

Kimura disease is not angiolymphoid hyperplasia with eosinophilia: clinical and pathological correlation with literature review and definition of diagnostic criteria*

*Doença de Kimura não é hiperplasia angiolinfóide com eosinofilia: correlação clinicopatológica com revisão da literatura e definição de critérios diagnósticos**

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Abstract: Kimura disease is a rare chronic inflammatory disease that presents as a tumor-like swelling in the head and neck region and is often associated with regional cervical lymphadenopathy. Cases have been described predominantly in the oriental literature. Kimura disease has been confused with angiolymphoid hyperplasia with eosinophilia, for having common characteristics, but both conditions should be differentiated. In this article, the clinical and histopathological characteristics are revised and the criteria to differentiate the two conditions are presented.

Keywords: Angiolymphoid hyperplasia with eosinophilia; Hemangioma; Histology

Resumo: A doença de Kimura é doença inflamatória crônica que se manifesta como crescimento tumoral indolor na região da cabeça e do pescoço, freqüentemente associada à linfadenopatia cervical. Por ser doença rara, ter sido descrita inicialmente na literatura oriental e ter características em comum com a hiperplasia angiolinfóide com eosinofilia, a doença de Kimura tem sido confundida com essa enfermidade, da qual deve ser distinguida. Neste artigo, revisam-se as características clínicas e histopatológicas e apresentam-se critérios para a diferenciação dessas duas entidades. **Palavras-chave:** Hemangioma; Hiperplasia angiolinfóide com eosinofilia; Histologia

INTRODUCTION

Kimura disease (KD) was initially described in 1937, in the Chinese literature, by Kimm and Szeto¹ as an “eosinophilic hyperplastic lymphogranuloma” and it became known as KD after its publication by Kimura et al.² of similar cases in Japan under the title “Atypical granulation associated with hyperplastic abnormalities in the lymphoid tissue.” It is a chronic inflammatory disease involving the dermis and subcutaneous tissue characterized by one or multiple nodules or unpainful masses. It occurs predominantly as a unilateral manifestation in the head and neck and it is

frequently associated with regional lymphadenopathy with or without involvement of salivary glands.³ Histopathologically, this condition is characterized by a lymphocytic inflammatory infiltrate, forming lymphoid follicles interspersed with aggregates of eosinophils and variable fibrosis in a richly vascular stroma. The pathophysiology of KD remains unknown, although allergic reaction, trauma and autoimmune process have been implicated as triggering factors.^{3,4}

Angiolymphoid hyperplasia with subcutaneous eosinophilia (ALHE) was described in 1969, by Wells

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and Whimpster,⁵ who studied nine patients with persistent subcutaneous nodules in the head and neck. In the pathological examination, these cases presented exuberant vascular proliferation, inflammatory infiltrates containing lymphocytes, eosinophils and mast cells, but with no fibrosis. The authors considered that ALHE late stage would correspond to Kimura disease and they were followed in their observations by Reed et al.⁶ and Eveson et al.⁷ Eventually, numerous articles⁸⁻¹⁰ considered the two denominations as synonyms.

Although recent articles^{11,12} have established consistent criteria for differentiation between ALHE and Kimura disease, several authors still confuse the two entities.¹³⁻¹⁵

Kimura disease

KD is a rare inflammatory disorder of unknown origin. Most of patients are male and oriental young adults. The prevalence in patients of other ethnicities is considered low. The disease is characterized by a triad of painless subcutaneous masses in the head and neck, eosinophilia in the peripheral blood and in tissues, and marked increase in serum levels of immunoglobulin E (IgE).^{16,17}

At physical examination, patients with KD present one or more subcutaneous masses in the head and neck, accompanied by satellite adenomegalies and/or increased volume of salivary glands, especially the parotid and submaxillary glands. (Figure 1).

The lesions are firm at palpation, not painful and progressively increase in size with some of them reaching a diameter between 3 and 10 cm. There is a marked predominance of male patients; the

male/female ratio is 2:1; and the onset of the disease occurs mostly in the third decade of life.^{18,19} Kung et al.³ studied 21 patients distributed as 18 men and 3 women, and they observed that the age of onset of lesions ranged from 7 to 50 years, with a mean age of 28 years. Such patients frequently reported pruritus in the overlying skin. In this study, most of the lesions were in the regions of head and neck; seven cases also presented involvement of the parotid gland. Lesions in other areas were also described such as the inguinal area, upper limbs and chest wall.³

Although KD pathogenesis remains unknown, it is considered nowadays an allergic disease and it seems to be a systemic immunological disorder. Eosinophilia and increased serum IgE levels make KD be considered a CD4(+) T helper 2 (Th2) allergic reaction. Th2 cells would produce interleukins (IL) IL-4, IL-5 and IL-13, which, in turn, would act in B cells favoring the production of antigen-specific IgE. Th2 cell proliferation and the overexpression of cytokines would play an essential role in the development of the disease.^{16,20}

The histopathological changes in KD consist of a massive, nodular, diffuse and mixed inflammatory infiltrate composed mainly of lymphocytes and eosinophils, occupying all the extension of reticular dermis, subcutaneous tissue and, sometimes, the muscle fascia and the skeletal muscle (Figure 2). The inflammatory infiltrate is poorly circumscribed and contains numerous lymphoid follicles; infiltration of adjacent salivary glands may also occur.^{13,15} Lymphoid follicles are hyperplastic and contain prominent germination centers (Figure 3). Eosinophilic infiltration may occur occasionally with areas of necrosis (Figure 4).



FIGURE 1: Kimura disease: subcutaneous masses in the neck, accompanied by increased volume of salivary glands
Source: Ackerman AB, Briggs PL. Differential diagnosis in dermatopathology. Vol III. Pennsylvania: Lea & Febiger; 1993. p.62-5.

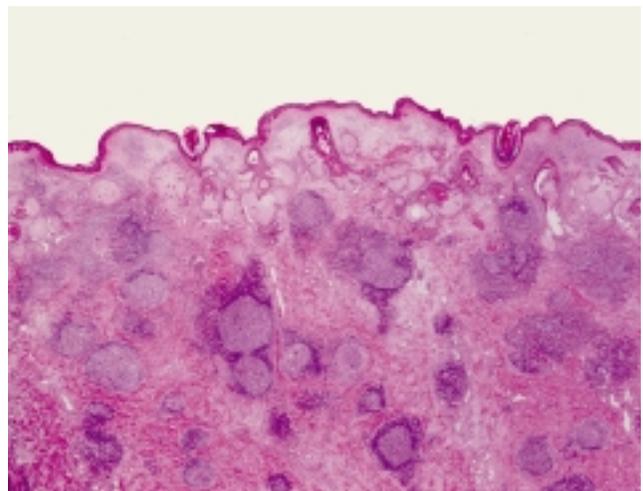


FIGURE 2: Kimura disease: massive nodular, diffuse and mixed inflammatory infiltrate, occupying all the extension of reticular dermis. The infiltrate is poorly circumscribed and contains several lymphoid follicles (HE x 50)

Although plasma cells and histiocytes are present, no epithelioid cells, multinucleated giant cells or granulomas are seen.^{3,10} Fibroplasia is seen in the subcutaneous tissue and around the lesion. Fibrosis can be sometimes observed as septa. Fibroplasia cellularity varies and tends to hyalinization of older lesions.^{13,21}

The lesions are markedly of vascular type; capillaries are numerous and their endothelium is prominent and with no cytological atypias.^{13,21} Small arteries present hyperplasia or fibrosis of tunica intima and tunica muscularis. Large caliber arteries are rarely seen. Older lesions show more pronounced fibrosis, less active lymphoid follicles, less intense inflammatory infiltrate and a relatively less exuberant vascular component.^{13,15,21}

Due to KD benign nature, treatment may range from observation and follow-up of mild and asymptomatic cases to conservative surgical excision, although lesions sometimes tend to recur. Other therapeutic options less commonly used include intralesional corticosteroids, cyclosporine, pentoxifylline and radiotherapy.²²⁻²⁷

Angiolymphoid Hyperplasia with Eosinophilia (ALHE)

In 1969, Wells and Whimster⁵ studied nine patients with persistent subcutaneous nodes in the head and neck and described them as “angiolymphoid hyperplasia with subcutaneous eosinophilia” (ALHE). Wilson-Jones and Bleehen²⁸ described similar lesions and published them in the same year and in the same journal under the name “inflammatory angiomatous nodules with abnormal blood vessels in the scalp and ears – pseudo or atypical pyogenic granuloma”. In 1983, Enzinger and Weiss,²⁹ in their book *Soft Tissue Tumor* suggested the expression “epithe-

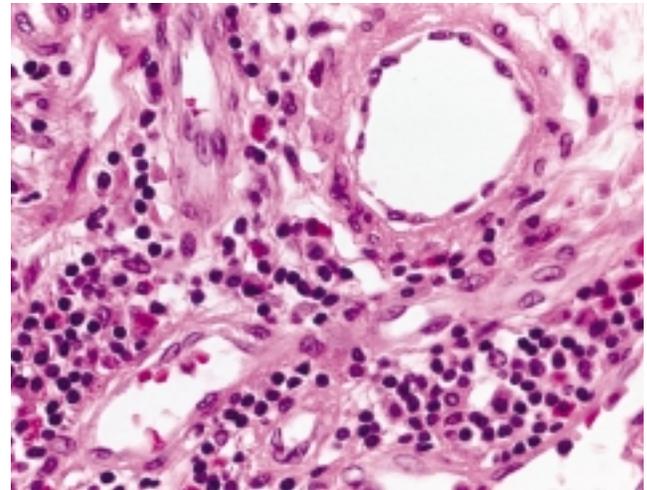


FIGURE 4: Kimura Disease: dense inflammatory infiltrate containing numerous eosinophils (HE x 400)

lioid hemangioma” for this uncommon and distinct vascular formation.

ALHE is a rare disease which manifests with the presence of dermal papules and nodules measuring 2-3 cm and a color varying between light brown and pink (Figure 5). It predominantly observed in the head and neck, especially around the external ear in young patients. There seems to be a higher incidence in females and it is more common in patients aged 20-50 years (peak incidence between 30-33 years).^{21,30} Although its pathogenesis remains undefined and some authors consider it an abnormal vasoproliferative reaction, recent studies^{11,13} tend to consider this disease as a benign vascular neoplasm or a vascular malformation secondary to a subcutaneous arteriovenous shunt which sporadically can be associated with a previous trauma. Eosinophilia in the peripheral blood is frequently absent in ALHE, as well as the lev-

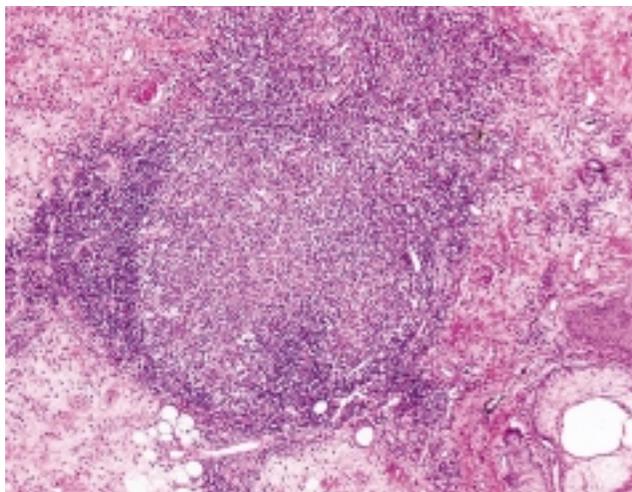


FIGURE 3: Kimura disease: lymphoid follicles are hyperplastic and contain prominent germinal centers (HE x 100)



FIGURE 5: ALHE: dermal papules and nodules, located in the head region

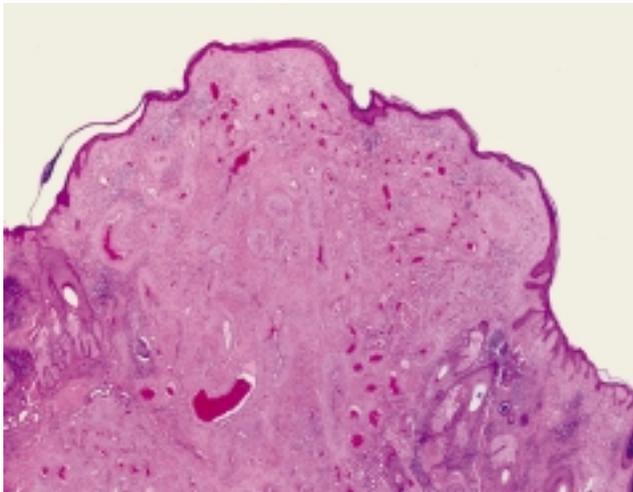


FIGURE 6: ALHE: vascular proliferation and inflammatory infiltrate in all the extension of reticular dermis (HE x 50)

els of IgE which are normal.¹³

Histopathologically, ALHE is predominantly characterized by vascular proliferation and inflammatory infiltrate (Figure 6).^{13,15,30} The vascular component includes capillaries clustered around arterial or venous vessels, dilated and atypical, forming a lobular architecture and sometimes surrounded by a fibromixoid stroma (Figure 7).¹³ These capillaries have a protruded endothelium with rounded and sometimes polygonal nuclei (Figure 8). One or more cytoplasmic vacuoles can be seen in the abnormal endothelial cells. The lesion can grow entirely in a blood vessel or it can originate from the vascular wall.²¹

The inflammatory component is characterized

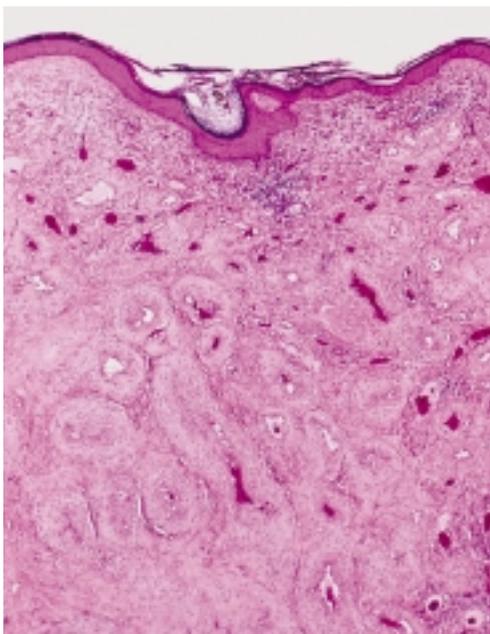


FIGURE 7: ALHE: dilated blood vessels, some with bizarre and irregular shapes in the reticular dermis. Inflammatory infiltrate containing lymphocytes and eosinophils (HE x 100)

by a superficial and deep, nodular and diffuse infiltrate, composed predominantly of lymphocytes, a variable number of eosinophils, plasma cells and mast cells. Lymphoid follicles are rare or are absent in most cases. The inflammatory infiltrate tends to be less conspicuous in papulous lesions than in nodular lesions.^{13,21}

In addition to KD, the differential diagnoses for ALHE should include angiosarcoma, hemangioma, hemangioendothelioma and a reaction to insect bite.¹⁵

Angiosarcomas could be distinguished from ALHE for presenting nuclear atypia with hyperchromatism, mitotic activity and scarce eosinophils in the inflammatory infiltrate.

Hemangiomas do not present an intrinsic inflammatory infiltrate and they rarely show enlarged and protruding endothelial cells or with an eosinophilic cytoplasm. In addition to the characteristics above, a hemangioendothelioma has a characteristic reticular growth.^{15,21}

Reactions to insect bites or reactions to vaccines may present inflammatory characteristics in common with ALHE, but they rarely show a prominent vascular component.¹⁵

Treatment to ALHE is always a challenge.^{20,31} Surgical removal, including the arterial and venous segments at the base of the lesion, seems to be the most efficient alternative. Recently, a surgical technique developed by Mohs³² was used as a way to spare a larger amount of tissue and to control the margins. Other therapeutic options less commonly used include isotretinoin, interferon, pentoxifylline, imiquimod, cryotherapy and laser.³³⁻⁴⁰

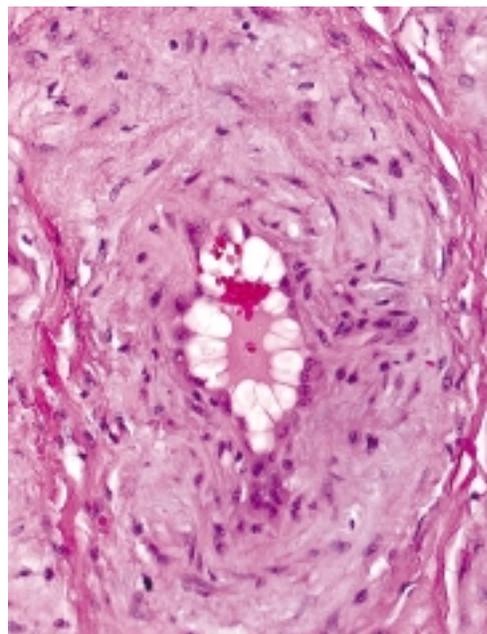


FIGURE 8: ALHE: numerous enlarged endothelial cells in the lumen of an abnormal blood vessel. Presence of lymphocytes and eosinophils (HE x 400)

CHART 1: Common histopathological characteristics of ALHE and KD

- ◆ They could involve the dermis and the subcutaneous tissue
- ◆ They present an inflammatory infiltrate composed of lymphocytes and eosinophils
- ◆ They present blood vessels with endothelial cells that may be protruded and with abundant cytoplasm
- ◆ They present fibroplasia
- ◆ They may contain plasma cells in the inflammatory infiltrate
- ◆ They spare epithelial and non-epithelial adnexal structures

DISCUSSION

For many years, the authors of medical literature in English used the expressions ALHE and KD as synonyms.¹³ Even today, in the last edition of *Dermatology in General Medicine* (Fitzpatrick et al¹⁴) there is still some doubt if the two entities represent distinct diseases. The difficulty to distinguish them is in part due to the rarity of KD in the occidental literature and to characteristics that are common to both diseases.^{3,13}

ALHE and KD have the following histopathological characteristics¹³ in common: both may involve the dermis and subcutaneous tissue; present an

inflammatory infiltrate composed by lymphocytes and eosinophils, blood vessels with endothelial cells that can be protruding and with abundant cytoplasm, and fibroplasias; have plasma cells in the inflammatory infiltrate; and spare the epithelial and non-epithelial structures in adnexal structures (Chart 1).

Despite these characteristics in common, ALHE and KD can be easily differentiated from each other (Chart 2). At low magnification, ALHE is characterized by dilated blood vessels which sometimes have bizarre and irregular shapes, in addition to enlarged and protruding endothelial cells with abundant cytoplasm. These vessels are frequently surrounded by a ring of fibroplasia containing mucin. In contrast, KD is histopathologically characterized as a small enlargement due to nodular and diffuse inflammatory infiltrate throughout the dermis and containing lymphoid follicles associated with fibroplasias, which replaces a great deal of the subcutaneous tissue.^{13,21}

At larger magnifications, ALHE is characterized by enlarged and sometimes polygonal endothelial cells with prominent vacuoles in the cytoplasm. These vacuoles are not present in KD. Although eosinophils are present in both diseases, they may be in a small number or practically absent in ALHE, but they are always abundant in KD. Lastly, while the lymphoid follicles are absolutely necessary for the diagnosis of KD, they are present in less than 10% of cases of ALHE.¹³

CHART 2: Differential histopathological diagnosis between ALHE and KK

Angiolymphoid hyperplasia with subcutaneous eosinophilia	Kimura Disease
◆ It does not look like lymphoid tissue in low magnification	Similar to lymphoid tissue in low magnification
◆ Predominantly blood vessel disorder	Predominantly lymphoid follicle disorder
◆ Dilated blood vessels, some of them with bizarre and irregular shape in the dermis and/or subcutaneous tissue	Absence of irregular and dilated blood vessels
◆ Few or none lymphoid follicle	Numerous lymphoid follicle
◆ Presence of smooth muscles in blood vessel wall	Absence of smooth muscles in blood vessel wall
◆ Abundant mucin in blood vessel walls	Absent mucin in blood vessel walls
◆ Blood vessels with enlarged and protuberant endothelial cells, some of the of polygonal shape and with abundant cytoplasm	Non-protuberant endothelial cells in vascular lumen
◆ Presence of one or more vacuoles in the cytoplasm of abnormal endothelial cells	Absence of vacuoles in endothelial cell cytoplasm
◆ The number of eosinophils ranges from none to many	There are numerous eosinophils
◆ Subcutaneous tissue is not replaced by fibrosis	Subcutaneous tissue is not highly replaced by fibrosis
◆ It does not extend to muscle fascia	It extends to muscle fascia and sometimes to skeletal muscle

Clinically, there are also important differences which enable differentiating KD from ALHE, particularly the larger diameter of lesions, the longer time of evolution and the erythematous or purpuric color that is typical of ALHE, thus reflecting the vascular nature of the process.^{4,13}

CONCLUSION

ALHE is considered a vascular malformation resulting from an arteriovenous shunt. The process is predominantly vascular and other changes such as lymphoid follicles and eosinophils seem to be secondary.

In contrast, KD seems to have an immunological basis reflecting the numerous lymphoid follicles and eosinophils. The idea that is still present in some works considering that ALHE and KD are part of the same disease does not have a clinical, pathological or biological support. Histopathologically, the two conditions can be distinguished at first with a low microscopic magnification and other characteristics detected with higher magnification are useful to confirm diagnosis and enable allow the differentiation. □

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