatic aggregations of histiocytes were collected retrospectively from the files of the authors. Clinical information was obtained from the hospital records, clinicians, or laboratory request forms. The following data were recorded, if available, in each patient: age, sex, location of the lesions, clinical appearance, clinical diagnosis, associated diseases, and follow-up. In cases with livedo reticularis–like lesions, cutaneous biopsy included both dusky and white central areas.

For conventional light microscopy, tissue was fixed in 4% formalin, embedded in paraffin wax, and cut and stained with hematoxylin–eosin. For immunohistochemical studies, representative sections of all cases were examined by the labeled streptavidin–biotin method using appropriate positive and negative controls throughout. Automated immunostaining was performed on a BioTek Solutions Tech Mate (TechMate 500; Biotech Solutions, Dako, Glostrup, Denmark) using commercially available antibodies to the following antigens: CD3 (clone F7.2.38, dilution 1:200; Dako); CD4 (clone IF6, dilution 1:10; Novocastra, Newcastle, United Kingdom); CD8 (clone DK25, dilution 1:50; Dako); TIA-1 (clone 2G9, dilution 1:600; Immunotech, Krefeld, Germany); CD20 (clone L26, dilution 1:500; Dako); CD79a (clone JCB117, dilution

1:50; Dako); CD45 (clone PD7/26, dilution 1:400; Dako); S-100 protein (clone S-100, dilution 1:4000; Dako); CD1a (clone O10, dilution 1:1; Immunotech), Ki-67 (clone MIB-1, dilution 1:40; Dako); CD68 (clone PGM1, dilution 1:200; Dako), myeloperoxidase (clone MPO-7, dilution 1:2000; Dako), alpha-smooth muscle actin (clone IA4, dilution 1:300; Dako), CD31 (clone JC/70A, dilution 1:10; Dako); CD34 (clone Qbend/10, dilution 1:100; Dako); Podoplanin (polyclonal, dilution 1:200; Acris, Hiddenhausen, Germany); Prox-1 (polyclonal, dilution 1:200; Relia Tech, Braunschweig, Germany); LYVE-1 (polyclonal, dilution 1:200; BmT, Meerbusch, Germany); and D2-40 (clone D2-40, dilution 1:100; Dako). In 4 selected cases (cases 2, 3, 4, and 15), double immunostaining for both histiocytic and lymphatic endothelial cell markers was performed in the same slide using a different chromogen for each marker.

RESULTS

Clinical Findings

Table 1 summarizes the clinical data of the 16 patients. Briefly, there were 6 men and 10 women. The age range of the patients was 46–85 years (mean, 70 years). The lesions were predominantly located on the upper and lower limbs. The clinical appearance was variable, but poorly demarcated erythematous plaques and livedo reticularis–like lesions were frequently described in the reports accompanying the biopsy specimens. There was not pitting or other signs of localized lymphedema in the involved areas. Five cases were affected of rheumatoid arthritis, and the lesions were located on the extremities in the vicinity of the affected joints. In one of these patients (case 5), the intralymphatic histiocytosis was probably an incidental histopathologic finding at the periphery of the excision specimen of a Merkel cell carcinoma on the left thigh. Another patient with rheumatoid arthritis and lesions on the upper arm had history of melanoma and lymphadenectomy. Two patients had history of breast carcinoma (cases 7 and 9) and the lesions developed on the surgical scar of the mastectomy. Curiously, in 2 cases (cases 11 and 13), the lesions developed on surgical scars from hip replacement with a metal prosthesis, whereas in another patient (case 1), the lesions disappeared spontaneously after prosthetic joint knee replacement (Fig. 1). In another patient (case 15), the lesions consisted of unilateral eyelid swelling, which was clinically interpreted as Melkersson–Rosenthal syndrome (Fig. 2). Five patients did not have any associated condition, and in one case, clinical data were not available.

Histopathologic Findings

All cases showed similar features. The epidermis and papillary dermis were essentially normal, but the reticular dermis contained dilated vascular structures. Some of these dilated vessels had empty lumina, whereas others contained collections of mononuclear epithelioid cells, with eosinophilic, finely granular cytoplasm and vesicular, oval, uniform nuclei (Fig. 3). In some cases, the intravascular aggregations of these cells seemed to be cohesive; however, in other cases, there were individual cells that appeared to be "floating" within the dilated lumina. In addition to the mononuclear

TABLE 1. Clinical Data of 16 Patients With Intralymphatic Histiocytosis

Case	Sex	Age (yrs)	Lesion Location	Clinical Features	Associated Diseases or Findings	Follow-up
1	F	79	Thighs, knees	Erythematous violaceous confluent patches	Rheumatoid arthritis	Lesions disappeared after knee joint replacement
2	F	46	Left lower leg	Poorly demarcated erythema	Rheumatoid arthritis Klippel–Trenaunay syndrome	N/a
3	M	48	Left chest, left thigh	N/a	N/a	N/a
4	F	84	Right arm	Indurated plaque: intravascular lymphoma?	None	Lesions have persisted
5	F	57	Left thigh	Erythema and induration	Merkel cell carcinoma at the same site of the original biopsy, rheumatoid arthritis, PCR negative for EBV, *Borrelia*, and *Treponema pallidum*	N/a
6	M	79	Abdominal skin	Multiple excoriated papules: scabies?	None	N/a
7	F	69	Right breast	Erythema on the surgical scar: carcinoma erysipeloides?	Previous right breast carcinoma	N/a
8	F	85	Left upper arm	Livid erythema: dermatomyositis?	PCR negative for *Borrelia*, *Streptococcus*, *Staphylococcus*, and *Bartonella*	N/a
9	F	66	Left breast	Livid erythematous patch	Excision of left breast carcinoma 9 yrs ago	N/a
10	F	78	Right elbow	Scaly induration: granuloma annulare, allergic eczema, herpes simplex?	None	N/a
11	M	63	Right hip	Indurated erythema of the surgical scar	The lesions developed on the scar after hip joint replacement with a metal prosthesis	N/a
12	F	75	Right upper arm	Livid erythema after insect bite: mycosis fungoides?	PCR negative for *Borrelia* and HHV-8, polyclonality of light chain expression (kappa and lambda light chains)	N/a
13	M	65	Right thigh	Erythema on the surgical scar	The lesions developed on the surgical scar after hip joint replacement with a metal prosthesis	N/a
14	F	84	Right upper arm	Persistent reticulate erythema	Rheumatoid arthritis, PCR negative for *Borrelia*, IgH and TCR clonality	N/a
15	M	68	Upper eyelid	Melkersson–Rosenthal syndrome?	Melanoma in situ in the overlying epidermis Unilateral eyelid swelling histopathologically showing suppurative granuloma	N/a
16	M	73	Left upper arm	Large vascular radiating patch present for 2 months: angiosarcoma, inflammatory carcinoma, Kaposi's sarcoma?	Rheumatoid arthritis, malignant melanoma S/P lymphadenectomy	N/a

HHV-8, human herpesvirus 8; N/a: Not available; PCR, polymerase chain reaction; TCR, T-cell receptor; EBV, epstein-barr virus.

epithelioid cells within the lymphatic lumina, there were occasional sparse numbers of the same cells admixed neutrophils and small lymphocytes. An inflammatory response of variable intensity from case to case was also present in the adjacent dermis. This inflammatory infiltrate was composed mostly of small mature lymphocytes and a variable number of histiocytes and plasma cells. In rare instances, large lymphoid aggregates of small lymphocytes and plasma cells were identified adjacent to the vessels, and these aggregates, in places, appeared to protrude into the lumen of the vessels.

The dilated vessels exhibited thin walls of irregular shape, and a single discontinuous layer of flat endothelial cells lined their lumina. There was no nuclear pleomorphism or heterochromasia of endothelial cells nor were their endothelial nuclei protruding within the lumina. In some of the dilated vessels containing the mononuclear epithelioid histiocytes, the endothelial cells showed a presumed hyperplastic proliferation with some folding of endothelial strands into the lumina,

which were intermingled with intraluminal histiocytes, lymphocytes, and neutrophils, resulting in an intravascular papillary or glomeruloid pattern that almost occluded the lumina. There was no evidence of leukocytoclastic vasculitis or thrombosis of the involved vessels.

Immunohistochemical Findings

The endothelial cells lining the dilated lumina expressed immunoreactivity for CD31, CD34, podoplanin (Fig. 4), D2-40, Lyve-1, and Prox-1, which confirmed their lymphatic endothelial cell nature. Intralymphatic mononuclear epithelioid cells were positive for CD68 (PGM1), confirming their histiocytic nature (Figs. 5 and 6), although in some cases, they also showed variable immunoexpression for myeloperoxidase, CD31 (Figs. 7–10), and podoplanin. S-100 protein and CD1a were negative in the intravascular mononuclear cells. Sparse numbers of CD3 positive lymphocytes were identified within the lumina of some of the dilated lymphatic vessels, whereas

FIGURE 1. Case 1. A, Livedo reticularis–like lesions involving the anterior aspect of the knees and legs. B, The lesions disappeared spontaneously on the right leg after prosthetic joint right knee replacement. C, The lesions persisted on the left leg.

the inflammatory infiltrate of the adjacent dermis was composed of a variable number of CD45, CD3, CD4, and CD20 positive lymphocytes, CD79a-positive plasma cells, and CD68 (PGM1)-positive histiocytes. In most cases, within the inflammatory dermal infiltrate, the number of CD20 and CD79a-positive lymphocytes was usually higher than that of CD3, CD4, and CD45 positive lymphocytes. CD8 and TIA1 were negative. Ki67 antibody showed variable nuclear positivity from case to case in the macrophages (histiocytes), but in general, the proliferative index was low. Rare endothelial cells lining the dilated vessels expressed Ki67 immunoreactivity as well. Immunostaining for alpha-smooth muscle actin (1A4) demonstrated that most of the dilated vessels containing histiocytes lacked smooth muscle cells or pericytes at the periphery of their walls, whereas some alpha-smooth muscle (1A4) positive spindle shaped cells, probably myofibroblasts, were identified in the dermal infiltrate. In the 4 cases employing double immunohistochemistry, with podoplanin, in conjunction with CD68 (PGM1) (Fig. 6), or Lyve-1, in conjunction with CD68 (PGM1), each marker stained their specific target cells; endothelial cells expressed podoplanin

or Lyve-1 immunoreactivity, and intralymphatic histiocytes showed CD68 (PGM1) immunoexpression.

DISCUSSION

Intralymphatic histiocytosis seems to be a rare disorder, and Table 2 summarizes those cases previously described in the literature. Analyzing all the previously reported 18 cases with the 16 cases described in this series, some clinicopathologic features seem to be relatively characteristic of this process. The disorder seems to be relatively more common in women than in men, it develops mostly in adult or elderly patients, and the cutaneous lesions show predilection for the extremities. The clinical lesions are characterized by poorly demarcated and irregularly shaped erythematous patches or plaques, sometimes with a livedo reticularis–like pattern and other times with papular, vesicular, or nodular areas on their surface.

There is a frequent association of intralymphatic histiocytosis with rheumatoid arthritis. Of the 34 patients (including both the cases of our series and those previously described in

FIGURE 2. Case 15. A, The lesions consisted of unilateral eyelid swelling. B, Close-up view of the eyelid swelling.
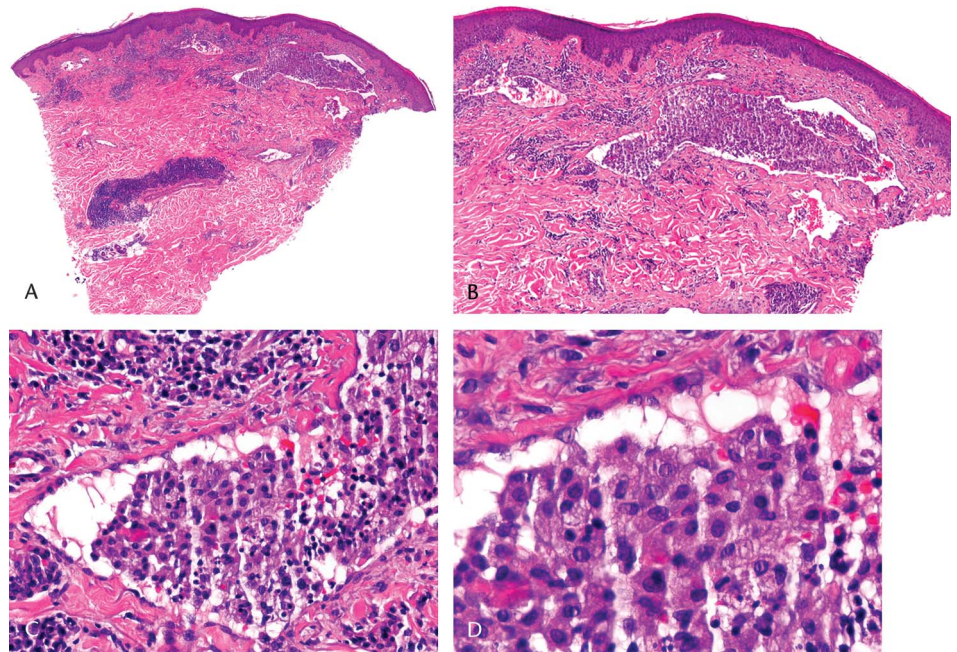
FIGURE 3. Case 2. Histopathologic features. A, Dilated vessels at different levels of the dermis. B, Intravascular collections of mononuclear epithelioid histiocytes. C, Intravascular histiocytes showed eosinophilic finely granular cytoplasm. D, Intravascular histiocytes showed vesicular oval uniform nuclei.

the literature), 18 patients (5 cases of our series and 13 from the literature) suffered from rheumatoid arthritis, and 2 additional patients from the literature showed positive rheumatoid factor. Furthermore, the cutaneous lesions developed in the vicinity of the involved joints. However, the clinical course of the cutaneous lesions of intralymphatic histiocytosis does not seem to parallel the activity of the rheumatoid arthritis. The lesions seem to be evanescent with an indolent biological behavior but show a chronic course. Although partial

responses have been achieved with different therapies, including local radiotherapy,[1] topical corticosteroids,[2] cyclophosphamide,[2] pentoxifillin,[8] amoxicillin + acetylsalicylic acid,[10] and arthrocentesis,[11] relapses were common, and presently, there is no specific or consistent treatment for them. In fact, there is no real evidence that any of the reported treatments had any efficacy.

Morphologically, the intraluminal cells seen in the cutaneous lesions of our patients showed the cytologic
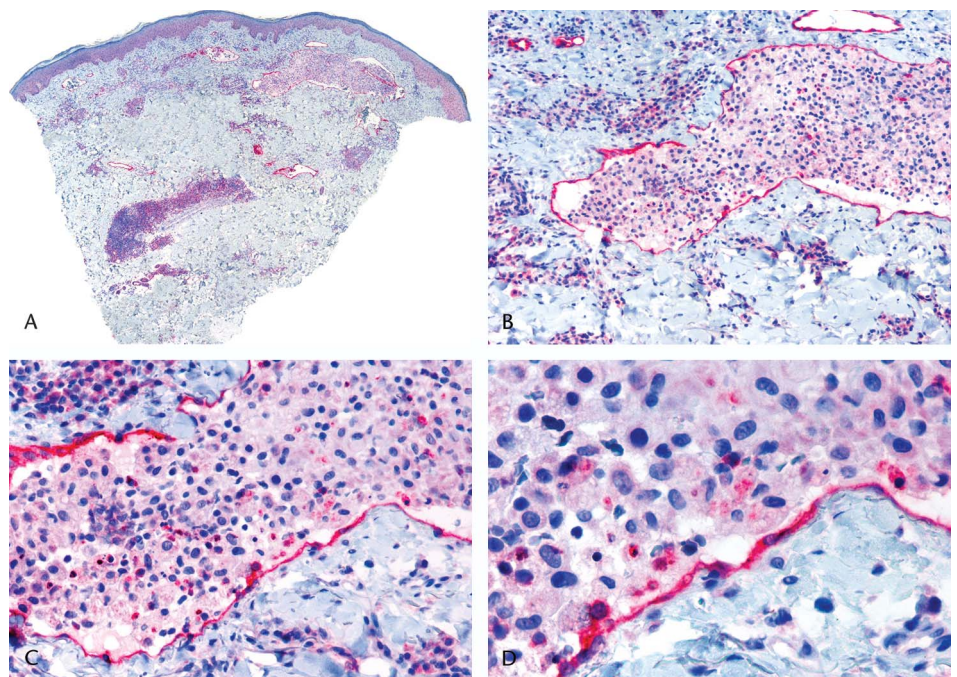

FIGURE 4. Case 2. Immunostaining for podoplanin. A, Scanning power. B, Podoplanin positivity of the flat endothelial cells lining the dilated vascular structures. C, Endothelial cells expressed podoplanin, whereas intraluminal histiocytes were podoplanin negative. D, Higher magnification showing the podoplanin positivity only in the flat endothelial cells.
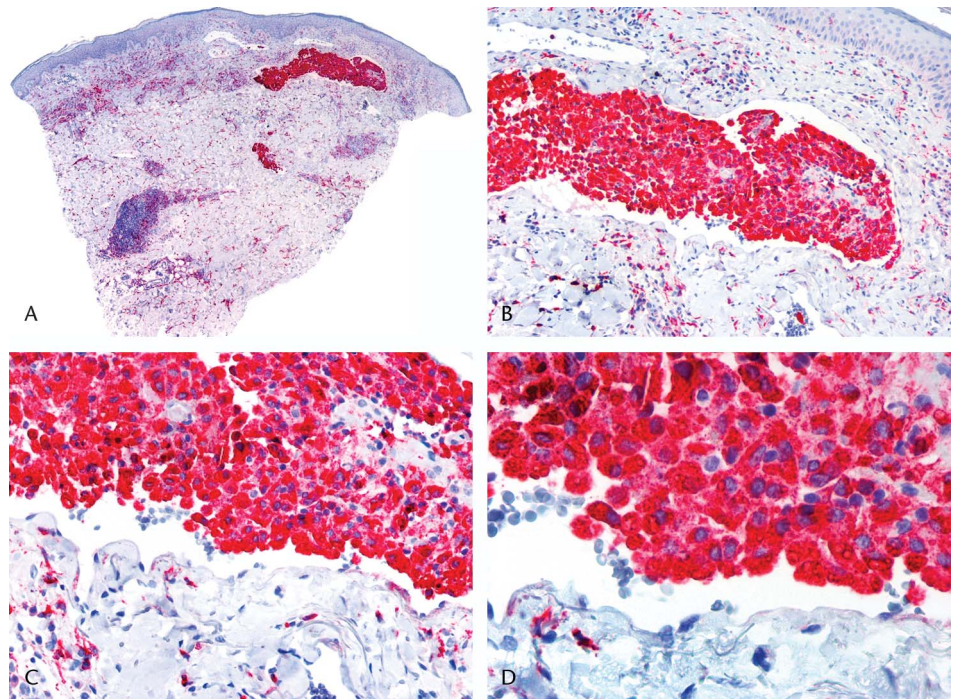
FIGURE 5. Case 2. Immunostaining for PGM1. A, Scanning power. B, PGM1 positivity of the intravascular histiocytes. C, Intravascular histiocytes expressed PGM1, whereas endothelial cells did not. D, Higher magnification showing the PGM1 positivity of the histiocytes, whereas flat endothelial cells were negative.

characteristic of histiocytes, and furthermore, they showed immunoexpression of histiocytic markers. In contrast, the endothelial cells lining the dilated vascular structures expressed the immunophenotype of lymphatic endothelial cells. However, some of the investigated immunohistochemical markers are not entirely specific for histiocytes and for lymphatic endothelial cells. PGM1 is probably the best immunohistochemical marker for cells of monocyte/macrophage

lineage, and it recognizes the CD68 cluster with higher specificity than Kp1 antibody, but PGM1 immunoreactivity has been also detected in mast cells, synovial cells, and plasmacytoid monocytes.[12] Parallel to this, the usual immunohistochemical markers for endothelial cells are CD34 and CD31, but they also have been detected in other nonendothelial cells, such as hematopoietic precursors (CD34[13]) and intratumoral histiocytes (CD31[14]). Moreover, CD31 and
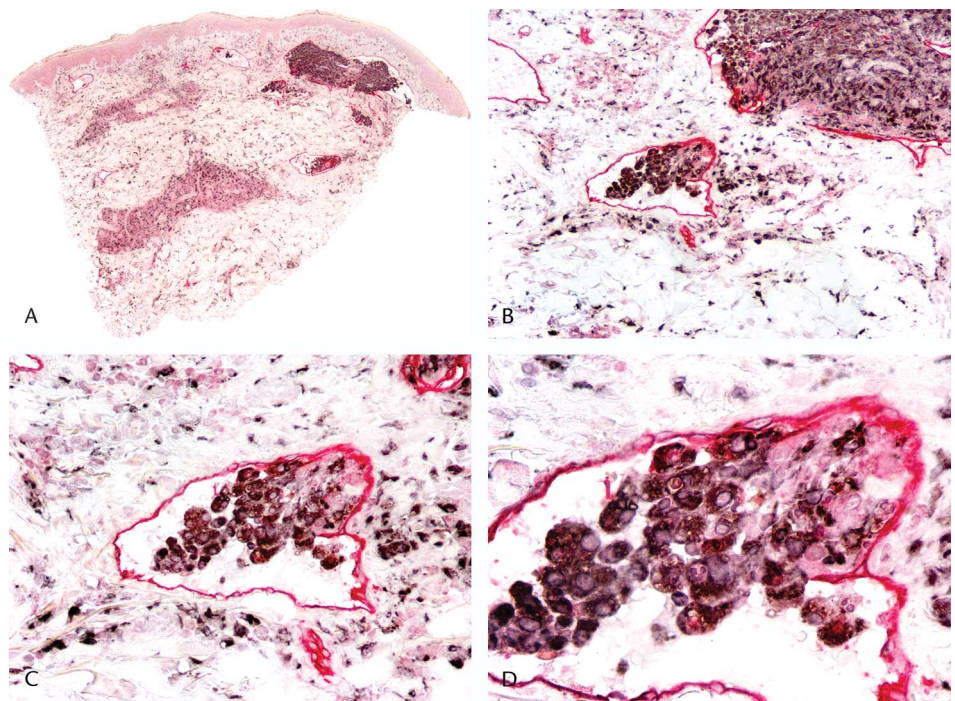

FIGURE 6. Case 2. Double immunostaining for podoplanin (red color) and PGM1 (brown color). A, Scanning power. B, Podoplanin stained the endothelial cells and PGM1 stained the intravascular histiocytes. C, Podoplanin-positive endothelial cells in red color and intravascular histiocytes in brown color. D, Higher magnification showing the double immunostaining for podoplanin with red color in endothelial cells and for PGM1 with brown color in intravascular histiocytes.
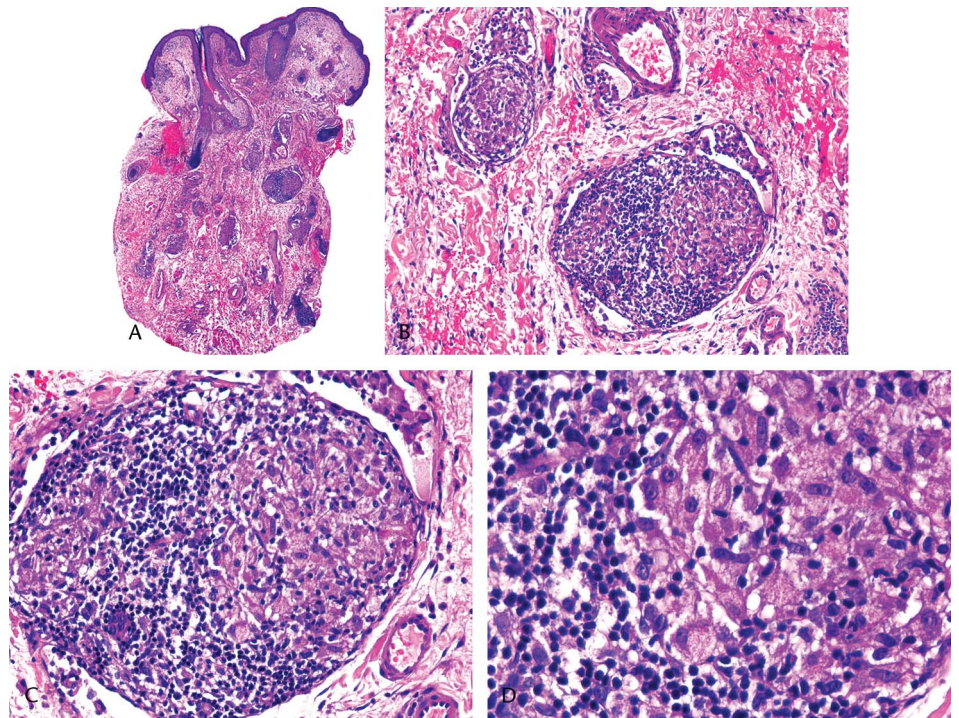
FIGURE 7. Case 15. Histopathologic features of intralymphatic histiocytosis. A, Scanning power. B, Dilated vessels with their lumina filled by mononuclear cells. C, Intravascular cells consisted of histiocytes intermingled with lymphocytes. D, Higher magnification of intravascular histiocytes and lymphocytes.

CD34 do not distinguish between blood and lymphatic endothelial cells because they are usually expressed in both. In recent years, however, a new group of antibodies have been employed to immunohistochemically differentiate between endothelial cells of blood and lymphatic vessels. Recently, podoplanin,[15] D2-40,[16] Lyve-1,[17] and Prox-1[18] have been

proposed as relatively specific markers for lymphatic endothelial cells because they are expressed in embryonic and adult endothelial cells of normal lymphatic vessels as well as in endothelial cells of lymphatic malformations and in proliferating cells of some neoplasms of presumed lymphatic differentiation. In contrast, these markers are negative in
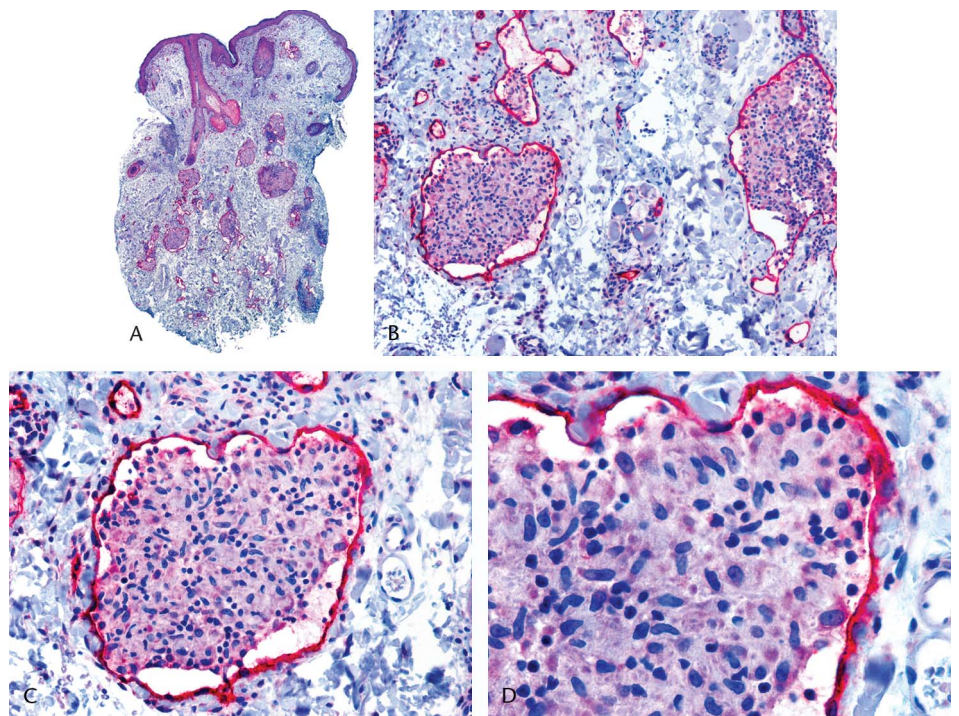

FIGURE 8. Case 15. Immunostaining for podoplanin. A, Scanning power. B, Dilated vessels with their lumina filled by mononuclear cells. C, Podoplanin is only expressed in flat endothelial cells. D, Higher magnification showing podoplanin positivity of endothelial cells.
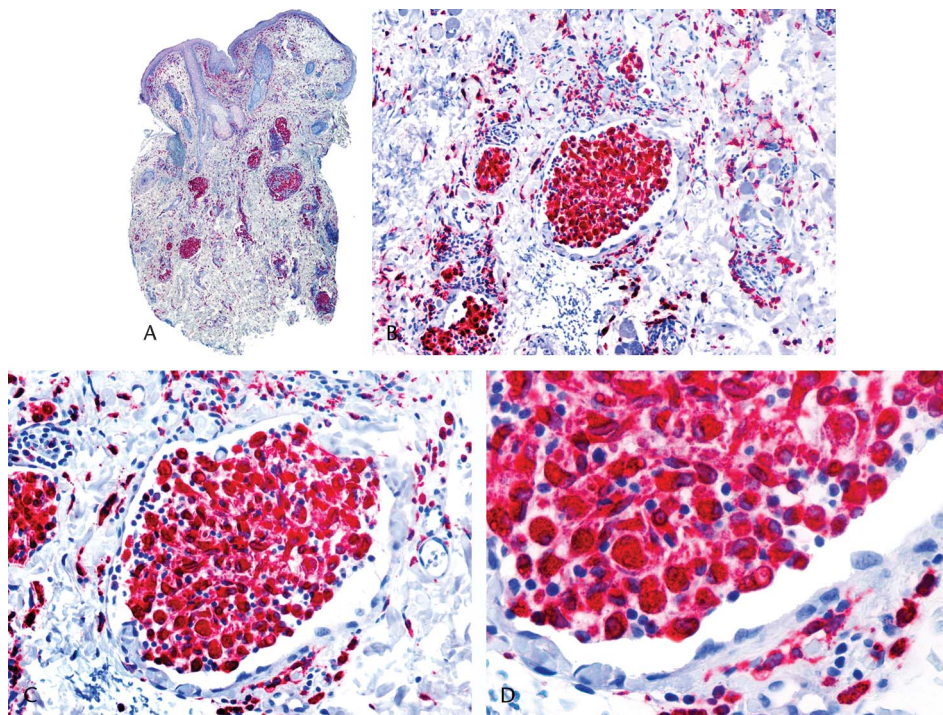
FIGURE 9. Case 15. Immunostaining for PGM1. A, Scanning power. B, Dilated vessels with their lumina filled by PGM1-positive mononuclear cells. C, PGM1 is only expressed by intravascular cells but no by flat endothelial cells. D, Higher magnification showing PGM1 positivity of intravascular cells.

endothelial cells of normal blood vessels, infantile hemangiomas, and other vascular proliferations of putative blood vessel endothelial cell differentiation. Therefore, in our cases, the immunoreactivity of podoplanin, D2-40, Lyve-1, and Prox-1 in the endothelial cells lining the dilated vessels containing histiocytes within their lumina supports the lymphatic nature

of those vessels and reinforces the name of intralymphatic histiocytosis as the best nomenclature for this condition.

The histopathologic differential diagnosis of intralymphatic histiocytosis includes intravascular reactive angioendotheliomatosis, intravascular lymphoma, leukemia, and other inflammatory conditions with intralymphatic collections
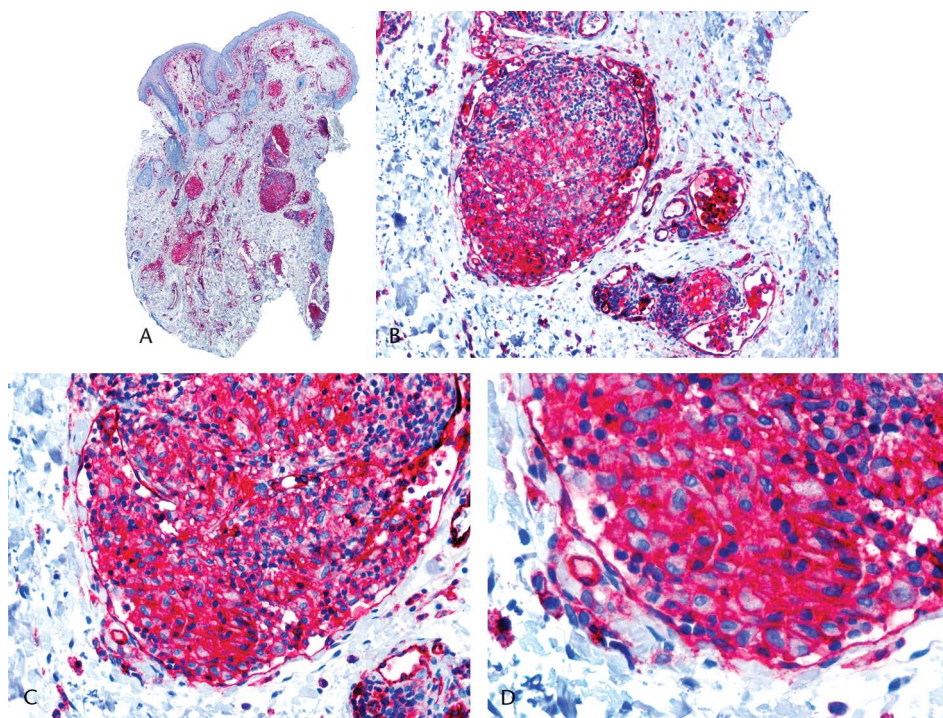

FIGURE 10. Case 15. Immunostaining for CD31. A, Scanning power. B, Dilated vessels with their lumina filled by CD31-positive cells. C, CD31 is expressed by both intravascular cells and flat endothelial cells. D, Higher magnification showing CD31 positivity of both intravascular and endothelial cells.

TABLE 2. Summary of the Cases of Intralymphatic Histiocytosis Previously Described in Literature

Case, Reference	Age (yrs)/Sex	Clinical Diagnosis	Histopathology/Immunohistochemistry	Associated Diseases
1, O'Grady et al[1]	70/F	Erythematous rash below the left knee	Intravascular collections of histiocytes (Mac 387 and Kp1 + histiocytes and F-VIII + endothelial cells)	ND
2, Rieger et al[2]	80/F	Red macules and plaques on face and arms	Intravascular collections of histiocytes (Mac 387 and PGM1 + histiocytes and CD31, F-VIII, and *Ulex europaeus* + endothelial cells	Cardiac insufficiency osteoporosis, positive rheumatoid factor
3, Rieger et al[2]	77/F	Violaceous patches with livedo-like erythema on both elbows	Intravascular collections of histiocytes (Mac 387 and PGM1 + histiocytes and CD31, F-VIII, and *U. europaeus* + endothelial cells)	Rheumatoid arthritis, bilateral breast cancer
4, Pruim et al[3]	63/M	Violaceous lesions with livedo-like erythema on the left elbow	Intravascular collections of histiocytes (HAM 56 and CD68 + histiocytes and CD31, CD34 + endothelial cells)	Rheumatoid arthritis
5, Pruim et al[3]	59/F	Erythematous rash on the left wrist	Intravascular collections of histiocytes (HAM 56 and CD68 + histiocytes and CD31, CD34 + endothelial cells)	Rheumatoid arthritis
6, Magro and Crowson[4]	82/M	Contact dermatitis on shoulder	Intravascular collections of histiocytes	Rheumatoid arthritis
7, Magro and Crowson[4]	46/M	Urticaria on buttocks, thighs, and lower back	Intravascular collections of histiocytes	Rheumatoid arthritis
8, Magro and Crowson[4]	41/F	Lymphoma on forearm	Intravascular collections of histiocytes	Rheumatoid arthritis
9, Takiwaki et al[5]	69/F	Indurated erythema and papules on the elbow	Intravascular or intralymphatic collections of histiocytes (CD68 + histiocytes and CD31, CD34, and F-VIII + endothelial cells)	Rheumatoid arthritis
10, Takiwaki et al[5]	74/M	Livedo-like erythema on the elbow and forearm	Intravascular or intralymphatic collections of histiocytes (CD68 + histiocytes and CD31, CD34, and F-VIII + endothelial cells)	Rheumatoid arthritis
11, Takiwaki et al[5]	66/F	Livedo-like erythema on the elbow and forearm	Intravascular or intralymphatic collections of histiocytes (CD68 + histiocytes and CD31, CD34, and F-VIII + endothelial cells)	Rheumatoid arthritis
12, Takiwaki et al[5]	62/F	Erythema and confluent papules on forearm	Intravascular or intralymphatic collections of histiocytes (CD68 + histiocytes and CD31, CD34, and F-VIII + endothelial cells)	Rheumatoid arthritis
13, Okazaki et al[6]	52/M	Livedo-like erythema with vesicles on lower leg	Intralymphatic collections of histiocytes (CD68 + histiocytes and D2-40 + endothelial cells)	Rheumatoid arthritis
14, Asagoe et al[7]	17/M	Painful induration of the scrotum	Intravascular collections of histiocytes (CD68 + histiocytes and CD31 + D2-40 endothelial cells)	Tonsillitis
15, Catalina-Fernández et al[8]	50/F	Erythematous plaques with livedo-like pattern on shins	Intralymphatic collections of histiocytes (CD68 + histiocytes and D2-40 + endothelial cells)	Rheumatoid arthritis, fibromyalgia
16, Okamoto et al[9]	75/F	Violaceous, infiltrated erythema on left forearm	Intralymphatic collections of histiocytes (PGM-1 + histiocytes and D2-40 + endothelial cells)	Rheumatoid arthritis, lymphedema
17, Mensing et al[10]	68/F	Reticular, bizarre-shaped livid macules on the face, livid macules on the face, back, and thighs	Intravascular collections of histiocytes (CD68 + histiocytes and CD31, CD34, and F-VIII + endothelial cells	Heart attack, diabetes
18, Waranabe et al[11]	75/M	Erythematous nodules on the left knee	Intravascular collections of histiocytes (PGM-1 + histiocytes and D2-40 + endothelial cells)	Orthopedic metal implants

F-VIII, factor-VIII–related antigen; F, female; M, male; ND, not described.

of histiocytes. Angioendotheliomatosis refers to an intravascular proliferation of endothelial cells that fill and sometimes obliterate vascular lumina. Initially, angioendotheliomatosis was considered by Tappeiner and Pfleger[19] as a neoplastic proliferation of endothelial cells. Later, clinical experience led to the conclusion that there were 2 variants of angioendotheliomatosis: a malignant (lymphomatous) and a benign (hyperplastic) variant, which we now regard as completely different diseases.[20] Currently, immunohistochemistry, electron microscopy, and gene rearrangement analysis of B-cell and T-cell receptor genes have clearly demonstrated that the examples originally considered as malignant

angioendotheliomatosis were actually a malignant and usually very aggressive *lymphoma*, an intravascular lymphoma, whereas the benign angioendotheliomatosis is a reactive intravascular proliferation of *endothelial* cells.

Intravascular lymphoma represents a rare variant of lymphoma characterized by a proliferation of neoplastic lymphocytes almost exclusively within blood vessels. Most of the reported cases are B-cell lymphomas, although a few cases of intravascular T-cell lymphomas have also been described in the literature.[21–34] In contrast with other lymphomas, lympho-reticular organs such as lymph nodes, bone marrow, spleen, and liver are not commonly involved by intravascular lymphoma except in the terminal stages of the disease, and circulating neoplastic lymphocytes are not identified, as a rule, in the peripheral blood. The lesions typically involve the central nervous system and the skin with an aggressive biological course and poor prognosis in most of the cases. In our cases of intralymphatic histiocytosis, immunohistochemical studies excluded the lymphocytic nature of the intravascular cells, the lesions showed an indolent biological behavior without systemic involvement, and, therefore, the diagnosis of intravascular lymphoma was excluded unequivocally.

The histopathologic differential diagnosis of intralymphatic histiocytosis with the so-called intravascular reactive angioendotheliomatosis is more controversial, and in fact, some investigators have raised the possibility that both disorders are actually 2 different aspects of the same phenomenon,[2,10] whereby intraluminal histiocytes appear with the organization of microthrombi followed later by endothelial cell proliferation. Reactive angioendotheliomatosis is the term used to name a rare benign process of unknown etiology that has been described in association with systemic infections, such as subacute bacterial endocarditis[35–39] or tuberculosis;[20,40,41] microvascular occlusive disorders, such as those related to intravascular deposition of cryoproteins,[42,43] antiphospholipid syndrome,[44] or dysglobulinemia[45]; vascular disorders such as hypertensive portal gastropathy in patients with hepatopathy,[46] severe peripheral vascular atherosclerotic disease,[47] iatrogenic arteriovenous fistulas for hemodialyisis,[48] or amyloid angiopathy;[49] hematologic malignancies, like chronic myeloid leukemia[50] or Castleman disease and POEMS syndrome (raising a relationship between reactive glomeruloid angioendotheliomatosis and glomeruloid hemangioma[51]); renal disease or postrenal transplantation;[52] and other miscellaneous conditions such as valvular cardiac disease,[52] glioblastoma multiforme in patients on systemic chemotherapy,[52] hepatic failure resulting from alcohol-induced cirrhosis,[52] and patients with rheumatoid arthritis.[52] Finally, human herpesvirus 8 positivity demonstrated recently by immunohistochemistry was identified in 4 of 10 cases of reactive angioendotheliomatosis, suggesting that some cases may be secondary to infection by this virus.[52] Some authors have suggested that reactive angioendotheliomatosis may represent a residual lesion of leukocytoclastic vasculitis,[20] but strong evidence for this hypothesis is lacking. From a histopathologic perspective, there are 2 variants of reactive angioendotheliomatosis, namely intravascular angioendotheliomatosis, which is characterized by a proliferation of intravascular endothelial cells that obliterate the lumina of the involved vessels,[35–46,48–54] and

the so-called diffuse dermal angioendotheliomatosis, which consists of a diffuse proliferation of endothelial cells interstitially arranged between collagen bundles of the reticular dermis.[47,48,52,55] The microscopic distinction between intravascular reactive angioendotheliomatosis and intralymphatic histiocytosis is difficult, and in fact, some of the described cases of intravascular reactive angioendotheliomatosis associated with rheumatoid arthritis[56] may also be examples of intralymphatic histiocytosis. Furthermore, conventional immunohistochemical markers may be unable to differentiate between these 2 processes because CD31, the marker used commonly for endothelial cells, may be also expressed by histiocytes,[14] and intralymphatic histiocytosis is often accompanied by putative hyperplasia with folding of endothelial strands into the lumina, and a combination of endothelial cells and histiocytes is usually identified within the lumina of the vessels involved by both intravascular reactive angioendotheliomatosis and intralymphatic histiocytosis. Therefore, only the new lymphatic endothelial markers, namely podoplanin, D2-40, Lyve-1, and Prox-1, allow for the identification and differentiation of intraluminal histiocytes and putative hyperplastic lymphatic endothelial cells. In short, although it has been proposed that intralymphatic histiocytosis and intravascular reactive angioendotheliomatosis represent 2 different stages of a single inflammatory process, in our experience, they are 2 entirely different disorders because intravascular reactive angioendotheliomatosis invariably involves only blood vessels (lymphatic endothelial markers are not expressed in the vessels involved by reactive angioendotheliomatosis, observations not shown), whereas intralymphatic histiocytosis is a process affecting exclusively lymphatic vessels.

The presence of some intraluminal myeloperoxidase-positive cells seen in some of our cases also raises the possibility of cutaneous lesions of myelogenous leukemia, but the clinical course of the patients and the absence of leukemic expression in the peripheral blood ruled out that possibility.

Finally, intralymphatic collections of histiocytes have also been described in lesions of Destombes–Rosai–Dorfman disease,[57] Melkersson–Rosenthal syndrome,[58–63] sclerosing lymphangitis of the penis,[64,65] and granulomatous lymphangitis of the scrotum and penis.[66] In contrast to the histiocytes of Destombes–Rosai–Dorfman disease, the intraluminal histiocytes seen in our patients showed no emperipolesis and they did not expressed S-100 protein immunoreactivity. Melkersson–Rosenthal syndrome shows a completely different clinicopathologic setting from that of intralymphatic histiocytosis, although, curiously enough, one of our cases (case 15) showed unilateral eyelid swelling that was clinically considered as unilateral Melkersson–Rosenthal disease, but histopathologically, the lesion consisted of suppurative granulomas with negative cultures and polymerase chain reaction investigations for microorganisms. However, it is also possible that this case represents an example of the so-called granulomatous lymphangitis[66,67] or a case of the so-called localized lymphedema,[68] and in this context, some authors consider orofacial granulomatosis as a forme frustes of Crohn disease.[67] Finally, sclerosing lymphangitis of the penis and granulomatous lymphangitis of the scrotum and penis also

show a complete different clinicopathologic picture from that of intralymphatic histiocytosis.

The pathogenesis of intralymphatic histiocytosis remains unknown. In all reported cases of this process, the lesions were histopathologically characterized by lymphangiectasis with intraluminal aggregates of histiocytes. Lymphangiectases result from obstruction of lymphatic drainage due to congenital abnormal vessels' development or acquired damaged lymphatic vessels from infection, trauma, surgery, radiation, and persistent inflammation or obstruction due to lymphatic metastases or parasite infection.[68,69] The frequent association of intralymphatic histiocytosis with rheumatoid arthritis and joint replacement or surgery suggests that chronic inflammation or the surgical wound could be the cause of lymph stasis with subsequent development of lymphangiectases. Lymph stasis may lead to poor clearance of antigen, localized immune dysfunction, and persistent inflammation. Thus, the aggregations of histiocytes within the lymphatic vessels may indicate the presence of persistent antigen that is stimulating histiocytes to proliferate and aggregate. However, because the association of intralymphatic histiocytosis with entirely disparate disorders such as rheumatoid arthritis, breast cancer, or joint replacement with metal prosthesis, it is also conceivable that intralymphatic histiocytosis is just a histopathologic pattern that may be seen in different inflammatory disorders.

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