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KIMURA'S DISEASE AND ANGIOLYMPHOID HYPERPLASIA WITH EOSINOPHILIA: A COMPARATIVE STUDY

DERMATOLOGY

KEYWORDS: Kimura's disease, angiolymphoid hyperplasia with eosinophilia, epitheloid hemangioma

Dr KaranInder Singh Mehta	Associate Professor, Department of Dermatology, Venereology & Leprosy, Dr Rajendra Prasad Govt Medical College, Tanda, Kangra, Himachal Pradesh-176001
Dr Pushpinder Singh Chauhan	Assistant Professor, Department of Dermatology, Venereology & Leprosy, Dr Rajendra Prasad Govt Medical College, Tanda, Kangra(HP)
Dr Vikram Mahajan	Professor and Head, Department of Dermatology, Venereology & Leprosy, Dr Rajendra Prasad Govt Medical College, Tanda, Kangra(HP)
Dr Harjit Kaur	Medical officer, Department of Pathology, Dr Rajendra Prasad Govt Medical College, Tanda, Kangra(HP)

ABSTRACT

Much confusion exists in literature regarding the relationship between Kimura's disease and angiolymphoid hyperplasia with eosinophilia (ALHE). They were initially thought to represent the same disease spectrum, but it has now been widely accepted that they are unrelated and represent different entities. The former represents a lymphoid hyperplasia and the latter a benign vascular tumor. Recognition of the clinical characteristics and histological features of Kimura's disease and ALHE is very important in making this distinction. We evaluated the clinical and histopathologic features of ALHE and Kimura's disease in our patients and also reviewed the differences between ALHE and Kimura's disease to emphasize that they are two distinctive entities.

INTRODUCTION

Kimura's disease is a chronic inflammatory disease involving the dermis and subcutaneous tissue characterized by one or multiple painless nodules. It affects the subcutaneous tissues, major salivary glands, and lymph nodes, chiefly in the head and neck region. It is often accompanied by peripheral blood eosinophilia and elevated serum IgE. The pathogenesis of Kimura's disease remains unknown, although allergic reaction, trauma, autoimmune process and infective causes have been implicated. Angiolymphoid hyperplasia with eosinophilia is a rare benign vasoproliferative disease of an unknown cause which occurs in older patients and it usually presents as superficial, light pink to red-brown papules and nodules that are frequently found in the dermis and superficial fascia of the head and neck, and particularly in the periauricular region. Western authors believed Kimura's disease and ALHE to be the same disease because they share similar clinico-histopathological features: predilection for head and neck, lymphoid infiltration with eosinophils, vascular proliferation and absence of adnexal structure involvement. However, there are also many differences between the two conditions that suggest they are distinct entities. We present two cases, each representing either of the two conditions, similarities and differences between them in terms of clinical and histopathological features are discussed and the literature is reviewed.

CASE 1:-

A 15-year-old-male child presented with multiple, progressively increasing skin-colored swellings over scalp and post-auricular region for the last 5 years. The lesions were at times painful and mildly itchy. Dermatological examination revealed multiple non tender, freely mobile subcutaneous masses varying in sizes from 3 to 5cm in the occipital scalp and post-auricular region. The overlying skin color was normal (Figure1). There was significant right cervical lymphadenopathy of size 2x2cm non-tender and not attached to the underlying structures. There was apparently no involvement of salivary glands. Systemic examination revealed no abnormality. Urine analysis, blood examination including complete blood count, erythrocyte sedimentation rate and blood chemistry were normal except for eosinophilia of 15%. . Surgical excision of the lesions was done and biopsy was sent for histopathological examination keeping ALHA and Kimura's disease as differentials. Microscopy revealed normal epidermis, multiple lymphoid follicles in the deep dermis and subcutaneous tissue. There was diffuse and dense

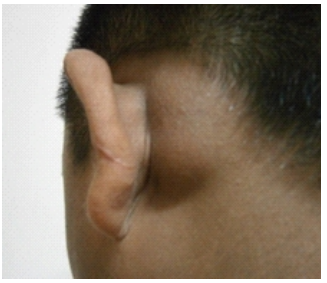

Figure 1:Subcutaneous nodules with overlying normal skin over left post-auricular region

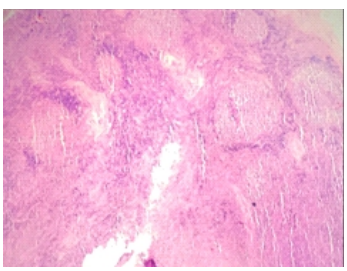

Figure 2: Multiple lymphoid follicles with germinal centers, the inflammatory cells are predominantly eosinophils and lymphocytes.(H&E, x10)

infiltration of lymphocytes and eosinophils. Marked vascular proliferation consisting of small to medium sized blood vessels lined by plump endothelial cells

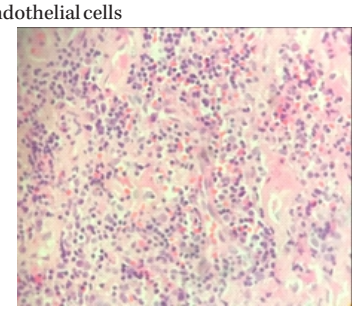

Figure 3: Hyalinization of blood vessels and interstitial fibrosis (H&E, x40)

was seen. Variable sclerosis and hyalinization around the blood vessels was also noted (Figure 2&3). There was no evidence of cellular

atypia or vasculitis. A diagnosis of Kimura's disease was made based upon the clinical and histological findings. There was no recurrence after a follow up period of one year.

CASE 2:-

A 49-year-old male presented to our outpatient clinic with a 1 year history of multiple dome-shaped dull red nodular lesions over right side of scalp and pre-auricular area. The lesions had developed spontaneously. The lesions were increasing in size and had a tendency to bleed after minor trauma. There were no palpable regional or systemic lymph nodes. Systemic examination and routine laboratory investigations including including a complete blood cell count, erythrocyte sedimentation rate, urine analysis and blood chemistry, demonstrated no abnormalities. The total eosinophil count was within normal range. Skin examination revealed multiple,

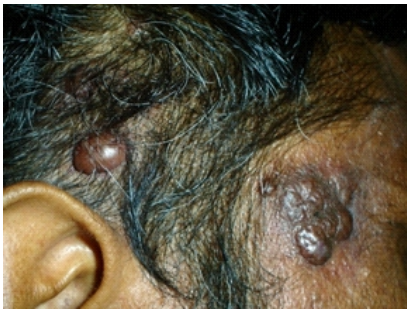

Figure 4: Dull red soft nodules and plaque over parieto-temporal region

dull erythematous, dome shaped nodules and plaques of sizes 1-3cm over the right parieto-temporal region. The lesions were discrete and most of them had a smooth hairless surface. The lesions were firm in consistency; mobile, non-tender and non-compressible (Figure 4). Histopathology from the lesion showed features of mild acanthosis, proliferation of blood vessels lined with epitheloid endothelial cells and these cells projected into the lumen. Few endothelial cells showed cytoplasmic vacuoles, prominent perivascular lymphocytic infiltrate along with eosinophils (Figure 5&6). No mitosis or atypical cells were observed. Thus on the basis of history, clinical findings, and histopathological evaluation, a final diagnosis of

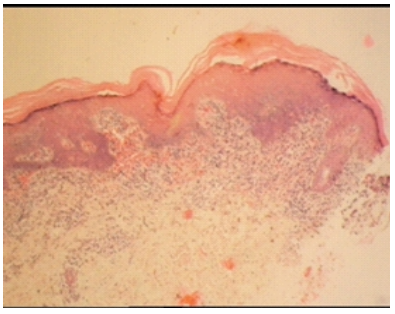

Figure 5: Histopathology showing mild acanthosis with proliferation of angioid tissue and dermal infiltrate (H&E, x10)

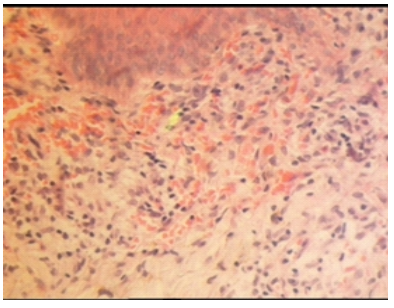

Figure 6: Vascular hyperplasia with lymphocytic and eosinophilic dermal infiltrate & epitheloid appearance of endothelial cells (H&E,x40)

"Angiolymphoid hyperplasia with eosinophilia" was made. Intralesional triamcinolone acetonide (40mg/ml) was infiltrated in the lesions once a month. At 2-month of follow up all the lesions had regressed but the patient did not turn up further.

DISCUSSION

Kimura's disease was initially described in 1937 by Kimm and Szeto[1] as an "eosinophilic hyperplastic lymphogranuloma" .Subsequently, in 1948, this condition was more widely known as Kimura's disease after Kimura et al[2] reported similar cases in Japan. In the West, a disease entity called angiolymphoid hyperplasia with eosinophilia was described in 1969 by Wells and Whimster[3], who studied nine patients with persistent subcutaneous nodules in the head and neck and they were the first to link Kimura's disease to ALHE. They felt that the two conditions represented two ends of the same disease spectrum i.e., an initial marked vessel proliferation and later a lymphocyte proliferation and thus considering Kimura's disease as the late stage of ALHE. Eventually, these two conditions have been regarded by many authors either as the same disease or as different stages of the same disease[4,5,6,7]. However, Rosai et al[8] first recognized that Kimura's disease and ALHE differed in terms of their histopathological features and they suggested that they are distinct entities. Subsequently, many authors highlighted clinical and histopathological differences and thus regarded the two conditions as two separate disease entities[9-15]. In some recent case reports, authors[16-18] still believes the concept that ALHE and Kimura's disease form a spectrum in one disease.

Kimura's disease is a chronic inflammatory disease involving the dermis and subcutaneous tissue characterized by single or multiple asymptomatic nodules or masses involving the subcutaneous tissue or salivary glands. This is mostly accompanied by regional lymphadenopathy with or without involvement of salivary glands, peripheral blood eosinophilia and sometimes elevated serum IgE levels. It mostly occurs in young, oriental males. 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 pathogenesis of Kimura's disease remains unknown. Several etiological factors including allergic, trauma, infective, neoplastic and autoimmune process have been implicated. In addition to ALHE, the differential diagnoses for Kimura's disease include, lymphoma, nodal metastasis, salivary gland tumor and Mikulicz's disease. Treatment may range from observation and follow-up of mild and asymptomatic cases to conservative surgical excision. Other therapeutic options which have been tried with variable success include corticosteroids (both intralesional and oral), oral retinoids, non-steroidal anti-inflammatory drugs, cyclosporine, pentoxiphylline and radiotherapy[13,16].

Angiolymphoid hyperplasia with eosinophilia or also known as epithelioid hemangioma is an uncommon cutaneous vascular disorder characterized by solitary or multiple, superficial or subcutaneous, red to brown firm papules and nodules. Approximately 80% of patients present with isolated lesions, while the remaining patients usually demonstrate grouped papules or nodules in a single region. The lesions are often associated with pruritus, pain, and spontaneous bleeding, and may coalesce into confluent plaques. ALHE can occur in all races, but is reported more frequently in Asians. Women are more commonly affected than men, and the disease typically arises in early to mid-adult life. The head and neck are characteristically affected, but the disease is also known to affect the trunk and extremities especially the arms and hands. Serum hypereosinophilia is inconstant and is not required to make the diagnosis. The etiology is currently unclear. Various hypotheses have been put forth, including a reactive process, a neoplastic process, or is thought to be associated with infection and arteriovenous malformation. Histopathologically, there is proliferation of large endothelial cells lining vascular spaces, and lymphocytic and eosinophilic inflammatory infiltrations in the dermis. Plump endothelial cells show scalloped borders, lobulated nuclei, and mitoses. The "epitheloid" endothelial cells which protrude into the

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vascular lumen have "cobblestone" appearance. Vacuolated endothelial cells can also be seen. The main differential diagnosis is Kimura disease but other disorders such as pyogenic granuloma, Kaposi sarcoma, lymphocytoma cutis or sarcoidosis may imitate the clinical picture of ALHE[16,19,20]. Treatment is often challenging for ALHE, as spontaneous regression is rare. Complete surgical excision is the treatment of choice and if completely excised, it rarely reoccurs. Other alternative treatments which have been reported with variable levels of success are:-laser therapy, intralesional corticosteroids, cryotherapy, imiquimod, tacrolimus, isotretinoin, radiotherapy, interferon alfa 2a, and methotrexate[21].

The relationship between ALHE and Kimura's disease has been a subject of much controversy in the literature. ALHE and Kimura's disease, which share many common clinical and histological features, must be distinguished because they are unrelated and represent distinct entities. These two conditions present as nodules and have similar predilection, preferably on the head and cervical region especially in the peri-auricular area. Histologically, they also show some overlapping features, such as involvement of dermis and subcutis, lymphoid infiltration with eosinophils and vascular proliferation, proliferation of endothelial cells and the absence of adnexal structure involvement. The main histological features of ALHE are the vascular component, characterized by proliferation and swelling of the endothelial cells, whereas in Kimura's disease, prominent cellular areas with lymphocytes forming follicles are observed and are surrounded by an inflammatory infiltrate with eosinophilia and fibrosis. ALHE may be seen in any race and is characterised macroscopically by erythematous or plum colored papules or nodules, without lymphadenopathy and may be accompanied by a mild peripheral eosinophilia. Kimura's disease, on the other hand, is mostly observed in young adults of asian descent and occurs as deep nodules with lymphadenopathy, peripheral eosinophilia and salivary gland involvement. The comparative epidemiological, clinical and histopathological features of the two diseases are summarized in Table 1& Table 2[13,15,16,18,22].

TABLE 1:

Clinical features	Kimura's disease	Angiolymphoid hyperplasia with eosinophilia
Age	2nd-3rd decade	3rd-5th decade
Sex	Male predominance (85%)	Female predominance (70%)
Ethnicity	Asians commonly	All races
Presentation	Subcutaneous nodules	Dermal papules or nodules
Size	2-10cm	0.2-6cm
Site	Usually head and neck	Usually head and neck
Depth	Deep	Superficial
Overlying skin	Normal	Erythematous
Duration	Longer	Shorter
Pruritis	No	May be severe
Lymphadenopathy	Common	Uncommon
Eosinophilia	Invariably present	20% of cases
Serum IgE	Usually increased	Usually normal
Renal involvement	Common	Rare
Salivary gland involvement	Common	Rare
Recurrence	15-40%	30%
Other features	Raynaud'sphenomenon,asthma,temporal arteritis,ulcerative colitis	Rare

TABLE 2:

Histopathological features	Kimura's disease	Angiolymphoid hyperplasia with eosinophilia
Depth	Subcutaneous	Dermis, subcutaneous
Endothelium	Flat to low cuboidal	Cuboidal to dome-shaped, epitheloid or histiocytoid
Vacuoles in endothelial cytoplasm	Absent	Present
Mucin in blood vessel walls	Absent	Abundant
Smooth muscles in blood vessel walls	Absent	Present
Neoangiogenesis	Less prominent	Prominent
Inflammation	Abundant lymphocytes with few plasma cells	Sparse to heavy infiltrate of lymphocytes
Infiltrate	Nodular	More diffuse
Lymphoid follicles	Common	Rare
Germinal center	Always	Uncommon
Eosinophils	Abundant	Sparse to abundant
Eosinophilic abscesses	Present	Rare
Fibrosis	Usually marked	Mild
Edema	Often marked	Minimal
Immunohistochemistry	IgE reticular staining	CD34,CD31, F VIII positive in vascular component

Our patients had classical clinical and histopathological features of Kimura's disease (case 1) and Angiolymphoid hyperpalsia with eosinophilia (case 2). Common features were head and neck involvement in both patients and histologically presence of lymphocytic and eosinophilic infiltration along with vascular proliferation. As in typical ALHE, our patient (case 2) histologically showed plump epitheloid endothelial cells protruding into the lumen and vacuolated endothelial cells. There were no clinical manifestations such as palpable lymph nodes, laboratory abnormalities, and peripheral eosinophilia. Our second patient had characteristic subcutaneous nodules; lymphadenopathy, peripheral eosinophilia and microscopically there were well formed lymphoid follicles, thus confirming the diagnosis of Kimura's disease. In conclusion, although ALHE and Kimura's disease may share some similarities, these are two distinct disease entities and they can be differentiated by their characteristic clinical and histopathological features.

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