Case Report

Angiolymphoid Hyperplasia with Eosinophilia Located on the Forehead: A Possible Association with Oral Contraceptive Use?

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Keywords

Angiolymphoid hyperplasia with eosinophilia · Skin · Pathogenesis · Contraceptive pill

Abstract

Angiolymphoid hyperplasia with eosinophilia (ALHE) is an uncommon benign vasoproliferative tumor characterized by nodules, papules or plaques localized principally in the head and neck region. Histopathological examination reveals hyperplastic blood vessels lined by large endothelial cells, accompanied by an infiltrate of inflammatory cells including eosinophils. The pathogenetic mechanism remains unclear, although different theories have been proposed. Various treatment strategies have been described, but surgery remains the treatment of choice. We describe the case of a young woman with ALHE taking an oral contraceptive pill suggesting a possible etiopathogenetic relationship.

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Introduction

Angiolymphoid hyperplasia with eosinophilia (ALHE) is a benign tumor that is characterized by a vascular proliferation associated with infiltration from lymphocytes and eosinophils. It was first described in 1969 by Wells and Whimster and considered as a late stage of Kimura disease [1]. Nowadays, the two disorders are considered separate entities.

A systematic review of the literature conducted in 2016 by Adler et al. [1] confirmed 908 cases. From 2016 to 2019, an additional 60 cases have been reported in the literature. Young

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Fig. 1. Patient presenting at the emergency department with a subcutaneous nodule.

to middle-aged adults are usually affected, with a mean age of 37.6 years with no gender predilection [1]. Some authors report a higher incidence in women but Adler et al. found no statistically significant differences between genders. A possible explanation – that was suggested by Guo and Gavino [2] – is that in one of the biggest series of 116 patients by Olsen and Helwig [3], the population was predominantly masculine due to the selection of patients from a group of military and Veterans Health Administration hospitals leading therefore to a male sex bias [2].

The lesions are localized mainly on the head and neck, especially affecting the ear and preauricular area (36.3%) [1]. Locations less frequently encountered are the oral mucosa, salivary glands, parapharyngeal space, breast, colon, lung and upper limbs and fingernails [1, 4–6].

They typically manifest as intradermal or subcutaneous single or multiple papules or nodules, or plaques. Symptoms reported include pruritus, pain, bleeding and pulsation [1].

Approximately 20% of patients have blood eosinophilia without elevation of immunoglobulin E (IgE) levels [3].

Histopathologically, ALHE is characterized by prominent vascular hyperplasia. The main pathognomonic characteristic is the presence of epithelioid endothelial cells lining the vascular wall and projecting inside the vascular lumen giving a “cobblestone” appearance. These cells have large nuclei and abundant eosinophilic cytoplasm. The second defining characteristic of ALHE is inflammation. Lymphocytes and eosinophils diffusely surround and may infiltrate the blood vessels [1].

Differential diagnosis must be made between ALHE and Kimura disease which were thought to be the same pathology in the past [1, 7].

The pathogenetic mechanisms of ALHE remain uncertain. Many hypotheses have been proposed [1, 3, 8–14].

Surgery is the main treatment, but various treatment strategies have been described in the literature with varying results (e.g., tacrolimus, propranolol, cryotherapy) [2].

We describe a case occurring in a patient taking oral contraceptive pills suggesting a possible association between hormones and ALHE.

Fig. 2. Histopathology showing proliferation of vascular channels surrounded by a chronic, inflammatory infiltrate with eosinophils. The vessels are lined by plump endothelial cells. HE. $\times 20$.

Fig. 3. Higher magnification showing proliferated vascular channels and infiltration by numerous eosinophils. HE. $\times 32$.

Case Report

A 34-year-old woman was transferred to the emergency department, University Hospitals of Geneva, after an unsuccessful attempt by her general practitioner to excise a subcutaneous nodule located on the forehead. The procedure was stopped due to excessive bleeding intraoperatively. Her medical history was uneventful. She had been taking contraceptive pills for 20 years. She reported that the nodule had been present for 5 months and that a nodule on the scalp had been successfully excised by her general practitioner several years before. We failed to retrieve information about whether histopathological examination was performed at that time or not. Upon clinical examination, a well-circumscribed, subcutaneous nodule was observed, with a diameter of about 2 cm, located on the left side of the forehead, associated with an inflammatory reaction (Fig. 1). Surgical excision was performed under local anesthesia. An elliptical incision was performed respecting the Langer lines of minimal tension on the skin. The lesion was resected in totality, and the skin was closed using simple interrupted sutures. Histopathological examination revealed a florid lobular vascular CD31-positive proliferation, lined by

Table 1. Cases of angiolymphoid hyperplasia with eosinophilia associated with pregnancy or contraception

	Cases	Age, years	Pregnancy/contraception	Localization of lesions	Lesions, <i>n</i>	Occurrence/aggravation/regression after discontinuation	Treatment
Olsen and Helwig [3], 1985	5	Not mentioned	Pregnancy	Not mentioned	Single, multiple	Occurrence, aggravation	Not mentioned
Moy et al. [15], 1992	2	28 28	Pregnancy, contraception	Forehead, scalp	Multiple	Occurrence, aggravation, regression	Electrodessication curettage, laser/surgical excision
Hollo et al. [16], 2005	1	28	Pregnancy	Eyebrow, temporal region	2	Occurrence	Surgical excision
Zarrin-Khameh et al. [17], 2005	1	33	Pregnancy	Ear	1	Occurrence	Surgical excision
Ceyhan et al. [18], 2011	1	33	Pregnancy	Ear	1	Occurrence	Surgical excision
Marcum et al. [19], 2011	1	29	Pregnancy	Occipital scalp	Multiple	Aggravation and occurrence of new lesions	Laser
Parimalam and Thomas [21], 2016	1	33	Pregnancy, history of contraception	Ear	Multiple	Occurrence	Surgical excision
Haritha et al. [20], 2016	3	27 25 32	Pregnancy	Postauricular, scalp	Multiple	Occurrence, aggravation, regression	Surgical excision, cryotherapy

hypertrophic endothelial cells, occasionally protruding inside the lumen (Fig. 2) and surrounded by inflammatory infiltrate of variable density containing lymphocytes, eosinophils and mast cells (Fig. 3). Rare lymphoid follicles were noted. A diagnosis of ALHE was established. Her serum eosinophilic count was normal. No recurrence was noted at the 12-month follow-up visit.

Discussion

Many hypotheses about the pathogenetic mechanisms of ALHE have been made. A reactive mechanism secondary to vascular damage has been suggested [3, 8]. Other authors have claimed that ALHE is of neoplastic origin and specifically that it is a T-cell lymphoproliferative disorder [9–11]. The role of the renin-angiotensin system in provoking vessel proliferation has equally been discussed [12]. Another hypothesis is that the disorder could be explained by an immunological pathogenetic mechanism [13]. A possible association with the HIV virus has also been reported in the literature [14], as well as human T-cell lymphotropic virus or human herpesvirus 8 [1]. An etiopathogenetic factor that has not been adequately studied is the impact of sex hormones, especially estrogen.

Olsen and Helwig [3] observed a development of lesions in 4 patients and also an increase in nodular size of preexisting nodules in 1 patient during pregnancy and thus were the first to suggest an association with hyperestrogen states in the pathogenesis of ALHE. Since then, other cases of occurrence or recurrence or aggravation of ALHE during pregnancy have been reported in the literature [15–20]. By contrast, to the best of our knowledge, only 2 cases of ALHE occurring in patients with a history of contraceptive pill use have been described [15,

20, 21]. Resolution of lesions after discontinuation of contraceptive pills and decrease in size after pregnancy have also been described [15, 20].

All reported cases of ALHE associated with hormones are presented in Table 1.

The occurrence and aggravation of the disease during pregnancy as well as the regression of the lesions after discontinuation of the hormonal effect could lead to the hypothesis that hormones play a role in the pathogenesis of ALHE, but the mechanism remains undetermined.

The hormonally responsive behavior of many other vascular tumors has been studied. An etiopathogenetic link between pyogenic granuloma and pregnancy is widely accepted [22, 23]. The impact of hormones on the development of hemangiomas has also been studied by various authors [24–27].

The pathogenetic pathways by which hormones lead to vascular tumors have been well established. More precisely, estrogen enhances endothelial changes that lead to angiogenesis [28]. The stimulation of growth factors such as basic fibroblast growth factor, insulin-like growth factor, transforming growth factor- β , vascular endothelial growth factor, matrix metalloproteinase-9, endothelial progenitor cells and nitric oxide by estrogen [29, 30] is a crucial mechanism that results in proliferation of vascular endothelial cells leading to the development of lesions such as ALHE. Further studies need to be conducted to prove that hypothesis.

As far as differential diagnosis is concerned, ALHE should be distinguished from Kimura disease, which is typically characterized by a large subcutaneous mass localized in the periauricular or submandibular region. Young Asian males are most commonly affected. It is a systemic immunological process characterized by lymphadenopathy, eosinophilia and increased serum levels of IgE. Renal disease and asthma are commonly present [7]. Histologically, florid lymphoid follicles and eosinophilic infiltrates are typical histological findings of Kimura disease [7].

Many therapeutic options have been used for ALHE including radiotherapy, laser therapy, photodynamic therapy, cryotherapy, electrodesiccation and medications such as corticosteroids, pentoxifylline, interferon- α , imiquimod, tacrolimus, thalidomide, oral isotretinoin, acitretin and intralesional chemotherapeutic agents [31]. However, surgical excision remains the gold standard treatment [2]. A recurrence rate of 30% has been reported in the literature in cases of incomplete excision [32].

Statement of Ethics

The patient has given written informed consent to publish the case (including publication of images).

Disclosure Statement

The authors have no conflicts of interest to declare.

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