

## Research Article

# Kimura's Disease: A case series with literature review

B.V. Suguna and M. Hemalata\*

Department of Pathology, Kempegowda Institute of Medical Sciences (KIMS), BSK II stage, Bangalore 560070, India

### \*Correspondence Info:

M. Hemalata

Associate Professor of Pathology

Department of Pathology

Kempegowda Institute of Medical Sciences (KIMS)

BSK II stage, Bangalore 560070 India

E-mail: [hemalatajreddy@gmail.com](mailto:hemalatajreddy@gmail.com)

### Abstract

**Objective:** Kimura's disease is a rare chronic inflammatory disorder of unknown etiology prevalent in middle-aged Asian men. It usually involves deep subcutaneous tissues and lymph nodes of the head and neck region with frequent regional lymphadenopathy and/or salivary gland enlargement. We report histopathologic features of Kimura's disease and briefly review the literature.

**Method:** Four cases of swellings in head and neck region were included in the study. Histopathological findings are reported.

**Results:** Histopathologically characteristic findings were angiolymphoid proliferation and eosinophilia. Peripheral blood eosinophilia and raised ESR were the other findings.

**Conclusion:** We report characteristic histologic findings in four patients with Kimura's disease.

**Keywords:** Kimura's disease, eosinophilic lymphogranuloma, lymphadenopathy, eosinophilic lymphadenitis

## 1. Introduction

Kimura disease was first described by Kimm and Szeto as "eosinophilic hyperplastic lymphogranuloma" in Chinese literature in 1937.<sup>1</sup> The disease born the name Kimura after Kimura et al, described definitive histological findings in 1948.<sup>2</sup> The disease is endemic in Asia (especially China, Japan and Indonesia), however, sporadic cases from the West have also been reported.<sup>3-5</sup> Although the disease can become apparent at any age, most of the cases described have occurred in the second and third decades of life, with 80-87% of the affected patients being males.<sup>6</sup> We report here four cases of this rare disease and briefly review the literature.

## 2. Method

Four cases with subcutaneous swellings in the head and neck region were referred for histopathological examination by various surgical specialties at the Kempegowda Institute of Medical Sciences (KIMS), Bangalore, India. All specimens were fixed in 10% buffered formalin and processed routinely for paraffin embedding. Sections of 5 µm thickness were cut and stained with Hematoxylin and Eosin (H & E). Ethics approval was not sought because the study was retrospective in nature.

## 3. Results

### 3.1 Case 1

An 18 year old boy presented with 2-year history of a slow growing painless swelling in the right post-auricular region.

On clinical examination, the swelling was non-tender and measured around 3x3cm; there was no discharge and the overlying skin was normal. Clinically, it was diagnosed as chronic otitis media with post auricular lymphadenitis. We received two grey white globular masses, the larger one measured 2.5x1.5x0.5cm and the smaller measured 1.5x1x1cm.

### 3.2 Case 2

A 32 year old male presented with left post auricular painless swelling of 4 months duration. Clinically, the swelling was around 3x3cm, soft, non-tender, mobile, and had a smooth surface. With the clinical diagnosis of dermoid cyst, the mass was excised and sent for histopathological evaluation. The two grey white masses measured 2 x 1.8 x 0.5cm each.

### 3.3 Case 3

A 56 year old man presented with 6 months history of a painless, slow growing swelling of the right upper lip. On clinical examination, the swelling measured around 4 x 4cm. It was firm, non-tender, well circumscribed and had a smooth surface. The skin over the swelling was normal. With the above features, a diagnosis of probable salivary gland tumour was offered. On gross, the mass was grey brown measuring 4.5 x 3 x 1cm.

### 3.4 Case 4

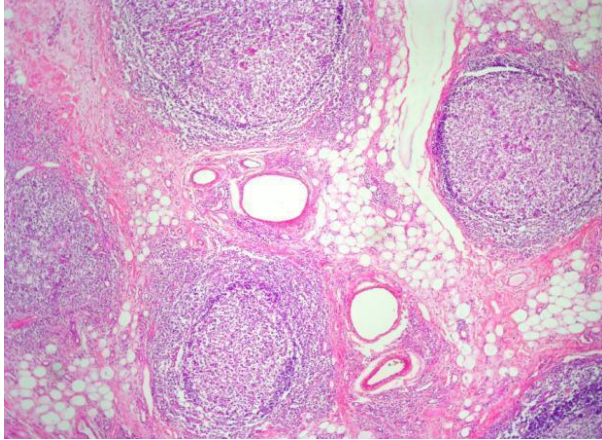
A 41 year male presented with a painless, slow growing swelling in the preauricular region of 3 months duration. On clinical examination, the swelling measured 3 x 2 cm and was firm, non-tender and fairly circumscribed with a smooth surface. Based on these features, a clinical diagnosis of pleomorphic adenoma was made.

Cut sections of all the above-mentioned lesions were grey white with large grey yellow areas.

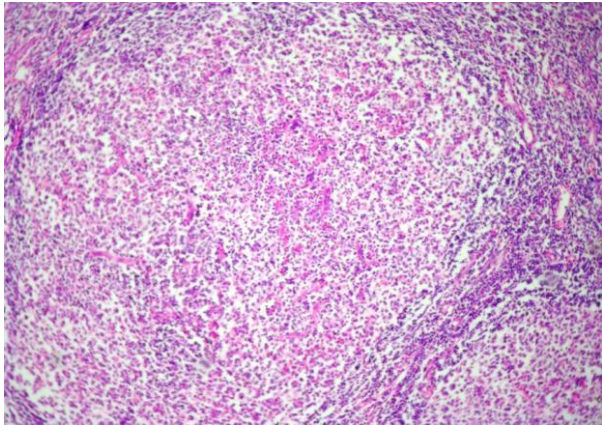
### Microscopy

Microscopically, all cases showed similar features in different tissues namely, lymph node (case 1 and 2), salivary gland tissue (case 3) and subcutaneous tissue (case 4). The basic histologic features were hyperplastic lymphoid follicles having prominent germinal centers (figure 1 & 2). Few of the lymphoid follicles showed vascularization of the germinal centers, in which capillary venules grew into the germinal centers. Some of the germinal centers showed interstitial homogenous eosinophilic material between the germinal centre cells (figure 3). Also seen was moderate to dense eosinophilic infiltration and many proliferating thin walled blood vessels with flattened to cuboidal endothelial lining (figure 4). With the above findings, a diagnosis of Kimura's disease was made. All patients had raised erythrocyte sedimentation rate (ESR) and eosinophil count.

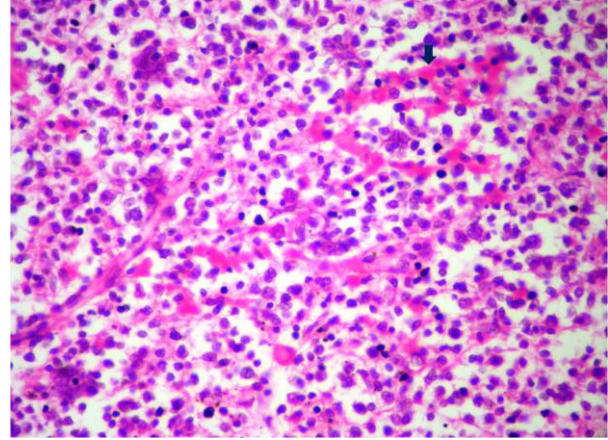
**Figure 1: Lymphoid tissue comprising numerous lymphoid follicles with well formed germinal centres in the subcutaneous tissue (H&E x 10)**



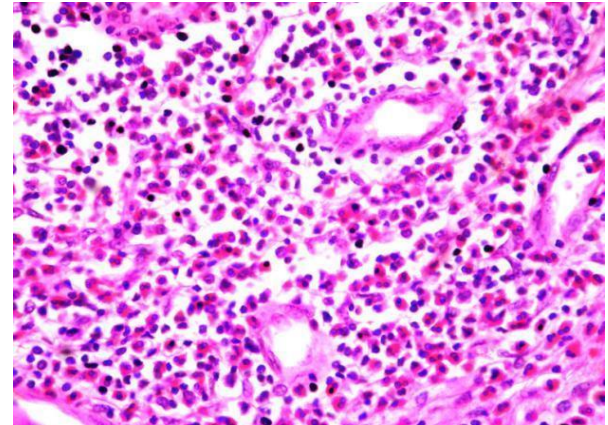
**Figure 2: Lymphoid tissue comprising numerous lymphoid follicles with well formed germinal centres and proliferating small capillaries within (H&E x 40)**



**Figure 3: Germinal centre with homogenous eosinophilic material (arrow) between the germinal centre cells (H&E x40)**



**Figure 4: Moderate to dense eosinophilic infiltrate and thin walled proliferating vessels with flattened to low cuboidal lining. (H&E x40)**



#### 4. Discussion

Kimura's disease is a chronic inflammatory disorder of unknown origin. The disease can become apparent at any age, but most commonly occurs in the second and third decades of life, with 80-87% of the affected patients being males.<sup>6,7</sup> In the present study also, all four patients were males and the youngest was 18 years and the oldest was 56 years old. The usual clinical presentation is one or more slowly increasing subcutaneous nodules in the head and neck regions, accompanied by regional lymphadenopathies and/or salivary gland enlargement. The nodules can be pruritic and painful with normal overlying skin.<sup>4,8</sup> Other sites of involvement including the oral cavity, axilla, groin, limbs, and trunk have also been described.<sup>9</sup> Two of our cases (1&2) presented with post-auricular swelling, one presented with swelling over upper lip (case 3) and the last case presented with subcutaneous nodule in the pre-auricular region. Clinically, all swellings were painless, long standing, solitary and occurred in the head and neck region. The overlying skin did not show any significant changes. Laboratory findings in Kimura disease include raised peripheral blood eosinophil counts and markedly elevated serum immunoglobulin E (IgE) level.<sup>7</sup> In our study, all patients showed increased eosinophil count and raised ESR. However, we did not assess serum IgE.

The etiology and pathogenesis of Kimura disease is unknown. The disease is classified as a reactive benign process. Allergic reactions, infections, and autoimmune reactions with aberrant immune reaction have been suggested.<sup>10</sup> The findings of increased eosinophils, mast cells, and increased levels of interleukin 5 and IgE suggest an abnormal T-cell stimulation to a hypersensitivity-type reaction<sup>11</sup>. Molecular studies for immunoglobulin heavy-chain and T-cell receptor gene arrangement support a reactive nature.<sup>12,13</sup> Recently, Chim et al. described a clonal T-cell receptor gamma gene rearrangement in an elderly man with Kimura disease.<sup>14</sup>

Excision biopsy is required for a correct diagnosis and the basic histologic features are similar in different tissues which includes hyperplastic lymphoid tissue containing well-developed lymphoid follicles, infiltration of eosinophils, vascular proliferation and varying degrees of fibrosis.<sup>2</sup> Lymphoid follicles may be few to numerous and are round to oval in shape with well delineated mantles and prominent germinal centers. Some of the lymphoid follicles show features of vascularization of the germinal centers, in which capillary venules grow into the germinal centers. Some lymphoid follicles show interstitial homogenous eosinophilic material between the germinal centre cells. There is also a tendency for eosinophils to infiltrate the germinal centers resulting in necrosis of the centre structures. This phenomenon has been termed eosinophilic folliculolysis.<sup>7</sup> Between the follicles are seen many small lymphocytes, plasma cells, eosinophils, immunoblasts, histiocytes and mast cells. Moderate to massive eosinophilic infiltrate is a consistent feature in Kimura's disease, usually seen as a diffuse pattern in the interfollicular areas or becoming denser in perivascular areas. Eosinophilic microabscesses are occasionally seen. A varying degree of vascular proliferation is frequently observed in a 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. Furthermore, perivascular sclerosis in the form of concentric rings of collagen is frequently seen, with the affected venules showing endothelial atrophy.<sup>15</sup> Fibrosis is always present, most prominently in subcutaneous and salivary gland lesions. In the present study, all the cases showed above mentioned histopathological features in various tissues namely lymph nodes, minor salivary gland

and subcutaneous tissue. The lesion involving salivary gland did show more fibrosis in comparison with the other tissues. Immunohistochemistry (IHC) can be used as an additional aid to diagnose Kimura's disease although it was not employed in this study. Immunohistochemical stains typically show IgE reticular network in the germinal centers with IgG, IgA and lysozyme-positive cells scattered mainly in interfollicular granulomatous areas.<sup>16</sup>

Kimura's disease should be histopathologically differentiated from the following diseases: angiolymphoid hyperplasia with eosinophilia (ALHE), Hodgkin lymphoma, angioimmunoblastic T-cell lymphoma, Langerhans cell histiocytosis, florid follicular hyperplasia, Castleman disease, dermatopathic lymphadenopathy, allergic granulomatosis, parasitic lymphadenitis and drug reaction.<sup>17-19</sup> ALHE is the most easily confused for Kimura's disease which is now considered to be a kind of endothelial neoplasm related to inflammatory stimulation. ALHE often affects middle-aged women who typically present with a superficial mass. Histopathologically, it is an angioproliferative lesion which shows characteristically plump epithelioid or histiocytoid endothelial cells, accompanied by an inflammatory infiltrate that consists mainly of lymphocytes and eosinophils. Lymphadenopathy, blood eosinophilia, and elevated IgE level are uncommon.<sup>19,20</sup>

Generally, Kimura's disease is a localized condition with a benign clinical course but recurrence is not uncommon. In approximately 12% of patients, there is a related renal disease, usually presenting as nephrotic syndrome. On renal biopsy, IgE deposits can be seen on the glomerular basement membrane.<sup>21,22</sup> However, neither renal dysfunction nor proteinuria were detected in our cases reported here. Therapeutic options include surgery, radiotherapy, laser fulguration, photodynamic therapy and steroids.<sup>23,24</sup> Steroid is effective in reducing size of the mass, but the lesions may recur while reducing the dose of steroid.<sup>25-27</sup> Recently, it has been reported that cyclosporine,<sup>28</sup> azathioprine,<sup>29</sup> pentoxifylline,<sup>30</sup> pranlukast<sup>31</sup> and Imatinib<sup>24</sup> are valid treatment options for Kimura's disease.

## References

1. Kim HT, Szeto C. Eosinophilic hyperplastic lymphogranuloma, comparison with Mikulicz's disease [in Chinese]. *Chin Med J*. 1937; 23:699–700.
2. Kimura T, Yoshimura S, Ishikawa E. On the unusual granulation combined with hyperplastic changes of lymphatic tissue. *Trans Soc Pathol Jpn*. 1948; 37:179–180.
3. Kase Y, Ikeda T, Yamane M, et al. Kimura's disease. Report of 4 cases with a review of 130 reported cases. *Otolaryngol Head Neck Surg* 1990; 63:413–418.
4. Li T-J, Chen X-M, Wang S-Z, et al. Kimura's disease. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1996;82:549–555.
5. Hirokawa Y, Ikeda K, Ha-Kawa SK, et al. A case of eosinophilic lymphoid granuloma with fibrosis. *Jpn J Clin Radiol* 1987;42:357–360.
6. Sawada Y, Nomura K. Kimura's disease: a case report. *J. Dermatol*. 1984; 11:487-492.
7. Kuo, T., Shih, L.Y., and Chan, H.L. Kimura's disease: involvement of regional lymph nodes and distinction from angiolymphoid hyperplasia with eosinophilia. *Am J Surg Pathol* 1988; 12:843-856.
8. Chan, J.K.C., Hui, P.K., Ng, C.S., Yuen, N.W.F., Kung, I.T.M., and Gwi, E. Epithelioid hemangioma angiolymphoid hyperplasia with eosinophilia and Kimura's disease in Chinese. *Histopathology*. 1989; 15:557-574.
9. Kawada, A. Kimura's disease. Manifestation of the disease and its differential diagnosis. *Hautarzt* 1976; 27:309 -317.
10. Mitsui M, Ogino S, Ochi K, Ohashi T. Three cases of eosinophilic lymphofolliculoid granuloma of the soft tissue originating from the parotid gland. *Acta Otolaryngol Suppl*. 1996; 522:130–132.
11. Rajput DK, Pahl M, Clark J. Nephrotic syndrome associated with Kimura's disease. *Pediatr Nephrol*. 2000; 14:486–488.
12. Chim CS, Shek WH, Liang R, Kowng YL. Kimura's disease: no evidence of clonality. *Br J Ophthalmol*. 1999; 83:878–879.
13. Jang KA, Ahn SJ, Choi JH, et al. Polymerase chain reaction (PCR) for human herpes virus 8 and heteroduplex PCR for clonality assessment in angiolymphoid hyperplasia with eosinophilia and Kimura's disease. *J Cutan Pathol*. 2001; 28:363–367.
14. Chim C, Fung A, Shek T, Liang R, Ho WK, Kwong YL. Analysis of clonality in Kimura's disease. *Am J Surg Pathol*. 2002; 26:1083–1086.
15. Tie-Jun LI and Motoo KITANO : Oriental Kimura's Disease and its Relation to Angiolymphoid Hyperplasia with Eosinophilia (ALHE) *Surg Pathol*. 1992; 12:843-856.
16. Motoi M, Wahid S, Horie Y, Akagi T. Kimura's disease: clinical, histological, and immunohistochemical studies. *Acta Med Okayama*. 1992; 46(6):449-455.
17. Kung ITM, Gibson JB, Bannatyne PM. Kimura's disease: a clinicopathological study of 21 cases and its distinction from angiolymphoid hyperplasia with eosinophilia. *Pathol*. 1984;16:39-44
18. Urabe, A., Tsuneyoshi, M., and Enjoji, M. Epithelioid hemangioma versus Kimura's disease: a comparative clinicopathologic study. *Am J Surg Pathol* 1987; 11:758-766.
19. Don DM, Ishiyama A, Johnstone AK, Fu YS, Abemayor E. Angiolymphoid hyperplasia with eosinophilia and vascular tumors of the head and neck. *Am J Otolaryngol*. 1996; 17:240–245.
20. Bartralot R, Garcia-Patos V, Huetto 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.
21. Qunibi WY, Al-Sibai MB, Akhtar M. Mesangio-proliferative glomerulonephritis associated with Kimura's disease. *Clin. Nephrol*. 1988; 30:111-114.
22. Matsuda O, Makiguchi K, Ishibashi K, Chida Y, Ida T, Matsuda K, Tomita K, Marumo F, Hiruma M. Long-term effects of steroid treatment on nephrotic syndrome associated with Kimura's disease and review of the literature. *Clin. Nephrol*. 1992; 37:119-123.
23. Avinash K.Shetty, Charles R.Woods and Laurence B.Givner: Kimura's Disease: A Diagnostic Challenge. *Pediatrics* 2002; 39:110
24. Sun QF, Xu DZ and Pan SH. Kimura disease: review of the literature. *Intern Med J*. 2008; 38:668–672.
25. Chang AR, Kim K and Kim HJ. Outcomes of Kimura's disease after radiotherapy or nonradiotherapeutic treatment modalities. *Int J Radiat Oncol Biol Phys*. 2006; 65:1233–1239.
26. Kim GE, Kim WC and Yang WI. Radiation treatment in patients with recurrent Kimura's disease. *Int J Radiat Oncol Biol Phys* 38:607–612.
27. Wang YS, Tay YK and Tan E. Treatment of Kimura's disease with cyclosporine. *J Dermatolog Treat*. 2005; 16:242–244.
28. Sato S, Kawashima H, Kuboshima S and Takekuma K. Combined treatment of steroids and cyclosporine in Kimura disease. *Pediatrics*. 2006; 118:921-923.
29. Ben-Chetrit E, Amir G and Shalit M. Cetirizine: an effective agent in Kimura's disease. *Arthritis Rheum*. 2005; 53:117–118.
30. Itami J, Arimizu N and Miura K. Radiation therapy in Kimura's disease. *Acta Oncol*. 1989; 28:511-514.
31. Yoshikazu Ohtsuka and Yuichiro Yamashiro. Pranlukast regulates tumour growth by attenuating IL-4 production in Kimura disease. *Eur J Pediatr* 2004; 163: 416–417.