Intravascular/Intralymphatic Histiocytosis: A Report of 3 Cases

Cuyan Demirkesen, MD, Tugce Kıran, MD,* Cem Leblebici, MD,† Deniz Yücelten, MD,‡ Ayşe Esra Koku Aksu, MD,§ and Cem Mat, MD¶*

Abstract: Intravascular/intralymphatic histiocytosis (IV/ILH) is a rare, reactive cutaneous condition, with uncertain pathogenesis. It may be associated with various inflammatory and neoplastic diseases. Although the clinical presentation is various, the biopsies reveal dilated vessels, mostly lymphatics, containing aggregates of histiocytes within their lumina. We described 3 cases of IV/ILH with different clinical presentations. In the first case, the patient presented with lymphedema in the genital region without any underlying disease. However, the second and third cases had reticular erythematous skin lesions. The second case had common variable immunodeficiency disease, rheumatoid arthritis, inflammatory bowel disease, and a history of a lymphoproliferative lesion. The third case had metal prostheses at both his right and left knees. In all these 3 cases, histopathologic and immunohistochemical findings were similar to each other and to those cases reported in the literature. In addition, the third case was admixed with reactive angioendotheliomatosis. In the second case, the endothelium of the ectatic vessels expressed CD31 and CD34, but not D2-40/podoplanin, pointing out that these vessels were blood vessels rather than lymphatics, differing from the other 2 cases. In conclusion, we believe, the most convincing statement about IV/ILH is that it is not a distinct clinicopathologic entity, but a histopathologic feature found as a part of a constellation of inflammatory changes or many other conditions.

Key Words: intravascular histiocytosis, intralymphatic histiocytosis, reactive angioendotheliomatosis

(*Am J Dermatopathol* 2015;37:783–789)

INTRODUCTION

Intravascular/intralymphatic histiocytosis (IV/ILH) is a rare, reactive cutaneous condition, with a total of 53 cases reported in the literature.[1] It is characterized by the presence of dilated vessels, mostly lymphatics, containing aggregates of histiocytes within their lumina. The clinical presentation is various, including poorly demarcated erythematous plaques, lesions similar to livedo reticularis, endurated painful patches, red macules, excoriated multiple papules similar to scabies, edema resembling Melkerson–Rosenthal syndrome, and lymphedema/lymphangitis at the genital region.[2–5] Although the pathogenesis of this condition is uncertain, it has been associated with various inflammatory and neoplastic diseases, such as rheumatoid arthritis (RA), breast, Merkel cell, and colon carcinomas, joint replacements by metal implants, tonsillitis, and vulvar necrosis.[4,6–14] The role of lymphatic stasis secondary to chronic inflammation or surgery has been suggested.[4,10] This is a benign process with chronic course without any efficient treatment.

We describe 3 cases of IV/ILH with different clinical presentations and various etiologies underlying.

CASE 1

A 16-year-old boy presented with a 1-year history of scrotal and penil edema, multiple papules, and vegetative lesions after trauma to the genital region (Fig. 1). His first biopsy had been diagnosed as lymphangioma circumscriptum in another medical center. A surgical operation had been proposed as a treatment of choice, and he was referred to the departments of dermatology and urology in our hospital. In the incisional biopsy, underneath the hyperkeratotic and acanthotic epidermis, there was a proliferation of ectatic lymphatic vessels predominantly at the upper parts of the dermis. Within the lumina of some ectatic lymphatics, there were histiocytes with finely granular, distinct, and pale eosinophilic cytoplasm (Fig. 2). These histiocytes were mostly detected as densely packed sheets of cells. Additionally, sparse inflammatory cell infiltration, including lymphocytes, histiocytes, plasma cells, and some scattered eosinophiles, was present around the vessels. There was a mild fibroblastic proliferation in the dermis. Immunohistochemically, the endothelial cells of ectatic vessels stained with the antibody against D2-40/podoplanin, a selective marker for lymphatic endothelium.[15] The histiocytes, within the lumina expressed CD68 (Fig. 3). After the diagnosis of ILH, the patient was investigated for other inflammatory diseases, such as Crohn disease, sarcoidosis, and tuberculosis but no concomitant disease was found. Viral serology and serology for antinuclear antibodies were negative. Treatment with topical steroid, and a trial of Tetradox and Deltacortril, was not useful. Therefore, surgical treatment was performed; however, scrotal swelling recurred 1 year later. The patient still has scrotal lesions.

CASE 2

A 27-year-old woman presented with a poorly demarcated, asymptomatic erythematous rash at both her breasts for 6 months (Fig. 4). The rash was somewhat reticular in appearance and was quite faint. She had a history of common variable immunodeficiency disease since the age of 6 years and was receiving intravenous

From the *Department of Pathology, I.U. Cerrahpasa Medical Faculty, Istanbul, Turkey; †Department of Pathology, Istanbul Training and Research Hospital; ‡Department of Dermatology, Marmara University; §Department of Dermatology, Istanbul Training and Research Hospital; and ¶Department of Dermatology, I.U. Cerrahpasa Medical Faculty, Istanbul, Turkey.

The authors declare no conflicts of interest.

Reprints: Tugce Kıran, MD, Department of Pathology, I.U. Cerrahpasa Medical Faculty, Fatih, Istanbul, Turkey (e-mail: tugceesen@msn.com).

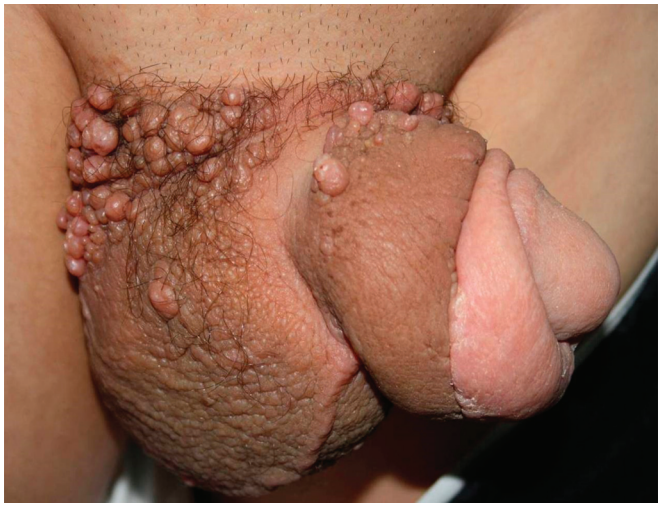

FIGURE 1. Scrotal and penil edema with multiple papules and vegetative lesions.

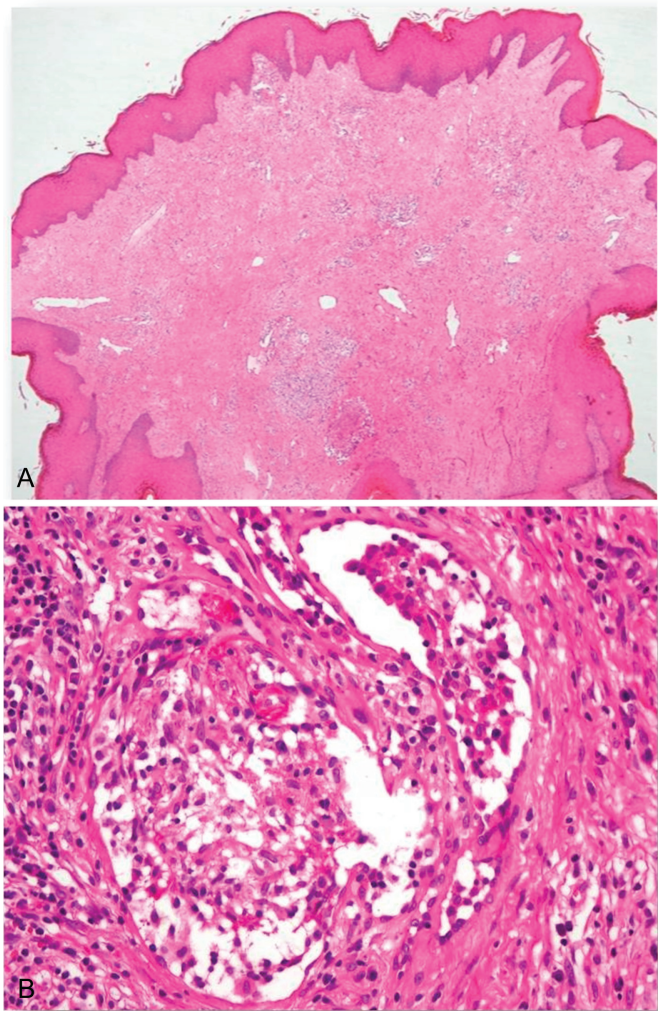

FIGURE 2. A, The ectatic lymphatic vessels predominantly at the upper and mid regions of the dermis (HE, ×40). B, The histiocytes with finely granular, distinct pale eosinophilic cytoplasm within lumina of these vessels (HE, ×400). HE, hematoxylin and eosin stain.

immunoglobulin for 17 years. Moreover, her medical history revealed the diagnosis of inflammatory bowel disease at the age of 15 years, in addition to the immunodeficiency, and she had used systemic steroids for about 7 years. At the age of 24 years, she had developed enlarged intraabdominal lymph nodes, therefore lymph node and bone marrow biopsies were performed. The diagnosis of mantle zone lymphoma and hypersplenism had been established. Afterward, she received 6 cycles of chemotherapy. A recent rebiopsy from an enlarged intraabdominal lymph node together with reevaluation of previous biopsies was interpreted as reactive lymphoproliferative disease secondary to primary immunodeficiency rather than a real lymphoma. During the follow-up and currently, she has had no signs of lymphoma. One year ago, she had a bout of arthritis and was given steroids for a short period of time, but because of ongoing complaints of artralgias and arthritis, the diagnosis of RA was established recently. Punch biopsy was performed from the erythematous skin lesions at the periareolar region. The proliferation of vascular structures and ectasia were seen in the dermis. Dilated vessels exhibited thin walls with a single layer of endothelial cells. There was neither nuclear pleomorphism nor protruding endothelial nuclei within the lumina. There were groups of histiocytes with distinct eosinophilic cytoplasm, together with a few number of lymphocytes and neutrophils within the lumina of the ectatic vessels (Fig. 5). Intraluminal histiocytes stained positively for CD68 without showing any immunoreactivity for CD20, CD3, CD31, and CD34 (Fig. 6). The endothelial cells of the vessels displayed immunoreactivity for only CD31 and CD34 but were negative for D2-40/podoplanin (Fig. 6). After the diagnosis of intravascular histiocytosis (IVH), she did not receive any treatment for this skin lesion, but it regressed within 4–5 months while she was under the treatment of steroids and methotrexate due to RA.

CASE 3

A 76-year-old man presented with a livid reticular plaque lesion, at the lateral side of his right thigh, extending to his knee. There were 2 nodular lesions within this plaque, measuring 1 and 3 cm in diameter (Fig. 7). The patient had no history of any other disease except hypertension and the replacements of metal prostheses at his right and left knee because of gonarthrosis, 7 and 3 years ago, respectively. These lesions were not overlying the surgical scar areas, but it was close to it. The punch biopsy, performed from the skin of the right thigh, displayed prominent vascular proliferation. Some of the vessels had swollen endothelial cells, sometimes obliterating the vascular lumina (Fig. 8). The others were thin-walled ectatic vessels, filled with histiocytes, expanding the vascular channels (Fig. 9). These histiocytes were seen as minor collections or cohesive sheets of cells. Around the vessels, there was an inflammatory infiltration, containing neutrophils, lymphocytes, and plasma cells. The endothelium of thin-walled vessels with intraluminal histiocytes showed immunoreactivity with D2-40/podoplanin and less prominently with CD31 antibodies, whereas it was negative for CD34. The histiocytes stained positively for CD68 (Fig. 10). After the diagnosis of ILH with reactive angioendotheliomatosis, he received daflon and cefazolin treatment for 1.5 years. There was no response to daflon, but partial response to cefazolin. After the injection of intralesional steroid, the lesion partially regressed.

The summary of the clinical data of all 3 cases is depicted in Table 1.

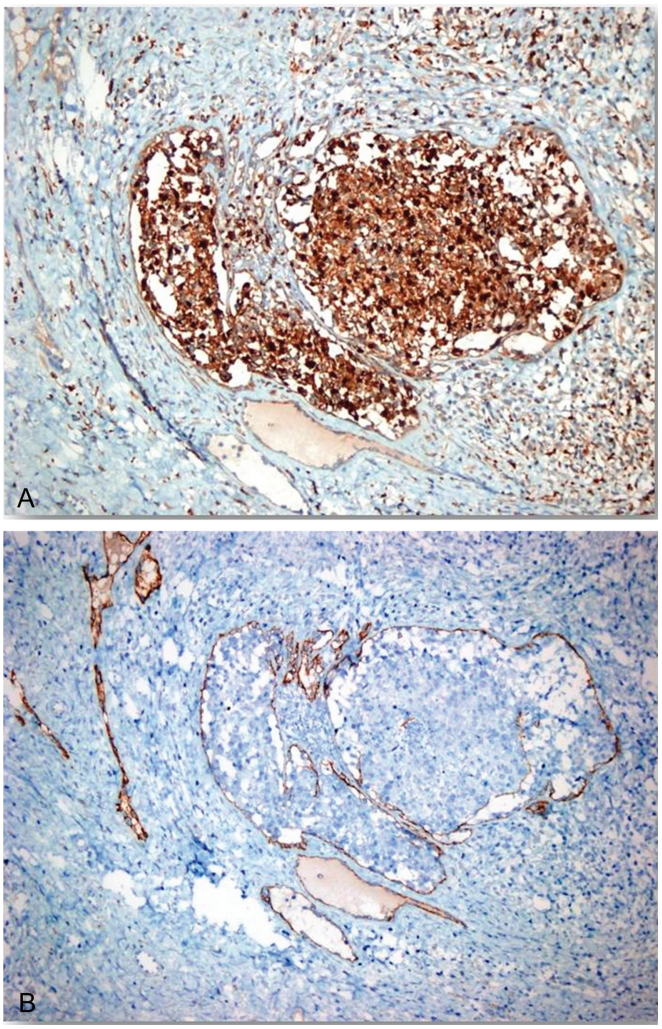

FIGURE 3. A, The histiocytes stained strongly positive for CD68. B, The endothelial cells of ectatic vessels expressed D2-40/podoplanin (×200).

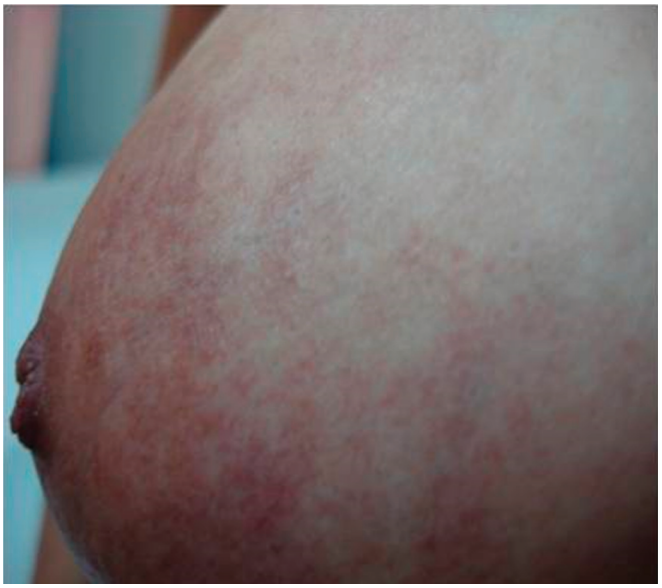

FIGURE 4. Poorly demarcated, reticular erythematous rash on her breasts.

DISCUSSION

The rare condition known as IVH was first described in 1994 by O'Grady et al.[16] They reported a 77-year-old healthy woman with a solitary, nontender erythematous rash below the left knee. Histopathologically, the lesion was characterized by ectatic dermal vessels, some of which contained histiocytes within their lumina. These cells were positive for Mac 387 and CD68, whereas the endothelial cells stained positively with the antibodies to factor VIII–related antigen. According to immunohistochemical findings, they called this condition as IVH. After this description, the association of IVH especially with RA and other chronic inflammatory processes that lead to lymphatic stasis was noted in many studies.[3,5,17] Pruim et al[17] believed that the vessels with a single layer of flat endothelial cells were more suggestive of lymphatics than blood vessels, and they were the first authors calling the term "histiocytic lymphangitis." This suggestion was confirmed after the development of more specific immunohistochemical markers, such as podoplanin, Lyve-1, Prox-1 which are specific markers for lymphatic endothelium.[15,17–19]

Although 2 of our cases were male, 1 of whom was a child, this condition is relatively more common in women than in men, and it develops mostly in adults and elderly patients.[4] The lesions are localized predominantly on the skin over and around the effected joints of the patients' extremities, as in our third case.[4] Some authors pointed out that these lesions are relatively resistant to topical and systemic therapies and showed an indolent and chronical behavior. By some authors, it was noted that the lesions disappeared after the treatment of the inflammatory or neoplastic diseases, which lead to lymphatic stasis.[6] The first and third cases demonstrated partial response to the treatment and had a chronic course, whereas the second case regressed totally while she was under treatment because of RA.

In our cases, histologic features were similar to each other and to those cases reported in the literature.[1–3,8,16,20,21] The main findings were ectatic thin-walled vessels with aggregates of histiocytes within their lumina (Table 1). Differing from the other 2 cases, the third case had admixed reactive angioendotheliomatosis. It should be emphasized that intravascular reactive angioendotheliomatosis and IVH are 2 non-related processes, because the endothelial cells of the involved vessels affected by intravascular reactive angioendotheliomatosis express an immunophenotype of blood endothelial cells ($CD31^+$, Prox-1−, Lyve-1−, and podoplanin−), whereas endothelial cells lining the involved vessels of IVH usually express an immunophenotype of lymphatic endothelial cells ($CD31^+$, Prox-1+, Lyve-1+, and podoplanin+). Moreover, reactive angioendotheliomatosis never contains large quantities of intravascular histiocytes. In the first and third cases, by the immunohistochemistry performed, the vessels containing histiocytes

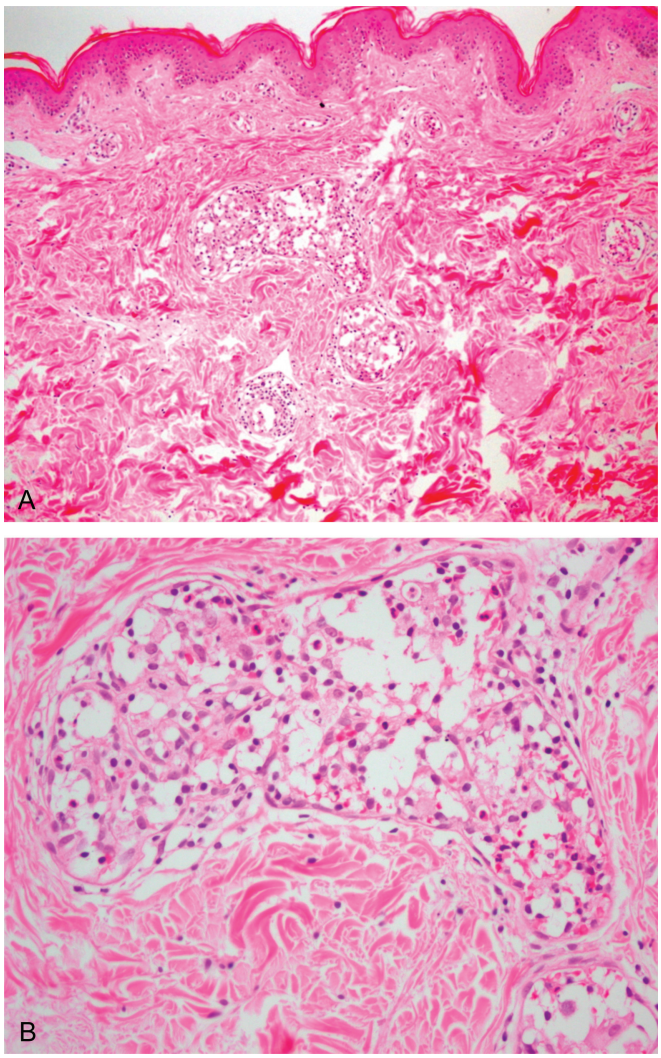

FIGURE 5. A, The proliferation of thin-walled vascular structures and ectasia at the upper and mid regions of the dermis (HE, ×40). B, The histiocytes with distinct eosinophilic cytoplasms and a few number of lymphocytes and neutrophils within lumina of ectatic vessels (HE, ×400). HE, hematoxylin and eosin stain.

were shown to be lymphatics, expressing D2-40/podoplanin, a specific marker for lymphatics. However in the second case, the endothelium of ectatic vessels expressed CD31 and CD34, but not D2-40/podoplanin, pointing out that these vessels were blood vessels rather than lymphatics.

The potential role of tumor necrosis factor-alfa, a mediator of inflammation in RA, in the pathogenesis of IV/ILH has been suggested by Okamoto et al.[20] In conjunction with this hypothesis, the skin lesions have been shown to improve in some cases using infliximab, an anti–tumor necrosis factor-alfa.[1] However, the relationship between inflammation and IV/ILH is not straightforward, as Requena et al[21] pointed out that the activity of RA and the skin lesions of IV/ILH is not parallel to each other.

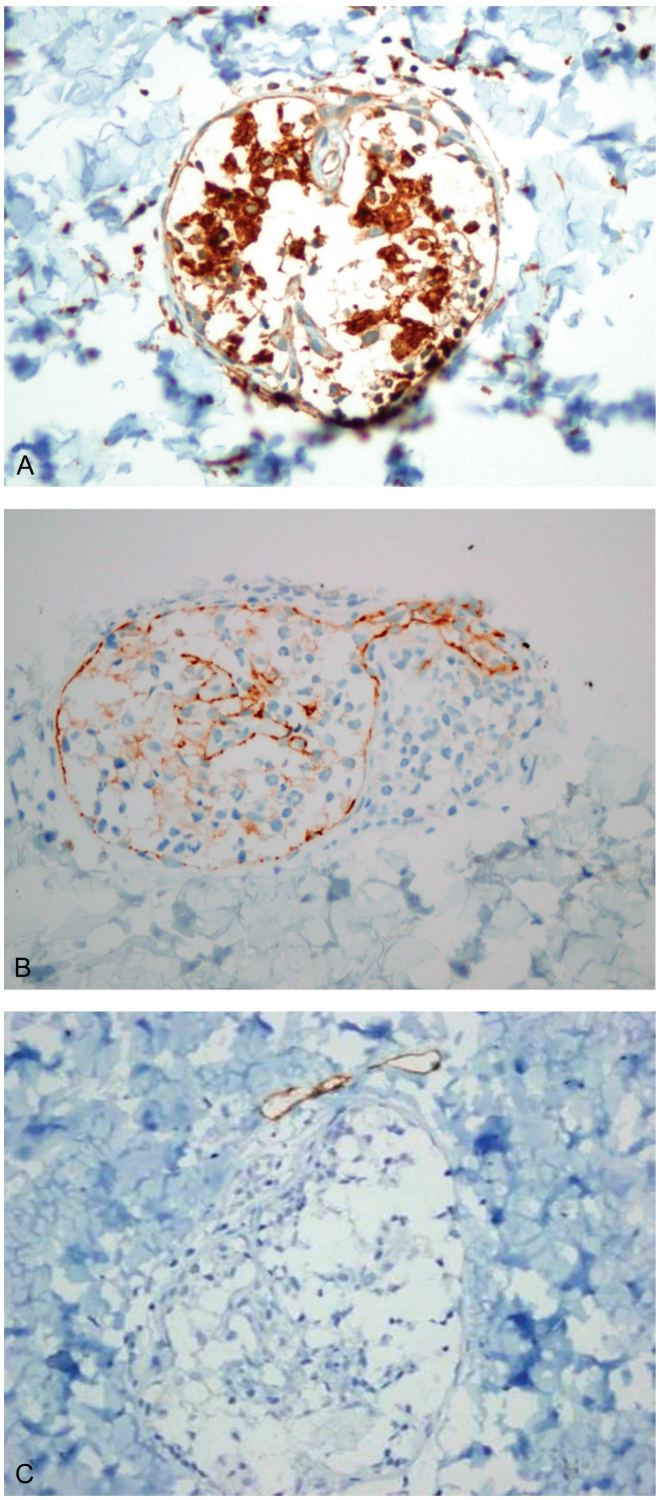

FIGURE 6. A, Intraluminal histiocytes stained positive for CD68. B, The endothelial cells of the vessels showed immunoreactivity for only CD34, (C) but not for D2-40/podoplanin (×200).

Histopathologically, the differential diagnosis of IV/ILH includes many disorders, such as reactive angioendotheliomatosis, intravascular lymphoma, metastatic carcinoma,

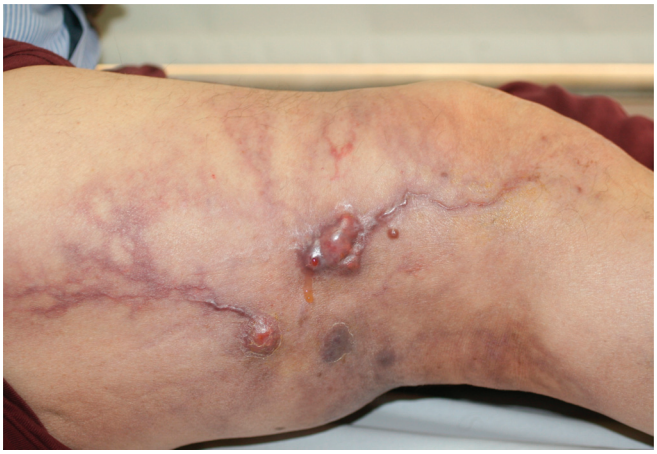

FIGURE 7. Arboriform livid plaque with 2 nodular lesions.

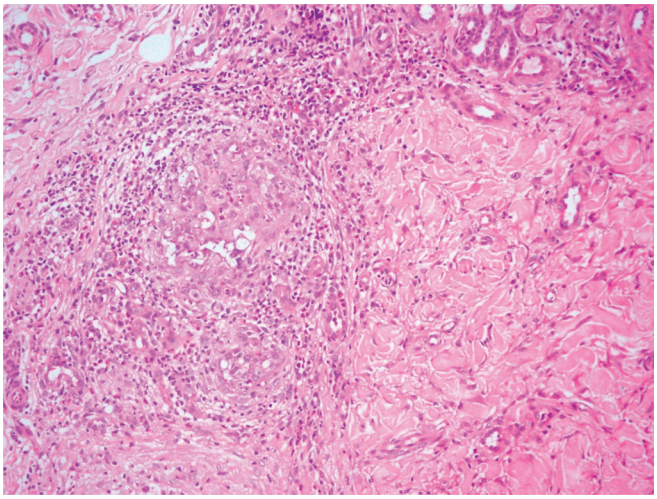

FIGURE 8. Prominent, vascular endothelial proliferation, occluding the lumen of the vessel (hematoxylin and eosin stain, ×200).

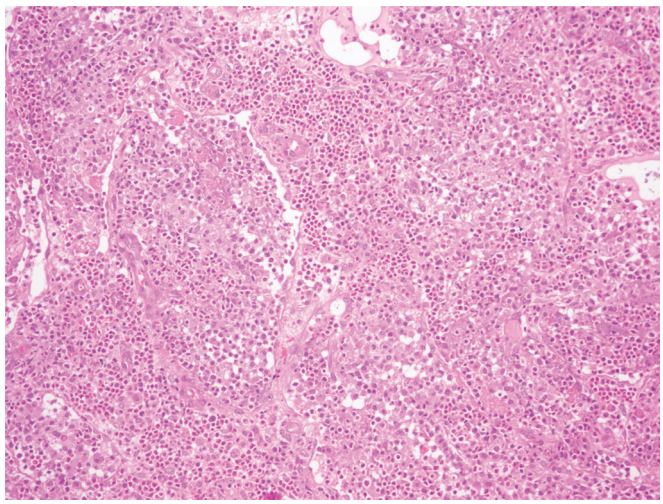

FIGURE 9. The ectatic thin-walled vessels with intraluminal histiocytes (hematoxylin and eosin stain, ×400).

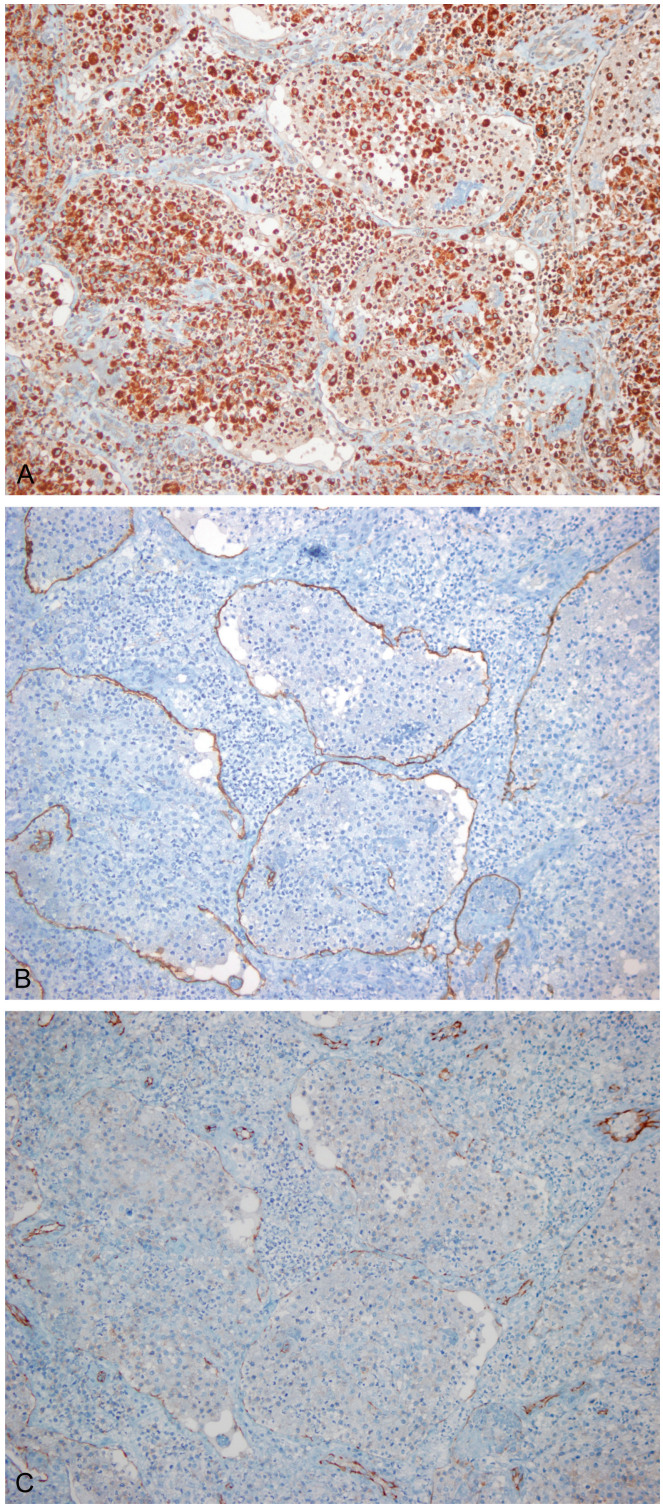

FIGURE 10. A, The histiocytes stained strongly positive for CD68. B, The endothelial cells of ectatic vessels stained with D2-40/podoplanin, (C) they stained less prominently with CD31 (×200).

TABLE 1. Clinical Data of 3 Patients With IV/ILH

Case	Sex	Age, yrs	Lesion Localization	Clinical Features	Associated Diseases or Findings	Follow-up
1	M	13	Scrotum, penis	Edematous, multiple papules and vegetative lesions	None	Scrotal swelling recurred 1 yr later after the operation
2	F	27	Bilateral breasts	Reticular erythematous rash	CVID, IBD, RA, reactive lymphoproliferative disease	Lesions resolved within 4–5 mo during the treatment for RA
3	M	76	Right thigh and knee	Livid plaque lesion containing livid, erythematous nodular lesions	Replacement of a metal prosthesis on both his right and left knees	Lesion regressed prominently with medical treatment

CVID, common variable immunodeficiency; IBD, inflammatory bowel disease.

acroangiodermatitis, and inflammatory conditions with intralymphatic collections of histiocytes.[4]

Intravascular lymphoma is a rare variant of lymphoma characterized by proliferation of neoplastic lymphocytes within blood vessels. The lesions mostly involve central nervous system and skin. In contrast to IV/ILH, it has an aggressive biologic behavior and poor prognosis. In our cases, intravascular cells had histiocytic nature, confirmed by the positive staining for CD68. Although the second case had a suspicious history of mantle zone lymphoma, which was later on interpreted as reactive lymphoproliferative lesion because of primary immunodeficiency, the cells within the lumina were negative for lymphoid markers.

Microscopically, the differential diagnosis of intravascular reactive angioendotheliomatosis and IV/ILH is difficult. Moreover, some cases of IV/ILH are reported to be together with reactive angioendotheliomatosis, as in our third case.[1] It is not possible to differentiate these 2 conditions with conventional immunohistochemical markers, such as CD31 and CD34, because CD31 may be also expressed by histiocytes. Therefore, only the new lymphatic markers, D2-40/podoplanin, Lyve-1, and Prox-1 can identify and differentiate luminal histiocytes and hyperplastic lymphatic endothelial cells. Some authors have suggested that both reactive angioendotheliomatosis and IV/ILH are actually 2 different aspects of the same condition.[3,22] According to this opinion, histiocytes appear with the organization of microthrombi followed later by endothelial cell proliferation. Some authors disagree with this suggestion because intravascular reactive angioendotheliomatosis invariably involves only blood vessels.[4] We believe that the condition resulting in IV/ILH may also give rise to intravascular reactive angioendotheliomatosis, which are actually 2 different histopathologic findings.

All of our patients had different clinical features. In the first case, the patient presented with lymphedema in the genital region and was similar to the cases reported as "granulomatous lymphangitis of the scrotum and penis" by Murphy et al.[5] This patient had no underlying diseases, such as sarcoidosis, tuberculosis, or inflammatory bowel diseases. However, the second and third cases had erythematous skin lesions. The second case had common variable immunodeficiency disease, RA, inflammatory bowel disease, and a history of a lymphoproliferative lesion. The third case had metal prostheses at both his right and left knees, which may be related to IV/ILH.[4,10]

In conclusion, we believe, the most convincing statement about IV/ILH is that it is not a distinct clinicopathologic entity, but a histopathologic feature found as a part of a constellation of inflammatory changes or many other conditions, almost as an incidental finding, but sometimes as the major abnormality in biopsies. Still, it should be kept in mind that these patients should be sought for inflammatory diseases, such as RA, Crohn disease, sarcoidosis, tuberculosis, and neoplastic diseases.

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