Oriental Kimura's Disease and its Relation to Angiolymphoid Hyperplasia with Eosinophilia (ALHE)

Tie-Jun LI[1] and Motoo KITANO[1]

Abstract

Kimura's disease, a chronic inflammatory condition of unknown cause, is endemic in Orientals. The clinical features of this disease include young and middle aged male predominance, predilection for the head and neck regions and a long duration. The disease may present as single or multiple lesions, mainly involving subcutaneous tissues, major salivary glands and lymph nodes in isolation or in combination. Histopathologically, the lesion is characterized by hyperplasia of lymphoid tissue with well-developed lymphoid follicles, marked infiltration of eosinophils, proliferation of thin-walled capillary venules and varying degrees of fibrosis. This paper reviewed the current understanding of this disease and discussed its distinctions to angiolymphoid hyperplasia with eosinophilia (ALHE).

Key words: Kimura's disease, Angiolymphoid hyperplasia with eosinophilia, Eosinophilic lymphogranuloma, Lymphadenopathy, Salivary gland, Eosinophils, Eosinophilia

Introduction

Kimura's disease, a chronic inflammatory condition, often produces subcutaneous tumor-like nodules with a predilection for the head and neck regions. The condition is apparently more prevalent among Orientals (Kimura *et al*., 1948; Kawada *et al*., 1966; Jin & Shi, 1937; Jin *et al*., 1957; Chang & Chen, 1962; Li, 1988) and often associated with major salivary glands involvement and regional lymphadenopathy (Leong *et al*., 1971; Tham *et al*., 1981; Kung *et al*., 1984; Urabe *et al*., 1987; Kuo *et al*., 1988; Chan *et al*., 1989; Hui *et al*., 1989). The majority of the cases had been reported in China and Japan. Similar cases were also reported from Hong Kong (Tham *et al*., 1981; Kung *et al*., 1984; Chan *et al*., 1989; Hui *et al*., 1989), Taiwan (Kuo *et al*., 1988), Malaysia (Ng *et al*., 1991) and Singapore (Leong *et al*., 1971). Angiolymphoid hyperplasia with eosinophilia (ALHE), however, was first reported in English literature in 1969 as a lesion similar to Kimura's disease (Wells & Whimster, 1969). Many authors since then have regarded these two conditions either as the same entity or as different stages of one disease (Mehregan & Shapiro, 1971; Reed & Terazakis, 1972; Castro & Winkelmann, 1974; Buchner *et al*., 1980;

1) Department of Oral Pathology, Kagoshima University Dental School, Kagoshima 890, Japan.

Olsen & Helwig, 1985; Iguchi *et al*., 1986). ALHE superficially resembles Kimura's disease because of the similar predilection for the head and neck regions, the frequent recurrence, and the pathologic findings of a vascular lesion accompanied by infiltration of lymphoid cells and eosinophils. However, it has been recently suggested that Kimura's disease can be distinguished from ALHE by clinical, histological and immunohistochemical criteria and constitutes its own clinical identity (Rosai *et al*., 1979; Kung *et al*., 1984; Urabe *et al*., 1987; Googe *et al*., 1987; Chan *et al*., 1989).

In the light of our recent report of 54 cases of Kimura's disease occurred in mainland Chinese patients (Li *et al*., 1996), we intended to have a comprehensive review of the clinical and pathological background of this Asian disease and to discuss its distinctions to the mainly Western-reported ALHE.

Clinical features of Kimura's disease

Kimura's disease usually presents as subcutaneous masses, lymph node enlargement and /or swelling of the parotid or submandibular glands, with predilection of head and neck regions in young and middle aged men (Chan *et al*., 1989; Li *et al*., 1996). A previous review (Kawada, 1976) of 194 cases in Japanese literature revealed a male and female ratio of 7:1. A little over one-third of the cases arose in the second decade. The lesion was most often solitary but may be multiple. Of the 194 cases, 163 had facial involvement. Other sites of involvement were the neck (43 cases), axilla (23 cases), groin (35 cases), popliteal region (40 cases) and forearm (2 cases). Similarly, in a review of 158 cases reported in Chinese literature since 1937 (Li, 1988), 149 were male and 9 were female. The age of 94 recorded cases ranged from 2 to 59 years with a peak group in the third decade (34 cases). The disease also showed a predilection for the head and neck regions (86.5%) with occasional occurrences in forearm and inguinal areas. In our recent reported series (Li *et al*., 1996), the age varied from 1–66 years but peaked at the third and fourth decades (Fig. 1). There was a male predominance with a male to female ratio of 3.5:1. Multiple lesions were detected in 23 cases, among those three patients showed bilateral involvement of parotid glands and one presented with bilateral submandibular glands involvement and inguinal lymphadnopathy. Kimura's disease usually presents as a painless subcutaneous swelling. Skin itchiness, pigmentation only occur in some patients with most cases showing no significant changes of the overlying skin (Li *et al*., 1996). Deeply seated lesions usually show no distinct borders, but more superficial lesion or enlarged lymph nodes are well-demarcated. The course of the disease is relatively long and benign, but recurrences are common after surgical excision of the lesion. Eosinophilia is almost always present, although there is no systemic visceral involvement. There have been no reported fatalities. In about 12% of patients, there may be associated with renal disease, usually presenting as

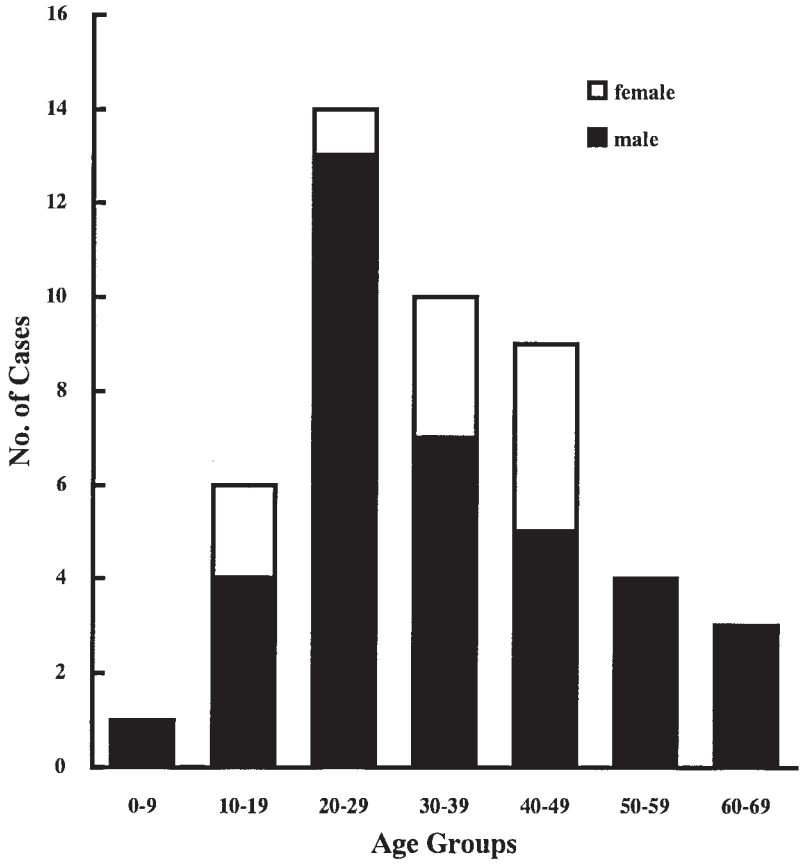


Fig. 1 Age and sex distribution of 47 patients with Kimura's disease (data taken from reference Li *et al*, 1996).

proteinuria and occuring almost exclusively in male patients (Yamada *et al*., 1982).

Multiple tissue involvement by Kimura's disease

The disease involves subcutanous tissues, major salivary glands, and lymph nodes in isolation or in combination, chiefly in the head and neck region. Table 1 summarizes the detailed tissue involvement by Kimura's disease in our recently reported series (Li *et al*., 1996). In the soft tissue, the subcutis is the predominant site of involvement, but the contiguous lower and mid dermis, fascia and skeletal muscle could also be involved. Most lesions have infiltrative borders. However, rare ones are circumscribed, simulating lymph nodes on low magnification but differing in the absence of sinusoids (Chan *et al*., 1989). Involvement of the salivary glands by the disease has been frequently reported (Miyamoto

Table 1. Clinical features of Kimura's disease[1]

Sex	
42 male, 12 female	
Age of diagnosis (47 cases recorded)	
1–66 years (mean 33.1 years, peak age at the third decade)	
Tissue involvement[2]	
Subcutaneous tissue	29 cases
Lymph node	17 cases
Parotid gland	18 cases
Submandibular gland	3 cases
Lacrimal gland	1 case
Number of lesions	
Single	31 cases
Multiple	23 cases
Location of lesions	
Head and neck (major salivary glands, face, neck, perauricular and eyelid)	54 cases
Inguinal[3]	3 cases
Axilla[3]	3 cases
Forearm[3]	1 case
Duration (51 cases recorded)	
One month–13 years (mean 3 years)	
< One year	15 cases
1–< 5 years	24 cases
5–10 years	7 cases
> 10 years	5 cases
Size (43 cases recorded)	
< 2 cm in diameter	17 cases
2–5 cm	15 cases
> 5 cm	11 caese

[1] data adopted from reference (Li et al, 1996)
[2] tissue involvement either in isolation or in combination
[3] from cases with multiple lesions

& Tani, 1977; Urabe *et al*., 1987; Li, 1988; Kuo *et al*., 1988; Chan *et al*., 1989; Li *et al*., 1996). In our 54 cases, involvement of salivary glands occurred in 21 patients (39%) and one patient also showed involvement of lacrimal gland (Li *et al*., 1996). Clinically and pathologically, the affected glands resemble benign lymphoepithelial lesion of salivary glands to a certain extent but the latter lesion contains myoepithelial islands and eosinophilic infiltration is absent. Bilateral salivary glands swellings, which had been occasionally reported (Tham *et al*., 1981; Iguchi *et al*., 1986; Li, 1988), were found in 4 cases of our present series (Li *et al*., 1996). Lymphadnopathy in Kimura's disease has been reported to range from 42% to 100% (Chang & Chen, 1962; Kung *et al*., 1984; Kuo *et al*., 1988). Our series revealed a slightly lower incidence of 31.5% (Li *et al*., 1996).

However, it is worth mentioning that there may be cases with early lymphadenopathy which are free from clinically detectable lymph nodes (Kung *et al*., 1984). Histopathological confirmation of that can be difficult because in most cases only the clinically positive nodes are usually available for examination. The frequent involvement of salivary glands and regional lymph nodes in patients with Kimura's disease quite often leads to an incorrect clinical impression, such as salivary gland tumors, Mikulicz's disease and even lymphomas.

Histological features of Kimura's disease

The basic histologic features are similar in the different tissues and predominantly those of hyperplastic lymphoid tissue containing well-developed lymphoid follicles, infiltration of eosinophils, vascular (capillary) proliferation and varying degrees of fibrosis (Kimura *et al*., 1948; Kawada *et al*., 1966; Jin & Shi, 1937; Jin *et al*., 1957; Chang & Chen, 1962; Li, 1988; Leong *et al*., 1971; Miyamoto & Tani, 1977; Tham *et al*., 1981; Kung *et al*., 1984; Urabe *et al*., 1987; Kuo *et al*., 1988; Chan *et al*., 1989; Hui *et al*., 1989; Li *et al*., 1996).

Lymphoid cells. There is a moderate to massive lymphoid infiltration associated with few to numerous lymphoid follicles. The lymphoid follicles are round or oval, and possessed well delineated mantles and prominent germinal centres (Fig. 2a). An interstitial homogeneous eosinophilic material between the germinal centre cells is often present (Fig. 2b). When infiltrated by eosinophils, some germinal centres appear to undergo progressive folliculolysis (Fig. 2c), and some show features of the so called "vascularization of the germinal centres", in which capillary venules grew into the germinal centres (Fig. 2d). Between the follicles, there are many small lymphocytes, plasma cells and eosinophils, some immunoblasts, histiocytes and mast cells.

Eosinophils. Moderate to massive infiltration of eosinophils is a consistent feature in Kimura's disease, usually showing a diffused pattern in the interfollicular areas or becoming denser in perivascular areas. Eosinophilic microabscesses are occasionally seen (Fig. 3). There is also a tendency for eosinophils to infiltrate the germinal centres resulting in necrosis of the centre structures. This phenomenon has been termed as eosinophilic folliculolysis (Fig. 2c; Kuo *et al*., 1988).

Blood vessels. Various degrees of vascular proliferative changes are frequently observed in the majority of the lesions. However, the blood vessels are usually thin-walled, high endothelial venules. The venules have slit-like lumina, and are lined by either flattened or low cuboidal endothelium with pale staining oval nuclei. The cytoplasm is scanty and light-staining, and is never vacuolated (Fig. 4a). Furthermore, perivenular sclerosis in the form of concentric rings of collagen is frequently seen, with the affected venules showing endothelial atrophy (Fig. 4b).

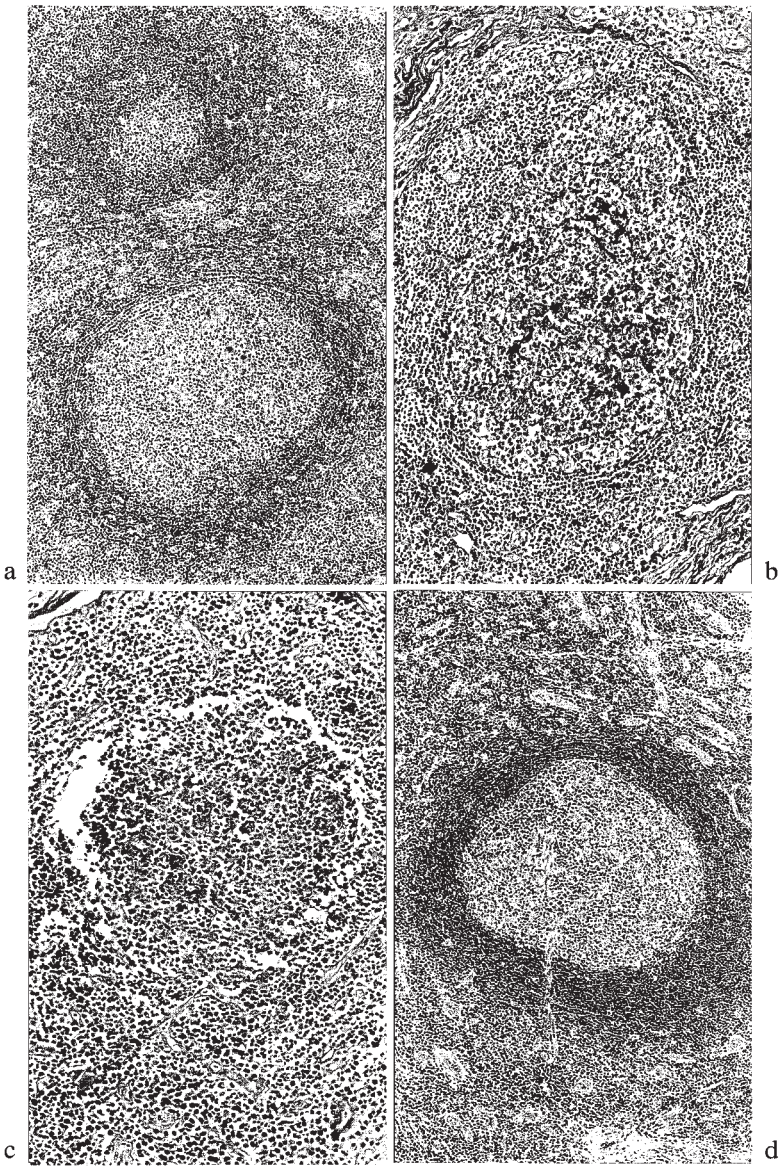


Fig. 2 Various appearances of lymphoid hyperplasia in Kimura's disease. The lymphoid tissue usually contains numerous lymphoid follicles with well-formed germinal centers (a, Hematoxylin-eosin stain; x40); In some cases, the germinal centers may contain an interstitial homogenous eosinophilic material between the germinal center cells (b, Hematoxylin-eosin stain; x50); Some may undergo folliculolysis (c, Hematoxylin-eosin stain; x60) or 'vascularization'. The latter shows capillary venules growing into the germinal centre (d, Hematoxylin-eosin stain; x40).

Fibrous tissue. Fibrosis is always present, most prominently in subcutaneous and salivary gland lesions. The fibrous tissue is poorly cellular, and is either homogeneous or in the form

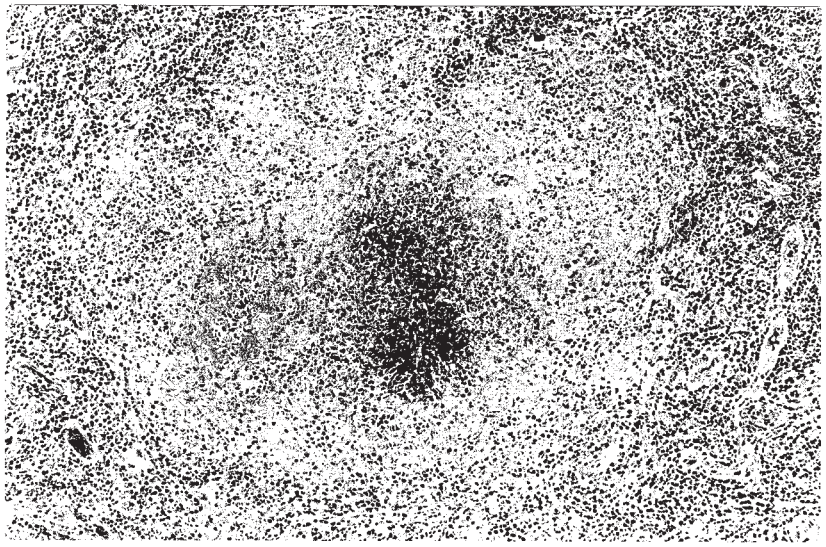
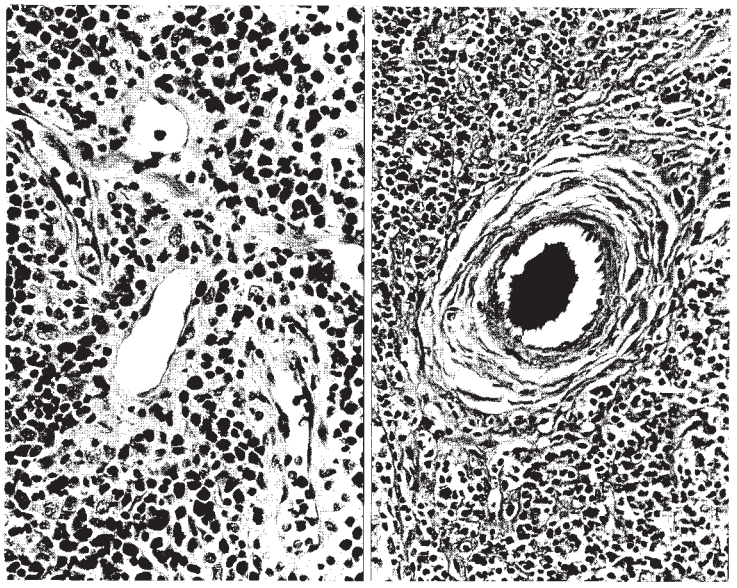


Fig. 3 Massive infiltration of eosinophils in the lesion leads to formation of a eosinophilic microabscess (Hematoxylin-eosin stain; x60).



a b

Fig. 4 a, Proliferated vessels are thin-walled capillaries lined by either flattened or low cuboidal endothelium. Many eosinophils and plasma cells are present (Hematoxylin-eosin stain; x120). b, A blood vessel shows concentric fibrosis accompanied with atrophy of endothelial cells (Hematoxylin-eosin stain; 100).

of thick keloid-like bundles with scattered infiltration of plasma cells and eosinophils (Fig. 5). There are frequent fibrous septa partitioning the lesion into irregular nodules. Sclerotic zones devoid of inflammatory cells are prominent in lesions of long duration. It appears that

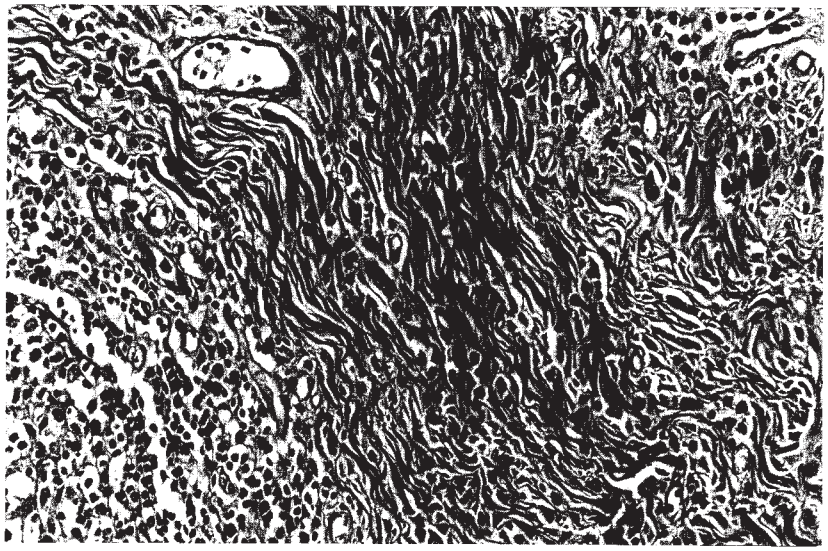


Fig. 5 In advanced lesions, the stroma shows dense collagenous fibrosis with scattered infiltration of plasma cells and eosinophils (Hematoxylin-eosin stain; x100).

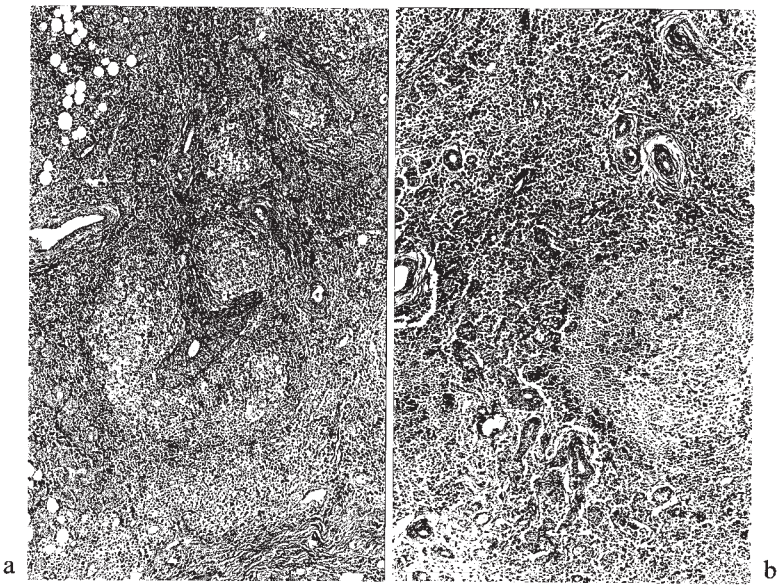


Fig. 6 The involved parotid gland (a) and submadibular gland (b) show marked infiltration of lymphocytes, plasma cells and eosinophils which resulted in atrophy and loss of acini. The lymphoid follicles often wrap around a small duct (a) and concentric fibrosis of the residue ducts (b) is commonly seen (Hematoxylin-eosin stain; x40).

the earliest form of sclerosis appeared to begin around the venules, either in the form of a thin fibrous sheath or concentric rings of collagen (Fig. 4b). Further sclerosis results in

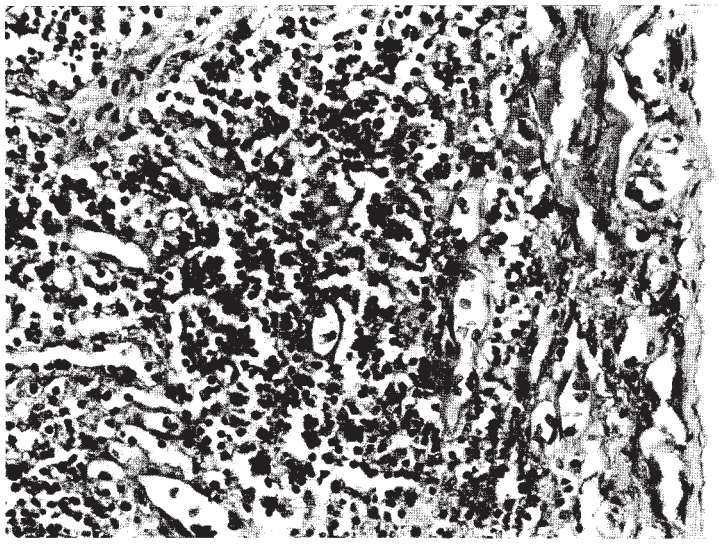


Fig. 7 In the involved lymph nodes, infiltration of eosinophils is mainly present in interfollicular areas and marginal sinuses (Hematoxylin-eosin stain; x100).

complete obliteration of the affected venules.

Salivary gland. The paroid or submandibular gland is often involved in a patchy fashion. Related lesions show irregular areas of inflammation and varying degrees of glandular destruction. In severe cases, the gland lobules are replaced by fibrous tissue and densely infiltrated by lymphocytes, plasma cells, mast cells and eosinophils, resulting in atrophy and loss of acini. Concentric periductal fibrosis is common (Fig. 6a). The lymphoid follicles often appears to wrap around of the residule ducts (Fig. 6b). In less affected salivary lobules, only ductal dilatation and periductal eosinophilic and lymphocytic infiltration are seen. The main glandular structures, i.e. acini and ducts, are relatively undamaged.

Lymph node. The architecture of the involved lymph nodes is usually preserved (Fig. 7a). The enlarged lymph nodes show follicular hyperplasia with large germinal centres and focal eosinophilic infiltration of interfollicular areas and subcapsular sinuses (Fig. 7b). Similar to subcutaneous lesions, homogeneous material between the germinal centre cells is often seen and folliculolysis is often associated with apparent eosinophilic infiltration. Although not pathognomonic, these nodal changes should alert the pathologist to the possibility of Kimura's disease, especially in cases where only the lymph node biopsy specimen is available.

Etiology of Kimura's disease

The pathogenesis of Kimura's disease remains obscure. In view of tissue and blood eosinophilia, allergy and parasitic infestation were suspected but not proved. Tests for *Paragonimus westermani, Dibothoriocephalus latus, Schistosoma japonicum, Gnathostoma spinigerum, Wuchereria bancrofti*, and for ascariasis and ancylostomiasis are all negative (Tham *et al*., 1981). Evidence of an insect bite is also not identified (Kawada, 1976). The deposits of IgE in the germinal centres of Kimura's disease, the elevated serum IgE, eosinophilia and the appearance of mast cells suggest that the disease is atopic in nature (Googe *et al*., 1987; Kuo *et al*., 1988). It has been proposed that Kimura's disease is probably an immunologically mediated disorder (Iguchi *et al*., 1986; Googe *et al*., 1987; Kuo *et al*., 1988). Occasional reports of its possible association with systemic nephrotic syndrome (Yamada *et al*., 1982; Kuo *et al*., 1988; Matsuda *et al*., 1992) lend further support for the above hypothesis. On the other hand, the prevalence of Kimura's disease in Asian population (Li *et al*., 1996) and its rarity in the West suggest that racial and/or cultural factors may also contribute to the etiology of this disease.

Distinctions between Kimura's disease and ALHE

In literature, there is much confusion between Kimura's disease and angiolymphoid hyperplasia with eosinophilia (ALHE). The detailed comparisons of the two conditions are summarized in Table 2.

Since its first description (Wells & Whimster, 1969), ALHE has been widely stated as the same entity to Kimura's disease, probably representing the different stages of the disease (Mehregan & Shapiro, 1971; Reed & Terazakis, 1972; Castro & Winkelmann, 1974; Buchner *et al*., 1980; Olsen & Helwig, 1985). Clinically, young people are affected by both lesions and other similarities include predilection for the head and neck regions, a relatively long course and good prognosis. Furthermore, common histopathological features such as lymphoid hyperplasia, eosinophilic infiltrates and vascular proliferation suggests these two diseases are identical. However, several papers have recently argued that the clinicopathologic differences are more than sufficient to justify their separation into two distinct entities (Rosai *et al*., 1979; Kung *et al*., 1984; Urabe *et al*., 1987; Googe *et al*., 1987; Kuo *et al*., 1988; Chan *et al*., 1989; Li *et al*., 1996). There is a male predominance in Kimura's disease, while patients with ALHE show roughly equal sex distribution (Olsen & Helwig, 1985; Iguchi *et al*., 1986); The lesions of Kimura's disease are usually large (about 2–5 cm in diameter) and deeply seated without a distinctive border. Initially, there is little visible change in the overlying skin. However, the eruptions of ALHE are usually small (about 1 cm in diameter) and superficially located. They form elevated papules or

Table 2. Comparison of clinicopathological changes between Kimura's disease and ALHE

	Kimura's disease	ALHE
Clinical features		
Sex	Male predominance.	Overall no sex predilection.
Age	1–80 years (reported mean range 27–40 years).	10.5–80 years (mean 35 years).
Race	Prevalence in Orientals.	Occurs in all races (more frequent in the West)
Presentation	Discrete nodules or localized swelling. Solitary or multiple (bilateral or in multiple regions). Size 1–20 cm, average 3 cm. Insidious onset, often of long duration (mean range 4–10 years).	Nodules or erythematous papules which may ulcerate or bleed. Solitary lesion or multiple lesions clustered in the same region. Size 0.2–1.5 cm, average 1 cm. Of shorter duration (mean 13 months).
Sites	Subcutaneous and deep soft tissue, major salivary glands, lymph node and sometimes oral cavity. Superficial dermal and visceral involvement do not occur. Usually in head and neck region, but can involve axilla, groin, limbs and trunk.	Skin, subcutaneous tissue, blood vessel, and almost any tissue, e.g. muscle, bone, lymph node, oral cavity, orbit and penis. Usually in head and neck region.
Regional lymph node enlargement	Common (over 50%). The lymph nodes often show histological evidence of involvement.	Uncommon, if enlarged, show reactive changes only.
Peripheral blood eosinophilia	Present in majority of cases.	Occurs in about 20% of cases.
Course	The course is progressive, often becoming stationary after years. Recurrence is common (15–40%), but there is no fatality. Rarely, there may be association with a nephrotic syndrome.	Benign lesion which recurs in about 30% of cases. However, recurrence is rare if excision is complete.
Histological features		
Outline	Usually non-circumscribed.	Often circumscribed except dermal lesions.
Lymphoid component	Abundant lymphocytes and plasma cells; lymphoid follicles are always found, diffusely or patchily distributed throughout the lesion. Interstitial homogeneous eosinophilic material between the germinal center cells, vascularization and necrosis of germinal centers are common.	Sparse to heavy infiltrate of lymphocytes and plasma cells, with or without lymphoid follicles. Vascularization and necrosis of germinal centers are uncommon.
Eosinophils	Moderate to abundant; eosinophilic abscesses, some of which occur within germinal centers, are common.	Sparse to abundant; eosinophilic abscess is rare.
Blood vessels	Degree of vascular proliferation (high endothelial venules) does not exceed that seen in florid lymphoid hyperplasia. No uncanalized cords. Involvement of wall of muscular vessels and intravascular growth do not occur. Endothelial cells are flat to low cuboidal and possess oval nuclei with fine chromatin. Cytoplasm scanty and light-staining with on vacuoles. Perivenular sclerosis is common.	Florid angiomatous proliferation of capillary-sized vessels to muscular vessels. Uncanalized cords may occur. Fibromyxoid matrix commonly present. Involvement of endothelium and muscular vessels are common; sometimes lesions are entirely intravascular. Endothelial cells are cuboidal to dome-shaped, and possess nuclei with irregular folding. Cytoplasm moderate in amount and deeply eosinophilic; vacuoles can often be found.
Fibrosis	Significant at all stages, particularly prominent in long-standing lesions.	Not a prominent feature.
Nature of lesion	Primarily chronic inflammatory lesion in which there are high endothelial venules. An aberrant immune response to an unknown stimulus.	Atypical endothelial proliferation, possibly neoplastic, which is associated with a variable inflammatory component.

Note: All data summarized from the references with a '*' mark in the reference list.

nodules and bleed easily when irritated (Kuo *et al*., 1988; Chan *et al*., 1989); The frequent feature of regional lymph nodes and salivary glands involvement in Kimura's disease is less frequent in ALHE (Wells & Whimster, 1969; Mehregan & Shapiro, 1971; Reed & Terazakis, 1972; Castro & Winkelmann, 1974; Buchner *et al*., 1980; Olsen & Helwig, 1985; Iguchi *et al*., 1986; Chan *et al*., 1989). Whilst cases identical to ALHE have also been reported among Orientals (Urabe *et al*., 1987; Kuo *et al*., 1988; Chan *et al*., 1989), their occurrences appear to be less common. According to our experience, only one case identical to ALHE was encountered during the same period when 54 cases of Kimura's disease were diagnosed (Li *et al*., 1996).

The most important histopathological difference is in the blood vessel component of the two conditions. Vascular changes of Kimura's disease reveal mainly capillary proliferation and increased number of the thin-walled blood vessels, which never reach the degree of the vascular change described in ALHE. The latter contains thick-walled blood vessels with the so-called histiocytoid or epithelioid endothelial cells characterized by hypertrophied or vacuolated endothelial cells protruding into the vascular lumen or even occluding the lumen (Wells & Whimster, 1969; Mehregan & Shapiro, 1971; Reed & Terazakis, 1972; Castro & Winkelmann, 1974; Buchner *et al*., 1980; Olsen & Helwig, 1985; Iguchi *et al*., 1986). This feature has led some to classify ALHE under the name of "histiocytoid hemangioma" (Rosai *et al*., 1979; Chan *et al*., 1989), representing the benign end within a broad spectrum of epithelioid vascular tumors (Tsang & Chan, 1993). While hyperplastic lymphoid follicles with well-developed germinal centres are consistently present in Kimura's disease, infiltration of lymphocytes is more variable in ALHE lesions, sometimes, without the presence of lymphoid follicles (Tham *et al*., 1981; Kung *et al*., 1984; Chan *et al*., 1989). Frequent folliculolysis and vascularization of germinal centers in Kimura's disease are also uncommon in ALHE (Chan *et al*., 1989). Fibrosis is prominent at all stages in Kimura's disease, but is often absent or only detectable at the edge of the lesion in ALHE (Wells & Whimster, 1969; Reed & Terazakis, 1972). Based on these substantial clinicopathological differences between the two conditions, we concur with the view that Oriental Kimura's disease is different from ALHE.

Conclusion

Kimura's disease is an important category of chronic inflammatory condition in the Oriental population. Its frequent involvement of salivary glands, simultaneous multiple lymphadenopathy and occasional association with the nephrotic syndrome often pose problems in diagnosis and treatment. Furthermore, the rarity of this disease in the Western countries helps to obfuscate its relation to the mostly Western-reported angiolymphoid hyperplasia with eosinophilia (ALHE). Although the precise nature and etiology of both

conditions are still unknown, the spectrum of the clinicopathological changes suggests that Kimura's disease most likely represents an aberrant immune reaction to an unknown stimulus, whereas ALHE might be a vascular neoplastic disease in nature.

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