ANGIOLYMPHOID HYPERPLASIA WITH EOSINOPHILIA-ACQUIRED PORT-WINE-STAIN–LIKE LESIONS: ATTEMPT AT TREATMENT WITH THE ARGON LASER

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An unusual case of angiolymphoid hyperplasia with eosinophilia (ALHE) simulating port-wine stain in a 50-year-old woman is reported. The lesions of ALHE are typically papules or subcutaneous masses that range from light pink to red-brown in color. In addition to the usual histologic findings of ALHE, the biopsy in our patient showed some fibrin-like material and fibrous long-spacing collagen on ultrastructural examination. This unusual lesion necessitates biopsy because the differential diagnosis includes port-wine stain, sarcoidosis, lupus erythematosus, and non-Hodgkin lymphoma (mycosis fungoides). Many different forms of treatment have been attempted for ALHE including radiotherapy, cytotoxic chemotherapy, corticosteroids, and antibiotics. The lesions in our patient responded to argon laser therapy and surgical excision, though there has been recurrence on the border of the treated area. Because laser energy is noncumulative in the tissues and effective in removing the lesions, we recommend it as the treatment of choice for these lesions.
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Angiolymphoid hyperplasia with eosinophilia (ALHE) is an uncommon acquired benign vascular lesion that appears most frequently in the head and neck region, particularly around or on the ears.[1–3] This entity has been previously described under a variety of names, which creates nosologic confusion[4–24] (Table 1).

To date, no consensus exists on whether Kimura's disease (reported in Oriental literature) and ALHE (reported in the European and U.S.A. literature) are identical conditions. Many authors have claimed that Kimura's disease and ALHE are the same,[10,15,25–27] others have hesitated to include Kimura's disease in the group of ALHE,[14] and some have detailed numerous and significant differences in the clinical, histologic, and laboratory aspects of these two entities.[17,21,28–33]

The main differences between Kimura's disease and ALHE are listed in Table 2. Kimura's disease appeared in younger patients, mostly between the first and third decade.[27,28,34] ALHE, on the other hand, was observed in older patients during the third–fifth decades.[28] A major predilection for males (85%) was found in Kimura's disease,[9,17,28,29,35] while 70% of patients with ALHE were females.[34,35]

Clinically, the skin lesions of Kimura's disease were very similar to those of ALHE.[10,14,27]

Table 1. Synonyms of vascular-inflammatory, tumor-like lesions of the skin.

Authors	Year	Synonyms
Kimura et al.[4]	1948	Unusual granulation combined with hyperplastic changes of lymphatic tissues
Winer and Levin[5]	1959	Acquired vascular tumors of the skin in adults
Cramer[6]	1962	Multiplen eosinophilen Granulomen der Kopfhaut
Summerly and Wells[7]	1963	Subcutaneous lymphoid hyperplasia with eosinophilia
Peterson et al.[8]	1964	Atypical pyogenic granuloma
Kawada et al.[9]	1965	Eosinophilic lymphfolliculosis of the skin (Kimura's disease)
Wells and Whimster[10]	1969	Subcutaneous angiolymphoid hyperplasia with eosinophilia
Wilson-Jones and Bleehen[11]	1969	Inflammatory angiomatous nodules with abnormal blood vessels (pseudo or atypical pyogenic granuloma)
Wilson-Jones and Marks[12]	1970	Papular angioplasia
Kandil[13]	1970	Dermal angiolymphoid hyperplasia with eosinophilia
Mehregan and Shapiro[14]	1971	Angiolymphoid hyperplasia with eosinophilia
Reed and Terazakis[15]	1972	Subcutaneous angioblastic lymphoid hyperplasia with eosinophilia
Kitabatake et al.[16]	1972	Eosinophilic granuloma of the soft tissue
Rosai and Ackerman[17]	1974	Intravenous atypical vascular proliferation
Inada et al.[18]	1977	Eosinophilic lymphfolliculosis of the skin
Bendl et al.[19]	1977	Nodular angioblastic hyperplasia with eosinophilia and lymphfolliculosis
Eady and Wilson-Jones[20]	1977	Psuedopyogenic granuloma
Rosai et al.[21]	1979	Histiocytoid hemangioma
Chang and Chen[22]	1982	Eosinophilic granuloma of lymph nodes and soft tissue
Weber et al.[23]	1982	Bullose angiolymphoide Hyperplasie mit Eosinophilie
Enzinger and Weiss[24]	1983	Epithelioid hemangioma

They were soft, single or multiple red-brown papules, or subcutaneous tumors[2,10,18] in the head and neck region.[10,14,28] They were also observed on the trunk and in the axillary, cubital, or inguinal area.[34,36] Lesions on the oral mucous membranes,[25,28,37-42] heart,[43] penis,[44] knee,[45] and hands[46,47] were seen in a few cases of ALHE. The lesions of Kimura's disease were larger (2–10 cm) than those of ALHE (0.2–6 cm).[24,27,28,34,36] The lesions in both entities were usually painless, but sometimes pruritus and pulsation were present.[2,5,9,16,21] Regional lymphadenopathy was common in Kimura's disease[34,36] but it was unusual in ALHE.[28]

Histologically, the lesions in Kimura's disease were located more often in deep subcutaneous tissue[34] rather than in the dermis, as in ALHE.[2] The blood vessels in Kimura's disease were numerous and proliferative but not as prominent as in ALHE.[2,9,17,21,29] In ALHE, the endothelial cells, which formed solid uncanalized masses, were large and slightly pleomorphic and/or lined newly formed blood vessels.[2,26,48] These endothelial cells possessed a large vesiculated nucleus with numerous fissures and prominent vacuolated cytoplasm resembling histiocytes.[29] The inflammatory infiltrates of lymphocytes, eosinophils, and histiocytes were indistinguishable in the two conditions.[11,21] In some cases of ALHE, however, tissue eosinophilia was absent.[2,48] Infiltrates of mast cells were more numerous in ALHE than in Kimura's disease.[10,31,32] Nodular lymphoid follicles with germinal centers were almost always present in Kimura's disease,[30-32,49,50] but only sporadically noted in ALHE.[31,32,51] In all stages of Kimura's disease there was marked fibrosis,[31,32] but in ALHE fibrosis was absent.[10,30]

Blood eosinophilia was more prominent in Kimura's disease than in ALHE.[27,52] A high serum level of IgE was present in Kimura's disease,[18,30,34,50,53] while it was low in ALHE.[25,27] IgE deposition within lymphoid follicles was usually noted in Kimura's disease,[18,34,54] but was present only in a few cases of ALHE.[45,55] Iguchi et al.[30] suggested that serum IgE level may be an important factor during differentiation of Kimura's disease and ALHE. Also, serum anti-Candida albicans antibody was reported in Kimura's disease,[54] but only occasionally observed in ALHE.[45,56] Skin tests for Candida in Kimura's disease were usually positive,[54] but negative in ALHE.[27]

The pathogenesis of ALHE remains unclear. Opinions are divided on whether the lesion represents a true neoplastic proliferation of blood vessels,[11,21,29] a response to trauma, infection, and humoral imbalance,[2] or a reactive process secondary to immunologic injury.[56]

Various methods of treatment for Kimura's

Table 2. Kimura's disease vs. angiolymphoid hyperplasia with eosinophilia.

Synonyms	In the Oriental literature: Eosinophilic lymphfolliculosis of the skin[9] Eosinophilic granuloma of lymph nodes and soft tissue[16,41]	In the English literature: Subcutaneous lymphoid hyperplasia with eosinophilia[7] Subcutaneous angiolymphoid hyperplasia with eosinophilia[10]
First publication	Kimura et al. 1948[4]	Wells and Whimster 1969[10]
Occurrence	During the 1st to 3rd decade[27,28,32]	During the 3rd to 5th decade[28,32]
Sex	Mostly in males (85%)[9,28,40]	More often in females (70%)[27,40]
Geographical distribution	China, Southeast Asia, Japan	Europe and U.S.A.—in non-Oriental persons
Number of cases	113 cases[36]	102 cases[28]
Clinical morphology	Single or multiple red-brown papules or subcutaneous tumors[10,18]	Dome-shaped, light pink to red-brown papules or subcutaneous masses. Multiple lesions form a "grape-like"plaque[2]
Size of lesions	Larger than 2 cm in diameter[28]	Smaller than 2 cm in diameter[28]
Site of predilection	Head and neck area. May occur anywhere in the body[17,28,34]	Head and neck area in 86% of the cases[28]
Symptoms	Localized or generalized pruritus[9,16]	Sometimes pruritus, pain, bleeding, and pulsation present[2,5,21]
Histopathology		
Location of lesions	Deep subcutaneous tissue or dermis[27]	Subcutis or dermis[2]
Blood vessels	Moderate proliferation of capillaries. Large and thickened vessels with prominent endothelial cells without distinctive morphology[2,9,17,34]	Abundant angiomatoid proliferation of capillaries with prominent endothelial cells. Solid, uncanalized masses of histiocytoid endothelial cells[31,42] with a large, vesiculated, fissured nucleus and a vacuolated cytoplasm.[34] Large vessels with intravascular endothelial proliferation and cutaneous AV shunts[2]
Infiltration	Intensive infiltrates of lymphocytes, eosinophils, and histiocytes; a few mast cells[18,21,37,38]	Diffuse infiltrates of lymphocytes, eosinophils, and histiocytes; numerous mast cells[10,37,38]
Lymphoid follicles	Hyperplasia of lymphoid tissue with germinal centers[25,36–38,43]	Sometimes a few lymphoid follicles usually without germinal centers[37,38,44]
Fibrosis	Marked fibrosis in all stages[37,38]	No fibrosis[10,36]
Regional lymphadenopathy	Common[27]	Unusual; present only in 11% of the cases[28]
Peripheral eosinophilia	Almost always present[32]	Usually normal[27]
Serum IgE	High level[18,27,36,45,46]	Low level[29,32]
Deposition of IgE	Present within lymphoid follicles[18,27,45]	Only in a few cases within lymphoid follicles[30,47]
Serum anti-Candida alb. antibody	Present[45]	Occasionally present[35,47]
Skin test with Candida	Positive[45]	Negative[27]
Course and prognosis	Long, good[16]	Long, good[2]

disease and ALHE have been used, including radiotherapy,[11,16,28,30,57] systemic[15,23] or intralesional corticosteroids,[27,41,58] antibiotics,[23] cytotoxic agents (vinblastine),[42] retinoic acid,[59] electrodesiccation and curettage,[14,58] surgical excision and grafting,[28,30,46,60,61] and recently the CO_2 laser[62] and the argon laser.[34,42]

We report here a case with atypical, flat lesions resembling port-wine stains in which light and electron microscopic and immunohistochemical studies revealed the features of ALHE. Treatment options, specifically laser therapy, of these rare, apparently benign lesions will be discussed.

CASE REPORT

Clinical Findings. A 50-year-old woman presented with two flat, port-wine–stain-like lesions on the right postauricular region and the neck (both 4 × 2.5 cm in diameter). (Figures 1A and 2A). These lesions appeared 5 years ago and slowly increased in size without any subjective symptoms or lymphadenopathy. Family history revealed that her father and her niece have port-wine stains on the abdomen and face, respectively.

Routine laboratory examinations, including complete blood count and serum chemistry, were within normal limits. Biopsies of the lesions, on

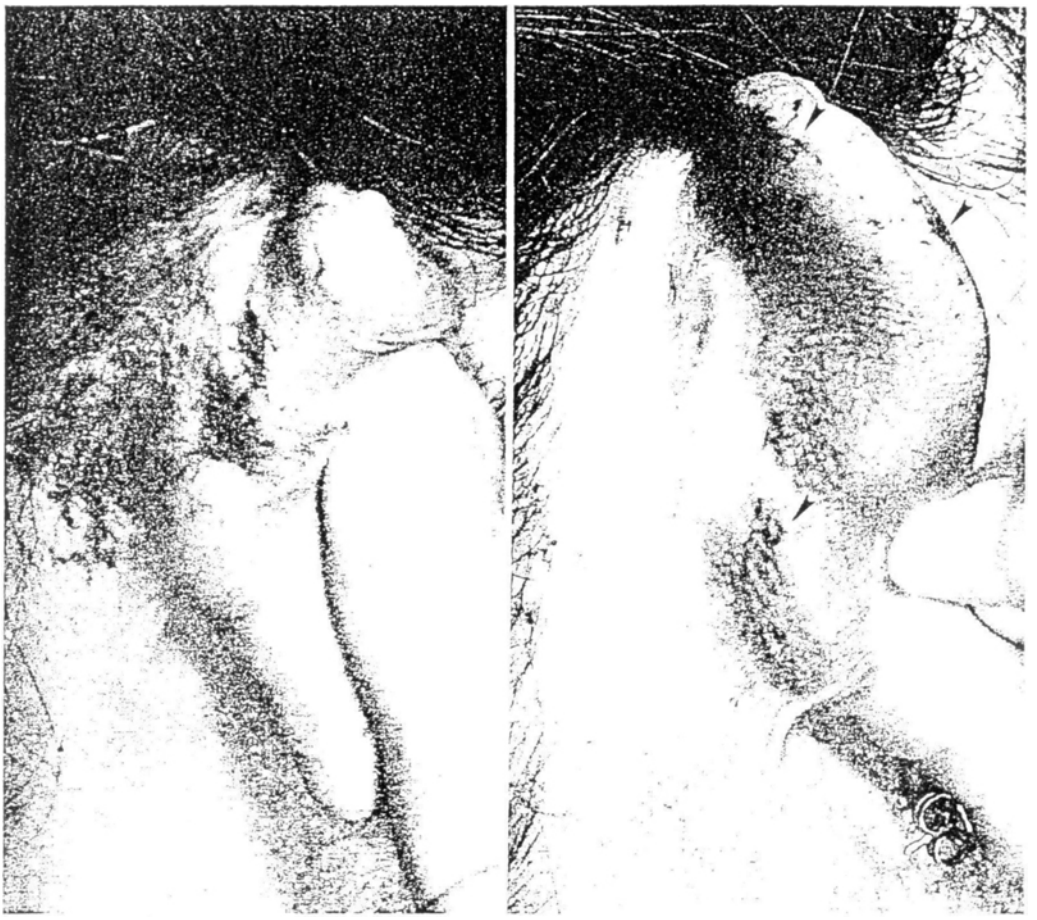

FIGURE 1. A 50-year-old woman with a flat, red lesion behind the ear simulating a port-wine stain. (A) Before treatment; (B) the same patient 17 months after argon laser surgery. Note telangiectatic vessels on the border of the treated area (arrowheads).

histopathologic examination, showed features that corresponded to criteria of ALHE.

Histopathology and Immunohistochemistry. The lesion was localized in the midportion of the dermis and was characterized by proliferation of blood vessels that were surrounded by a dense cellular infiltrate (Figure 3). Some dilated vessels formed tortuous, irregular channels. Others were uncanalized or only partially canalized. Thin-walled, dilated capillaries or lymphatic vessels and venules were lined by large endothelial cells, very similar to histiocytes, and surrounded by lymphocytes, histiocytes, mast cells, and a few eosinophils (Figure 4). Focal extension of the "inflammatory" cellular infiltrate to the hair follicles was also noted. There was no cellular atypia or increased mitoses in the endothelium and infiltrating cells. Wilder's stain demonstrated delicate reticular fibers surrounding the blood vessels, which were also visible within the cellular infiltrations.

Immunohistochemical study was performed on formalin-fixed tissue in paraffin sections using the immunoperoxidase technique for factor VIII-related antigen. The endothelial cytoplasm was faintly positive. Muramidase stain, a potential marker of histiocytes, was negative.

Electron Microscopy. Ultrastructural examination showed vascular structures lined by plump endothelial cells that protruded into the lumen. These cells possessed convoluted or multilobulated nuclei and cytoplasm with relatively normal organelles including numerous filaments and sparse Weibel-Palade bodies. Many cytoplasmic protrusions were seen on the luminal surface of the endothelial cells (Figure 5A). The basal lamina was multilayered in some areas and absent in others. Occasional fenestrations of the

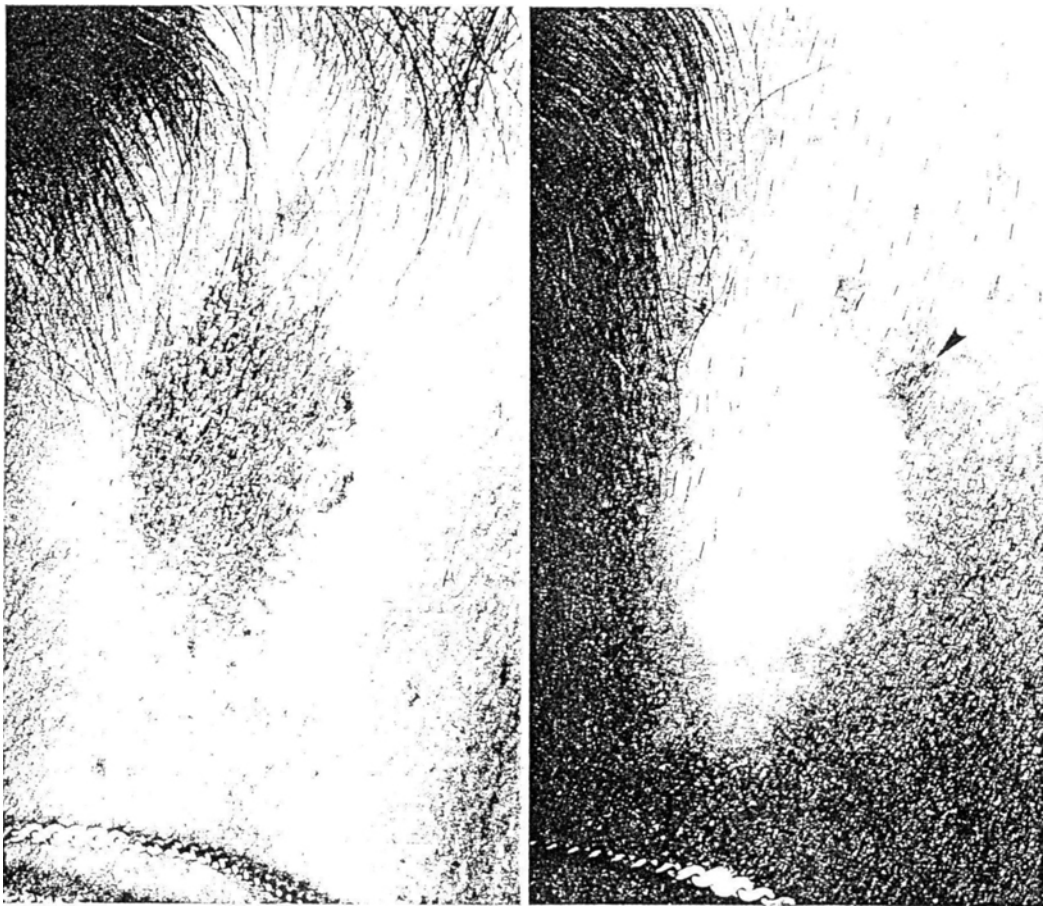

FIGURE 2. Port-wine–stain-like lesion on the neck in the same patient. (A) Before treatment; (B) after argon laser surgery showing new vascular lesions close to the treated area (arrowheads).

vessel walls were also found (Figure 5B). The mixture of histiocyte-like cells, lymphocytes, and mast cells were very close to the vessels. The histiocytoid cells formed solid clusters without formation of a lumen. Their nuclei were large and irregular with multiple indentations, dense rims of heterochromatin, and prominent nucleoli. The cytoplasm contained mitochondria, microtubules, microfilaments, abundant vacuoles, lysosomes, relatively large Golgi elements, and prominent smooth and rough endoplasmic reticulum. The cell surface possessed numerous folds and finger-like processes. Stroma consisted of an amorphous substance, a few collagen fibers, reticular fibers, and fibrin-like material. Additionally, "banded structures" or fibrous long-spacing collagen were also observed (Figure 6).

Treatment. An argon laser (System 1000 Dermatologic Argon Laser, Coherent, Palo Alto, CA) test treatment was performed using a power density of 153 watts/sq cm (exposure time 0.2 s; power 1.3 watts; spot size 1 mm) on an area 1.5 × 1.5 cm under local anesthesia with 2% lidocaine without epinephrine. After 4 months, good results were observed in the tested area and the rest of the lesions were treated under similar laser conditions. The lesions received 1,847 exposures with a power density of 153 watts/sq cm. On examination at 5 months and again at 1 year after treatment there were no lesions in the treated area, but, in some parts of the margin, new vessels were seen (Figures 1B and 2B). They were coagulated, with the argon laser using the same power density as before. After 1 more year, lesions spreading from the border of the treated part were observed again. At this time, the lesions were excised and for the second time histologically examined. Nine months after excision, the patient noted new vascular spots close to the

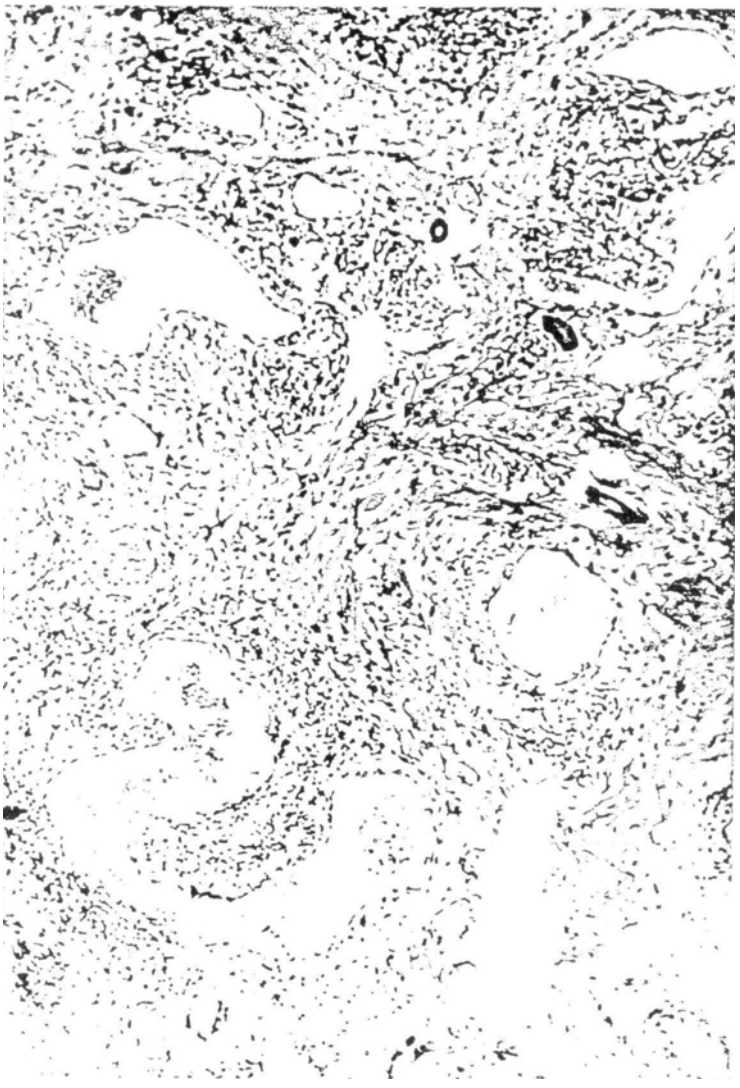

FIGURE 3. Micrograph of dilated, thin-walled blood vessels in the dermis. Note dense infiltration of lymphocytes and histiocytes very close to the vessels. Hematoxylin and eosin, Original magnification ×50.

margin of the surgical scar and on the ear. These lesions will be treated with the argon laser using a higher power density than was used before.

DISCUSSION

The lesions in our patient were unusual in that they resembled port-wine stains rather than the tumor-like nodules that appear both in Kimura's disease and ALHE. Lesions similar to those of our patient were reported by Weber et al[23] to have occurred on the head in two patients. These lesions were also flat and pinkish-red, but recurred with bullous eruptions despite treatment with antibiotics and corticosteroids.

As in most reported cases with ALHE,[28,34,48,52] our patient did not have tissue and blood eosinophilia or peripheral lymphadenopathy. On light and electron microscopy, our patient's lesions possessed a histologic pattern characteristic of ALHE, which is the heading under which we prefer to classify these lesions. They were located in the midportion of dermis showing histiocytic-type endothelial cells and infiltration of lymphocytes, histiocytes, and mast cells. The presence of fibrin-like material and fibrous long-spacing collagen are new findings in ALHE and they both require further study.

Immunoperoxidase technique for factor VIII-related antigen—a marker for endothelial cells at the tissue level—demonstrated a weakly pos-

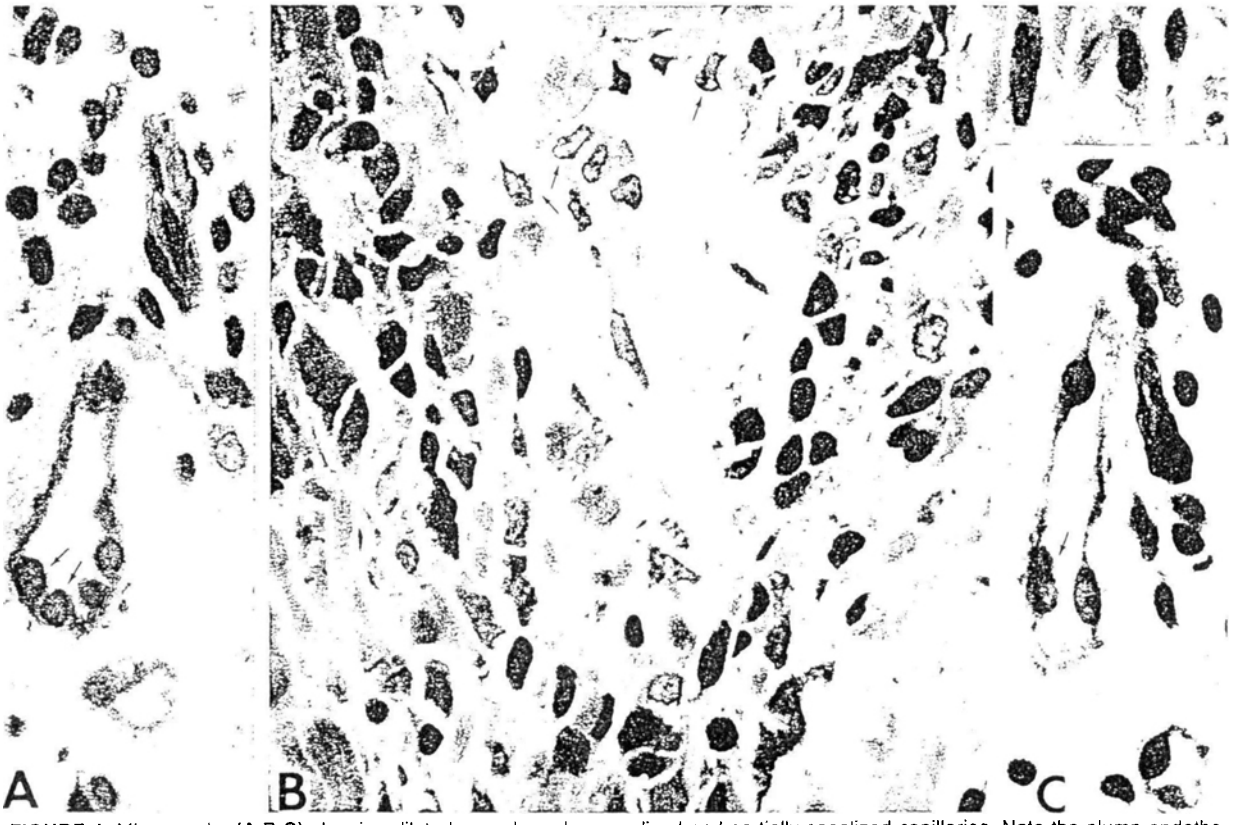

FIGURE 4. Micrographs (A,B,C) showing dilated vessels and uncanalized and partially canalized capillaries. Note the plump endothelial cells resembling histiocytes (arrows). Epon, toluidine blue, Original magnification ×500.

itive reaction in the endothelial cells. Variable positive staining of the proliferating endothelial cells for factor VIII-related antigen was also observed in ALHE by some authors,[2,50] and in some malignant and benign vascular tumors.[63,64] Ose et al.[50] noted in their immunohistochemical study on histiocytoid hemangioma that the intensity of staining for factor VIII/von Willebrand factor antigen decreased. False-negative results may be explained, however, by a high lability of factor VIII-related antigen, which may not survive routine formalin fixation and processing.[65] An indirect immunoperoxidase procedure for the presence of lysozyme as a specific histiocytic marker was negative in ALHE.[48,50] Results of our study with muramidase stain were also negative.

The morphology of the lesion in ALHE seems to vary with duration. The lesions in an early phase display a higher degree of vascular proliferation and larger endothelial cells, while those of long duration have more lymphoid tissue and a less prominent endothelium.[10,27,36,52]

The histogenesis of Kimura's disease and ALHE is still not clear. Direct immunofluorescent studies of tissue with ALHE have shown deposits of IgA, IgM, and complement C3 around small vessels within the lesions.[56] These data may indicate an immunologic phenomenon in this entity. Marsten[66] has even postulated that ALHE represents an autoimmune disorder similar to that in Hashimoto's thyroiditis.

The course of ALHE is chronically progressive, though benign. Spontaneous resolution of lesions may occur after many months,[10,12,13,15] but prolonged duration is more common.[1,14,67] Due to the nonspecific nature of the entity, it can be mistaken for a number of other conditions including malignant angioendothelioma, pyogenic granuloma, eosinophilic granuloma, angiomatous lymphoid hamartoma, granuloma faciale, Jessner's lymphocytic infiltrate, pseudolymphoma, atheroma, hemangioma, or persistent reaction to insect bites.[2,10,14,25,36,49,55] The flat, red lesions, as our patient presented, should be differentiated from port-wine stain, sarcoidosis, lupus erythematosus, and non-Hodgkin lymphoma such as mycosis fungoides. Hence, a biopsy is usually necessary to establish the diagnosis.

Many methods have been used to treat the

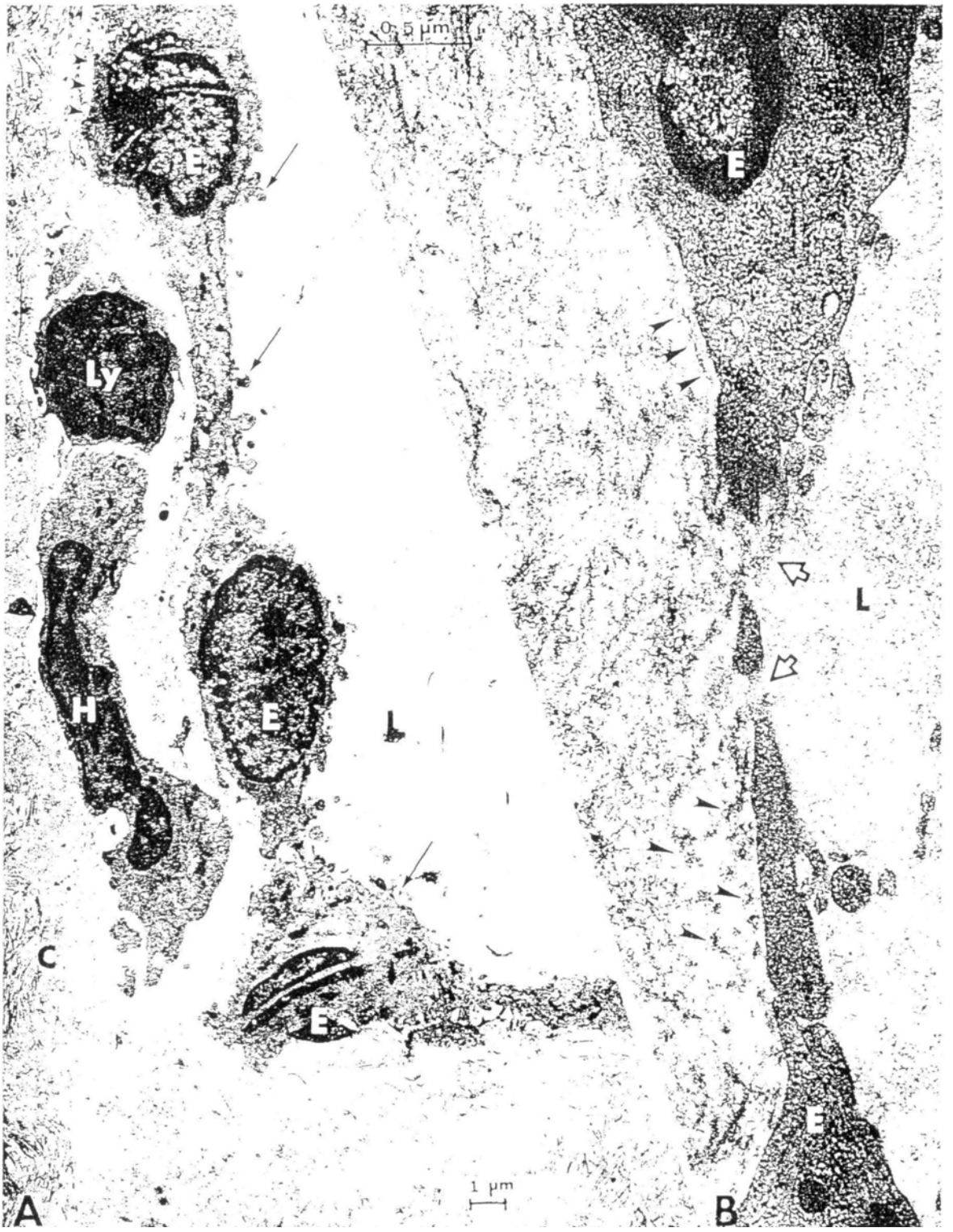

FIGURE 5. Electron micrograph (A). Dilated blood vessel with prominent endothelial cells (E) and numerous cytoplasmic projections, especially on the luminal surface (arrows). Lumen (L); basal lamina (arrowheads); lymphocyte (Ly); histiocyte (H); collagen fibers (C). Magnification · 36.250.

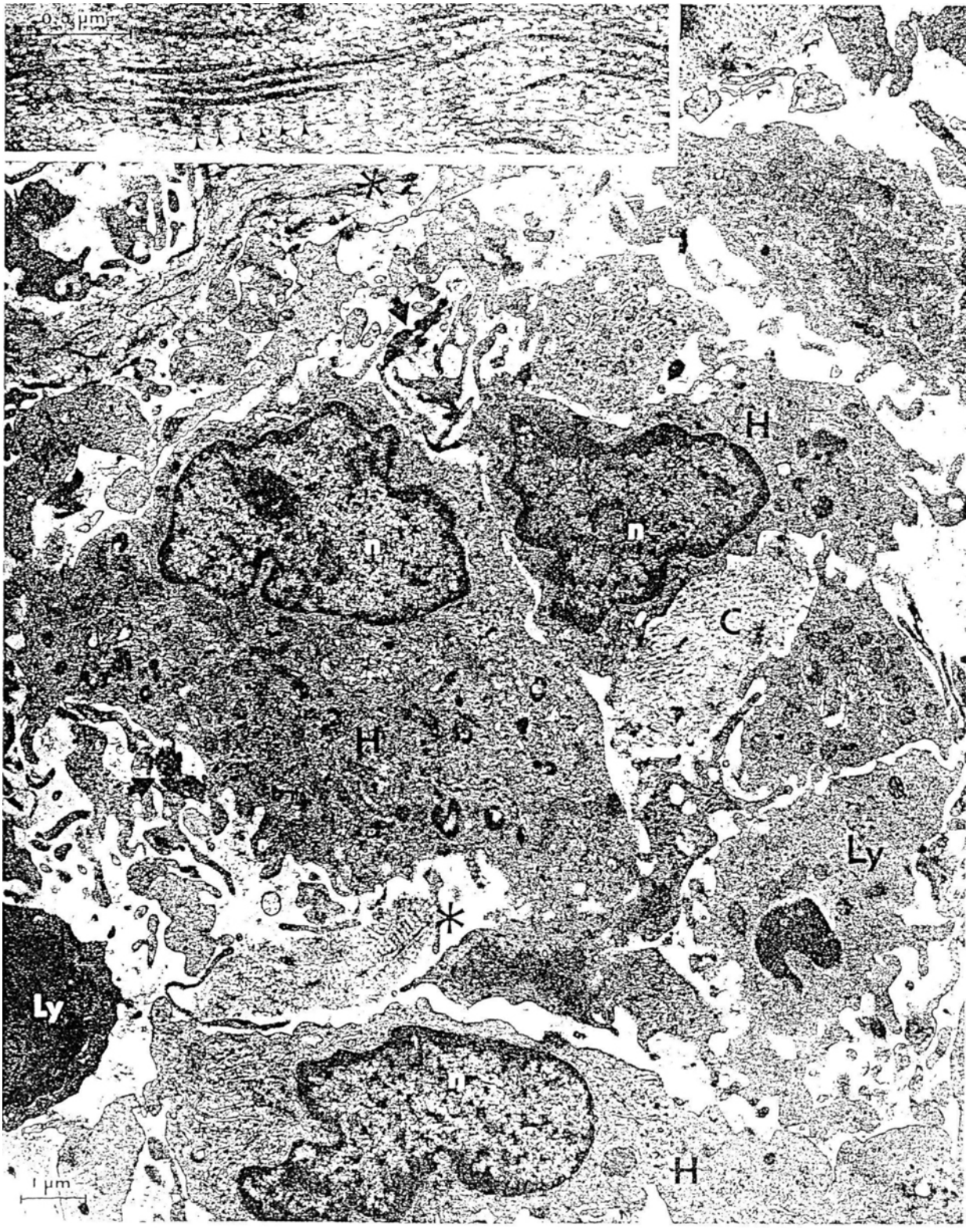

FIGURE 6. A few histiocytoid cells (H) forming clusters. Note large, irregularly shaped nuclei (n) with dense rims of heterochromatin and indented nuclear margins, as well as abundant cytoplasm with numerous protrusions. Note also lymphocytes (Ly), fibrin-like material (arrows), and long-spaced collagen (asterisks). Collagen fibers (C). Inset: Long-spaced collagen (arrowheads). Original magnification ×47,850.

skin lesions in ALHE and Kimura's disease. Radiation therapy, while effective, poses long-term risks for the patient; its value in treating a relatively benign lesion is questionable. Antibiotics and steroids provide a less aggressive form of treatment, but many clinicians reported inconsistent results.[13,23,55,68] Cytotoxic agents were rarely beneficial[9,42] and their systemic toxicity needs to be taken into account in this benign disorder.[69] Retinoic acid can reduce the size of lesions, but does not lead to complete regression.[59] Excision of the lesions and laser surgery appear to be the treatments of choice, although some of the lesions did recur, as was the case in our patient.[13,19,42,49,56,57] The red, vascular lesions were very easily coagulated by argon laser energy, but a few months later they started to spread from the margin of the treated areas. After surgical excision of the new lesions, spreading of dilated vessels was again observed. We intend to treat these lesions with the argon laser using a higher power density. The use of laser energy is more beneficial than surgical excision for two reasons. First, laser beams can easily coagulate or vaporize lesions that are located in areas very difficult to approach surgically, and second, because the laser energy is not cumulated in tissues; it may be used repeatedly for re-treatment of these recalcitrant lesions.

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