

Kimura's disease: a diagnostic and therapeutic challenge

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ABSTRACT

Introduction: Kimura's disease (KD) is a rare, benign, chronic inflammatory disease with unknown aetiology. Its manifestation is protean. KD has a predilection for the head and neck area, and typically presents as tumour-like lesions that could be easily misdiagnosed. We review our experience with four recent cases.

Methods: Over a four-year period, all patients admitted to Singapore General Hospital with KD of the head and neck region were retrospectively reviewed. Biodata, presenting symptoms and clinical parameters, especially serum eosinophil levels, preoperative investigations, type of surgical procedures and outcome were documented.

Results: Four patients presented with KD of the head and neck and displayed varied manifestations of the disease. All the patients had raised serum eosinophil levels. None of them had renal involvement. Preoperative computed tomography were performed in two of the patients and showed features suggestive of KD. Fine-needle aspiration cytology that was performed in two patients was not useful in the diagnosis. All the patients underwent surgical excision of the lesions. Only one patient had multiple recurrence, both at the original and remote sites in the head and neck.

Conclusion: The clinical presentation and behaviour of KD is very variable. Preoperative imaging is useful in the diagnosis of the disease but the final diagnosis is histological. Surgical excision is the current treatment of choice but recurrence is common. A high index of suspicion and awareness is vital in the early diagnosis and management of KD.

Keywords: angiolymphoid hyperplasia, eosinophilia, immunoglobulin E, Kimura's disease, lymphadenopathy

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INTRODUCTION

Kimura's disease (KD) is a rare, chronic inflammatory disease of unknown aetiology. First described in China by Kim and Szeto⁽¹⁾ in 1937, this disease was given its name and became more widely known after a systematic description by Kimura⁽²⁾ in 1948 in Japan. KD occurs endemically in the Far East, and only a small number of cases have been reported in the West. The typical clinical presentation of this condition is characterised by subcutaneous masses, predominantly in the head and neck region. It often accompanied by regional lymphadenopathy, raised serum eosinophil counts, and markedly-elevated serum immunoglobulin E (IgE) levels^(3,4). Histologically, the lesions are characterised by proliferating blood vessels and eosinophilic infiltration⁽⁴⁻⁶⁾. The condition seldom resolves spontaneously, and malignant transformation has not been reported to date. The optimal treatment for KD remains controversial. However, early diagnosis of KD could spare the patient unnecessary and potential harmful diagnostic procedures. We describe a series of four recent cases and review the literature.

METHODS

Between 1992 and 2000 in the Department of Otorhinolaryngology/ Head and Neck Surgery at the Singapore General Hospital, four patients were diagnosed with Kimura's disease of the head and neck region. Their records were reviewed and evaluated for the following variables: age, sex, comorbidities, previous history of KD, nature and site of lesion, leukocyte and eosinophil counts, renal function test results, types of preoperative investigations, results of preoperative imaging studies, types of surgical procedure, findings on histopathological examination, site of recurrence, if any, management of recurrence, and status on follow-up.

RESULTS

Of the four patients, three were male and one was female. Their ages ranged from 13 years to 47 years. All

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Table I. Patient case information.

Case	Age (in years)/gender	Previous lesion/site	Physical signs on presentation	Preoperative investigations of lesions/findings	Leukocyte count ($\times 10^9/L$)	Eosinophil count (%)	Treatment	Recurrence/site	Treatment of recurrence
1	47/M	None	Firm 2 x 2 cm right mastoid mass with bilateral small cervical lymph nodes	FNAC: reactive lymphoid hyperplasia	6.0	7.0	Excision	Left and right parotid masses at 1 year and 6 years post-excision of initial lesion respectively	Systemic steroids then right superficial parotidectomy at 5 years followed by left superficial parotidectomy a year later
2	40/F	None	Soft, 5 x 4 cm left parotid swelling, anterior to tragus	FNAC: non-diagnostic CT: 5 cm hyperdense lesion in left parotid	5.68	9.8	Superficial parotidectomy	None at 2.5 years	Not applicable
3	42/M	Both groins	Firm, 2 x 1 cm left post-auricular lymph node	None	7.2	19.7	Excision	None at 3 years	Not applicable
4	13/M	None	Firm, 3 x 3 cm left supraclavicular mass with bilateral small mobile lymph nodes	CT: features of left supraclavicular lymphadenitis and bilateral subcentimetre lymph nodes	3.5	9.9	Excision	None at 3 years	Not applicable

the patients exhibited raised eosinophil counts ranging in value from 7.0% to 19.7%. However, the leukocyte counts were within normal range. Serum creatinine level were normal in all the patients and no urinary protein excretion were detected. Serum IgE levels were not performed for our patients. None had any comorbidity. Two of the patients had associated regional cervical lymphadenopathy.

Only one patient had a previous history of KD (Table I). In this patient, the previous lesions had occurred in both inguinal regions one year prior to the current presentation. The inguinal lesions were soft in consistency and non-tender, and an initial clinical diagnosis of lymphangioma was made. Magnetic resonance (MR) imaging revealed ill-defined lesions in the subcutaneous tissue on the medial aspect of both groins, measuring 5 cm on the right and 4 cm on the left. Vascular channels were present within these lesions and showed marked enhancement with intravenous contrast. The diagnosis of KD was made on histology after excision of the lesions. Fine-needle aspiration (FNA) was performed on the lesions in two of the patients. The cytology was non-diagnostic in one patient and revealed reactive lymphoid hyperplasia in the other. Computed tomography (CT) performed on two patients (Fig. 1) showed features suggestive of KD.

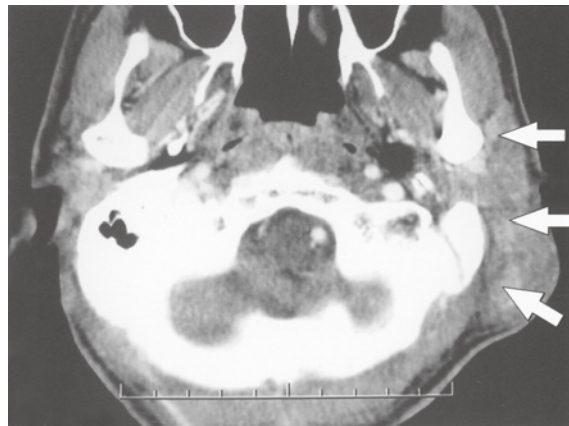


Fig. 1 Enhanced axial CT image (case 2) shows a large, ill-defined and moderately-enhancing nodular mass in the subcutaneous tissue lateral to the left parotid gland and extending into the superior lobe of the parotid gland (arrows).

All four patients underwent surgical excision of their lesions, with histological confirmation of the diagnosis. The lesions displayed similar histological features which were characteristic of KD, including prominent lymphoid hyperplasia and eosinophilic infiltrates. There were also lymphoid infiltrates with germinal centres, with focal eosinophilic microabscesses and prominent capillaries lined by endothelial cells. Involved lymph nodes also demonstrated similar characteristics with preservation of nodal architecture, prominent germinal centres, many of which show

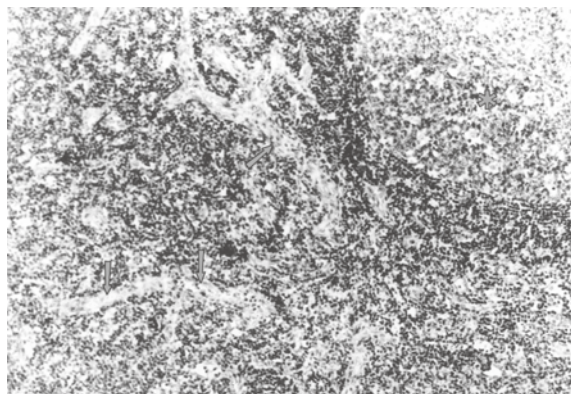


Fig. 2 Photomicrograph of the post-auricular lymph node (case 3) shows dense infiltrate of lymphocytes with germinal centre formation (asterisk) and numerous blood vessels with prominent endothelial cells (arrows). There are foci of eosinophilic infiltrates forming eosinophilic microabscesses, which encroach into the germinal centre (haematoxylin & eosin, x 100).

interstitial deposition of eosinophilic proteinaceous material and hypervascularity (Fig. 2). Stains and cultures of the lesions and any associated lymph nodes for bacteria, fungi and mycobacteria were negative.

One of the patients experienced recurrence of the disease. This patient presented initially with a postauricular node. One year post-excision of this lesion, the patient reported an isolated left pretragal nodule. The nodule was small, about 1 cm diameter, and located over the left parotid gland. Fine-needle aspiration cytology (FNAC) showed abundant lymphoid cells, probably due to reactive hyperplasia. It was noted that there was also bilateral cervical lymphadenopathy. The patient was not keen for any surgery and was started on systemic steroids. The left parotid nodule and cervical lymphadenopathy persisted. A few months later, he also developed a right parotid gland mass measuring 5 x 4 x 3 cm. It was non-tender with no evidence of sialadenitis. Full blood count showed eosinophilia of 18.6%.

The patient eventually acceded to a right superficial parotidectomy. Intraoperatively, there were multiple enlarged lymph nodes on the surface of the parotid gland. Histology confirmed the diagnosis of KD. The surgical margins were noted to be clear of disease. One month later, the patient complained that the left parotid mass had increased in size. A left superficial parotidectomy with excision of adjacent lymph nodes was performed. Recurrence of KD was confirmed on histology. One year later, the patient developed a recurrent mass over the right parotid gland measuring about 4 cm in diameter. However, the patient refused further surgery. On last follow-up, the mass has remained unchanged in size.

DISCUSSION

Since its initial description more than 50 years ago, KD remains an enigmatic condition and its

pathogenesis still has not been elucidated. KD is endemic in the Far East, although it has also been reported in Caucasians and non-Orientals. The clinical presentation is very variable as can be seen in our patients. Often occurring in the younger middle-aged males between the second and third decades of life, it typically presents as non-tender, subcutaneous lumps and swellings involving the head and neck region. However, it is also known to present in many other sites including the limbs, groin, trunk and scalp, and is often associated with regional lymphadenopathy^(3,4,7). The disease is also reported to be associated with systemic connective tissue disease and the nephrotic syndrome, occurring in up to 60% of patients with the latter condition^(3,8-10).

The lesions of KD may precede or coincide with the development of renal disease. Our patients were not affected by renal disease. Patients almost always have marked peripheral eosinophilia, (which was present in all our patients) and elevated serum IgE levels^(3,4). The latter, however, was not measured in our patients. The mechanisms of these manifestations continue to be the subject of controversy and research. Several mechanisms have been postulated but none have gained widespread acceptance to date. These include atopy to persistent fungal or parasitic antigenic stimulation^(11,12) and alterations of immune regulation⁽¹³⁻¹⁵⁾. The onset of KD is insidious and the lesions are benign, following an indolent course, gradually increasing in size over months or years. The overall prognosis is good. Although spontaneous involution is rare, malignant transformation has not been documented.

Diagnosis of KD is frequently difficult. A biopsy and/or excision of the involved lymph node or the lesion itself is frequently required for definitive histopathological diagnosis, and is often therapeutic as well. The histopathological findings in KD are the same, regardless of the site of involvement, and are characterised by lymphoid follicles formation with prominent germinal centres, infiltration of eosinophils, sometimes forming microabscesses, fibrosis, increased postcapillary venules and vascular proliferation^(3,4,6). Vessels remain thin-wall with cuboidal endothelial cells^(9,12). Polykaryocytic giant cells of the Warthin-Finkeldey type are a common feature. These features are also present in affected lymph nodes, in which their nodal architecture is preserved. The paracortex and sinuses showed striking eosinophilic infiltration with eosinophilic microabscesses and increased postcapillary venules. Although FNAC can be performed for the diagnosis of KD, its role is largely in the diagnosis of recurrent lesions and it may obviate the need for repeated

open biopsies^(16,17). For two of our patients in whom FNAC was performed, the procedure was not useful in the diagnosis.

Clinical differential diagnoses for KD include reactive lymphadenopathy, lymphoma, salivary gland tumour, nodal metastasis (breast, colorectal and nasopharyngeal cancer), and Mikulicz's disease^(3,4). Lesions of KD are also frequently diagnosed as angioma, lymphangioma or haemangioma, as in case 2, and other tumours. The differential diagnosis frequently highlighted in the literature is angiolymphoid hyperplasia with eosinophilia (ALHE). Although there has been controversy in the past, it is now widely accepted that ALHE and Kimura's disease are separate entities with different clinical and histopathological features^(3,4,16).

Although not diagnostic, imaging studies can play a major role in aiding the diagnosis of KD and distinguishing the disease from other conditions. It is also useful in delineating the extent and progression of the disease. Radiological features, particularly on CT and MR imaging, have been reported to be useful in the diagnosis of KD. Tissues involved in KD, for example the parotid gland and lymph nodes, show intense enhancement on CT, reflecting the vascular nature of the lesions⁽¹⁸⁻²⁰⁾. The borders are usually ill-defined and there is usually adjacent enhancing cervical lymphadenopathy. The CT findings in our patients were compatible with KD. On MR imaging, these lesions demonstrate intermediate to high signal intensities on T1-weighted images and hyperintense signals on T2-weighted images^(18,19).

The optimal treatment for KD is not well established. However, treatment should aim to preserve cosmesis and function while preventing recurrences and long-term sequelae. The range of treatment options include conservative treatment, steroid therapy (as in case 3), radiotherapy, cryotherapy, laser fulguration, and surgical excision. Other therapeutic options, including cytotoxic agents, cyclosporin and pentoxifyline, have been used with variable results^(21,22). At initial presentation, surgical excision is the choice for both diagnosis and therapy^(3,12,23). The value of achieving negative surgical margins for local control in excision has not been studied. Nevertheless, the treatment outcome after excision is variable and recurrence is common. In cases treated with surgical excision alone, the recurrence can be as high as 25%⁽²⁴⁾.

Localised recurrences can often be managed by surgical excision. However, if recurrence is frequent or there is symptomatic nephrotic syndrome, systemic steroids should be started. Steroid dosages should be initiated at high doses and then tapered to effect^(8,9,11).

Unfortunately, there is a tendency for lesions to recur when steroid therapy is stopped⁽²³⁾. For recalcitrant cases or lesions not amenable to surgery due to size or unacceptable resultant morbidity, radiotherapy can be considered⁽²⁵⁾. Low-dose local irradiation (about 25 to 30 Gy) has been reported to yield good control and obviates the need for long-term corticosteroids^(23,25). However, in addition to the side-effects of radiotherapy, there is also concern regarding secondary malignancies in the irradiated field, although none has been reported yet.

These four cases are presented to increase awareness of KD and to highlight features which may aid the diagnosis of this condition. With its predilection for the head and neck region and its variability in presentation, it will frequently be mistaken for other conditions and even malignant tumours. A high index of suspicion is required and KD should be considered in the differential diagnoses of head and neck masses in Oriental patients, especially if it is associated with imaging findings of a moderately- or densely-enhancing mass with adjacent cervical lymphadenopathy and peripheral blood eosinophilia.

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