Kimura's disease: A clinical case related to a mosquito bite

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TMB de Chalain, J Culbertson. Kimura's disease: A clinical case related to a mosquito bite. *Can J Plast Surg* 1995;3(4): 205-208. Kimura's disease is a benign, but locally injurious disease with a marked predilection for the head and neck. Of uncertain etiology, its tendency to present as a discrete, enlarging mass with associated lymphadenopathy makes it a condition of interest to clinicians who see head and neck pathology. Although rare, there are increasing numbers of reports of the condition and it should become part of the standard differential diagnosis. A typical case of this rare disease, apparently originating from a mosquito bite several years before presentation is presented.

Key Words: *Angiolymphoid hyperplasia with eosinophilia; benign tumours of head and neck; Kimura's disease*

Maladie de Kimura : Cas clinique lié à une piqûre d'insecte

RÉSUMÉ: La maladie de Kimura est bénigne, mais provoque une lésion locale surtout au niveau de la tête et du cou. D'étiologie incertaine, sa tendance à se présenter sous forme de masse distincte qui grossit, associée à une lymphadénopathie, rend cette maladie intéressante pour le clinicien consulté pour une pathologie de la tête ou du cou. Bien qu'encore rares, les cas signalés voient leur nombre croître et la maladie devrait faire partie du diagnostic différentiel standard. Nous présentons ici un cas typique de cette maladie rare, apparemment liée à une piqûre d'insecte subie quelques années auparavant.

Kimura's disease is an unusual condition in several respects. It was first reported by Chinese authors Kimm and Szeto in 1937 (1) and, besides its eponym, has been variously known as epithelioid hemangioma, atypical pyogenic granuloma and cutaneous eosinophilic lymphofolliculosis. The definitive description was published by Kimura et al in Japan in 1948 (2) and since that time, there has been a slowly increasing number of reports. While most cases have originated in China, Japan or Southeast Asia, there have been sporadic case reports from Europe and the Americas and by late 1994 there had been some 120 cases described in the world literature. The majority of patients have originated in the Eastern hemisphere, but ongoing emigration and population mixing have resulted in increased incidence in Western countries. The disease is most prevalent in Asians, uncommon in Caucasians and rare in Blacks. It has been suggested that the common factor is a degree of Asian ancestry (1).

Kimura's disease is a chronic inflammatory condition which presents with a characteristic triad of signs and symptoms, namely a painless, slowly enlarging soft tissue mass (or masses), associated lymphadenopathy and peripheral eosinophilia. Eighty-five per cent of cases occur in men.

Clinically, the subcutaneous soft tissue masses occur predominantly in the head and neck, and often involve the parotid glands. Approximately 67 to 100% of patients develop regional lymphadenopathy and, in longstanding disease, this may become generalized (3). Patients may complain of local or generalized pruritus and subacute or chronic dermatitis. There may be proteinuria and laboratory investigations will invariably reveal peripheral eosinophilia and increased serum immunoglobulin (Ig)E.

While there has been considerable discussion in the pathology literature concerning this disease, it is still unknown by most surgeons. This report seeks to increase awareness of an interesting condition.

CASE REPORT

A 59-year-old Black male presented with a complaint of a slowly enlarging mass in the right fronto-temporal region (Figure 1). History revealed that he was an engineer who had been employed by an oil company in Alaska some 10 years previously. At that time, he could recall being bitten by a mosquito on the right forehead, and the resultant pruritic nodule never seemed to completely clear up. Rather, a slowly enlarging soft tissue mass occurred at the site and this led him to seek medical attention a few years later when he returned to Atlanta. He was seen by a local surgeon who recommended excisional biopsy of the 2 x 2 cm tumour, and this was performed via a lenticular incision, directly over the lesion above the lateral brow. This removed the lesion, but unfortunately the frontal branch of the seventh nerve was also injured. Histology at this time revealed masses of inflammatory cells with a marked eosinophilic infiltrate, but a firm diagnosis was not reached.

The patient did well for the next two to three years, at which time he noted that the mass seemed to be growing again. By the time he consulted the plastic surgery service in late 1994, he had a 3 x 4 cm mass over the right fronto-temporal region, as well as easily palpable nodes in the ipsilateral pre-auricular area and anterior triangle of the neck.

On clinical examination, the mass was firm, densely inherent to the overlying skin, but not to the underlying bone or adjacent structures. At this stage the patient was clinically well, with no systemic signs or symptoms. On his blood workup, the only abnormality detected was a moderate eosinophilia.

The patient was scheduled for surgery and at operation a bicoronal flap was raised using a sine wave incision (Figure 2). This allowed the tumour to be sharply dissected from the overlying skin and surrounding soft tissues (Figure 3). Underlying periosteum was kept intact. To fill the resulting hollow, secondary to tumour extirpation, a pericranial flap was elevated and rotated, before closing the wound in layers. The tumour was submitted for histology and a diagnosis of Kimura's disease was made. The histology slides from the previous resection in the area were also obtained, and these could be shown to mimic the recurrent pathology precisely.

Figure 1) *The patient before re-excision of recurrent tumour in the fronto-temporal region. The scar of the first excision is readily apparent*

Figure 2) *The mass in situ, as approached via a superior bicoronal sinewave incision. For orientation, the right ear is visible at the right hand margin of the picture*

Figure 3) *The soft tissue mass after extirpation. The tag suture marks the infero-medial limit*

Within one month of excision of the recurrent primary mass, the lymphadenopathy had spontaneously resolved; by three months the access incision was virtually invisible with complete survival of the skin overlying the site of excision (Figure 4).

PATHOLOGIC FINDINGS

The gross surgical specimen (Figure 3), a mass of pinky-tan coloured soft tissue, measured 7 x 5.8 x 1.4 cm and was submitted in formalin. After paraffin wax embedding, representative sections were cut and stained with hematoxylin and eosin.

Histologically, the specimen consisted of fibro-adipose tissue and skeletal muscle containing a dense inflammatory infiltrate and fibrosis (Figure 5). The infiltrate was characterized by lymphoid tissue with germinal centres and numerous eosinophils with eosinophilic microabscess formation. A prominent proliferation of small venule-sized vessels was noted. There was no evidence of malignancy and no organisms were noted.

Figure 4) *The patient's appearance three months after surgery. The access incision is virtually invisible, and there has been complete survival of the skin overlying the site of excision. The hyperpigmentation is thought to be a result of the chronic inflammatory changes over the 10 year course of the lesion's history*

Figure 5) *Histology of the lesion. Note the dense inflammatory infiltrate with eosinophilia and germinal centre arrangement of the lymphoid tissue*

The pathological material relating to the patient's prior excisional biopsy, performed at another institution some years prior to this, was requested and reviewed. These sections also showed an identical dense inflammatory infiltrate extending into deep muscle and subcutaneous tissue, lymphoid reactive follicles, marked eosinophilia and microabscess formation, confirming the clinical impression that this was a true recurrence and not a new lesion.

DISCUSSION

With the increasing influx of Asian immigrants into North America, Kimura's disease is an entity of which physicians need to be aware. The differential diagnosis, while including obvious lesions such as dermatofibrosarcoma protuberans and cylindroma (turban tumours), will ultimately be determined by both the clinical picture and the histopathology. Clinically, malignant lymphoma, parotid tumours, hemangioma, pyogenic granuloma, Mikulicz's disease and Kikuchi's disease are all conditions for which Kimura's disease has been mistaken in the past (3). Other conditions to consider include Kaposi's sarcoma, angiosarcoma, eosinophilic lymphoma and angioimmunoblastic lymphadenopathy; parasitic diseases responsible for subcutaneous masses with an associated lymphadenopathy, such as tissue-invasive helminth infections, cysticercosis, sparganosis, toxocariasis and several forms of invasive myiasis may also need to be ruled out (1).

In Kimura's disease there is classically a dense inflammatory infiltrate characterized by eosinophilic lymphoid tissue with germinal centres and microabscesses. There is often marked fibrosis found within the typical lesions. Pathologically, the picture is perhaps most difficult to distinguish from angiolymphoid hyperplasia with eosinophilia (ALHE), and for a long time these two conditions were thought to represent one and the same pathology, but the current consensus is that they represent two ends of a spectrum of similar diseases (4-6).

In contrast to that of Kimura's disease, the histology of ALHE is typified by an exuberant proliferation of capillary vessels with marked irregularity of luminal sizes. Lining endothelium comprises plump, vacuolated cells. While there is an inflammatory infiltrate, the associated lymphocytes are not arranged in germinal centres as they are in Kimura's disease. Further, while ALHE is marked by the presence of histiocytoid endothelial cells, these are absent from Kimura's lesions.

Clinically, Kimura's disease is believed to be a disease of the Far East and Asia, and ALHE one of the western world. Jambhekar et al (4) suggest that while ALHE is known to occur in the Far East and Asia, Kimura's has yet to be established in the west. This case report, as well as that of Irish et al (1), clearly refute this contention. Finally, while ALHE occurs in older, predominantly female populations, Kimura's disease is primarily a disease of younger males.

The cause of Kimura's disease remains enigmatic and the low incidence of the condition makes clinical research in this regard difficult. There are, however, several theories of etiology.

The eosinophilia and elevated IgE levels seem to favour a parasitic cause, but this has never been established. Somewhat more appealing is the suggestion that this entity may represent a form of unusual atopic response. Evidence for this stems from the observation that the histologic features vary with site and duration of the lesion (7), as well as the local tissue eosinophilia, mast cell hyperplasia, polytypic lymphoplasmacytic infiltration with reactive germinal centres and a blood picture typified by eosinophilia and raised serum IgE levels.

Some authors have claimed that Kimura's disease represents yet another manifestation of an immune dysfunction, and cite as evidence the discovery of cryoglobulins in one patient's serum, an association with renal diseases and an unclassified systemic connective tissue disorder in another case (8). Trauma has been suggested as an antecedent condition, but in the series of 116 cases collected by Olsen and Helwig (7), there was a history of prior injury or local irritation in less than 10%.

Akosa et al (8) reported on three cases, all apparently related to prior injection with tetanus toxoid. They present the speculation that these inoculations may have been causal, and argue, in support of their hypothesis, that a known adverse effect of the tetanus vaccine is formation of a persistent nodule at the site of injection, especially if the injection is into the superficial layers of the subcutis. In the present case, the patient insisted that the lesion began as a mosquito bite. It is perhaps significant, in the light of Akosa's hypothesis, that the mosquito obtains its meal by injecting a mixture of foreign proteins into the superficial subcutis; conceivably, one or more of these could have acted as the appropriate trigger for what would appear to be an abnormal atopic reaction.

The mainstay of treatment for Kimura's disease remains oral corticosteroid therapy. Apart from the potential risks of long-term steroid use (suppression of the

adrenal-pituitary axis, thinning of skin with poor wound healing), there is also the distinct risk of tumour relapse when steroids are withdrawn, even after years of treatment. Furthermore, a proportion of tumours become refractory to ongoing oral steroid therapy, and the response to intralesional steroid injections has met with little success (1).

For refractory lesions, low-dose radiation, of the order of 25 to 30 Gy, with appropriate fractionation, may be effective. This appears to give local control, but again, the use of radiation, especially in younger patients, is not without risks, and only 50% of the patients in a Japanese study could be weaned off oral steroids after radiation therapy (9).

The treatment of choice for localized disease would thus appear to be surgical excision (1,3), although some authors make a plea for conservative management, particularly in anatomically sensitive areas such as the periorbital (10). The wisdom of sparing patients overly radical surgery, if possible, is readily apparent in the present case, in which the patient sustained an iatrogenic injury to the frontal branch of the right facial nerve, at the time of the primary excisional biopsy, before referral to our centre. In fairness to the surgeon concerned, histology did show involvement of all tissue planes from the dermis to the deep muscle layer, so that the frontal branch was, in all probability, heavily involved in the tumour mass.

There have also been reports of recurrence in 15 to 40% of cases (10), even after apparently adequate surgical excision and excisional biopsies (3), but this may be because of the poor delineation of the borders of Kimura's lesions, suggesting that adjunctive frozen sections may be useful, especially in re-excision of recurrences. In summary, Kimura's disease is an indolent, benign, but locally disfiguring disease, whose true importance lies in its ability to mimic a number of other benign inflammatory and neoplastic conditions of the head and neck. Knowledge of the condition, its clinical appearance, course and histopathology puts the practitioner in a better position to answer questions from concerned patients and primary caregivers, and optimize management strategies.

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