CASE SERIES

Kimura Disease: A Case Series Presenting as Orbital Mass

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ABSTRACT

Introduction: Kimura disease (KD) is a chronic inflammatory process that can occur within the head and neck region involving deep subcutaneous tissue. Tumour-like nodules were the usual presentations. Albeit rare, there have been reports on orbital KD occurrence in recent years. **Case series:** We reported seven cases of orbital KD of patients aged 12 to 67 years old from a tertiary referral center in Malaysia. Painless orbital swelling was the most common presentation. The duration of presentation ranges from 2 months up to 6 years. Peripheral blood investigations demonstrated eosinophilia (>5% of white blood cells) and elevated serum immunoglobulin E (IgE) level. The orbital mass measures from 1cm to 5cm in dimension. Differentials include Hodgkin lymphoma, haemangioma, angiolymphoid hyperplasia with eosinophilia (ALHE) or a pseudotumour. In all cases, surgical excision was performed. Histopathological examination showed various degrees of lymphoid hyperplasia with germinal centres, eosinophilic infiltrates, hyalinized vascular proliferation and fibrosis. Diagnoses of KD were made. There were no recurrences seen on available follow up data of 2 cases. **Conclusion:** Albeit rare, orbital KD alerts to its common existence within the head and neck region. It mimics ALHE microscopically and malignant neoplasm clinically and radiologically. Thus, awareness for this entity, its histological characteristics with clinical and radiological correlations are essential in achieving a correct diagnosis. As there is no consensus on its optimal treatment, and its unpredictable response to the therapeutic interventions, the choice and extent of treatments also varied according to individual response and disease recurrence.

Keywords: Kimura disease, Orbital, Eosinophilia, Vascular hyalinisation

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INTRODUCTION

Kimura disease (KD) is historically described as unusual granulation with hyperplasia or lymphatic tissue by Kimura et al in 1948 (1). It is characterised by an inflammatory process of prolonged duration involving the subcutaneous tissue and associated with lymph nodes enlargement particularly in the head and neck region (1-3). KD is prevalent among young male with preference of Asian descendants (2). It is a benign disorder of unknown aetiology that may clinically mimic a neoplastic process.

The usual presentation is nontender subcutaneous masses with indolent growth associated with lymph nodes enlargement. Most occurs within the head and neck region. Salivary gland involvement is also seen in association with lymph nodes involvement (4). Involvement of the orbit is not frequent however when it occurs, the eyelid or the lacrimal gland are usually affected (5). Kimura disease is also often associated with increased level of serum eosinophils and markedly elevated serum immunoglobulin E (IgE) level (2,4). If left untreated, this idiopathic lesion usually remains static or may show regression. In some cases, it may recur if surgical resection is incomplete.

Over the years, increased number of case reports of KD from various sites were observed. Despite having a defined criteria for diagnosis, KD still represents an entity with diagnostic uncertainties, as it may resemble both benign and malignant conditions which causes difficulty in making the diagnosis (5). Its differentials extend from benign vascular lesions such as angiolymphoid hyperplasia with eosinophilia (ALHE) to angiosarcoma. Neoplastic lymphoid proliferation or a pseudotumour are also considered (2).

CASE SERIES

A summary of the clinical presentation from seven

cases of orbital KD from year 2007 to 2019 is presented in Table I. All data were retrieved from the hospital and laboratory information system of Department of Pathology, Hospital Serdang, Selangor, Malaysia.

Our seven cases of KD comprised of four male and three female patients. The age ranges from as young as 12 years to 67 years old. The mean age was at 38.4 years old. All patients exhibit similar clinical presentation as

TABLE I: Cases of Kimura disease presented as orbital mass

Case	Age (years)	Gender	Presentation	Location	Specimen size	WBC count (x10 /L)	Eosinophils count (1- 6 x10 /L)	Absolute Eosinophils Count (0.04-0.4)	Pre op visual assessment (VA-visual acuity) RE-right eye LE-left eye IOP-intraocular pressure	Post op visual assessment (VA-visual acuity) RE-right eye LE-left eye IOP-intraocular pressure	Management	Follow-up
1	44	F	Right eye swelling, duration of first presentation not known; developed contralateral eye swelling one year after right eye surgery	Right lower eyelid (first), left upper eyelid (second)	5cm (first), 1.5cm (second)	8.9	18	1.58	(First) No visual disturbances No diplopia No nystagmus or strabismus VA RE/LE 6/6 (Second) VA LE 6/36 with PH 6/24	Right lower lid swelling and eye discharge Complicated with right eye proptosis VA LE 6/12 -6/9 Left upper eyelid become swollen No visual disturbances	Surgical resection with steroid therapy Radiotherapy was suggested but patient was keen on surgery.	Lost to follow up after second surgery
2	22	F	Eye swelling for two months, known case of eczema dermatitis	Right lower eyelid	4cm	8.1	9	0.76	No visual disturbances No nystagmus or strabismus VA RE 6/24 LE 6/9 Lesion biopsied and swelling progressively worsen with almost totally obscured vision, Eye discharge and ulcer Conjunctiva congested, clear cornea	Post biopsy VA RE unaided 6/18 with PH 6/12, LE 6/9 unaided and with PH Post surgical excision VA RE 6/12, LE 6/9 AC deep and quiet (D/Q) Conjunctiva mildly injected, clear cornea	Biopsied with lid hygiene, antibiotics and Surgical resection with maxitrol	Not known
3	12	M	Eye swelling for three years, known case of asthma and eczema	Left upper eyelid	1cm	18.5	21	3.86	No visual disturbances, blurring of vision, No strabismus, no nystagmus. VA RE 6/6, LE 6/12 IOP both eye 14mmHG	No visual disturbance Developed swelling in both eyes. VA RE 6/6, LE 6/9	Surgical excision and cold compress Referred for chemotherapy in another paediatric tertiary centre	Not known
4	45	F	Eye swelling for one year	Right upper eyelid	2.5cm	12.7	13	1.59	No visual disturbance No strabismus, no nystagmus. VA RE 6/12 -1, LE 6/9 -1 AC D/Q, IOP 20mmHg	Developed ptosis, upper lid oedema, laxity of peri wound skin No proptosis VA RE/LE 6/9,	Surgical resection with steroid Cold compress and massage	Not known
5	40	M	Palpable lesion for one year	Right lower eyelid	In fragments, 1cm, 1cm and 1.1cm	6.6	7	0.45	No visual disturbance, pain, blurred vision/diplopia. EOM full VA RE with glasses 6/9, LE 6/12 with glasses 6/6, IOP 14mmHg RE, 13mmHG LE	Developed RE lower lid swelling No proptosis VA RE/LE 6/9, IOP RE/LE 16mmHg	Surgical resection with steroid (Swelling increase with tapered steroid dosage) Methotrexate added Cold compress	2 months, no eye complaints
6	39	M	Eye swelling for three months	Left lower eyelid	2.3cm	7.6	10	0.8	Left poor vision (since small), Right vision poor (last few years) Iris Coloboma RE. Nystagmus present. Strabismus absent. Lens cataract with phacododenesis Retina-no fundal view. Left micropthalmos VA RE unaided 6/60 with PH 6/36 LE unaided NPL.	LE lid mild swelling Subconjunctival haemorrhage Microcornea Iris coloboma Lens brunescent cataract with phacododenesis.	Surgical resection alone (subciliary)	Not known
7	67	M	Eye swelling for six years	Left upper eyelid	3cm and 1.5cm	11.1	7	0.72	No visual disturbance, blurring of vision, double vision or red eye No strabismus, nystagmus Lens cataract, No maculopathy VA 6/6 both eyes IOP 16mmHg both eyes	VA RE 6/9, LE 6/6 No recurrence Suspect glaucoma IOP RE 17mmHg and 16mmHg	Surgical resection alone Cold compress	2 years, no eye complaints, no recurrence

painless eye swelling of a duration that varied from two months to six years. There is no predilection to upper or lower eyelid as both eyes were equally affected. One patient developed a new lesion in the contralateral eye after one year of surgical removal. The associated signs and symptoms include proptosis and blurring of vision. All patients have associated eosinophilia and show increased in absolute eosinophilic count (AEC) in the peripheral blood. Serum IgE was however not done.

For Case 5, axial contrast enhanced computed tomography (CT) of the orbit illustrates heterogeneously enhancing soft tissue density mass at the right lower eyelid while for Case 6 axial T1 weighted fat suppressed, post gadolinium MR image showed enhancing left lower eyelid mass. Both features may suggest suspicions for a neoplastic process (Fig. 1). In addition to the finding of a mass, CT of the orbit for Case 7 showed a retrobulbar enhancing mass that encircles the optic nerve. There is poor fat plane separating the surrounding extraocular muscles and lacrimal gland. In this case, a neoplastic process would also be favoured.

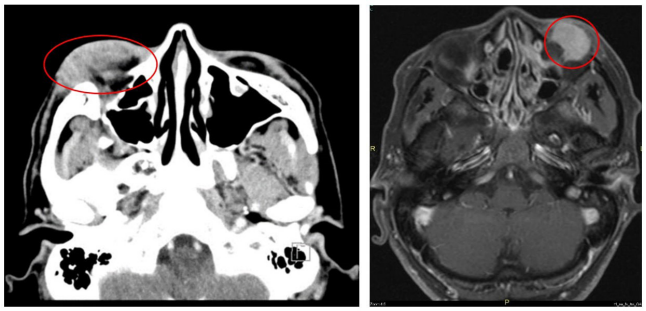

Figure 1: (left) (Case 5). Axial contrast enhanced CT orbit showing heterogeneously enhancing soft tissue density mass at the right lower eyelid. (right) (case 6). Axial T1 weighted fat suppressed, post gadolinium MR image showing enhancing left lower eyelid mass.

Macroscopic examination of the resected mass from all cases revealed tumour mass measuring from 1cm to 5cm in greatest dimension. Various degree of lymphoid hyperplasia with germinal centres, eosinophilic infiltrates, hyalinized vascular proliferation and fibrosis were observed histologically (Fig. 2). There is lacked of atypical endothelial proliferations that is seen in ALHE. A panel of immunohistochemistry were essentially done to exclude neoplastic differentials. Neither CD30-positive Reed Sternberg/Hodgkin cells nor CD1a expressed Langerhan cell histiocytes were present in all cases. Thus, with the combination of histological features and clinical presentations, diagnosis of Kimura disease were established.

DISCUSSION

KD was precisely described by Kimura 1948 as the 'unusual granulations with hyperplastic changes of the lymphoid tissue' (1). Despite having an unknown aetiology, it is most likely representing an

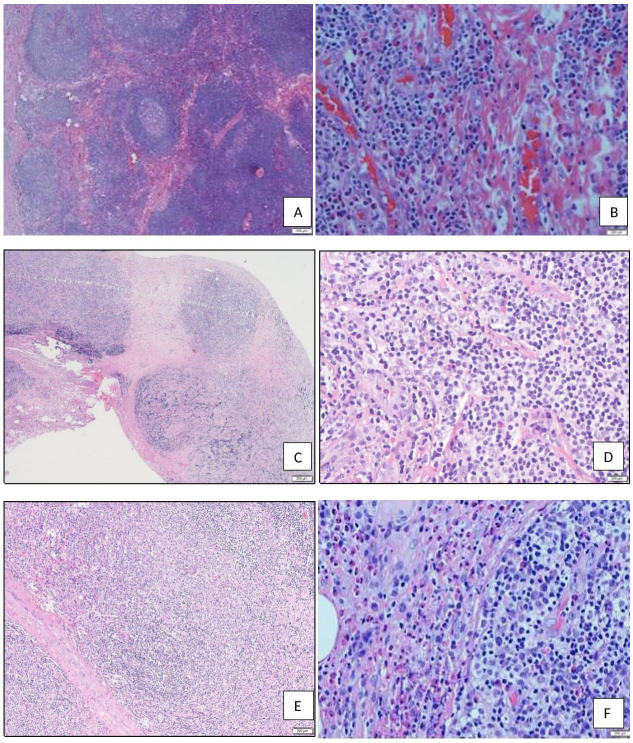

Figure 2: A-C (Case 3,7). A. The tumour shows lymphoid hyperplasia with prominent germinal centres (H&E, 40x). B. Infiltrates of eosinophils and mononuclear cells (H&E, 400x). C. In areas, stromal fibrosis is prominent (H&E, 100x). D-F (Case 5,7) D. Hyalinised vessels surrounded by lymphocytes and eosinophils (H&E, 400x). E. Expanded paracortex with lymphocytes, eosinophils and plasma cells (H&E, 100x) F. Infiltrates of eosinophils and mononuclear cells, and some of the eosinophils extend to germinal centres (H&E, 400x).

aberrant chronic immune response. There has been postulation relating to infectious aetiologies, however based on laboratory investigations, an autoimmune reaction or a delayed hypersensitivity reaction were favoured. This is also evident by some accompanying hypersensitivity responses such as atopic dermatitis, asthma, conjunctivitis, allergic rhinitis, peripheral hypereosinophilia and elevated level of serum IgE (2,4,5).

Studies have reported that Kimura disease may involve the oral cavity, trunk, axillae, limbs and groin. However, orbital, extraocular muscle and eyelid involvement is rare (1). The time frame prior to the diagnosis is typically several years (1), because the lesion may be enlarged gradually or show newly developed nodules or even regress spontaneously. Two case index (Case 2 and 6) however showed a very short presentation of less than a year which was uncommon.

Morphological features that define KD include follicular hyperplasia with germinal centers, eosinophilic infiltrates with occasional eosinophilic abscesses, vascular proliferation and fibrosis 1,4). Histologically, KD is characterized by florid hyperplasia of the follicular and germinal centre with expansion of the

paracortex and associated prominent high endothelial venules. However, there is lacked of atypical vascular proliferation as seen in ALHE (3). Often at times, proteinaceous precipitate is seen in the germinal centers. Presence of immunoglobulin E (IgE) deposition by immunohistochemistry detection on the follicular dendritic cell network do occur. Foci of necrosis may be seen in the germinal centers with marked eosinophilic infiltration, sometimes forming eosinophilic microabscesses. The expanded paracortex may contains small lymphocytes, plasma cells, mast cells and polykaryocytes. Patchy fibrosis may occur around the venules. However, the definitive diagnosis of Kimura disease is made by histopathological examination in concordance with clinical and radiological findings (4). Laboratory investigations usually demonstrate eosinophilia (>5% of white blood cell) as well as elevated serum immunoglobulin E (IgE) level (5).

The closest benign mimicker of KD with eosinophilic infiltration include ALHE and insect bites. Despite having an indolent course, KD clinical presentations may also mimic aggressive diseases such as lymphomatous infiltration including Hodgkin lymphoma, angioimmunoblastic T cell lymphoma. Langerhans cell histiocytosis, Castleman's disease, florid follicular hyperplasia, eosinophilic granulomatosis with polyangiitis, drug-induced lymphadenitis and parasitic lymphadenitis were also included as some of the differentials (6).

KD and ALHE are recognised as two different entities (1,3). In comparison, KD is endemic among Asians and sporadic in the rest of the world. Young and middle-aged men are typically affected by KD while ALHE affects all ethnic groups and age groups (2,6). KD tends to occur in deeper soft tissue with endothelial proliferation lacking the atypical histiocytoid endothelial cells as compared to ALHE. Patchy fibrosis may occur around the venules. ALHE on the other hand usually presents with a smaller, more superficial and well-defined lesion. It demonstrates prominent epithelioid endothelial cell proliferation which may represent a benign vascular neoplasm. Eosinophilic microabscesses are unusual in this type of lesion (3).

Classical Hodgkin lymphoma (CHL) and Langerhans cell histiocytosis are other conditions to be considered as differentials for KD especially in cases with associated lymphadenopathy. Even so, morphological recognition of classical Reed Sternberg cells and Langerhans histiocytes with reniform nuclei would help in distinguishing between these entities (7). Yet, the reactive background of inflammatory infiltrates comprising numerous eosinophils, lymphocytes, plasma cells may cause dilemma in distinguishing between CHL and KD. Nonetheless this can be resolved by subjecting to immunohistochemical detection of CD30-expressed Reed Sternberg cells. Similarly, Langerhans cell histiocytosis that exhibits sinusoidal dilation with prominent eosinophilic infiltrations associated with neutrophils and histiocytes can be excluded through expression for CD1a or S100 or Langerin immunohistochemistry.

The unpredictable response to the therapeutic interventions is the reason why there is no optimal treatment for KD. Nevertheless, successful treatment modalities of orbital KD in some reports have included surgical resection, steroid therapy and used of cytotoxic drug such as methotrexate for steroid resistant lesions, H-2 blockers as well as radiotherapy as the first line treatment (8,9). Anti-IgE therapy (omazilumab) has also been introduced in a study (9). The lesional size and the peripheral blood eosinophil were all decreased after anti-IgE therapy, but complete remission was not observed. In our series, all were resected surgically. Two case index receiving surgical management only did not show disease recurrence. Three case index received steroids, one of whom did not respond. Thus, methotrexate was added with clinical improvement. None of our index cases had anti IgE treatment.

One case index had contralateral eye involvement after 1 year with lack of improvement of the first involved eye post operatively. Radiotherapy was suggested but patient was only keen on surgery and steroids. A case report described the use of single anterior oblique portal radiation to avoid exposure to the lens (10). The lesion gradually disappeared with improvements of visual symptoms and decreased eosinophilia with radiotherapy. Radiation therapy with or without concurrent steroid treatment has also been used successfully in refractory cases of KD (11). The only paediatric index case was referred for chemotherapy. Detail of response to chemotherapy was however unavailable. Extent of management of orbital KD varies according to individual response the treatment. Risk of recurrence in KD warrants long-term follow up of the patient, nevertheless most patients have excellent outcomes with low morbidity (2,4,9).

CONCLUSION

Albeit rare, KD is a differential diagnosis in patients with slow growing orbital swelling. It closely mimics benign condition such as ALHE microscopically and malignant neoplasm clinically and radiologically. In addition, its variable histologic patterns may pose diagnostic dilemmas. Thus, awareness for this entity, the histological features that characterised this lesion with clinical and radiological correlations are essential in achieving a correct diagnosis. Ancillary testing to exclude neoplastic process may be performed. Hence, diagnosis of KD should be carried out in a comprehensive manner on the basis of clinical, radiological and histopathological findings as KD has a desired outcome with occasional local recurrence. The choice and extent of treatment also varied according to individual response.

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