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ORIGINAL ARTICLE

The clinicopathological characteristics of Kimura disease in Chinese patients

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Abstract

Introduction Kimura disease (KD) is a rare idiopathic inflammatory disorder of unknown etiology. Unusual presentations of KD might cause diagnostic difficulty or be misdiagnosed as malignancy if clinical suspicion is insufficiently high. Here, we aimed to determine the clinicopathological features of Chinese KD patients to reveal further insights into the natural history and treatment of this disease.

Method The clinical data of 46 cases of KD diagnosed at Peking Union Medical College Hospital from January 1980 to December 2018 were analyzed retrospectively through case record review.

Results Of 46 cases, 40 were male and six were female. The age at onset ranged from 2 to 56 years (median 27 years). All patients presented with either single (26.1%) or multi-focal (73.9%) subcutaneous masses. Twenty-nine (63.0%) cases presented with head and neck subcutaneous masses, and 9 cases (19.6%) involved different parts of the body. Parotid, submandibular, and lacrimal gland involvement occurred in 17 (37.0%), 3 (6.5%), and 2 cases (4.3%), respectively. Nephrotic syndrome was present in three cases (6.5%), and thromboembolism was present in five cases (10.9%). During follow-up, thirteen patients (13/28, 46.4%) relapsed over 1–13 years (median 8.5 years). The recurrence rate in patients receiving corticosteroids, surgery, and combined surgery and radiotherapy was 30.8%, 66.7%, and 50.0%, respectively. One patient was diagnosed with T cell lymphoma 1 year after diagnosis of KD.

Conclusions KD is characterized by subcutaneous masses but it is also a systemic disease. Given the high rate of recurrence and reported association with lymphoma, patients require careful long-term follow-up.

Key Points
- *Kimura disease (KD) is a rare inflammatory disorder of unknown etiology that is endemic in Asia.*
- *Clinicians must regard and manage KD as a systemic disease.*
- *There is no consensus on optimal treatments and further studies are necessary to improve outcomes.*
- *Given the high rate of recurrence and reported association with lymphoma, patients require careful long-term follow-up.*

Keywords Clinical characteristics · Eosinophilic granuloma · Kimura disease · Natural history · Treatment

Introduction

Kimura disease (KD) is a rare, chronic, lymphoproliferative inflammatory disease [1–4]. KD was first described in 1937 in the Chinese literature as "eosinophilic hyperplastic lymphogranuloma" [5] but became known as Kimura disease after Kimura et al. published the definitive histologic description in 1948 [6]. KD is characterized by subcutaneous mass lesions occurring predominantly in the head and neck region, frequently with regional lymphadenopathy or salivary gland

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involvement. However, as more cases have been reported, it is becoming clear that KD may present with many different clinical manifestations, especially visceral involvement. KD with unusual presentations might create diagnostic difficulties or even be misdiagnosed as malignancy if clinical suspicion is insufficiently high. Here, we studied the clinicopathological manifestations of 46 cases of KD to reveal further insights into the natural history and treatment of this disease.

Material and methods

This retrospective study was performed at Peking Union Medical College Hospital, a 1800-bed university-affiliated tertiary hospital in Beijing, China. A retrospective review of all records of patients diagnosed with KD between January 1, 1980, and December 31, 2018, was performed. KD was diagnosed based on histopathological examination. Detailed clinical and laboratory data were extracted from the patients' medical records. Demographic information and details of these patients were analyzed.

All data were analyzed using IBM SPSS Statistics version 20.0 software (IBM Corp., Armonk, NY, USA). Categorical variables were described using counts and percentages. Quantitative variables were described using medians and ranges. The χ^2 tests were used to compare the rate of visceral involvements between the patients with and without head and neck involvement, as well as the recurrence rate between the different treatment modalities. $P < 0.05$ was considered statistically significant.

Results

Clinical characteristics

The clinical details of the 46 KD cases are summarized in Table 1. Forty (87.0%) were male and six (13.0%) were female (sex ratio 6.7:1). The age at onset ranged from 2 to 56 years (median 27 years), with incidence peaking during the third decade. The median time interval between symptoms and diagnosis was 24 months (range, 1 month–35 years). There was no family history of KD in any case.

All patients presented with firm, subcutaneous masses without compressive symptoms. The head and neck region (63.0%) was the most frequent site involved, but nine (19.6%) patients had lesions at different sites and two cases (4.3%) had subcutaneous masses on the forearm. Isolated lymphadenopathy was the initial presentation in five patients (two cases in the neck and three cases in the inguinal region). There was salivary gland involvement in 22 cases (47.8%, 17 in the parotid gland, three in the submandibular gland, and two in the lacrimal gland). The lesion was solitary in 12 (26.1%) patients and multifocal in 34 (73.9%) patients. Of the 39 patients with available data, the median diameter of the mass was 4.1 cm (range, 1.0–12.0 cm).

Table 1 Clinicopathological features of 46 cases of Kimura disease

Clinical characteristics	No. of patients (%)
Sex	
Male	40 (87.0%)
Female	6 (13%)
Age at onset, years	
< 20	11 (23.9%)
20–29	14 (30.4%)
30–39	6 (13.0%)
40–49	7 (15.2%)
≥ 50	8 (17.4%)
Number of lesions	
Single	12 (26.1%)
Multiple	34 (73.9%)
Locations of lesions	
Head and neck	29 (63.0%)
Forearm	2 (4.3%)
Inguinal	6 (13.0%)
Multiple parts of the body	9 (19.6%)
Size in diameter (39 cases recorded)	
< 2.0 cm	3 (7.7%)
2.0–4.9 cm	26 (66.7%)
≥ 5.0 cm	10 (21.7%)
Exocrine gland involvement	
Parotid gland	17 (37.0%)
Submandibular gland	3 (6.5%)
Lacrimal gland	2 (4.3%)
Modality to obtain tissue	
Subcutaneous mass excision	22
Mass from the parotid region	11
Enlarged lymph nodes excision	17

There were no signs of lesion redness, heat, or pain in any case. Twenty-one patients (45.7%) presented with pruritus, six (13.0%) with pigmentation, one (2.2%) with rough skin changes, and three (6.5%) with a diffuse itchy skin rash. Only one patient presented with fever.

There were renal manifestations in three cases (6.5%), presenting as nephrotic syndrome. Three patients presented with arterial occlusion (one in a lower extremity artery, one in a temporal artery, and one in both a temporal artery and a lower extremity artery). One patient had venous thromboembolism in a lower extremity. Further, one case presented with arterial occlusion and deep venous thromboembolism in a lower extremity simultaneously.

Of the thirty-six patients with lesions in the head and neck regions (including 29 patients whose disease is limited to the

head and neck region and 7 patients involving multiple parts of the body), only three patients (3/36, 8.3%) had visceral involvement. While of the ten patients without head and neck involvement, four patients (4/10, 40.0%) had visceral involvement. The rate was significantly different ($\chi^2 = 6.083$, $p = 0.014$).

Laboratory results

The laboratory results are summarized in Table 2. Of 45 patients with whole blood cell analysis, the median eosinophil percentage was 21.1% (range, 5.0–58.7%) and the median absolute eosinophil value was 1.85×10^9/L (range, 0.39–10.1×10^9/L). Of these, 44 cases (97.8%) had eosinophilia. Eighteen out of 19 cases (94.7%) had elevated serum immunoglobulin E (IgE) levels, with a median value of 1591 U/L (range, 41–5000 U/L). Liver and kidney function tests of all 45 tested cases were within the reference ranges. Twenty patients had erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) tested, all of which were normal, and all four patients with serum immunoglobulin G4 (IgG4) tests were also normal. Forty-four cases had urine analysis, three of which were positive: urine protein per 24 h of 4.8 g, 5.2 g, and 20.4 g, respectively. Of these three patients, two received ultrasound-guided kidney biopsy, which showed minimal change disease and membranous nephropathy stage 2, respectively, on histopathological analysis. Bone marrow aspiration was carried out in ten patients, all showing increased eosinophils of 13.0 to 26.5% (median 20.5%).

Histopathological findings

Material for histopathological examination was obtained from either the diagnostic biopsy or the surgical excision specimen: 18 cases from a subcutaneous swelling, 11 from the parotid gland, and 18 from excision of enlarged lymph nodes (three neck, one submental, one submandibular, eight inguinal, four epitrochlear, and one superior mesenteric).

In all cases, microscopic examination revealed the characteristic features of lymphoid hyperplasia with reactive germinal centers and massive eosinophil infiltration. Well-formed lymphoid follicles were observed in some cases. Germinal center necrosis, proteinaceous deposits, vascularization of germinal centers, and sclerotic areas were also seen. Eosinophilic microabscesses were occasionally present.

Management and prognosis

The treatments and prognoses of the 46 KD cases are summarized in Table 3. Sixteen patients underwent complete surgical resection alone, and nine patients with parotid masses received surgical excision combined with postoperative low-dose radiotherapy, but there was no association between receiving radiotherapy and tumor size. Oral corticosteroids (0.5–1 mg/kg/day) were given to 20 patients with multiple lesions or visceral involvement after surgical resection or biopsy. Six patients received cyclophosphamide (100 mg/day) in addition to corticosteroids, including three patients complicated with nephrotic syndrome, one patient with arterial occlusion and DVT, and two patients with generalized lymphadenopathy. All five patients with arterial occlusion and deep venous thromboembolism were treated with aspirin (100 mg/day).

The follow-up period ranged from 1 to 30 years. Eighteen patients (18/46, 37.8%) were lost to follow-up. During follow-up, thirteen patients (13/28, 46.4%) relapsed in 1–13 years (median 8.5 years). The recurrence rates in patients receiving corticosteroids, surgery, and surgery combined with radiotherapy group were 30.8%, 66.7%, and 50.0%, respectively; these rates were not significantly different ($\chi^2 = 2.794$, $p = 0.247$). It is worth noting that all three patients with recurrences in the surgery combined with radiotherapy group relapsed at other sites. All four patients in the corticosteroid group relapsed after the drug had been withdrawn. One patient was diagnosed as peripheral T cell lymphoma, not otherwise specified (PTCL, NOS) 1 year after the diagnosis of KD.

Discussion

Here, we present a retrospective clinicopathological analysis of 46 patients with KD. In doing so, we have better characterized this entity, particularly with respect to the relationship between treatment options and prognosis.

KD is a rare, chronic, benign inflammatory disease, which is endemic to Asia. In general, KD tends to affect young adults, most commonly in the second and third decades [3,

Table 2 Laboratory results of 46 cases of Kimura disease

Laboratory test	Median (range)	Reference
Eosinophil percentage in peripheral blood	21.1% (5.0–58.7%)	0.5–5.0%
Eosinophil value	1.85×10^9/L ($0.39–10.1 \times 10^9$/L)	$0.02–0.50 \times 10^9$/L
Serum IgE level	1591 KU/L (41–5000 KU/L)	0–60 KU/L
Eosinophil percentage in bone marrow aspiration	20.5% (13–24.5%)	0–7.6%

Table 3 Treatment and prognosis of 46 patients

Treatment	Number with follow-up	Number of patients with recurrences (%)	Number of recurrences in situ	Number of recurrences at other sites
Total ($n = 45$*)	28	13 (46.4%)	7	6
Surgery ($n = 16$)	9	6 (66.7%)	4	2
Corticosteroids ($n = 20$)	13	4 (30.8%)	3	1
Surgery + radiotherapy ($n = 9$)	6	3 (50.0%)	0	3

*One patient with KD was not included, since he was diagnosed with lymphoma 1 year later

7]. In the present series, the median age at onset was 27 years, consistent with the reported literature. The male-to-female ratio was 6.7:1, similar to the reported sex distribution of a striking male predominance (male:female 3.5–6:1) [1–3].

KD is characterized by painless subcutaneous masses occurring predominantly in the head and neck region and frequently associated with regional lymphadenopathy or salivary gland involvement. In our series, the head and neck region was the usual presentation site (63.0%), with 19.6% multifocal, as reported previously [1–3, 7]. In the present study, two-thirds of patients had skin involvement, and most patients had eosinophilia and elevated serum IgE levels, consistent with the previous literature [1–3, 7]. KD is frequently associated with melanin pigmentation or pruritus, elevated serum IgE, and eosinophilia. Gao et al. [2] observed nerve infiltration with lymphocytes and eosinophils in patients with pruritus or pigmentation, to some extent explaining the possible pathogenesis of these phenomena.

KD can be systemic and may involve multiple organs. Our study demonstrated that KD could involve the forearm, inguinal area, and visceral organs such as the kidneys and blood vessels. The main systemic manifestation of KD is renal involvement, and KD, in association with proteinuria and nephrotic syndrome, is well recognized. Proteinuria may occur in 12–16% of patients, 60–80% of whom have nephrotic syndrome [8, 9]. Renal involvement may occur simultaneously or months or years after the onset of mass lesions. Membranous glomerulonephritis is the commonest histopathological pattern, although other lesions include mesangioproliferative glomerulonephritis, minimal-change disease, focal-segmental glomerulosclerosis, IgM nephropathy, and IgA nephropathy [9, 10]. Most patients with renal impairment respond well to steroid therapy [8–11]. Only three patients (6.7%) had nephrotic syndrome in our study, which is lower than the 12–16% reported in the literature, perhaps due to the relatively low number of cases examined. The pathogenesis of nephrotic syndrome in KD is unclear. Several studies have speculated that the pathogenesis of KD with renal involvement may be related to high serum IgE levels and eosinophilia [8], while others have suggested that renal impairment is probably due to immunocomplex-mediated damage or T-helper 2 (Th2)-dominant immune response disorders [10]. Recently, there have been several reports of KD patients with renal involvement progressing to end-stage renal disease [10, 11]. In our study, no patients developed kidney failure, which may be explained by the relatively short course of KD in these patients.

In our study, five patients had some form of vessel thromboembolism, which has only rarely been reported. As these five patients had no risk factors leading to artery and deep venous thromboembolism and their blood tests showed no evidence of hypercoagulability, a KD-related thrombotic condition was suspected. There are some reported cases of an association between thromboembolic events and KD, with the few reports that do exist reporting coronary artery, popliteal artery, temporal artery, radial and ulnar arteries, mesenteric artery, superior mesenteric vein, portal vein, splenic vein, and renal vein involvement [12–17], all in the absence of vasculitis. Although the exact mechanism is unclear, eosinophilia in KD patients can cause hypercoagulability and thromboembolism. A postulated mechanism is that cytokines secreted by eosinophils, including eosinophil cationic proteins, eosinophil peroxidase, and major basic protein (MBP), are potent stimuli of platelet activation and aggregation and alter the clotting process by interfering with endothelial cell surface thrombomodulin [18]. Furthermore, eosinophils release reactive oxygen species and directly injure endothelial cells [19]. Thus, thromboembolism should be suspected when a KD patient presents with nonspecific symptoms such as vague abdominal pain or headache. To our knowledge, this is the first report involving the relationship between lesion distribution and the rate of visceral involvement. Our results showed that KD patients without head and neck regions had higher chances with visceral involvement. Though the reason for this phenomenon is unknown, this report may serve as a reminder that KD patients should get thorough examinations, especially the ones without head and neck involvement.

Salivary glands are often involved in KD patients, of which the parotid glands are the most common [1, 2, 7, 20, 21]. Our results are generally in accordance with previous studies: twenty patients (43%) had salivary gland involvement (17 cases parotid gland and three submandibular gland) and the lacrimal glands were involved in two patients. Bilateral salivary gland enlargement has been reported in KD patients [20, 21], which was present in four of our patients and may even be

higher due to the absence of biopsy or surgical specimens in all cases. The reason for frequent salivary gland involvement in KD patients is still unknown. Tham et al. [21] demonstrated that all cases of salivary gland involvement in KD were accompanied by neighboring connective tissue changes, with the lesions being more severe in the connective tissues than in the salivary gland itself and the gland structure far from the lymph node usually being histologically normal. These results suggest that the pathological changes in the salivary gland result from lesions in the lymph nodes or adjacent subcutaneous connective tissues [21].

The diagnosis of KD is based on characteristic clinicopathological features. The diagnostic challenge of KD is generally solved by histopathological examination, although there is no pathognomonic feature of KD histologically. In light of the importance of the histopathology, how to obtain specimens is particularly important in clinical practice, especially for patients with multiple lesions. In the past, although inguinal lymph node biopsy has been regarded as relatively safe, the specificity of inguinal lymph node enlargement is poor, so inguinal lymph node biopsy is not the first choice in clinical practice. However, inguinal lymph nodes were the most frequently selected site of biopsy in patients with suspected KD in our study, with acceptable diagnostic yield. Therefore, inguinal lymph nodes might be a suitable first choice for biopsy in patients when multiple lymph nodes are involved.

The differential diagnosis of KD includes other inflammatory and neoplastic conditions, for example, angiolymphoid hyperplasia with eosinophilia (ALHE), Hodgkin lymphoma, angioimmunoblastic T cell lymphoma, allergic granuloma, Langerhans cell histiocytosis, Castleman disease, and immunoglobulin G4-related disease (IgG4-RD). Although ALHE shares similar histological features with KD, the former is believed to be a more superficial, vascular lesion with an absence of regional lymphadenopathy; additionally, peripheral eosinophils and serum IgE concentrations are typically not elevated in ALHE [1, 4].

Some studies have suggested a relationship between KD and IgG4-RD [3, 22–26], the latter characterized by significant organ infiltration with IgG4-positive plasma cells and T lymphocytes [27]. Similar to KD, patients with cutaneous IgG4-RD are mostly male, with nodules occurring predominantly in the head and neck region, frequent lymph node involvement, and eosinophilia or high IgE levels [22, 23]. The clinicopathological manifestations of these two diseases overlap, but each has its own characteristics. IgG4-RD occurs in patients with a median age 63 years and has more lacrimal/salivary gland involvement and common pancreatic involvement [3], in contrast to KD, which usually affects young men and has no reports of pancreatic involvement to date. IgE is known to be expressed in follicular dendritic cells and eosinophilic microabscesses in KD but not in IgG4-RD [23]. Tsubouchi et al. [28] observed numerous IgG4-positive plasma cells in a lung biopsy from a KD patient, suggesting possible coexistence of the two diseases. Others have hypothesized that IgG4-RD might be an epiphenomenon of KD based on the reported presence of IgG4-positive plasma cells in KD and the results of immunohistochemical staining tests in accordance with IgG4-RD diagnostic criteria [24, 25]. Liu et al. [24] reported that a series of immune reactions due to chronic allergen exposure in KD patients may cause the clinical manifestations of IgG4-RD [24]. Antigens that induce IgE responses are also good inducers of IgG4 [23]. Both IgG4 and IgE production are dependent on T-helper 2 (Th2) cells, which ensure B cell proliferation and immunoglobulin class switching. KD and IgG4-RD can be considered a part of a clinical spectrum of abnormal immune reactions and they both require comprehensive consideration when differentiating them [3, 22].

The optimal treatment for KD remains uncertain. KD management differs depending on individual patient factors. Surgery is the usual primary approach for diagnostic and therapeutic purposes and should be considered in younger patients with local primary lesions or localized recurrences. For patients with incomplete resections or recurrences, radiotherapy may be a reasonable therapeutic choice and is advocated in patients with positive surgical margins and those with repeated recurrences after surgery [29, 30]. Systemically administered immunosuppressive drugs in the form of corticosteroids, azathioprine, and interferon-alpha; cytotoxic agents such as cyclophosphamide; and thalidomide are indicated for patients with unresectable swellings, multiple lesions, or visceral organ involvement and show good effects on disease progression. However, the optimal duration of these therapies has not been thoroughly investigated, and the application and length of immunosuppressive therapy remain to be elucidated.

Even though the disease usually follows a benign clinical course, recurrences are common, reported in up to 60 to 80% of patients [31]. Few studies have addressed the relationship between treatment options and recurrence rates. In one study of 46 patients undergoing 58 treatments, the recurrence rate in patients undergoing surgical excision combined with low-dose radiotherapy was much lower than that receiving surgical excision or radiotherapy alone. One meta-analysis revealed that radiation or surgical excision alone was inferior to surgical resection combined with postoperative radiotherapy for controlling local recurrences (risk ratio (RR) = 2.72, 95% confidence interval (CI), 1.47–5.04 and RR = 4.72, 95% CI 2.53–8.82). However, surgical excision alone did not show a significant advantage in controlling local recurrences compared with radiotherapy alone (RR = 2.13, 95% CI 0.88–5.17) [29]. Our study showed that there is no significant difference between the recurrence rate of surgery and surgery combined with radiotherapy. Nevertheless, the recurrence rate of patients on corticosteroids was much lower than that of patients receiving surgery and surgery plus radiotherapy. All four patients

receiving corticosteroids relapsed after withdrawing the medication. Previous literature [8, 9, 11] has highlighted that recurrences are not uncommon after steroid therapy discontinuation. Therefore, in our experience, patients with organ involvement may warrant immunosuppressive therapy to prevent recurrences during steroid reduction.

KD is believed to be a benign condition with a good prognosis. However, one of our patients was diagnosed with nonspecific peripheral T cell lymphoma in the first year of follow-up, similar to two case reports in China [32, 33], in which the time interval was 38 years and 2 years, respectively. The clonal analysis of T cell subsets may be helpful when distinguishing KD patients from lymphoma. But the diagnosis of lymphoma requires comprehensive application of morphology, immunohistochemistry, genetic, and molecular biology techniques. It is hard to rely on molecular data to get the diagnosis of lymphoma.

In conclusion, although Kimura disease is characterized by a subcutaneous mass occurring predominantly in the head and neck region, it is also a systemic disease that can involve many organs. KD should be considered in the differential diagnosis of patients presenting with primary lymphadenopathy and eosinophilia. In view of the high recurrence rate, patients need long-term follow-up.

Compliance with ethical standards

Disclosures None.

Ethics approval This study protocol has been approved by the Ethics Committee of Peking Union Medical College Hospital (protocol number: S-K 702). The ethics committee waived the requirement for informed consent because anonymous data were analyzed retrospectively.

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