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Research Article

Kimura's Disease of the Clinical Characteristics, Treatment, and Prognosis of 34 Cases: A Retrospective Cross-Sectional Study

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Abstract

Background: This study aimed to explore the clinical characteristics, diagnosis, treatment, and prognosis of Kimura's disease (KD), and to analyze the related factors of recurrence after treatment.

Methods: 34 patients with KD were diagnosed from Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan from June 2011 to March 2023. Retrospective analysis of clinical data, treatment, and prognostic information, recurrence was defined as the appearance of a mass at the treatment site, or the continued enlargement of the original mass, or the death of the patient.

Results: KD presents as a painless mass or regional lymph node involvement, with pruritus and hyperpigmentation of the skin. 26 patients showed peripheral blood eosinophilia, and 23 patients presented elevated eosinophil counts. Magnetic Resonance Imaging showed well-defined lymph nodular or ill-defined solid mass. 14 patients were treated by surgery alone, 16 patients received surgery combined with adjuvant therapy, 2 patients received chemotherapy and radiotherapy, and 1 received systemic corticosteroids alone. Follow-up data on 23 patients revealed that 8 patients recurred within 2 months to 3 years after the treatment, one of them died 4 months after radiotherapy. Univariate analysis showed duration and lymphocytes were related to recurrence. ($P<0.05$).

Conclusion: KD is characterized by painless masses or lymphadenopathy, with pruritus and hyperpigmentation, and laboratory tests show eosinophilia. After surgery, adjuvant therapy can be selected according to duration and lymphocytes to reduce the recurrence rate.

Keywords: Kimura's disease; Eosinophilia; Diagnosis; Treatment; Recurrence

Background

KD was first reported by a Chinese doctor in 1937 as an "eosinophilic hyperplastic lymphogranuloma", and described in detail by the Japanese scholar Kimura [1], and named the disease. KD is a rare chronic inflammatory disease that is much more prevalent in young males of Asian. The clinical characteristics are one or more painless masses with waxing and waning over time [2], some with pruritus and hyperpigmentation. It often involves the head and neck region, and also occurs in the salivary glands, subcutaneous tissues, regional lymph nodes, and other sites. Laboratory tests show peripheral blood eosinophilia and elevated immunoglobulin E (IgE) levels [3,4]. KD is a slowly progressive disease and the site, number of masses, and clinical presentation vary from patient to patient, which makes it difficult to diagnose. KD is rare, most of the clinical studies are case reports, and there is a lack of large, comprehensive clinical studies. Some treatments have been reported, including surgery, systemic steroids, immunosuppressive medications, and radiotherapy [5]. However, it is easy to recurrence and there is no current consensus on the optimal treatment.

KD is associated with pruritus for a long time, which affects people's quality of life. Furthermore, the disease is still prone to recurrence even after treatment. We reviewed the presentation and treatment of 34 patients and the relevant literature to deepen the understanding of this disease.

Methods and Analysis

Study Design and Procedures

This study was a retrospective cohort study and was approved by the ethics committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (TJ-JRB20231293). The need for obtaining informed patient consent will be waived due to the retrospective nature of this study.

Patients admitted to the hospital between June 2011 and March 2023. Inclusion criteria included (1) being treated in our hospital and diagnosed with Kimura's disease by pathology, (2) having complete medical history data. Exclusion criteria included (1) any mental

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illness, or other diseases that can lead to the legal recognition of restricted capacity, (2) life-threatening systemic diseases such as malignant tumors within 1 year before the consultation, (3) special infectious diseases such as Hepatitis B or HIV infection.

Analysis of clinical pathological features, treatment, and prognosis of KD. During follow-up, recurrence was defined as the appearance of a mass at the site of original treatment, the continued enlargement of the original mass, or the death of the patient.

Statistical Analysis

Continuous variables were analyzed using mean ±SD or median with IQR, while categorical variables were represented as counts and proportions. Univariate analysis, using the chi-square test or Fisher's exact test, was conducted for each selected recurrence factor (gender, age, disease location, symptom, physical findings, duration, laboratory values, and Systemic disease history). Values of $p<0.05$ were considered statistically significant. All statistical analyses were performed using SPSS V.23.0 (IBM SPSS).

Results

Clinical Characteristics

Clinical features are summarized and 34 cases with Kimura disease are listed in Table 1. 29 cases being male. The duration of symptoms was 10 days to 30 years. Most cases (30 of the 34, 88.2%) presented on the head and neck, and 4 cases involved other parts of the body. For glands, involvement of the parotid gland in 16 cases, the submandibular gland in 4 cases, the eyelids in 3 cases, the palate in 1 case, and the buccal in 1 case. The lesions were presented unilaterally in 20 cases and bilaterally in 14 cases. There were 19 cases of multiple lesions, 11 cases of skin pruritus and 9 cases had hyperpigmentation (Figure 1). 6 cases had a history of smoking and 5 cases had drinking, 11 cases had allergic diseases (such as drug allergy, bronchial asthma, atopic dermatitis and chronic urticaria), 3 cases with hypertension and 1 case was complicated with nephrotic syndrome.

Laboratory Tests

Among the 30 cases included, 26 cases showed elevated peripheral blood eosinophils, 23 cases had elevated eosinophil counts, 14 cases

Table 1: Clinical information of 34 patients with Kimura disease.

Patient No.	Age (yr)/ Gender	Duration of symptoms	Site	Clinical Presentation	size (cm)	boundary	pruritus	hyperpigmentation
1	28/M	2years	parotid gland, neck	painless mass	4*3	unclear	none	none
2	41/M	5years	parotid gland	painless mass	1.5*1.5	unclear	none	have
3	21/M	2years	parotid gland	painless mass	3.4*1.6	unclear	none	none
4	45/M	2years	parotid gland	painless mass	left2.5*2.5, right2*2.5	clear	none	none
5	11/M	1year	neck	painless mass	1.2*1	clear	have	none
6	66/M	1year	submandibular gland	lymphadenopathy	3*4	unclear	have	none
7	43/M	2months	submandibular gland	painless mass	2.0*1.7	clear	none	have
8	38/M	3months	parotid gland	painless mass	left3*4,right1*4	clear	none	none
9	50/M	3years	parotid gland	painless mass	2.5*3,1*1	unclear	have	have
10	50/M	20years	parotid gland	painless mass	right1*2,3*4.5, left3*4,2*4	unclear	none	none
11	39/M	10years	parotid gland	painless mass	2*2.5	unclear	have	have
12	29/M	4months	parotid gland	swelling	1.6*1	unclear	none	none
13	28/F	3months	parotid gland	painless mass	2* 1	unclear	none	none
14	5/M	3months	cheek	painless mass	1.5*1	unclear	none	none
15	39/M	10years	parotid gland	painless mass	2.5*2.5	clear	have	none
16	7/M	7months	eyelid	swelling	no	unclear	none	none
17	23/M	11years	submandibular gland, parotid gland	swelling	no	unclear	none	none
18	12/M	1year	neck, limb	painless mass	2.5*2.5	unclear	none	none
19	36/M	2months	groin, neck, brow	lymphadenopathy	2.5*2.5	unclear	have	have
20	48/F	10days	submandibular gland	swelling	no	no	none	none
21	8/M	3years	neck, groin, limb	lymphadenopathy	3*3	unclear	none	have
22	37/M	30years	parotid gland, neck	painless mass	left3*4,right1*1	clear	none	none
23	8/M	4years	eyelid, neck, limb	swelling lymphadenopathy	no	unclear	have	have
24	8/M	2years	neck	painless mass	4*4	unclear	none	none
25	66/M	2years	parotid gland	painless mass	2.5*2.5	unclear	have	none
26	47/M	1month	neck	lymphadenopathy	3*3	unclear	none	none
27	50/M	4years	occiput, parotid gland, neck, limb	painless mass	5*5, 3*3, 1*1.5	unclear	have	have
28	3.2/M	20days	neck	painless mass	3*4	unclear	none	none
29	46/M	15days	parotid gland	painless mass	3*5	unclear	none	none
30	67/M	15days	palate	painless mass	2*3	clear	none	have
31	67/M	2months	parotid gland	painless mass	left2.5*3,1.5*2.,right2.5*2.5,1*1	unclear	none	none
32	60/F	10years	parotid gland	painless mass	left4*4,1*1,right2*2	unclear	have	ne
33	58/M	1year	parotid gland	painless mass	2.0*0.8	unclear	none	none
34	15/M	3years	eyelid	painless mass, swelling	1.0*0.8	unclear	none	none

M, male; F, female.

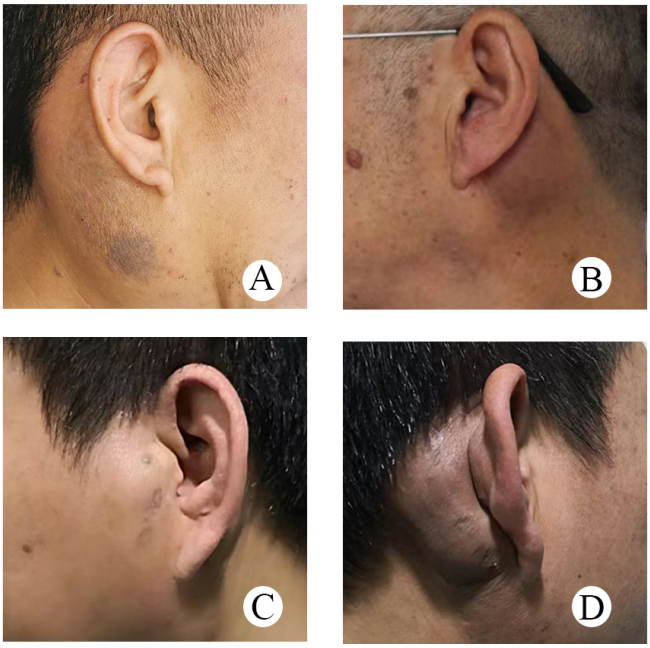

Figure 1: Preoperative picture of typical Kimura disease (A) Patient 1, unilateral mass with skin hyperpigmentation. (B) Patient 2, unilateral mass with skin hyperpigmentation. (C.D) Patient 3, Bilateral mass with hyperpigmentation on the right.

Table 2: Laboratory vales.

indicator	case(%)
Eosinophils (%)	
normal	4(13.33)
elevated	26(86.67)
Eosinophil count (10^9/L)	
normal	7(23.33)
elevated	23(76.67)
Neutrophils (%)	
decreased	14(46.67)
normal	15(50)
elevated	1(3.33)
Neutrophil count (10^9/L)	
decreased	4(13.33)
normal	23(76.67)
elevated	3(10)
Lymphocytes (10^9/L)	
decreased	3(10)
normal	25(83.33)
elevated	2(6.67)
Lymphocyte count (10^9/L)	
decreased	2(6.67)
normal	24(80)
elevated	4(13.33)

Table 3: Treatment and Outcome of 34 patients with Kimura disease.

Treatment	Total	Follow-up	Recurrence
Surgical	14	10	4
Surgery + Radiotherapy	6	4	1
Surgery + Radiotherapy + Chemotherapy	2	1	0
Surgery + Steroid	8	6	2
Surgery + Steroid + Chemotherapy	2	1	1
Steroid	1	0	0

had decreased neutrophils, 4 cases had decreased neutrophil counts, 3 had decreased lymphocytes, and 2 showed decreased lymphocyte counts (Table 2). Preoperative bone marrow puncture in 5 cases showed that granulocyte hyperplasia was active and the eosinophils increased, accounting for 20%~36%, and a few cells had vacuoles. Additionally, 2 cases showed decreased lymphocytes.

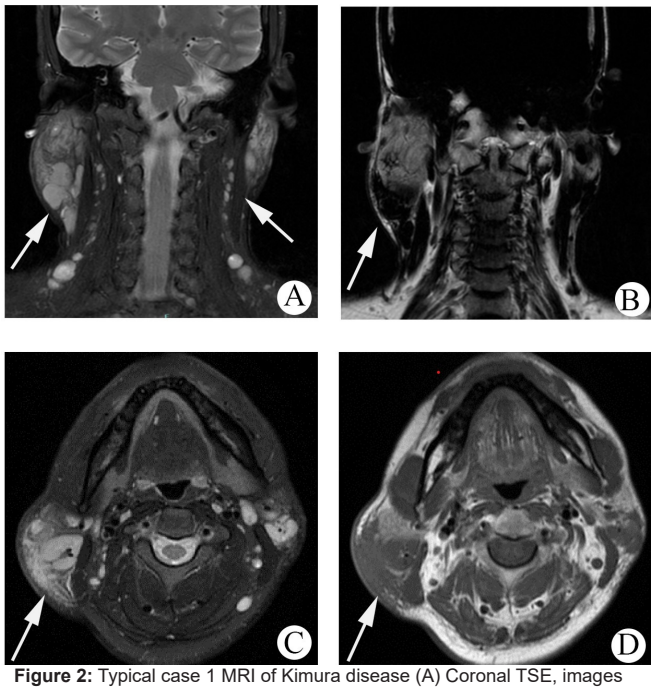

Figure 2: Typical case 1 MRI of Kimura disease (A) Coronal TSE, images show a lobulated heterogeneously hyperintense lesion, and beaded changes of lymph nodes. (B) Coronal TSE, images show diffuse atrophy of subcutaneous fat in the right parotid mass. (C, D) Axial TSE, the boundary of the lesion on the right is ill-defined, partial fusion, and vascular flow void signal can be seen.

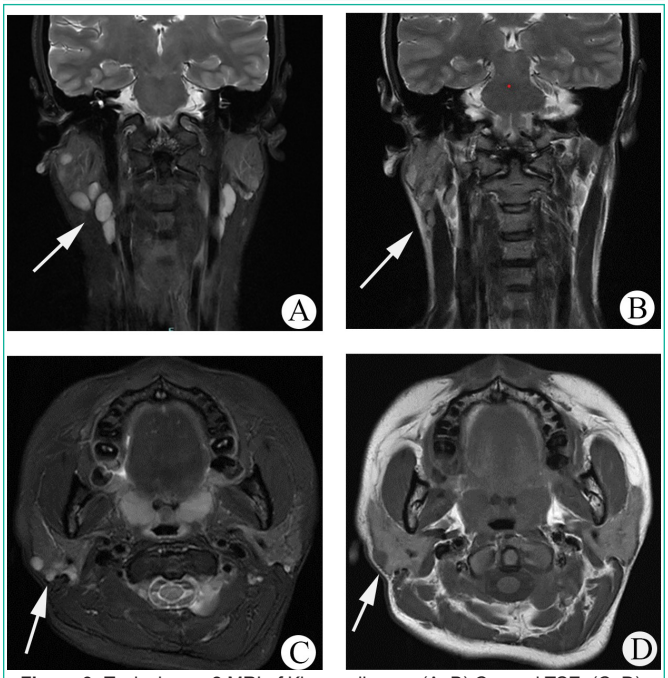

Figure 3: Typical case 2 MRI of Kimura disease (A, B) Coronal TSE, (C, D) Axial TSE. Only the glands and cervical lymph nodes are increased. The lymph nodes were elliptical, with a smooth margin and a relatively well-defined outline.

Magnetic Resonance Imaging Characteristics

Magnetic resonance imaging (MRI) was performed in 10 cases. 4 cases showed T1-weighted sequences isointense signal and hyperintense signal on T2-weighted sequences, 4 cases showed T1-weighted sequences hyperintense and T2-weighted sequences hyperintense, 1 case showed T1-weighted sequences hypointense and heterogeneously hyperintense lesion on T2-weighted sequences. 7 cases showed nodular lesions, 3 cases patchy or lobulated lesions were seen. The boundary was well-defined in 5 cases and ill-defined in 5 cases. Among them, 2 cases of multiple lesions were partially fused (Figure 2), and 2 cases only showed beaded changes of lymph nodes (Figure 3). 1 case showed diffuse atrophy of subcutaneous fat on T1-weighted sequences. Contrast-enhanced magnetic resonance imaging (CE-MRI) was performed in 10 cases, 3 cases were patchy heterogeneous enhancement and 1 case showed nodular homogeneous enhancement lesion. 4 cases were indicated Inflammation.

Treatment and Outcome

Among the 34 cases, 14 cases were treated by surgery alone, 6 cases with surgical combined with radiotherapy, 2 cases were treated with combined surgery, radiotherapy, and chemotherapy, 8 cases with surgery and steroid, 2 cases underwent combined surgery, steroid, and chemotherapy, 1 case with steroid only, and 1 case did not undergo any treatment after diagnosing KD by the cytological puncture. For 23 cases with follow-up data, 8 cases experienced recurrence, with a recurrence rate of 34.78%. Among recurrence cases, 4 cases were treated with surgery alone, 1 case was treated with combined surgery, steroid and, chemotherapy, 2 cases underwent surgical combined with steroid, 1 was treated by surgery and radiotherapy, died 4 months after radiotherapy. 7 cases recurred within 2 months to 3 years after treatment. 5 were showed pruritus, and 2 showed hyperpigmentation (Figure 4). 34 cases of Kimura's disease were treated. Methods and prognosis (Table 3).

Pathological Characteristics

In the study, the pathology report suggested partial glandular destruction, lymphoid follicular hyperplasia with massive eosinophilic infiltration, and prominent eosinophilic micro-abscesses and follicular lymphoid hyperplasia [6] (Figure 5). The immunohistochemical analysis of 16 cases, a lot of CD3-positive were present in 13 cases and a large number of CD20-positive in 13 cases, partial CD21 positivity can be seen in 9 cases, Bcl-6 was positive in 8 cases and Bcl-2 was positive in 2 cases. A few IgG-positive were observed in 8 cases. In situ hybridization, 8 cases showed EBER CISH negative and 2 cases showed Braf (V600E) negative.

Recurrence Predictors

Follow-up data on 23 patients revealed that and 8 patients recurred within 2 months to 3 years after the treatment, the recurrence rate was 34.78%. Table 4 shows predictors of recurrence. Univariate analysis showed duration (P=0.006) and lymphocytes (P=0.021) were associated with recurrence. There were no significant recurrence-related differences in gender, age, location, multiplicity, laterality, maximum size, symptom, eosinophils, eosinophil count, neutrophils, lymphocyte count, smoking and drinking history, past medical history (P<0.05).

Table 4: Recurrence predictors.

factor	Total	recurrence	P-value
Gender			0.482
Male	19	6	
Female	4	2	
Age			0.879
<40	11	4	
>=40	12	4	
Duration			0.006
<1	10	1	
1~5	9	3	
>5	4	4	
Smoking history			0.955
none	20	7	
have	3	1	
Alcohol history			0.651
none	19	7	
have	4	1	
Site			0.214
Head and neck	20	6	
Head, neck and other parts	3	2	
Multiplicity			0.363
Single	17	5	
Multiple	6	3	
Laterality			0.181
Unilateral	18	5	
Bilateral	5	3	
Maximum size, cm			0.113
<3cm	12	4	
≥3cm	9	4	
swelling	2	0	
Pruritus			0.591
None	16	5	
Have	7	3	
Hyperpigmentation			0.363
None	17	5	
Have	6	3	
Boundary			0.433
Clear	5	1	
Unclear	18	7	
Eosinophils (%)			0.175
Normal	3	0	
Elevated	20	8	
Eosinophil count (10^9/L)			0.175
Normal	3	0	
Elevated	20	8	
Neutrophils (%)			0.591
Decreased	7	3	
Normal	16	5	
Elevated			
Lymphocytes (10^9/L)			0.021
Decreased	3	2	
Normal	20	6	
Elevated	0	0	
Lymphocyte count (10^9/L)			0.175
Decreased	3	0	
Normal	20	8	
Elevated	0	0	
Cardiovascular history			0.455
None	22	8	
Have	1	0	
Allergic reaction history			0.591
None	16	5	
Have	7	3	

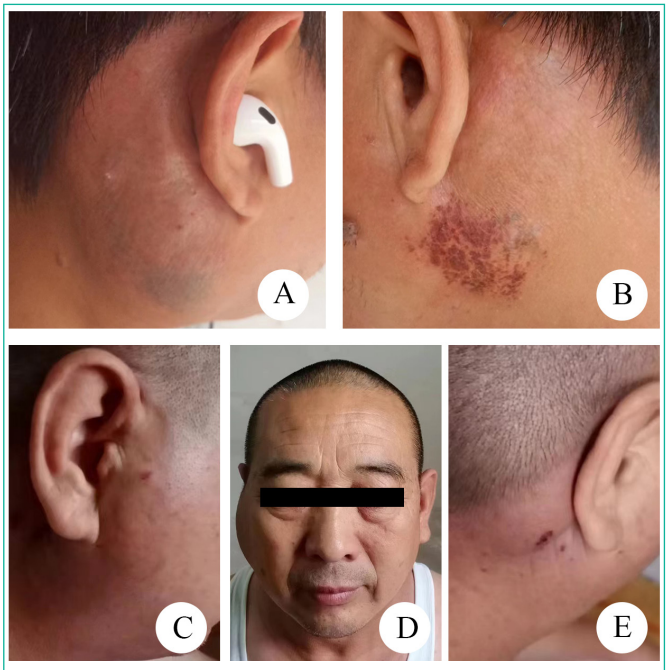

Figure 4: Recurrence after treatment for Kimura disease. (A, B) Patient 1, was treated by surgery and steroid, hyperpigmentation and pruritus of bilateral parotid glands showed 6 months after treatment. (C, D, E) Patient 2, was treated by surgery alone, relapsed two months after treatment, and manifested as bilateral painless masses.

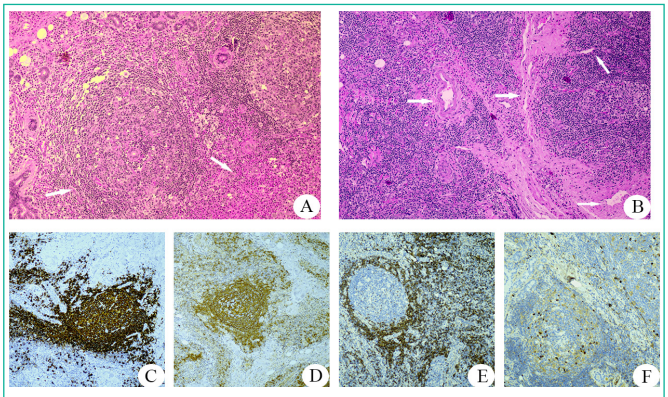

Figure 5: Histologic features (Hematoxylin–eosin staining magnification: ×100) (A) Prominent eosinophilic infiltrate with micro-abscesses formation, and lymphoid follicular hyperplasia. (B) Increased vessel. (C) A large number of CD20-positive. (D) Partial CD21 positivity. (E) Bcl-2 was positive; F: A few IgG4-positive cells.

Discussion

Kimura's disease is a chronic inflammatory disease and presents as a painless mass or subcutaneous nodule with pruritus occasionally. The lesions are single or multiple, and may appear in different locations over several years [7-11]. KD often involves the salivary glands, and cervical lymph nodes, and also involves other areas such as the armpits and groin. When salivary glands and cervical lymph nodes are involved, they need to be differentiated from malignant lymphoma, and parotid tumors such as Warthin's tumor.

In the study, the average duration of KD was 3.8 years, and the longest case was up to 30 years. 58.82% occurred unilaterally and 55.88% showed multiple. 30 cases developed in the head and neck region, of these, 53% involved the parotid gland, and 13.3% showed the eyelids. It may be considered that there are more lymph nodes in the head and face, so the parotid glands, eyelids, and other upper cervical lymph nodes were involved earlier. Gao et al [12] reported that increased eosinophils in the subcutaneous tissue induced the release of relevant cytokines and neurotransmitters, when delivered to the sensory nerve fibers in the subcutis, resulting in pruritus. In our study, all cases with pruritus were accompanied by elevated eosinophils, similar to our results. We found that the lesion skin was accompanied by hyperpigmentation, which has not been reported previously.

MRI helps identify the location and size of the mass and the diagnosis. Previously reported that KD was considered when MRI demonstrated an ill-defined lesion and increased lymph nodes, which is similar to this study [13,14]. In our study, it can be classified into two types according to the MRI, one is a well-defined nodular lesion and the other is an ill-defined patchy or lobulated lesion. Boundaries may be related to the duration of inflammatory infiltration around the lesion. In addition, increased lymph nodes and diffuse atrophy of subcutaneous fat at the lesion are characteristic imaging findings of KD.

The pathogenesis of KD is not clear. According to Munemura et al [15], when the body's immunity is disordered, a large number of T helper (Th) cells differentiate into type 2 helper T (Th2) cells and release cytokines, collectively activating eosinophils and causing serum eosinophilia. In our study, bone marrow puncture and blood routine showed eosinophils, which may be related to pathogenesis. Pathology is the gold standard for diagnosis, characteristics of KD include dense lymphoid follicular hyperplasia, massive eosinophilic infiltration, accumulation of micro-abscesses, venular hyperplasia, and differing extents of fibrosis [16-18]. Bi et al [19] reported of KD involving the eyelids, a lot of CD3-positive and partial CD20 positivity were present in the lymphoid follicles, and CD20-positive were observed in all areas. Gurram et al [20] showed CD3 and CD20 positivity in the submandibular region. BCL-6 is specific for B lymphocytes, and is often identified with reactive follicular hyperplasia, lymphomas, and malignant tumors [21]. In the study, it was found that a few IgG positives were because of the synthesis of B cells induced by cytokines released by Th cells [15,22,23].

Definite diagnosis is for better treatment, many treatment modalities have been proposed, including surgery, steroid, chemotherapy, radiotherapy, and combined treatment modalities, but there has been no consensus up to now. Some [24,25] reported recommending surgical resection with negative margins is preferred. Although it is considered to be a benign disease, KD is sensitive to radiotherapy and is the first choice for recurrent cases or patients with incomplete resections [26]. Multiple cases should be treated with steroids, but it is easy to relapse during the clinical course [27-30], therefore, it is a second-line regimen in the treatment of KD. In the study, the recurrence rate for those who were treated by surgery alone was 17.39%, the recurrence rate for those who were treated by surgery and steroid was 8.69%, the recurrence rate for those who underwent combined surgery, steroid and, chemotherapy was 4.35%, the recurrence rate for those who was 4.35%, and 1 case were treated by surgery and radiotherapy who died 4 months after radiotherapy.

Recurrence rates are high even after treatment, which is related to ill-defined lesions and increased lymph nodes. In previous reports, we found that eosinophilia, maximum size of the mass, and pruritus are associated with recurrence [31]. Yang et al [14] followed up on 29 patients and found that symptom duration, bilateral, size, eosinophilia, and ill-defined mass were the main predictors of recurrence. Our study shows that duration longer than or equal to 5 years and lymphocyte decrease are associated with recurrence, which helps us to better reduce the recurrence rate.

Conclusions

In the study of 34 patients, our study confirmed that KD is considered with painless masses or lymph node involvement, accompanied by pruritus and hyperpigmentation, and eosinophilia. MRI showed well-defined nodular lesions or ill-defined patchy or lobulated lesions, increased lymph nodes and diffuse atrophy of subcutaneous fat at the lesion are characteristic imaging findings of KD. Pathology is the best way of diagnosis, immunohistochemistry showed diffuse expression of CD3, CD20, and CD21, as well as partial expression of Bcl-6 positivity and weak IgG4 positivity. After surgery, we can choose appropriate adjuvant treatment according to duration and lymphocytes to control recurrence.

Abbreviations

KD: Kimura's disease; TIVA: Total intravenous anesthesia; Ig E: Immunoglobulin E; MRI: Magnetic resonance imaging.

Authors' Contributions

JX wrote the paper. PFX carried out data collection. CYH, CMH and KS were involved in statistical analysis. WQL and XQ modified the paper and designed this study concepts. All authors read and approved the final manuscript.

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Availability of Data and Materials

The raw data are confidential and cannot be readily shared. Researchers need to obtain permission from the institutional Review Board and apply for data access to The Ethics Committee of The study was approved by the ethics committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology.

Declarations

Ethics Approval and Consent to Participate

The study was approved by the ethics committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (TJ-JRB20231293). All participants volunteered for the study, were informed about the scope of the study and provided written consent.

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