

Clinical Paper  
Clinical Pathology

# Comparison of the efficacy of different treatment modalities for Kimura's disease

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**Abstract.** The objective of this study was to investigate the clinical features of Kimura's disease in the head and neck region and to compare the local recurrence rate between three therapies used for the treatment of this disease. The clinicopathological information of 46 hospitalized patients suffering from Kimura's disease in the head and neck region over a 10-year period was reviewed retrospectively. All lesions were clinically observed in the head and neck region. These 46 patients underwent a total of 58 treatments; nine patients underwent multiple treatments due to local recurrence. Of the 58 treatments, 32 involved surgical excision alone, 24 involved surgical excision and postoperative low-dose radiotherapy (20–40 Gy), one was a combination of ultrasound-guided core needle biopsy and radiotherapy, and one was a combination of incisional biopsy and subsequent radiotherapy. During the follow-up period, nine patients suffered 16 local recurrences. The recurrence rate of surgical excision combined with low-dose radiotherapy was much lower than that of surgical excision alone or radiotherapy alone (both  $P < 0.05$ ). It is concluded that Kimura's disease is a benign condition with a good prognosis, and surgical excision combined with postoperative low-dose radiotherapy is associated with the lowest local recurrence rate in the treatment of this disease.

**Key words:** Kimura's disease; recurrence; surgical excision; radiotherapy.

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In 1937, a Chinese oncologist named Kimm described seven patients with enlarged lymph nodes that exhibited pathological eosinophilic infiltration and termed this entity 'eosinophilic hyperplastic lymphogranuloma'.<sup>1</sup> Subsequently, Kimura et al. described the pathological features of this condition,<sup>2</sup> and since then Kimura's disease has become widely recognized.

Kimura's disease is a rare and chronic inflammatory lesion of unknown aetiology that most commonly presents in the head and neck region of Asian men. Clinical examination generally reveals subcutaneous swelling or nodules in the head and neck region that is partially associated with regional lymphadenopathy. The incidence peaks during the second and fourth

decades of life, and approximately 80–87% of patients are men.<sup>3</sup> With a prolonged indolent course, Kimura's disease is known as a disfiguring condition, carrying no risk of malignant transformation even without treatment.

The definite aetiology and pathogenesis of Kimura's disease remains unclear. A recent study demonstrated that the

interaction between type 1 and type 2 helper T-cells may be involved in the development of Kimura's disease.<sup>4</sup> Moreover, Day et al. suggested that Kimura's disease occasionally shows a clonal proliferation of T-cells.<sup>5</sup> As Kimura's disease has an unknown aetiology, there is currently no preventative management for this condition.

No optimum treatment modality for symptomatic Kimura's disease is reported in the literature, although surgery, radiotherapy, steroid therapy, and intravenous immunoglobulin have proven effective.<sup>4</sup> Surgical procedures are preferred for primary lesions without general contraindication, and postoperative steroid therapy is recommended, especially for patients with nephrotic syndrome.<sup>5</sup> However, radiotherapy is considered satisfactory for recurrent cases or poor surgical candidates. Hareyama et al. recommended a dose of approximately 26–30 Gy for irradiation, and the radiation field should be confined to the area of the lesion and regional lymph nodes.<sup>6</sup>

The details of 46 patients with Kimura's disease are presented here. An analysis was performed of the patient clinical characteristics, with a focus on treatment regimens and corresponding outcomes. Furthermore, a comparison of the local recurrence rate of three therapies used for the treatment of Kimura's disease was conducted.

## Patients and methods

Over a 10-year period (2004–2013), 46 patients with a clinicopathological diagnosis of Kimura's disease were treated at the study institution. Detailed clinical data were retrieved from the patients' medical charts, including sex, age, site involved, clinical duration, laboratory workup, treatment modality, and pathological diagnosis. Demographic information and details of these patients were analyzed. The clinical management of these cases was summarized, including the use of surgical excision, core needle biopsy, incisional biopsy, and low-dose radiotherapy.

Each treatment decision was made by a specific doctor based on their own experience. Surgical excisions were performed by different surgeons. As the salivary glands (submandibular gland, parotid gland, and minor salivary gland) were involved, the surrounding gland tissue was excised during surgery. Postoperative radiation of 20–40 Gy to a single field (2 Gy each day, 5 days a week) was delivered within 1 month after surgery.

The follow-up period ranged from 12 months to 120 months, with a mean period

of 65 months. Recurrence was evaluated through clinical and radiological examinations. The rate of loss to follow-up was 8.7%. Continued observation or further treatment for recurrent lesions was determined on the basis of the follow-up results.

For the statistical analysis, all data were analyzed using IBM SPSS Statistics version 20.0 software (IBM Corp., Armonk, NY, USA). The  $\chi^2$  test and Fisher's exact test were used to compare the recurrence rate between the different treatment modality groups;  $P < 0.05$  was considered statistically significant.

## Results

### Clinical characteristics

Out of the 46 patients examined, 40 were male and six were female, giving a male-to-female ratio of 6.7:1. The age at onset ranged from 5 to 78 years (median age 41 years). With regard to the anatomical distribution, 23 cases (50%) involved the parotid region (six cases involved the bilateral parotid regions), 14 cases involved the submandibular region, and six cases involved multiple regions. Twenty-nine patients developed a solitary lesion of Kimura's disease. The remaining patients demonstrated multiple lesions to differing extents in the head and neck region upon clinical examination (Fig. 1).

Eight patients (17.4%) in this series presented with melanin pigmentation, five (10.9%) with coarseness, and nine (19.6%) with pruritus of the affected overlying skin. Spontaneous growth and decline was observed in two patients.

Only one patient presented with nephrotic syndrome; this patient died of subsequent renal failure. The laboratory

Table 1. Clinical features of 46 patients with Kimura's disease.

Clinical characteristics	No. of patients
Age at onset, years	
≤20	6 (13.0%)
20–40	16 (34.8%)
>40	24 (52.2%)
Sex	
Male	40 (87.0%)
Female	6 (13.0%)
Anatomical location	
Parotid	23 (50%)
Submandibular	14 (30.4%)
Submental	1 (2.2%)
Cervical	2 (4.3%)
Multiple sites	6 (13.0%)
Peripheral blood eosinophilia	40 (87.0%)
Coarseness of overlying skin	5 (10.9%)
Pruritus	9 (19.6%)
Melanin pigmentation	8 (17.4%)
Spontaneous growth and decline	2 (4.3%)
Renal failure	1 (2.2%)

results of 40 patients (87.0%) revealed markedly elevated eosinophil counts in the peripheral blood (Table 1). Unfortunately, serum IgE levels were not recorded for this series.

The lesions most often appeared as hypoechoic masses or enlarged lymph nodes on preoperative ultrasonography. Typically, computed tomography revealed an expansive and ill-demarcated subcutaneous mass (Fig. 2). In addition, diffuse swelling of the nearby soft tissue could be seen in a few cases.

### Management and prognosis

The 46 patients examined underwent 58 treatments; nine patients underwent



Fig. 1. Kimura's disease: the patient presented with bilateral parotid subcutaneous swelling, seen on frontal view.

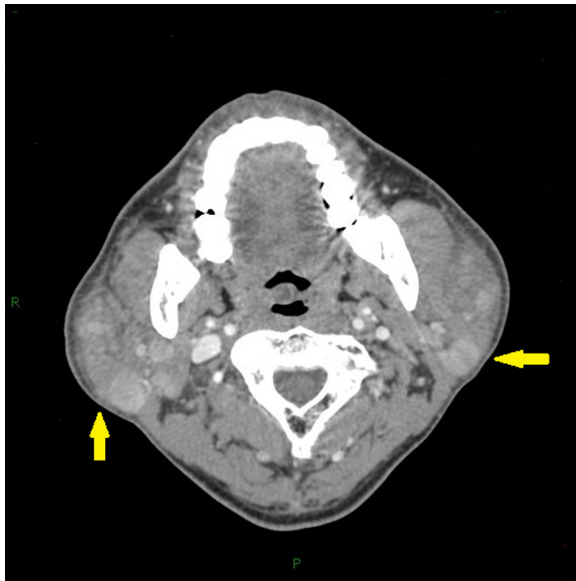


Fig. 2. Axial computed tomography scans demonstrated multiple bilateral ill-defined subcutaneous lesions involving the parotid gland tissue.

multiple treatments due to local recurrence. Treatment grouping was done according to the number of treatments, rather than the number of patients. Of the 58 treatments, 32 were surgical excision alone (the surgical margin was negative in all 32 cases), 24 were surgical excision combined with postoperative low-dose radiotherapy of 20–40 Gy (due to an ill-defined lesion border, partial excision was performed in all 24 cases; accordingly the surgical margins were all positive), one was a combination of ultrasound-guided core needle biopsy and subsequent radiotherapy (50 Gy), and one was a combination of incisional biopsy and subsequent radiotherapy (50 Gy). No patient was administered steroid drugs due to the frequent relapse after withdrawal of the medication.

This study was conducted retrospectively. Patients received different therapies from different consulting doctors. Each treatment modality was selected by a specific doctor based on their own experience.

Nine of the 46 patients suffered 16 local recurrences and underwent multiple clinical interventions. During the follow-up period (ranging from 12 months to 120

months), the overall recurrence rate was 27.6%. No radiation-induced carcinogenesis was observed after low-dose radiotherapy, and only a few elderly patients complained of slight xerostomia. With the exception of one patient who presented temporary facial nerve paralysis postoperatively (recovered 3 months later), no patient showed signs of nerve damage. Moreover, other common complications of salivary gland surgery such as salivary fistula and Frey syndrome were not observed in this series.

The recurrence rate in the group that underwent surgical excision alone was 37.5% and the recurrence rate in the group that underwent radiotherapy alone was 100%; surgical excision combined with low-dose radiotherapy showed a recurrence rate of 8.3%. There was no difference in anatomical site between the groups ( $P > 0.05$ ). The  $\chi^2$  test and Fisher's exact test were applied for statistical analysis and it was found that the recurrence rate in the surgical excision combined with low-dose radiotherapy group was much lower than the rates in the surgical excision alone and radiotherapy alone groups ( $P = 0.015$  and  $P = 0.018$ , respectively) (Table 2).

## Discussion

Kimura's disease is a rare and chronic inflammatory lesion with a peak incidence during the second and fourth decades of life; approximately 80–87% of patients are men.<sup>4</sup> Clinically, in the present series, the median age at onset of Kimura's disease was 41 years, consistent with the onset reported in the literature (second and fourth decades).<sup>3</sup> Forty of the 46 patients in this series were men, giving a male-to-female ratio of 6.7:1. This is similar to the sex distribution reported in a previous review of 194 cases, which presented a prominent male predominance.<sup>7</sup> However no possible pathogenesis for the male predominance associated with Kimura's disease has yet been described. Some immune system diseases like systemic lupus erythematosus (SLE) present a prominent female predominance, and it has been reported that sex hormones and genetic disparities account for the pathogenesis and incidence of SLE.<sup>8</sup> Therefore, it is suspected that sex hormones and genetics may also play an important role in the male predominance of Kimura's disease.

Kimura's disease commonly presents as a subcutaneous mass in the head and neck region. In terms of lesion sites, 23 cases in this series (50%) were located in the parotid region (including six that involved the bilateral parotid sites), 14 (30.4%) in the submandibular region, and 6 (13.0%) in multiple regions. It is concluded that the parotid and submandibular regions are the sites most commonly affected by Kimura's disease, as reported previously.<sup>9</sup> Thus, Kimura's disease should be considered when a relatively young man presents with subcutaneous swelling in the head and neck region (especially in the case of multiple lesions in the parotid, submandibular, or cheek regions).

Kimura's disease is frequently associated with melanin pigmentation or pruritus of the overlying skin, a history of spontaneous resolution, lymphadenopathy, elevated levels of serum IgE, and eosinophilia. Gao et al. observed nerve infiltration by lymphocytes and eosinophils in patients with pruritus or pigmentation, explaining

Table 2. Local recurrence rates for the three types of treatment modality used in patients with Kimura's disease.<sup>a</sup>

Clinical management	Number of treatments	Number of recurrences	Recurrence rate	Significance
Combination of surgical excision and radiotherapy	24	2	8.3%	
Surgical excision alone	32	12	37.5%	$P < 0.05^b$
Radiotherapy alone	2	2	100%	$P < 0.05^c$

<sup>a</sup>In total, 46 patients underwent 58 treatments; nine of the 46 patients developed 16 local recurrences and underwent multiple clinical interventions. Treatment grouping was done in terms of the overall number of treatments, rather than the number of patients.

<sup>b</sup> $P$ -value = 0.015 for the comparison with treatment by combination of surgical excision and radiotherapy.

<sup>c</sup> $P$ -value = 0.018 for the comparison with treatment by combination of surgical excision and radiotherapy.

the possible pathogenesis of pruritus to some extent.<sup>9</sup> In the present study, eight patients (17.4%) presented with melanin pigmentation, five (10.9%) with coarseness, and nine (19.6%) with pruritus of the affected overlying skin. Spontaneous growth and decline was observed in two patients. The laboratory results of 40 patients (87.0%) revealed markedly elevated eosinophil counts in the peripheral blood. Therefore, in the present authors' experience, Kimura's disease should be highly suspected when these manifestations are encountered in the clinic.

Being a systemic condition, with peripheral eosinophilia and an increased IgE concentration, Kimura's disease has the potential to involve multiple organs. This could be explained by disturbances in the immune regulation of IgE and eosinophil production.<sup>10</sup> The involvement of the axilla, groin, hand, spermatic cord, and prostate has been reported in several studies on Kimura's disease.<sup>11–14</sup> It has been reported previously that Kimura's disease may lead to nephrotic syndrome (up to 60% of patients) in addition to head and neck involvement as an initial manifestation.<sup>15</sup> Only one patient in this study developed chronic renal failure in addition to head and neck lesions, and this was after a long clinical course of Kimura's disease. This low number of cases with chronic renal failure might be explained by the fact that most of the patients had had a relatively short course of Kimura's disease. As follow-up continues, more patients may present with renal involvement to different extents.

Several treatment modalities have been introduced in the literature, such as observation, surgical excision, radiotherapy, and steroid therapy.<sup>5,6</sup> However, due to its common recurrence, no method is yet recognized as the optimal therapy. Previous studies have reported the efficacy of steroids in controlling local lesions, lymphadenopathy, and nephrotic syndrome, but recurrence has frequently been seen while tapering the steroid dose or withdrawing the medication,<sup>16,17</sup> and long-term steroid medication may lead to osteoporosis, digestive ulcers, and acquired diabetes mellitus. No steroid medication was used in the present series of patients, due to the high associated recurrence. Surgical excision can be performed for both diagnostic and therapeutic purposes. However, on clinical and pathological examination, the lesions of Kimura's disease tend to be ill-defined. Therefore, it is difficult to achieve negative borders during surgery, and the reported recurrence rate is approximately 25%.<sup>5</sup>

Kimura's disease has been widely reported to react well to radiation. Radiotherapy has been advocated for patients with positive surgical margins, those with repeated recurrences after surgery, and for refractory relapse during systemic steroid treatment.<sup>6,18</sup> In order to avoid radiation injury and the potential risk of carcinogenesis from radiation, a low dose of radiotherapy is advocated. Hareyama et al. achieved a 90% local control rate by applying a low dose of radiotherapy.<sup>6</sup>

It should be noted that radiotherapy in the head and neck area may hinder the physical development of children (especially the most important developing organ, the brain),<sup>19</sup> as well as having the side effects of skin injury and carcinogenesis. Hence, for the paediatric patient, surgery and systemic steroid medication may be preferable to radiation. The paediatric patients in the present series were managed with surgery alone.

In this study, 46 patients underwent 58 treatments, with nine patients undergoing multiple treatments due to local recurrence. The overall recurrence rate was 27.6%. The recurrence rate for the surgical excision alone group, the radiotherapy alone group, and the surgical excision combined with low-dose radiotherapy group was 37.5%, 100%, and 8.3%, respectively. The recurrence rate following surgical excision combined with low-dose radiotherapy was much lower than that of either surgical excision alone or radiotherapy alone (both  $P < 0.05$ ). This is similar to the results of a study by Chang et al., in which local control was obtained in nine of 14 patients (64.3%) in the radiotherapy group and two of nine patients (22.2%) in the non-radiotherapy group, leading to the conclusion that radiotherapy has an excellent local control rate.<sup>20</sup> In contrast, the present study (which included a higher number of patients) further identified different outcomes for these common treatment modalities and showed that surgical excision combined with low-dose radiotherapy is an effective treatment regimen with the lowest local recurrence rate for Kimura's disease. In this series, only five patients experienced two or more local recurrences. It was noted that all of the patients who suffered multiple local recurrences had undergone either surgical excision alone or radiotherapy alone for the primary and previous recurrent lesions, which suggests that the use of a single method of treatment might not control the lesions completely. Thus, it is concluded that the single application of surgical excision or radiotherapy tends to result in multiple recurrences, especially for primary lesions.

This study has some limitations. It was performed at only one institution, and for a chronic disease, the follow-up time was not long enough. Considering the benign nature of Kimura's disease, radiotherapy carries a risk of carcinogenicity. Although there were no secondary malignancies observed in these patients, a prolonged follow-up is necessary. Moreover, serum IgE levels were, unfortunately, not examined in this series, and the eosinophil count was not re-evaluated after treatment. In addition, the present authors have little experience with administering corticosteroids or other medications similar to cyclosporine (especially for paediatric patients), therefore information related to medical therapy is lacking in this study.

Kimura's disease is a benign condition with a good prognosis that usually occurs in the head and neck region. A definitive diagnosis is established by clinical and histopathological examination. Although it is reported in the literature that surgical excision, radiotherapy, and steroid therapy are effective, it was found in this study that surgical excision combined with subsequent low-dose radiotherapy should be carried out for Kimura's disease to reduce local recurrence.

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## Conflict of interest

The authors do not have any conflicts of interest.

## Ethical approval

Ethical approval was not required for this study.

## Patient consent

Written patient consent was obtained to publish the clinical photographs.

## References

1. Kimm HT, Szeto C. Eosinophilic hyperplastic lymphogranuloma, comparison with Mickulicz's disease. *Proc Chin Med Soc* 1937;23:699–700.
2. Kimura T, Yoshimura S, Ishikawa E. Unusual granulation combined with hyperplastic change of lymphatic tissue. *Trans Soc Pathol Jpn* 1948;37:170–80.

3. Nyrop M. Kimura's disease: case report and brief review of the literature. *J Laryngol Otol* 1994;**108**:1005-7.
4. Hernandez-Bautista V, Yamazaki-Nakashimada MA, Vazquez-García R, Stamatelos-Albarrán D, Carrasco-Daza D, Rodríguez-Lozano AL. Treatment of Kimura disease with intravenous immunoglobulin. *Pediatrics* 2011;**128**:e1633-5.
5. Day TA, Abreo F, Hoajsoe DK, Aarstad RF, Stucker FJ. Treatment of Kimura's disease: a therapeutic enigma. *Otolaryngol Head Neck Surg* 1995;**112**:333-7.
6. Hareyama M, Oouchi A, Nagakura H, Asakura K, Saito A, Satoh M, Tamakawa M, Akiba H, Sakata K, Yoshida S, Koito K, Imai K, Kataura A, Morita K. Radiotherapy for Kimura's disease: the optimum dosage. *Int J Radiat Oncol Biol Phys* 1998;**40**:647-51.
7. Kawada A. Kimura's disease. Demonstration of the disease and its differential diagnosis. *Hautarzt* 1976;**27**:309-17.
8. Tedeschi SK, Bermas B, Costenbader KH. Sexual disparities in the incidence and course of SLE and RA. *Clin Immunol* 2013;**149**:211-8.
9. Gao Y, Chen Y, Yu GY. Clinicopathologic study of parotid involvement in 21 cases of eosinophilic hyperplastic lymphogranuloma (Kimura's disease). *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006;**102**:651-8.
10. Wierenga EA, Backx B, Snoek M, Koenderman L, Kapsenberg ML. Relative contributions of human types 1 and 2 T-helper cell-derived eosinophilotropic cytokines to development of eosinophilia. *Blood* 1993;**82**:1471-9.
11. Daaleman TP, Woodroof J. Kimura's disease presenting as a subcutaneous facial plaque in an African American. *Cutis* 2000;**66**:201-4.
12. Tham KT, Leung PC, Saw D, Gwi E. Kimura's disease with salivary gland involvement. *Br J Surg* 1981;**68**:495-7.
13. Som PM, Biller HF. Kimura's disease involving parotid gland and cervical nodes: CT and MR findings. *J Comput Assist Tomogr* 1992;**16**:320-2.
14. Mitsui M, Ogino S, Ochi K, Ohashi T. Three cases of eosinophilic lymphfolliculoid granuloma of the soft tissue originating from the parotid gland. *Acta Otolaryngol Suppl* 1996;**522**:130-2.
15. Othman SK, Daud KM, Othman NH. Kimura's disease: a rare cause of nephrotic syndrome with lymphadenopathy. *Malays J Med Sci* 2011;**18**:88-90.
16. Nakahara C, Wada T, Kusakari J, Kanemoto K, Kinugasa H, Sibasaki M. Steroid-sensitive nephrotic syndrome associated with Kimura disease. *Pediatr Nephrol* 2000;**14**:482-5.
17. Viswanatha B. Kimura's disease in children: a 9 years prospective study. *Int J Pediatr Otorhinolaryngol* 2007;**71**:1521-5.
18. Itami J, Arimizu N, Miyoshi T, Ogata H, Miura K. Radiation therapy in Kimura's disease. *Acta Oncol* 1989;**28**:511-4.
19. Syndikus I, Tait D, Ashley S, Jannoun L. Long-term follow-up of young children with brain tumors after irradiation. *Int J Radiat Oncol Biol Phys* 1994;**30**:781-7.
20. Chang AR, Kim K, Kim HJ, Kim IH, Park CI, Jun YK. Outcomes of Kimura's disease after radiotherapy or nonradiotherapeutic treatment modalities. *Int J Radiat Oncol Biol Phys* 2006;**65**:1233-9.

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