Kimura disease: a clinical study of 7 cases and literature review

Rong Wang, Jingjing Wu, Ling Li, Zhaoming Li, Mingzhi Zhang

Department of Oncology, the First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan 450052, China
E-mail: mingzhi_zhang1@163.com

Abstract: We report seven patients with Kimura disease(KD) whose diagnoses were based on histopathology. Serum IgE and eosinophil level were elevated. Three patients underwent the regimen of sequential medication of prednisone, cyclophosphamide and cyclosporine. Another three were mainly treated with prednisone and radiation. Treatments resulted in a regression of the masses. One patient recurred whose LDH level was high, eosinophil count was 66.8% in bone marrow and mass was as large as 18cm*18cm at the first diagnosis. We conclude that large mass, high LDH and eosinophil level may serve as risk factors of progression of KD.
[Rong Wang, Jingjing Wu, Ling Li, Zhaoming Li, Mingzhi Zhang. **Kimura disease: a clinical study of 7 cases and literature review.** *Life Sci J* 2013;10(2):734-738].(ISSN:1097-8135). http://www.lifesciencesite.com. 102

Keywords: Kimura disease, treatment, prognosis

Introduction

Kimura disease (KD) is a rare benign disorder with unknown etiology. It mainly occurs to young males in Asia, especially in their 20s to 30s. However, it also occurs to non-Asian populations at any age (1,2,3). It manifests as slowly enlarging, painless subcutaneous masses in the head and neck regions (4). It often occurs to parotid glands, while salivary gland and submandibularis gland are seldom involved (5).Local diseases on extraocular muscles (6), epiglottis (7), trunk, limbs (8) and hips (3,9) are uncommon. Lymphadenopathy is another common clinical finding in KD.

Characteristic laboratory findings are elevated serum IgE level and peripheral blood eosinophilia. Renal implication has also been reported in KD with a rate of 12%~16% (10). Histologically it's characterized by eosinophilic abscess and follicular hyperplasia with germinal centers. Other common findings include vascular proliferation, stromal and perivenular sclerosis (11).There is no standard regimen to treat KD. The therapeutic strategies include surgery, radiation, systemic corticosteroids, cytotoxic agents, cyclosporine and so on (12,13).Although the prognosis of KD is generally good, the disease course is often chronic with common recurrence (14). In this report, we describe a series of seven recent cases and review the literature.

Case report

Seven patients with Kimura disease were admitted to the Department of Oncology of the First Affiliated Hospital of Zhengzhou University between 2009 and 2011. The information of these patients are summarized in table 1. There are six male patients and one female patient. The median age was 40 years (range 20–51 years). The initial manifestation was painless subcutaneous masses. The location of lesions were as follows: five on cervical region, two on axilla, four on groin, two on parotid gland, one on mediastinal, celiac and supratrochlear region, respectively. Meantime, one patient with big mass in celiac region had diarrhea. Another had purple tetter on trunk and bilateral upper limbs with itch. The other five had normal skin.

Elevated peripheral blood eosinophil count was detected in six patients, ranging from 7.1% to 39%. The median value was 12.1%. The leukocyte count was normal. Besides, eosinophil counts on bone marrow revealed elevated values ranging from 6.4% to 66.8% (the media 9.4%) in six patients. Serum IgE level was elevated in four patients. High level of lactate dehydrogenase(LDH) was detected in the patient with diarrhea only, and the rest were all in normal range. The values of β- microglobulin (β-MG) were normal in all the patients. Renal function were normal in all patients and no proteinuria was detected. In addition, one patient had eczema for more than 30 years, and one had history of allergic to lavo-ofloxacin. The other five had no comorbidities.

All patients underwent the surgery of excision of the lesions. The diagnosis was confirmed by histopathology. The histological features were that there was lymphoid infiltration with germinal centers in the lesions, with focal eosinophilic microabscesses (Figure 1).

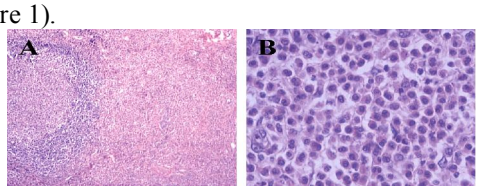

Figure1. A, lymphocyte infiltrate with germinal centre (HE, original magnification 100×). B, bunch of eosinophils infiltrate in eosinophilic microabscess (HE, original magnification 400×)

Table1. Clinical features and laboratory findings of 7 patients with Kimura disease

case	age/gender	Clinical Presentation	Leukocyte count (x10^9/L)	Eosinophil Count (%)	Eosinophil count (x 10^9/L)	IgE	β-MG	LDH	Eosinophil count of bone marrow (%)
Ⅰ	47/M	half-hard mass, 18cmx18cm, retroperitoneal with small lymph nodes	N	↑	↑	U	N	↑	↑
Ⅱ	37/F	soft lymph nodes, biggest 2cmx1cm, bi-lateral cervical, axil-lary and inguinal region, tetter associated with itch	N	↑	↑	U	N	N	U
Ⅲ	51/M	firm mass of parotid gland, 5cm×3cm, with welling lymph nodes in cervical region	N	↑	↑	U	N	N	U
Ⅳ	40/M	elastic mass,4cm×4cm, left inguinal,with swelling nodes in cervical,axillary and left supratrochlear region	N	↑	↑	U	N	N	↑
Ⅴ	43/M	two elastic mass, 8cm×8cm and 3cm×3cm, left inguinal region	N	↑	↑	↑	N	N	↑
Ⅵ	20/M	elastic mass, 2cm×3cm, right inguinal region,with swelling nodes in left cervical region	N	N	N	↑	N	N	↑
Ⅶ	25/M	soft mass of parotid gland,with swelling nodes in submental region	N	↑	↑	↑	N	N	↑

U= unmeasured; N=normal

Table 2. The treatments and outcomes in 7 patients

case	Treatment	Response	Recurrence/sites	Treatment of recurrence
Ⅰ	surgery→PDN(45mg/d)→CVP*2→PDN→CTX→CysA→PDN	mass/nodes reduce rapidly, some even disappear, eosinophil count in peripheral blood and bone marrow, serum IgE decrease to normal	initial lesion at half a year which was postexcision one year, after treatment there is none at 24 months	chemotherapy of CVP
Ⅱ	PDN(45mg/d)→CTX→CysA	as decribed aboved	none at 33 months	not applicable
Ⅲ	PDN(40mg/d)	as decribed aboved	none at 42 months	not applicable
Ⅳ	PDN(45mg/d)	as decribed aboved	none at 40 months	not applicable
Ⅴ	PDN(30mg/d)+Entanercept+radiotherapy	as decribed aboved	none at 28 months	not applicable
Ⅵ	obeservation	as decribed aboved	none at 21 months	not applicable
Ⅶ	PDN(30mg/d)→CTX→CysA	as decribed aboved	none at 22 months	not applicable

The treatments and follow-ups are listed in table 2. The detailed treatments were as follows: two patients received operations, and one of them was administrated with prednisone of 30mg/d for a month, Etanercept 25mg/d for twice and radiotherapy to the lesions 30Gy after the operation; and four patients received prednisone of 30~45mg/d for a month and then reduced the dose gradually, and three of them subsequently received cyclophosphamide with 50mg/tid for three months, then cyclosporine with 150mg/bid for three months, and one patient received no treatment. By now, there was only one had a recurrence who presented with severe diarrhea, and then we gave him chemotherapy of CVP (cyclophosphamide, vincristine and prednisone) for two cycles, then the diarrhea disappeared. The other five had a rapid response to the therapy and the masses or involved nodes shrinked apparently, and even some of them disappeared. What's more, during the follow-ups from 21 months to 42 months, all of them had no recurrence. The median time of no recurrence was 28 months, and one patient's recurrence-free time reached as long as 42 months. All the patients are alive now.

Discussion

Kimura disease was first described as "eosinophilic hyperplastic lymphogranuloma" by Kim and Szeto in 1937(15). It was known as Kimura disease

after report of similar cases by Kimura (1).It was described as "unusual granulation combined with hyperplastic changes of lymphatic tissue" in 1948 in Japan. KD primarily affects in Asians, as well as sporadic incidences occurred to non-Asians (1). The disease is uncommon in Caucasians, and rare in Africans (3). Although the disease can manifest at any age, it has been reported that the disease mainly occurred in their 20s to 30s of the patients' life (3). In a case series of 54 Chinese patients, the mean age of the patients was 33.1 years(16).

The typical clinical manifestation of this disease is painless subcutaneous masses, preferentially in the head and neck region. It is often accompanied by regional lymphadenopathy (5).In addition to noting the presence of masses, patients may complain of pruritus and dermatitis (17).The laboratory findings include raised peripheral blood eosinophil counts and markedly elevated serum immunoglobulin E (IgE) levels (18). In our study, we found all patients had raised peripheral blood eosinophil counts and serum IgE level, which are consistant with the reports of Kung and Kuo (18,19). We also detected the eosinophil counts in their bone marrow, which showed elevated values in all the patients, too. The renal involvement is also reported, presenting with proteinuria or even nephrotic syndrome which occur in up to 60% of patients (11,18). However, neither renal dysfunction nor proteinuria was detected in these patients we report here.

An excision biopsy of the involved lymph node or the lesion is usually required for definitive histopathological diagnosis. The characteristic pathologic findings of nodal implication in KD include follicular hyperplasia, eosinophilic infiltration in the germinal center, and the formation of eosinophilic microabscess or eosinophilic folliculosis (11). In our cases, all the patients were diagnosed on the basis of the pathological characteristics as eosinophilic infiltration in the germinal center and eosinophilic microabscesses and so on. In addition, in our patients 86% of them had raised eosinophil counts in peripheral blood and 71% had raised value in bone marrow; 43% had elevated serum IgE level. So we find raised eosinophil counts both in peripheral blood and bone marrow and the high serum IgE level are important evidence besides the pathology.

The cause and pathogenesis of KD is uncertain, although it might be a self-limited allergic or autoimmune response triggered by an unknown antigen (20). It has been speculated that a viral or parasitic trigger may regulate the T-cell activity or motivate an IgE-mediated type I hypersensitivity, which will lead to the release of eosinophiliotrophic cytokines (4,21,22). Immunohistochemical studies on skin, lymph nodes, and peripheral blood in Kimura disease have shown marked proliferation of human leukocyte antigen-DR CD4 cells (23). Activated CD4 cells of the Th2 phenotype can release cytokines such as granulocyte macrophage colony-stimulating factor and tumor necrosis factor(TNF)-α, IL-4 and IL-5, which may cause the high serum IgE level and raised eosinophil count as a result (24). This suggests that these cytokines may have a role in pathogenesis. It leads to the establishment of the treatment on the pathogenesis, like cyclosporine we used in our regimen. Sato et al (25)had reported they used cyclosporine successfully in combination with prednisolone for treatment of an 11-year-old boy. What' s more ,they showed a decline in serum levels of sIL-2R, IL-4, IL-5, IgE and eosinophil count. In our patients, it is also proved to be valid for decreasing patients' serum IgE level and eosinophil count.

KD should be differentiated from the following diseases: angiolymphoid hyperplasia with eosinophilia (ALHE), eosinophilic granuloma, Castleman disease, dermatopathic lymphadenopathy, allergic granulomatosis, parasitic lymphadenitis , drug reaction and scrofula, especially Hodgkin lymphoma and non-Hodgkin lymphoma (19,26). ALHE (26) is the most easily confused which is considered to be a kind of endothelial neoplasm related to inflammatory stimulation. ALHE often affects middle-aged women presenting with a superficial mass with a histology of the presence of inflammation around medium-sized arteries or veins and evidence of vascular damage (florid fibrointimal proliferation and cuboidal to dome-shaped endothelial cells), rather than the formation of lymphoid follicles and eosinophilic abscesses. Lymphadenopathy is uncommon, and blood eosinophilia is noted in <10% of cases (1,26,27).

There is no consensus on the way to treat this disease. Nevertheless, the management should aim to preserve cosmetic and function while preventing recurrences and long term sequels (28).Therapeutic options include surgery, radiotherapy, laser fulguration, photodynamic therapy and steroid (20,29). Steroid is effective to reduce the size of mass. But the lesions may recur during reducing the dose of steroid (30-32). Recently, it has been reported that cyclosporine (25), azathioprine (33), pentoxifylline (34), pranlukast (35) and Imatinib (29) are valid for KD.

In this report, some of these patients received prednisone, cyclophosphamide, cyclosporine sequentially. All the three drugs are effective as reported (25,29,31,32). Here, realizing the adverse effects such as water-sodium retention, buffalo hump, osteoporosis owing to taking prednisone for long time, we added cyclophosphamide and cyclosporine sequentially to avoid the adverse effects of prednisone when it was taken for long time. What's more, some patients are easy to relapse in the following two stages: ①when the patients keep taking the agents for a short

time (<half a year); ②when the patients taper the prednisone to the low dose(≤15mg/d).

For that reason, we design a regimen for KD which is the sequential medication of prednisone, cyclophosphamide and cyclosporine. The regimen has the following advantages:① avoid the serious adverse reaction of combination therapy;② a lower recurrence rate because of no resistance to the agents; ③good compliance.

Senel et al [36] reported a combination of cyclosporine, azathioprine and prednisolone to be successful in treatment of KD and decreasing serum levels of soluble IL-2 receptor (sIL-2R), IL-4 and IL-5 consequently. In our case, six patients get apparent remission not only in the mass but also in the laboratory results after the treatment of the sequential regimen, and the mean time of no recurrence was 28 months. This outcome is very meaningful.

Etanercept, an inhibitor of TNF-alpha, is used to treat autoimmune disease like rheumatoid arthritis and so on. Tsukadaira (24) reported that the high serum IgE level and raised eosinophil counts may result from the release of TNF-alpha, so we treated one of our patients with Etanercept. After he was treated with Etanercept , his serum IgE level dropped markedly, and his disease hasn't recurred by now.

In addition, if there is no response to the agents for the recurrent lesions, radiation (25-30 Gy) has been found to be effective for local lesions (37).

KD is a chronic benign disorder with an indolent clinical course. However, it frequently relapses. Here the only patient reported with a recurrence was whom receiving a steroid tapering with a large mass of 18cm×18cm at first diagnosis. The proportion of his eosinophil count on bone marrow was as high as 66.8%. Besides, the value of LDH, which is a prognosis affect factor of Malignant Lymphoma, was also high for him. However, the other patients had a normal value of LDH. So, we speculated that the patient with a large mass and an elevated eosinophil count and LDH level may have an aggressive course of the disease and may easier have a recurrence. The LDH value may serve as a prognosis factor of KD as well. But further research should be conducted in the future.

Although KD is a benign disorder, it has been reported that two patients with KD were diagnosed with Non-Hodgkin lymphoma years later in China (38, 39). So the correlation of KD and Lymphoma is to be further confirmed.

Correspondence Author:
Dr. Mingzhi Zhang,
Department of Oncology, the First Affiliated Hospital of Zhengzhou University,
Zhengzhou, Henan 450052, P.R. China.

References

[1] Kimura T, Yoshimura S and Ishikaura E(1948).Unusual granulation combined with hyperplastic changes of lymphatic tissue. Trans Soc Pathol Jpn 37:179– 180.
[2] Kim BH, Sithian N and Cucolo GF(1975). Subcutaneous angiolymphoid hyperplasia (Kimura disease). Report of a case. Arch Surg 110:1246–1248.
[3] Won Jun Choi and Hee Joon Yu(2010). An Unusual Clinical Presentation of Kimura's Disease Occurring on the Buttock of a Five-year-old Boy. Ann Dermatol 22: 57~60.
[4] Armstrong WB, Allison G and Kim JK(1998). Kimura's disease: two case reports and a literature review. Ann Otol Rhinol Laryngol 107 :1066–1071.
[5] Arun Saini and Ashok K(2009). Dutta.Kimura's Disease: An Unusual Glandular Involvement with Blood and Tissue Esinophilia. Indian J Pediatr 76 : 647-648.
[6] Sang Joon Lee, Ju Hwan Song and Shin Dong Kim(2009). Kimura's Disease Involving the Ipsilateral Face and Extraocular Muscles. Journal of Ophthalmology 23:219-223.
[7] Abdull Gaffar Badr A and Abdul-Haleem Eivind Carlsen(2008). Kimura Disease of the Epiglottis. Head and Neck Pathol 2:328–332.
[8] Enrico Beccastrini and Giacomo Emmi(2010). Kimura's disease: case report of an Italian young male and response to oral cyclosporine A in an 8 years follow-up. Clin Rheumatol published online: 19 April.
[9] Yoko Obata, Akira Furusu and Shigeru Kohno (2010). Membranous Nephropathy and Kimura's Disease Manifesting a Hip Mass. A Case Report with Literature Review. Inter Med 49: 1405-1409.
[10] Natov SN, Strom JA and Ucci A(1998). Relapsing nephrotic syndrome in a patient with Kimura's disease and IgA glomerulonephritis. Nephrol Dial Transplant 13:2358–2363.
[11] Hong Chen, Lester D. R. and Abbondanzo(2004). Kimura Disease: A Clinicopathologic Study of 21 Cases. Am J Surg Pathol 28:505–513.
[12] Day TA, Abreo F and Stucker FJ(1995). Treatment of Kimura's disease: a therapeutic enigma. Otolaryngol Head Neck Surg 112:333-337.
[13] HW Yuen, WK Low and SK Lim-Tan(2005). Kimura's disease: a diagnostic and therapeutic challenge. Singapore Med J 46:179-183.
[14] M. Abuel-Haija and M. T. Hurford(2007). Kimura disease. Archives of Pathology and Laboratory Medicine 131: 650–651.
[15] Kim HT and Szeto C(1937). Eosinophilic hyperplastic lymphogranuloma, comparison with Mikulicz's disease. Chin Med J 23: 699-700.

[16] Wang YS, Tay YK, Poh WT(2005).Treatment of Kimura's disease with cyclosporine. J Dermatolog Treat 16: 242-244.
[17] Tian LH and Chen X(2005). Kimura's disease: a case report. China J Lepr Skin Dis 21: 737–739.
[18] Kuo T, Shih L and Chan H(1988). Kimura disease. Involvement of regional lymph nodes and distinction from angiolymphoid hyperplasia with eosinophilia. Am J Surg Pathol 12:843-854.
[19] Kung ITM, Gibson JB and Bannatyne PM(1984). Kimura's disease: a clinicopathological study of 21 cases and its distinction from angiolymphoid hyperplasia with eosinophilia.Pathology 16:39-44.
[20] Avinash K.Shetty, Charles R.Woods and Laurence B(2002). Givner: Kimura's Disease: A Diagnostic Challenge. Pediatrics 39:110.
[21] Chusid MJ, Rock AL and Beste DJ(1997). Kimura's disease: an unusual cause of cervical tumor. Arch Dis Child 77:153– 154.
[22] Rajpoot DK, Pahl M and Clark J(2000). Nephrotic syndrome associated with Kimura disease. Pediatr Nephrol 14:486– 488.
[23] Tabata H, Ishikawa O, Ohnishi K and Ishikawa H(1992). Kimura's disease with marked proliferation of HLA-DR+ CD4+ T cells in the skin, lymph node, and peripheral blood. Dermatology 184:145– 148.
[24] Tsukadaira A, Kitano K and Okubo Y(1998). A case of pathophysiological study in Kimura's disease: measurement of cytokines and surface analysis of eosinophils. Ann Allergy Asthma Immunol 81:423– 427.
[25] Sato S, Kawashima H, Kuboshima S and Takekuma K(2006).Combined treatment of steroids and cyclosporine in Kimura disease. Pediatrics 118:921-923.
[26] Kang Zhou and Yushu Hao(2005). Kimura's disease. Chin J Hematol April 26: 4.
[27] Li TJ and Kitano M(1997). Oriental Kimura's disease and its relation to angiolymphoid hyperplasia with eosinophilia (ALHE). South Pacific Study 17: 287–300.
[28] Maleki et al(2010). Kimura's disease with eosinophilic panniculitis treated with cyclosporine: a case report. Allergy, Asthma & Clinical Immunology 6:5.
[29] Sun QF, Xu DZ and Pan SH(2008). Kimura disease: review of the literature. Intern Med J 38:668–672.
[30] Chang AR, Kim K and Kim HJ(2006). Outcomes of Kimura's disease after radiotherapy or nonradiotherapeutic treatment modalities. Int J Radiat Oncol Biol Phys 65:1233–1239.
[31] Kim GE, Kim WC and Yang WI(1997). Radiation treatment in patients with recurrent Kimura's disease. Int J Radiat Oncol Biol Phys 38:607–612.
[32] Wang YS, Tay YK and Tan E(2005). Treatment of Kimura's disease with cyclosporine. J Dermatolog Treat 16:242–244.
[33] Ben-Chetrit E, Amir G and Shalit M(2005). Cetirizine: an effective agent in Kimura's disease. Arthritis Rheum 53:117–118.
[34] Itami J, Arimizu N and Miura K(1989). Radiation therapy in Kimura's disease. Acta Oncol 28:511-514.
[35] Yoshikazu Ohtsuka and Yuichiro Yamashiro (2004). Pranlukast regulates tumour growth by attenuating IL-4 production in Kimura disease. Eur J Pediatr 163: 416–417.
[36] Senel MF, Van Buren CT, Kahan BD et al(1996). Effects of cyclosporine, azathioprine and prednisone on Kimura's disease and focal segmental glomerulosclerosis in renal transplant patients. Clin Nephrol 45(1):18-21.
[37] Hareyama M, Oouchi A and Satoh M(1998). Radiotherapy for Kimura'sdisease: the optimum dosage. Int J Radiat Oncol Biol Phys 40: 647-651.
[38] Huishu Chen and Hua'an Ji(2007). One case of Kimura disease for 38 years with cutaneous T-cell lymphoma. Chin J Hematol 28: 271-272.
[39] Xuyan Chen and Qiaoke Zheng(2005). One case of the Kimura disease develop into non-Hodgkin's lymphoma. Chin J Hematol 26: 615.

3/5/2013