Kimura’s disease: risk factors of recurrence and prognosis

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Abstract: Objectives: The aim of this study was to evaluate risk factors for recurrence and prognosis of Kimura’s disease. Methods: In this study, 32 patients received surgery alone, surgery followed by steroids orally and surgery followed by radiotherapy respectively from 2003 to 2015 (male/female: 27/5, ages: 6-64 years). Retrieval of clinical data and follow-ups have been done. The clinical features used as variables include age, gender, location, multiplicity, laterality, size, duration, primary outbreak, smoking, eosinophils, systemic disease and remedies. Statistical analysis including Kaplan-Meier method, Fisher’s exact test, Kruskal-Wallis H test, Mann-Whitney U-test and Cox proportional hazard regression model were performed with the SPSS 17.0. The threshold of statistical significance was set at $P=0.05$. Results: Median recurrence time was 29 months (2.42 years) after discharged and 56.3% patients relapsed. High recurrence rate was significantly associated with smoking habit ($P=0.036$). Patients who were diagnosed systemic disease ($P=0.027$) and were treated with surgery alone ($P=0.025$) or surgery followed by steroids orally ($P=0.025$) had short disease-free time. Furthermore, smoking habit (HR=3.383, 95% CI: 1.213-9.433, $P=0.02$), systemic disease (HR=4.462, 95% CI: 1.443-13.794, $P=0.009$), surgery alone (HR=4.668, 95% CI: 1.506-14.470, $P=0.008$) and surgery followed by steroids orally (HR=6.053, 95% CI: 1.330-27.556, $P=0.02$) were identified as risk factors for the prognosis of Kimura’s disease. Conclusions: Smoking habit, systemic diseases, surgery alone and surgery followed by steroids orally were associated with poor prognosis of Kimura’s disease, and they might be prognostic markers of Kimura’s disease.

Keywords: Kimura’s disease, recurrence, prognosis, smoking, radiotherapy

Introduction

Kimura’s disease (KD) is the benign, chronic inflammatory disorders with vague etiology, rarely found in Caucasians. It was firstly introduced in China by Kim and Szeto in 1938, but its name was given by Kimura in 1948 from Japan [1, 2]. About four hundreds patients with KD have heretofore been described worldwide [3]. Soft-tissue mass in the head and neck regions, elevated serum immunoglobulin E (IgE) and raised eosinophils are three most prominent features of this disease. Lymphatic tissue and major salivary glands could also be involved. The third decade male was predominately affected comparing to female. Head and neck regions were found to be affected more than any other regions, especially parotid glands and regional lymph nodes. Even though this disease have not shown any malignant transformation, it is often difficult to cope with because of its high recurrence rate. Surgery, steroids [4] and radiotherapy [5] have been used widely as first line recommendation, but none of them is standard procedure till now because of high recurrence rates. It was reported that rates of recurrence reached up to 62% [6].

Studies on the recurrence of KD are important in identifying factors that influence survival. It is also useful in counseling patients. Therefore, identifying new prognostic markers might enable a better treatment of the disease. To the best of our knowledge, investigation of recurrent rates with smoking, systemic disease and remedies were scarce. The aim of this paper is
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This is a retrospective study of 32 patients histopathologically proven as KD from 2003 to 2015 in our department. Pathological features could be found as follows: follicular proliferated of the lymphoid tissue, with different degrees of vascular proliferation and fibrosis, and a large number of eosinophils, lymphocytes, plasma cells, and mast cells infiltrated.

Clinical data were taken and follow-ups were undergone. Those who were lost in follow-ups were excluded. The main end point was recurrence, and recurrence was defined as complaint of swelling or pruritus after intervention as well as confirmed histopathologically. Disease-free time was calculated from the date of discharge to the recurrence or to the deadline of interview if did not relapse. Consent in written was obtained from patients after full explanation of the surgical procedures, likely outcomes and possible complications.

All patients underwent surgical treatment, then received follow-ups, steroids orally or radiotherapy respectively. Prednisone was prescribed 10-60 milligrams every day orally and then the dosage was reduced gradually in surgery followed by steroids orally group. The total radiation doses ranged from 36 to 40 Gray (Gy) with 2 Gy per fraction daily in the third therapy.

### Statistical analysis

Fisher’s exact test was used to clarify age, gender, location, multiplicity, laterality, size, duration, primary outbreak, smoking and systemic disease association with recurrence. Comparisons of disease-free time between age, gender, location, multiplicity, laterality, size, duration, primary outbreak, smoking, systemic disease, eosinophils and remedies were performed using the Kruskal-Wallis and Mann-Whitney U-test accordingly. The Kaplan-Meier method was used to estimate recurrence rates, and the univariate Cox-regression model was utilized to assess the difference between age, gender, location, multiplicity, laterality, size, duration, primary outbreak, smoking, systemic disease, eosinophils and remedies. The Cox proportional hazards model for multivariate survival analysis was performed to identify predictors related to prognosis if variables were considered statistically significant in univariate analysis. All statistical analyses were analyzed using SPSS software (SPSS 17.0, Chicago, IL, USA) and a

### Table 1. Clinical details and the rates of recurrence in KD

<table>
<thead>
<tr>
<th>Variables</th>
<th>Recurrence rate (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.072</td>
<td></td>
</tr>
<tr>
<td>&lt;35 years [14]</td>
<td>35.7</td>
<td></td>
</tr>
<tr>
<td>≥35 years [18]</td>
<td>72.2</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>0.631</td>
<td></td>
</tr>
<tr>
<td>Male [27]</td>
<td>59.3</td>
<td></td>
</tr>
<tr>
<td>Female [5]</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head and neck regions [26]</td>
<td>57.7</td>
<td>0.99</td>
</tr>
<tr>
<td>Others [6]</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Multiplicity</td>
<td>0.446</td>
<td></td>
</tr>
<tr>
<td>Single [10]</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Multiple [22]</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Laterality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral [16]</td>
<td>56.3</td>
<td>0.99</td>
</tr>
<tr>
<td>Bilateral [16]</td>
<td>56.3</td>
<td></td>
</tr>
<tr>
<td>Size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3.5 cm [10]</td>
<td>60</td>
<td>0.99</td>
</tr>
<tr>
<td>≥3.5 cm [22]</td>
<td>54.5</td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>&lt;5 years [14]</td>
<td>57.1</td>
<td></td>
</tr>
<tr>
<td>≥5 years [18]</td>
<td>55.6</td>
<td></td>
</tr>
<tr>
<td>Primary outbreak</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>Primary [21]</td>
<td>57.1</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>0.036</td>
<td></td>
</tr>
<tr>
<td>Yes [14]</td>
<td>78.6</td>
<td></td>
</tr>
<tr>
<td>Never [18]</td>
<td>38.9</td>
<td></td>
</tr>
<tr>
<td>Systemic disease</td>
<td>0.104</td>
<td></td>
</tr>
<tr>
<td>Yes [7]</td>
<td>85.7</td>
<td></td>
</tr>
<tr>
<td>No [25]</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Eosinophils</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>&lt;20% [14]</td>
<td>57.1</td>
<td></td>
</tr>
<tr>
<td>&gt;20% [18]</td>
<td>55.6</td>
<td></td>
</tr>
<tr>
<td>Remedies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery alone [10]</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Surgery + steroids [5]</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Surgery + radiotherapy [17]</td>
<td>41.2</td>
<td></td>
</tr>
</tbody>
</table>

to draw attention to recurrent risk factors and prognosis of KD which have been ignored.

### Material and methods

Approval from Institutional Review Board was obtained at the First Affiliated Hospital of Xinjiang Medical University prior to its conduct.
level of probability lower than 5% was considered as significant.

Result

Five were female and 27 were male in 32 patients, with a female to male ratio of 1:5.4. Age varied from 4 to 64 years ($\bar{x} \pm s = 33.4 \pm 18.0$), but peaked at the second and the fifth decades. The specimens were mostly resected from the periauricular regions with or without parotid glands involvement. Other sites involved by disease included submandibular gland, post ocipital region, parietal region, submental region, elbow, upper eyelid,inguinal region, bilateral breasts, neck region, and bilateral nasal cavity regions. The maximum size of lesion was 7.8 cm. The main findings were irregular masses with pruritus and pigmentation. Elevated peripheral blood eosinophil percentages ($\bar{x} \pm s = 25.01 \pm 18.58\%$) was identified in 28 patients (87.5%).

Systemic diseases defined as patients who were infected by hepatitis B virus, hepatitis C virus or diagnosed hypertension, cardiovascular disease, asthma or nephrotic syndrome by specialists. In our study, seven patients were diagnosed at least one of disease above.

Three different treatment modalities have been done for 32 patients: surgery alone, surgery followed by steroids orally and surgery followed by radiotherapy. Ten patients underwent surgery alone, five patients were given surgery followed by steroids orally and 17 patients were given surgery followed by radiotherapy.

Smoking habit ($P = 0.036$) was significantly associated with recurrence of KD. However, age, gender, multiplicity, laterality, size, location, duration of disease, primary outbreak, and systemic disease were not (Table 1).

The deadline of interview was Apr. 2015, with follow-ups of 1 to 102 months after discharge (median: 15 months). The overall cumulative recurrence rate was 56.3% (18/32) and median recurrence time was 29 months (2.42 years) after discharge (Figure 1). Ten patients who received surgery alone, two were cured but 8 did not. Among 5 patients from the surgery followed by steroids orally group, 2 were cured...
and 3 recurred. From the surgery followed by radiotherapy group, ten patients were cured but 7 relapsed.

Systemic disease (P=0.027) and remedies (P=0.021) were significantly associated with disease-free time (Table 2). We identified that those had longer disease-free time who were not diagnosed hepatitis B virus, hepatitis C virus, hypertension, cardiovascular disease, asthma or nephrotic syndrome and who were treated with surgery followed by radiotherapy. Differences in disease-free time were not statistically significant by gender, age, eosinophils, locations, laterality, multiplicity, size, duration, primary outbreak and smoking.

Univariate analysis was carried out to identify those factors significantly associated with KD recurrence. Statistically, smoking (P=0.029), systemic diseases (P=0.016) and remedies (P=0.014) were significantly associated with recurrence (Table 3), while age, gender, eosinophils, multiplicity, laterality, size, duration and primary outbreak were not.

Multivariate analysis indicated that smoking, systemic diseases, surgery alone and surgery followed by steroids orally were independent prognostic factors of recurrence (Table 3).

Discussion

KD is the chronic inflammatory disorders with T helper (Th) 2 predominant and strong dermatological manifestations such as: skin pruritus, overlying skin discolotation and coarseness of skin, reported firstly by Kimura and Szeto in 1938 but popularized after 1948 when Kimura from Japan elaborated its histological finding as “unusual granulation combined with hyperplastic changes in lymphoid tissues” [2, 7]. With unclear etiology, this disease was epidemic among the third decades male in Oriental. Many theories have been postulated regarding its etiology like allergic reaction, viral or parasitic trigger, impairment or interference with immune regulation, atopic reaction to a persistent antigenic stimulus by arthropod bites [8] and neoplasm. Clinical differential diagnoses include Angiolymphoid hyperplasia with eosinophilia, benign or malignant lesion of glands, Hodgkin’s disease, chronic inflammatory disorder of glands, and autoimmune diseases, such as Sjogren’s syndrome, granulomatous disorder of glands, etc. Hematologically, elevated serum IgE and peripheral eosinophils were distinguished KD from other disease. We have also shown eosinophilia ranging from 0.6% to 75.2%. But IgE level merely has been tested in 5 cases (not shown in data).

In our study, a female to male ratio was 1:5.4, which is similar to previous literature of 1:5.7 ratio [9]. The mean age was 33.4 years. KD was involved mostly in the head and neck region, especially major salivary glands and regional lymph nodes involvement. In 32 patients, lesions were also found in the postoccipital region, parietal region, submental region, elbow, upper eyelid, inguinal, bilateral breasts, neck region, and bilateral nasal cavities. Sporadic lesions have also been reported in epiglottis, scalp, lacrimal glands, larynx, spermatic cord, median nerve, heart, axillary or popliteal region and chest wall [10-13].

In this article, the median time of follow-up was 15 months with 56.3% recurrence. Median
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Recurrence time was 29 months (2.42 years) after discharged. In a series of articles, the mean follow-up time ranged from 1 to 5.8 years with 17%-62% recurrence [3, 6, 14-17]. This disagreement may be caused by various sample size and duration of follow-up. What's more, we included chief complaint, such as itching or tumefaction, as one of markers for recurrence, it might contribute to this high recurrence rate. Learning from other literatures, follow-up should be going on and sample size should be enlarged in our following research. It was first time to find the median recurrence rate owing to high recurrence rate in this article. Half of patients recurred at 29 months after discharged. Based on this data, it is the duration of 29 months that was recommended in follow-up to identify recurrence.

Previous studies unveiled that patients with eosinophil counts >50%, serum IgE levels >10,000 IU/mL, multifocal lesions outside the salivary glands, disease duration of greater than 5 years, bilateral involvement, a lesion diameter of greater than 3 cm, a blood eosinophil count greater than 20%, and ill-defined lesions suggested recurrence [3, 6, 14]. But in our study, none of those were found as markers of recurrence. These discrepancies may be attributed to different populations and sample size. Meanwhile, our diagnosis was supported by excisional biopsy, which was the top evidence for diagnosis, rather than core needle biopsy in some articles. We, however, found new prognosis indicators for KD. Among the evaluated prognostic factors, smoking, systemic diseases, surgery alone and surgery followed by steroids orally had prognostic value, which were not compatible with most literature data.

Smoking is a factor associated with recurrence. This might be explained by reasons that the IgE count and blood eosinophil count were relatively higher in smoker than in non-smoker [18-20] as well as elevated white blood cells and Th2 phenotype polarization [21-29]. In addition, smoking and higher IgE levels were independent risk factors for higher blood eosinophil counts. Although the relationship between smoking and activation of specific allergens was controversial [30], smoking may play a role for allergens [31, 32]. Also cigarette contains high levels of tar and other chemicals, which make patient’s immune system less effective at fighting against infections. Persistent weakening of the immune system could make them more vulnerable to diseases.

As for systemic diseases, they were associated with hepatitis B, hepatitis C, hypertension, cardiovascular disease, asthma and nephrotic syndrome. It was not well-established about relationships between hypertension, cardiovascular disease with recurrence of KD. Hypertension is one of top-risk factors in cardiovascular disease, including ischemic coronary disease, stroke, peripheral arterial disease, which were originated from atherosclerosis. Hypertension could accelerate the rate of atherosclerotic plaque maturity [33-35]. Specific and non-specific immunities were bound up with atherosclerosis [36], Th2 cells have been linked to atherosclerosis, even though controversy still existed [37, 38]. Not only were the dogma of Th1/Th2 paradigm of great importance in the progress, but also regulatory T cells and macrophages [39]. Speculation of immune system imbalance was inevitable.

Hepatitis B and hepatitis C stimulated production of great number of cytokines, especially pro-inflammatory ones. Both Th1 and Th2 lymphocytes have an influence on these processes. It was reported that HBeAg resulted in Th2-type cytokines responses [40]. Hepatitis C virus up-regulated Th2 cytokine [41]. Needless to say, asthma and nephrotic syndrome were immune impairment diseases with Th2 predominant either. Especially, nephrotic syndrome was one of complications in KD. It is obviously refractory to treatment.

Surgery, medical therapy [4] and radiotherapy [5] are three different modalities have been tried for the management of this disease, but none of them have been recommended to be first-line procedure because of high recurrence.

Surgery has been considered as first choice of management. But, as unclear boundaries and infiltrative nature, completely surgical removal was limited. Additionally, if the size of lesion was too large, surgery might cause unacceptable facial deformity. In our study, out of 32 patients, ten patients were given only surgical therapy. Two were cured and eight had recurrence.

Steroids have also been used popularly for KD, but high recurrence once the drug withdrawn
was reported in many researches [1, 4]. In several cases, steroids could alleviate the eosinophilia [42]. These reductions were transient and bounce-back was identified when the medicine was stopped. In our study, five patients were given surgery followed by steroids orally. Two were cured and 3 had recurrence.

Radiotherapy has been also considered as more effective therapy than long-term use of steroids and where surgery might not be accepted as severe cosmetic defect. Even though radiotherapy was controversial because of its indolent and non-malignant transformation, low dose radiation is effective and safe both in the short term and in the long run. Maybe radiotherapy was more beneficial than the long-term prescribed steroids orally. In accordance with literatures [43], our total radiation dosage was moderate. During the final follow-up, none of radiation induced malignant tumor was observed. It was impressive when combined with surgery. In our study, seventeen patients were given surgery and radiotherapy, ten were cured and 7 had recurrence.

In conclusion, Even though KD is benign in nature, it is often difficult to treat because of prolonged course and high recurrence rate. Smoking habit, systemic diseases, surgery alone and surgery followed by steroids orally were associated with poor prognosis of KD. Therefore, surgery followed by radiotherapy was considered as an optimal therapy in this data. Then, we should pay more attention to those patients with poor prognosis clinical characteristics. As KD is very rare, more patients were required.

Disclosure of conflict of interest
None.

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