Profound Proliferating Angiolymphoid Hyperplasia With Eosinophilia of Pregnancy Mimicking Angiosarcoma

Catherine B. Marcum, MD; Jonathan S. Zager, MD; Iriana P. Bélongie, MD; Jane L. Messina, MD; Neil Alan Fenske, MD

Angiolymphoid hyperplasia with eosinophilia (ALHE) is a rare benign vascular proliferation that clinically manifests as nodules and papules of the head and neck region. We report a profound, rapidly proliferating case of ALHE in a 3-week postpartum woman that clinically mimicked angiosarcoma. The clinical and histologic features of ALHE, Kitamura disease, and cutaneous angiosarcoma are reviewed, and the relationship between ALHE and pregnancy is discussed.
Cutis. 2011;88:122-128.

Angiolymphoid hyperplasia with eosinophilia (ALHE) is a rare disorder that usually presents as nodules and papules located on the head and neck in young adults. The lesions can be heterogeneous in appearance and number, ranging from flesh-colored subcutaneous nodules to violaceous papules and plaques from 0.2 to 8.0 cm in size. Rarely, regional lymphadenopathy is present. Histologically, ALHE is characterized by a dermal proliferation of vascular structures lined by plump vacuolated endothelial cells with a stromal infiltrate of lymphocytes and eosinophils. We report a case of ALHE that developed in a pregnant woman with extensive involvement of the scalp, rapid proliferation, and associated lymphadenopathy clinically mimicking a malignant vascular neoplasm.

Drs. Marcum, Bélongie, Messina, and Fenske are from the Department of Dermatology and Cutaneous Surgery, University of South Florida College of Medicine, Tampa. Dr. Zager is from and Drs. Messina and Fenske also are from the H. Lee Moffitt Cancer Center & Research Institute, Tampa.
The authors report no conflict of interest.
Correspondence: Neil Alan Fenske, MD, Department of Dermatology and Cutaneous Surgery, University of South Florida College of Medicine, 12901 Bruce B. Downs Blvd, MDC 79, Tampa, FL 33612.

Case Report

A 29-year-old 3-week postpartum woman presented to the dermatology clinic with a pruritic multinodular plaque of the superior occipital scalp of 1 year's duration. The patient reported bleeding with minor trauma but denied any history of trauma to the area. Although a small nodule was present approximately 3 months prior to conception, there was a rapid and continued increase in the size and number of lesions throughout her pregnancy, which stabilized upon delivery. The patient initially underwent a biopsy of a violaceous nodule by an otolaryngologist 2 months prior to presentation to our facility; this initial biopsy was interpreted as a benign hemangioma. She was otherwise healthy with no history of cutaneous disease. Her only medication was a prenatal vitamin. A thorough review of systems did not elicit any pertinent abnormalities.

On physical examination, multiple firm, erythematous to violaceous papules and nodules that focally coalesced into plaques were present on the superior and mid regions of the occipital scalp measuring 3.5×2.0 cm. Multiple satellite lesions ranging in size from 0.2 to 1.0 cm surrounding the plaque were noted (Figure 1). She exhibited bilateral submandibular and posterior cervical lymphadenopathy varying in size from 1.0 to 3.0 cm. Because of the large size of the lesion, its rapid growth, and the associated lymphadenopathy, there was concern regarding the possibility of a malignant vascular neoplasm. The patient was referred to the surgical oncology department for evaluation; a punch biopsy of the lesion and fine needle aspiration for histologic evaluation of a palpable right cervical lymph node were performed.

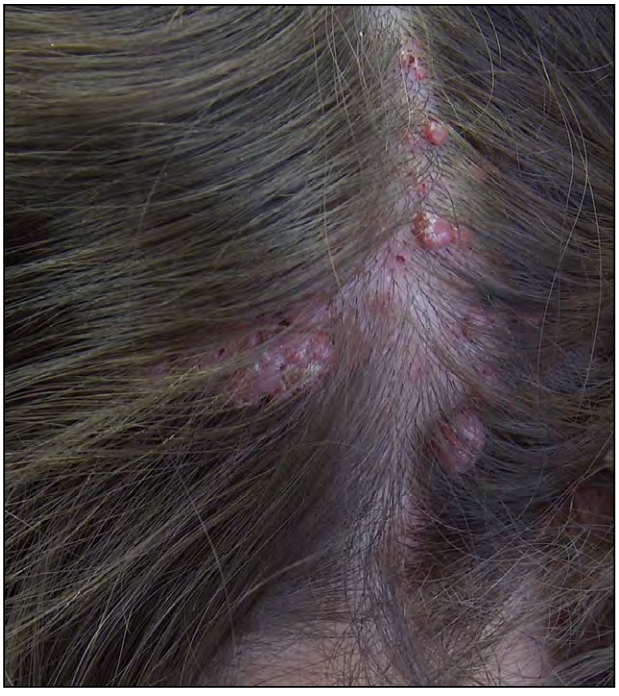

Figure 1. Multiple erythematous to violaceous papules and nodules with satellite lesions on the occipital scalp.

The skin biopsy demonstrated a proliferation of capillaries lined by epithelioid endothelial cells with oval vesicular nuclei and no cytologic atypia, which extended through the full thickness of the dermis. Intracytoplasmic vacuoles were noted within some of the endothelial cells. There was a dense surrounding inflammatory infiltrate of lymphocytes and eosinophils (Figure 2). No prominent dermal fibrosis or eosinophil microabscesses were present. Estrogen and progesterone receptor immunostains were negative within the specimen. These findings were diagnostic of ALHE. Histologic evaluation of a fine needle aspiration of the cervical lymph node as well as flow cytometry disclosed changes consistent with a reactive lymph node. Retrospective review of the initial biopsy diagnosed as a hemangioma revealed a dermal proliferation of thick- and thin-walled vascular structures of varying size amid dermal fibrosis, accompanied by a perivascular inflammatory infiltrate composed of lymphocytes and eosinophils, which was suggestive of ALHE.

Because of the benign nature of the lesion, the patient opted to postpone further workup to evaluate for an underlying vascular malformation, specifically magnetic resonance angiography, as well as definitive treatment until completion of breastfeeding. Fluocinonide solution 0.05% was prescribed in an attempt to alleviate the associated pruritus. Although the treatment of choice for ALHE is surgical resection, we have considered long-pulsed dye laser therapy as a treatment option for this patient due to the large size of the involved area and the patient's cosmetic concerns. During the last 2 years, residual papules and nodules have been sequentially removed by shave excision with almost complete clinical resolution.

Comment

Controversy has surrounded the term *angiolymphoid hyperplasia with eosinophilia* since it was first used in 1969.[1] The condition has been described using a variety of names including atypical pyogenic granuloma, epithelioid hemangioma, cutaneous histoid hemangioma, and inflammatory arteriovenous hemangioma.[2] Although previously regarded as a variant of Kimura disease, ALHE is now considered a distinct entity of uncertain pathogenesis. The lesions of ALHE typically affect the head and neck, though it has been reported to involve the trunk, extremities, genitalia, and inguinal region.[3] Extracutaneous lesions seldom occur but can involve the oral and nasal mucosa, orbit, salivary glands, colon, tympanic membrane, bone, and large arteries.[4,5] The lesions clinically appear as flesh-colored to violaceous, firm nodules and papules located superficially or subcutaneously. Associated features include pruritus, bleeding, pulsation, and tenderness.[6,7] In a minority of cases, lymphadenopathy (19%), an elevated IgE level, and/or peripheral eosinophilia (20%) have been reported.[6,8] The clinical behavior is characterized by frequent local recurrence following excision; however, to our knowledge, no metastatic spread has been reported.

Pathogenesis—It is unknown if the disease represents a reactive process or a true neoplasm of vascular origin. Interestingly, a clonal T-cell gene rearrangement has been detected in some lesions of ALHE, leading to speculation that the disorder could represent a benign or low-grade T-cell lymphoproliferative disorder with a secondary reactive vascular response.[9] However, numerous factors suggest that ALHE represents a localized reactive vascular process with an associated chronic inflammatory cell infiltrate. The presence of underlying vascular anomalies (55%) or adjacent vascular damage (63%) has been demonstrated in a considerable number of cases.[4,6,10,11] It has been speculated that the ischemia resulting from trauma or abnormal vasculature induces the endothelial proliferation and angiogenesis characteristic of this condition.[9] In addition, elevated renin levels have been demonstrated surrounding the vascular proliferation of ALHE. The resultant angiotensin II production also can stimulate angiogenesis. Other possible sources of neovascular induction include

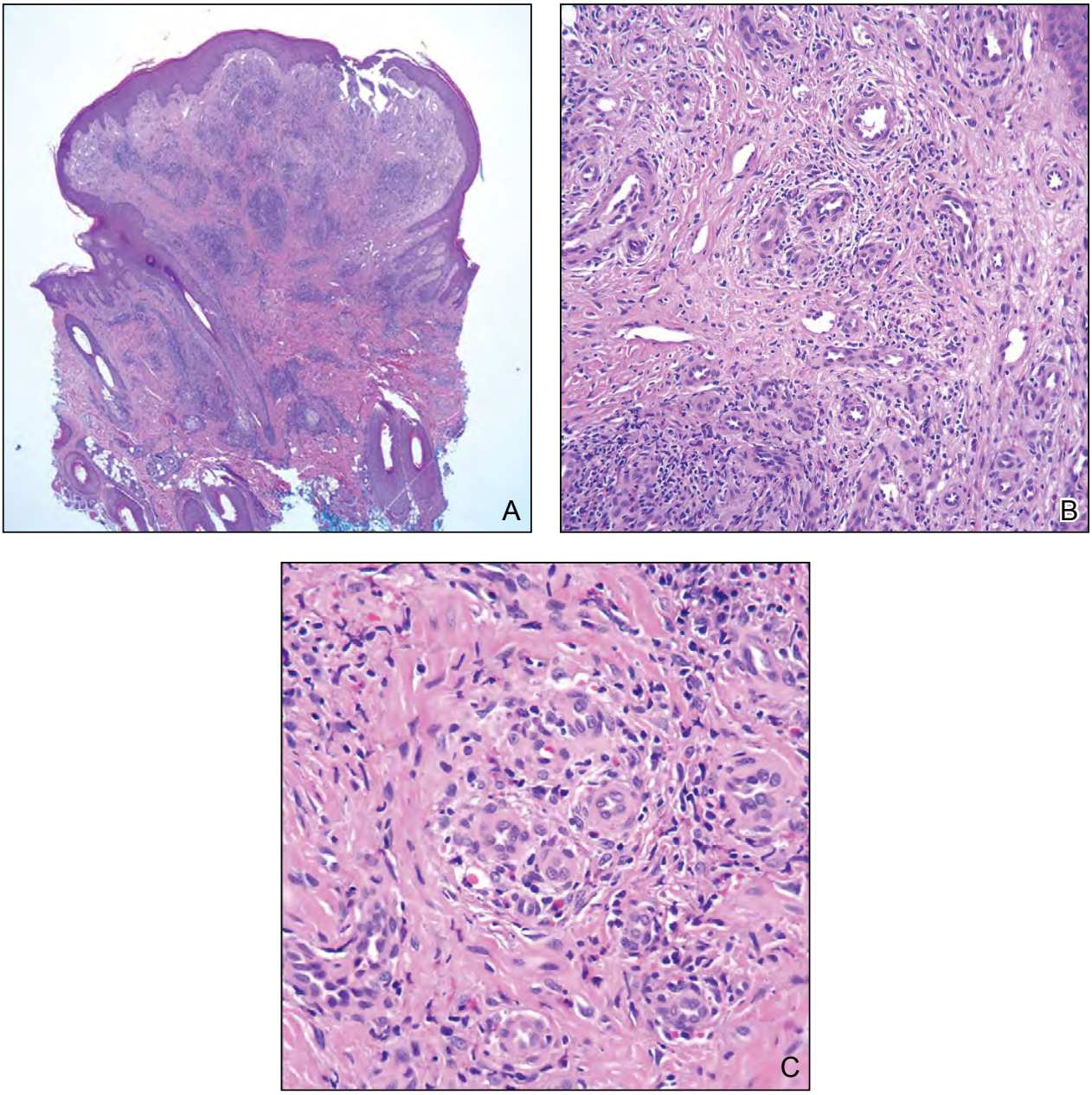

Figure 2. Histologic evaluation revealed a vascular proliferation within the dermis lined by epithelioid endothelial cells with intracytoplasmic vacuoles and no cytologic atypia. A dense inflammatory infiltrate of lymphocytes and eosinophils was present (A–C)(H&E; original magnifications ×2.5, ×20, and ×40, respectively).

vascular endothelial growth factor and IL-5 expression by lesional mast cells.[9]

Hormonal alteration, specifically hyperestrogenemia, also has been proposed as a possible etiologic mechanism.[12] Many vascular tumors exhibit hormonally responsive behavior, including pyogenic granulomas, hemangiomas, and hepatic vascular tumors. Lesions of ALHE also can appear or grow rapidly during pregnancy or with the use of oral contraceptives but decrease in size after delivery or with discontinuation of hormonal supplementation (Table 1).[12-14] In our case, the lesions increased rapidly in both size and number during pregnancy. However, unlike some reported hormonally responsive cases of ALHE,[13] lesional tissue was negative for estrogen and progesterone receptors. Although the patient's condition stabilized during the postpartum period, no remarkable decrease in tumor burden occurred. Because hormonal receptors were absent in our patient despite rapid growth of the lesions during pregnancy

Table 1.

Clinical Characteristics of ALHE

Case No.	Age, y	Location	Onset/Clinical Course[a]	Estrogen/ Progesterone Receptor Positivity	Peripheral Eosinophilia	Therapy	Follow-up
1	33	R auricle	2nd trimester; increase in size during pregnancy	Negative	No	Surgical excision	No recurrence after 13 months[8]
2	28	L brow, scalp	2nd trimester	Negative	No	Surgical excision	N/A[12]
3	28	Scalp	New lesions developed with administration of OCPs	N/A	N/A	IL vinblastine, electrodesiccation and curettage, CO_2 laser	No lesions developed after discontinuation of OCPs[13]
4	28	R forehead, R temple	Stable for 7 years; multiple new lesions appeared during pregnancy	Positive	N/A	Surgical excision	Decrease in lesion size by 50% in postpartum period[13]
5	25	Palate	Enlarged during 1st trimester	N/A	N/A	Surgical excision	No recurrence after 21 months[14]
6	24	R cheek	Onset and rapid growth during pregnancy	N/A	N/A	Surgical excision	No recurrence after 4 years[15]
7	N/A	N/A	1st trimester	N/A	N/A	N/A	N/A[5]
8	N/A	N/A	1st trimester	N/A	N/A	N/A	N/A[5]
9	N/A	N/A	1st trimester	N/A	N/A	N/A	N/A[5]
10	N/A	N/A	1st trimester	N/A	N/A	N/A	N/A[5]
11	N/A	N/A	Lesions present for years; increased in size during pregnancy	N/A	N/A	N/A	N/A[5]

Abbreviations: ALHE, angiolymphoid hyperplasia with eosinophilia; R, right; L, left; N/A, not available; OCP, oral contraception pill; IL, intralesional.

[a]The clinical course is not available for all cases.

and the initial lesions predated pregnancy, further investigation is needed to elucidate the mechanism of growth induction of ALHE in hyperestrogemic states.

Treatment—Although many treatment options have been utilized, including cryosurgical destruction, electrodesiccation and curettage, topical tacrolimus, corticosteroids (topical, intralesional, and oral), intralesional chemotherapeutic agents, intralesional interferon, pentoxifylline, isotretinoin, laser ablation, and surgical excision, there remains a high rate of recurrence.[15-21] The most efficacious treatment is surgical resection; however, the resected area should include an associated arteriovenous shunt to decrease recurrence. Thus pretreatment diagnostic workup should include a search for any associated vascular anomaly with angiography, magnetic resonance angiography, or computed tomographic angiography.[22] Various laser modalities, including pulsed dye, argon, and CO_2 lasers, have been utilized to treat ALHE recalcitrant to other therapies.[23,24] The pulsed dye laser has been advocated as a treatment option because of the selective targeting of hemoglobin within the vascular structures of ALHE. Further advances in pulsed dye lasers, such as long-pulsed and ultralong-pulsed varieties, have facilitated treatment of deep dermal vascular lesions and have successfully treated lesions of ALHE.[23,24]

Differential Diagnosis—Uncertainty has surrounded the precise relationship between ALHE and Kimura disease. Although Kimura disease initially was described as a late stage of ALHE, they are now regarded as 2 distinct entities. Similar to ALHE, Kimura disease also typically affects the head and neck; however, the 2 diseases exhibit numerous clinical differences (Table 2). Kimura disease more commonly affects Asian males and presents as flesh-colored subcutaneous nodules that can distort the contours of the head and neck due to massive infiltration of the dermis and subcutaneous tissue with lymphocytes. Contiguous lymphadenopathy and

Table 2.

Comparison of ALHE, Kimura Disease, and Cutaneous Angiosarcoma

	ALHE	Kimura Disease	Cutaneous Angiosarcoma
Mean age of onset, y	32	31	75
Sex predilection	F>M	M>F	M>F
Site	Head and neck	Head and neck	Head and neck (50%)
Recurrence	33%	15%–40%	72%
Histologic features	Vascular proliferation in the dermis with prominent plump endothelial cells with a hobnail appearance, often with intracytoplasmic vacuoles; inflammatory infiltrate comprised of lymphocytes, eosinophils, and mast cells	Lymphoid follicle formation with a surrounding inflammatory infiltrate of eosinophils, mast cells, plasma cells, lymphocytes, and histiocytes; marked fibrosis	Irregular dilated vascular channels lined by flattened endothelial cells, which may appear large, pleomorphic, and can protrude into the vascular lumina; intracytoplasmic vacuoles also are present; a lymphoid infiltrate is a common feature of lesions of the face and scalp
Lymphadenopathy	Rare	Common	Common
Peripheral eosinophilia	Rare	Common	Rare
Elevated IgE level	Rare	Common	Rare

Abbreviations: ALHE, angiolymphoid hyperplasia with eosinophilia; F, female; M, male.

peripheral eosinophilia are invariably present.[2,6,24-26] Moreover, ALHE and Kimura disease are histologically distinct. Kimura disease demonstrates lymphoid follicle formation with a surrounding inflammatory infiltrate of eosinophils, mast cells, plasma cells, lymphocytes, and histiocytes. Vascular abnormalities are not a prominent feature and plump endothelial cells are only focally present.[2]

Clinically, ALHE can be confused with an epidermal or pilar cyst, hemangioma, richly vascularized cutaneous metastasis, or angiosarcoma (Table 2). Angiosarcoma also commonly presents with lesions on the scalp but is more prevalent in the elderly population. The 3 well-characterized clinical variants of cutaneous angiosarcoma include angiosarcoma of the head and neck, angiosarcoma arising in the setting of chronic lymphedema (Stewart-Treves syndrome), and angiosarcoma induced by radiation. Epithelioid angiosarcoma is a rare variant of cutaneous angiosarcoma that affects the lower extremities, scalp, and face.[27,28] Although the initial cutaneous lesions of angiosarcoma appear as an ecchymotic patch or plaque, more advanced lesions can resemble the clinical presentation of ALHE and consist of firm, nodular, elevated plaques with satellite lesions. The lesions of angiosarcoma also tend to spread centrifugally in a short period of time,[29] similar to our case. Regional lymphadenopathy is not an unexpected finding in angiosarcoma because of its propensity for locoregional spread.

In addition to resembling advanced nodular lesions of angiosarcoma clinically, ALHE also can mimic epithelioid angiosarcoma histologically. The lesions of ALHE consist of well-circumscribed nodules located in the dermis and occasionally subcutaneous fat. Plump endothelial cells line the vascular channels and some immature endothelial cells may be present. The cytoplasm of the endothelial cells often contains intracytoplasmic vacuoles representing primitive vascular lumina. The surrounding stroma includes an inflammatory infiltrate comprised of lymphocytes, eosinophils, and mast cells.[2] An atypical form of ALHE also has been described that demonstrates a central epithelioid endothelial cell proliferation with an indeterminate growth pattern. However, the endothelial cells consistently exhibit peripheral maturation.[30]

A variety of vascular neoplasms have histologic similarities to ALHE, including epithelioid angiosarcoma, epithelioid hemangioendothelioma, and cutaneous epithelioid angiomatous nodule. Epithelioid angiosarcoma demonstrates sheetlike aggregations of rounded monomorphic epithelioid cells with abundant cytoplasm and vesicular nuclei. There may be focal areas of irregular vascular channels lined by flattened atypical endothelial cells. Intracytoplasmic vacuoles also can be present in the epithelioid cells. A lymphoid infiltrate is a common feature of angiosarcoma of the face and scalp. In contrast to ALHE, epithelioid angiosarcoma demonstrates mitoses, necrosis, and hemorrhage, while eosinophils in the inflammatory infiltrate are not considered a feature.[27,28] Epithelioid hemangioendothelioma also is composed of epithelioid cells within a fibromyxoid stroma. The endothelial cell proliferation exhibits a cordlike or lobular architecture, and many of the cells demonstrate cytoplasmic vacuolization. Unlike epithelioid angiosarcoma, cellular pleomorphism is mild and mitotic figures are rare. More distinct vascular channels can be present at the periphery of the lesion.[27] A solid proliferation of epithelioid endothelial cells characterizes an epithelioid angiomatous nodule. However, in contrast to a malignant vascular neoplasm, the proliferation is unilobular with a well-demarcated margin. The endothelial cells also contain frequent intracytoplasmic vacuoles. A chronic inflammatory infiltrate composed of lymphocytes and plasma cells often surrounds the proliferation with eosinophils present throughout the lesion. Although mitotic figures are common, there is a lack of nuclear atypia.[31]

Conclusion

Our case highlights the heterogeneous clinical presentation of ALHE. The large size of the lesion, rapid increase in size, and associated lymphadenopathy were concerning for a malignant vascular neoplasm. Additional biopsy of the lesion and evaluation of the palpable cervical lymph nodes were necessary to arrive at the correct diagnosis and guide therapeutic options. It is imperative to have a high index of suspicion regarding a malignant process when evaluating a growing, vascular-appearing lesion, especially in the setting of associated lymphadenopathy, to provide the most appropriate therapy to maximize cure. Our patient experienced dramatic proliferation and growth of the lesions of ALHE during pregnancy with subsequent stabilization after delivery. Hormonal alterations appear to be a contributing factor. Because lesional tissue did not exhibit estrogen or progesterone positivity, further study is needed to determine the precise role of hormonal alteration in the etiology of this vascular neoplasm.

REFERENCES

1. Wells GC, Whimster IW. Subcutaneous angiolymphoid hyperplasia with eosinophilia. *Br J Dermatol.* 1969;81:1-14.
2. Requena L, Sangueza OP. Cutaneous vascular proliferations. part II. hyperplasias and benign neoplasms. *J Am Acad Dermatol.* 1997;37:887-919.

3. Sezer E, Erbil H, Koseoglu D, et al. Angiolymphoid hyperplasia with eosinophilia mimicking Bowenoid papulosis. *Clin Exp Dermatol*. 2007;32:281-283.
4. Busquets AC, Sánchez JL. Angiolymphoid hyperplasia with eosinophilia induced by trauma. *Int J Dermatol*. 2006;45:1211-1214.
5. Bartralot R, Garcia-Patos V, Hueto J, et al. Angiolymphoid hyperplasia with eosinophilia affecting the oral mucosa: report of a case and a review of the literature. *Br J Dermatol*. 1996;134:744-748.
6. Olsen TG, Helwig EB. Angiolymphoid hyperplasia with eosinophilia: a clinicopathologic study of 116 patients. *J Am Acad Dermatol*. 1985;12:781-796.
7. Zeitouni NC, Hanna S, Loree TR, et al. Angiolymphoid hyperplasia with eosinophilia: a classic clinical presentation with histologic features of angiosarcoma. *Dermatol Surg*. 2002;28:772-775.
8. Don DM, Ishiyama A, Johnstone AK, et al. Angiolymphoid hyperplasia with eosinophilia and vascular tumors of the head and neck. *Am J Otolaryngol*. 1996;17:240-245.
9. Kempf W, Haeffner A, Zepter K, et al. Angiolymphoid hyperplasia with eosinophilia: evidence for a T-cell lymphoproliferative origin. *Hum Pathol*. 2002;33:1023-1029.
10. Onishi Y, Ohara K. Angiolymphoid hyperplasia with eosinophilia associated with arteriovenous malformation: a clinicopathological correlation with angiography and serial estimation of serum levels of renin, eosinophil cationic protein and interleukin 5. *Br J Dermatol*. 1999;140:1153-1156.
11. Fetsch JF, Weiss SW. Observations concerning the pathogenesis of epithelioid hemangioma (angiolymphoid hyperplasia). *Modern Pathol*. 1991;4:449-455.
12. Hollo P, Marschalko M, Sikos G, et al. Angiolymphoid hyperplasia with eosinophilia in pregnancy. *Eur Acad Dermatol Venereol*. 2005;19:645-646.
13. Moy RL, Luftman DB, Nguyen QH, et al. Estrogen receptors and the response to sex hormones in angiolymphoid hyperplasia with eosinophilia. *Arch Dermatol*. 1992;128:825-828.
14. Zarrin-Khameh N, Spoden JE, Tran RM. Angiolymphoid hyperplasia with eosinophilia associated with pregnancy: a case report and review of the literature. *Arch Pathol Lab Med*. 2005;129:1168-1171.
15. Akdeniz N, Kösem M, Calka O, et al. Intralesional bleomycin for angiolymphoid hyperplasia. *Arch Dermatol*. 2007;143:841-844.
16. Mashiko M, Yokota K, Yamanaka Y, et al. A case of angiolymphoid hyperplasia with eosinophilia successfully treated with tacrolimus ointment. *Br J Dermatol*. 2006;154:803-804.
17. Redondo P, Del Olmo J, Idoate M. Angiolymphoid hyperplasia with eosinophilia successfully treated with imiquimod. *Br J Dermatol*. 2004;151:1110-1111.
18. Woźniacka A, Omulecki A, Torzecka JD. Cryotherapy in the treatment of angiolymphoid hyperplasia with eosinophilia. *Med Sci Monit*. 2003;9:1-4.
19. Shenefelt PD, Rinker M, Caradonna S. A case of angiolymphoid hyperplasia with eosinophilia treated with intralesional interferon alfa-2a. *Arch Dermatol*. 2000;136:837-839.
20. Oh CW, Kim KH. Is angiolymphoid hyperplasia with eosinophilia a benign vascular tumor? a case improved with oral isotretinoin. *Dermatology*. 1998;197:189-191.
21. Person JR. Angiolymphoid hyperplasia with eosinophilia may respond to pentoxifylline. *J Am Acad Dermatol*. 1994;31:117-118.
22. Krapohl BD, Machens HG, Reichert B, et al. A rare vasoproliferative lesion: angiolymphoid hyperplasia with eosinophilia of the hand. *Br J Plast Surg*. 2003;56:168-170.
23. Abrahamson TG, Davis DA. Angiolymphoid hyperplasia with eosinophilia responsive to pulsed dye laser. *J Am Acad Dermatol*. 2003;49(suppl 2):S195-S196.
24. Angel CA, Lewis AT, Griffin T, et al. Angiolymphoid hyperplasia successfully treated with an ultralong pulsed dye laser. *Dermatol Surg*. 2005;31:713-716.
25. Chun SI, Ji HG. Kimura's disease and angiolymphoid hyperplasia with eosinophilia: clinical and histopathology differences. *J Am Acad Dermatol*. 1992;27:954-958.
26. Chen H, Thompson LD, Aguilera NS, et al. Kimura disease: a clinicopathologic study of 21 cases. *Am J Surg Pathol*. 2004;28:505-513.
27. Requena L, Sangueza OP. Cutaneous vascular proliferations. part III. malignant neoplasms, other cutaneous neoplasms with significant vascular component, and disorders erroneously considered vascular neoplasms. *J Am Acad Dermatol*. 1998;38:143-175.
28. Rudd RJ, Fair KP, Patterson JW. Aortic angiosarcoma presenting with cutaneous metastasis: case report and review of the literature. *J Am Acad Dermatol*. 2000;43:930-933.
29. Cooper PH. Angiosarcomas of the skin. *Semin Diagn Pathol*. 1987;4:2-17.
30. Fetsch JF, Sesterhenn IA, Miettinen M, et al. Epithelioid hemangioma of the penis: a clinicopathologic and immunohistochemical analysis of 19 cases, with special reference to exuberant examples often confused with epithelioid hemangioendothelioma and epithelioid angiosarcoma. *Am J Surg Pathol*. 2004;28:523-533.
31. Brenn T, Fletcher CD. Cutaneous epithelioid angiomatous nodule: a distinct lesion in the morphologic spectrum of epithelioid vascular tumors. *Am J Dermatopathol*. 2004;26:14-21.