CLINICAL CHARACTERISTICS AND OUTCOMES OF KIMURA DISEASE IN MALAYSIA: A CASE SERIES AND A LITERATURE REVIEW

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Abstract

Kimura disease is a rare benign chronic inflammatory disorder of the soft tissue with predominant occurrences in young Asian male adults. However, there is limited information of Kimura disease in Southeast Asia. Hence, the clinical characteristics and outcomes of Kimura disease in Malaysia was investigated. Published Kimura disease cases from Malaysia were comprehensively searched in PubMed and Google Scholar up to December 2020 using the keywords "Kimura Disease" and "Malaysia". Twenty-three papers were identified for review and case series of seven Kimura disease patients from a hospital in Malaysia were descriptively analysed. A total of 60 cases were obtained from both sources. Eighty-seven percent were men with a male:female ratio of 6.5:1 and majority of the cases were Malays (77.1%). Median age of onset was 22.0 (IQR 12.5-31.5) years, while the median duration before diagnosis of Kimura disease was 2.0 (IQR 0.8-5.0) years. Head and neck region (95%) were the most frequently involved anatomical site. Peripheral eosinophilia was detected in 88.9% of the cases at presentation and renal involvement was observed in four (22.2%) patients. Surgery (57.5%) was the commonest first choice of treatment, followed by a combination of surgery and steroid (29.8%), steroid alone (10.6%), and a combination of steroid and immunosuppressive agent (2.1%). Local recurrences were observed in 28.6% of the cases. In conclusion, a much younger age of disease onset was found among Malaysians. A high recurrence rate of one in every four patients was observed, indicating the need for further evaluations of treatment strategies.

Keywords: Kimura Disease, Malaysia, Histopathology, Treatment

Introduction

Kimura disease is a rare benign chronic inflammatory disorder of the soft tissue with unknown etiology. The disease was first described in 1937 by Kim and Szeto in China as "eosinophilic hyperplastic lymphogranuloma" (1). It was not well recognised until Kimura described the definitive histological findings in Japanese literature in 1948. This disease predominantly occurs among young male adults and is described as endemic in the Asian region, mainly in China and Japan (1, 2). Among Caucasians, the disease is rare although sporadic cases are being reported in America and Europe.

The most common presentation of Kimura disease is the occurrence of a painless subcutaneous mass, predominantly over the head and neck regions, with involvement of the salivary gland and regional lymphadenopathy. Renal involvement occurs in about 12-16% (3) of the cases, whereas vasculitis has rarely been reported as a complication (4). It is characterised by marked eosinophilia and elevated serum Immunoglobulin E (IgE) (1, 2). The common histological features are preserved nodal architecture, follicular hyperplasia with reactive germinal centers, well-formed mantle zones, eosinophilic infiltrates and proliferation of the postcapillary venules (3).

Although clinical characteristics and the outcomes of Kimura disease have been well described among the Chinese and Japanese, there is a lack of this information across the Southeast Asia region. As Southeast Asian countries have various ethnic groups, it is crucial to understand the nature of the disease among the different ethnicities. The aim of this study is to describe the clinical characteristics and outcomes of Kimura disease through a review of all published reports in Malaysia.

Materials and Methods

A total of seven patients diagnosed with Kimura disease from January 2015 to December 2020 at the Hospital Raja Perempuan Zainab II, Kota Bharu, Malaysia, were included

in this study. All records were retrospectively reviewed via hospital medical records. In addition to the above cases, PubMed and Google Scholar databases were screened for other reported cases in Malaysia. The keywords "Kimura Disease" and "Malaysia" were used during the database search. A total of 25 papers were published up to December 2020, with 23 papers being available for review. There were no responses from the authors of the two remaining papers.

Data on clinical characteristics, choice of treatment modality and clinical outcomes from both groups were extracted and analysed. Continuous variables were described using median (interquartile range, IQR), while categorical variables were reported as frequency and percentages. The SPSS version 26.0 software was used for statistical analysis. Ethical approval was not required in this study as data was extracted from published articles and from medical records retrospectively.

Results

Case series

In our case series, all seven patients were males and of Malay ethnicity. Majority of them had an onset at a median age of 11 years (IQR 10-16). Median duration from symptom onset to diagnosis were 2 years (IQR 0.4-5.0). All patients presented head and neck swelling masses of which, two patients had local pruritus overlying the mass. Two patients had history of atopy (one with asthma and eczema, another with allergic rhinitis). Renal involvement was observed in one case (Case No. 3). Peripheral eosinophilia was observed in six patients at presentation with a median count of 3.3 x 10^9/L (normal range <0.4x10^9/L, IQR 2.1-4.2) and a median percentage of 29.2% (normal range <6%, IQR 21.2-34.4). Total IgE levels in two patients were markedly elevated. Diagnoses for all cases were confirmed by histology, with the exception of Case No. 3.

Among these 7 patients, surgery was the main choice of treatment (6, 85.7%), followed by steroid medications (3, 42.9%) and azathioprine (2, 28.6%). A local recurrence of neck swelling was observed in four cases (out of six) during a median duration of follow up of 29.5 months (IQR: 20.0-47.5). Here we describe 2 cases with different clinical presentations.

Case No. 1 demonstrated a 13-year-old boy who presented a 2-year history of painless, slow and progressive enlargement of swelling on the right ear. A neck examination revealed masses at the right preauricular (2 cm x 1 cm) and posterior lobule of the right ear (3 cm x 1 cm). There were no overlying skin changes. His serum eosinophil count was 1.62x10^9/L, 18.8%. Surgical excision was done and the biopsy samples were histologically confirmed as Kimura lymphadenopathy (Fig. 1). Despite the surgery, local recurrence occurred after a few months following the excision. A trial of low dose prednisolone for 1 month resulted in minimal response. The patient was then initiated on azathioprine (2 mg/kg/day) with cetirizine for 1 year, but no size reduction of the swelling was observed. He proceeded with another surgical excision, in which the swelling reoccurred again within 5 months. Another surgical excision was done followed by the patient's transfer to another hospital due to logistic factor.

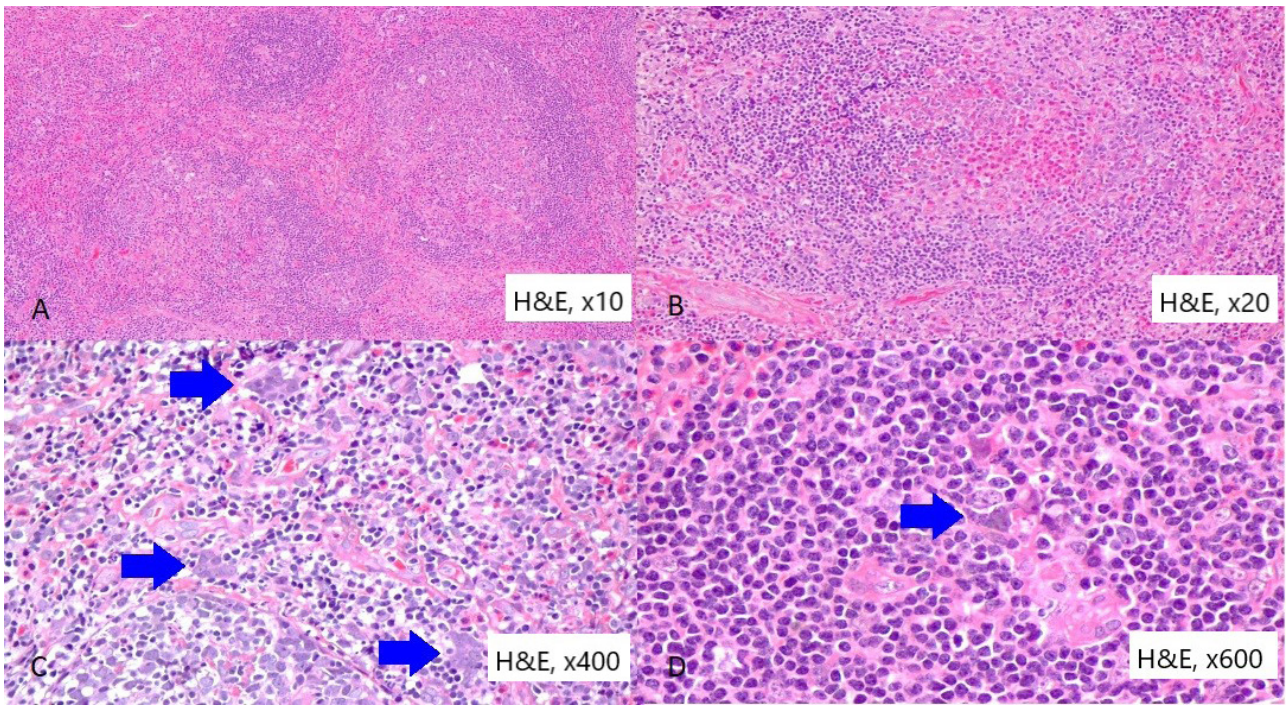

Fig. 1 (Case 1): **A**, Lymphoid follicles with reactive germinal centre. Intense eosinophilia with formation of eosinophilic micro-abscesses. The intervening stroma is collagenised (H&E, x10); **B**, Eosinophils and proliferation of capillaries (H&E, x20); **C** and **D,** Scattered polykaryocytes as shown by blue arrow (H&E, C: 400X, D: 600X). H&E, hematoxylin & eosin

In Case No. 3, a 16-year-old boy presented a 1-month history of painless left parotid (4 cm x 4 cm) and left cervical swelling. Laboratory tests confirmed peripheral eosinophilia (4.34x10^9/L, 31.3%) and a markedly elevated total IgE level of 4898kU/L (normal: <100kU/L). Peripheral blood film revealed eosinophilia without abnormal blast cells. Fine needle aspiration cytology (FNAC) of the masses revealed heterogenous population of lymphoid cells composed of mature lymphocytes, immunoblasts, plasmacytoid lymphocytes, and a high number of scattered eosinophils with the presence of a few Warthin-Finkeldey polykaryocytes (Fig. 2). No malignant cells were seen. A diagnosis of Kimura disease was made and the patient opted for conservative management. About 9 months after his first presentation and conservative management, he returned to the hospital with facial puffiness and generalised body edema. Although normotensive, urinalysis revealed high readings of protein (4+) and red blood cells were detected (1+), while 24 hours urine protein measured nephrotic range proteinuria at 4.1g per day. A lowered serum albumin at 13g/L (normal: 34-50g/L) was detected with a preserved renal function (serum creatinine 87µmol/L). Renal biopsy confirmed a diagnosis of minimal change glomerulonephritis. The patient was started on prednisolone 50mg daily (1 mg/kg/day) and perindopril was added for an antiproteinuric effect. Complete remission was achieved after 5 months of prednisolone. Swelling of the neck was also resolved with the use of steroid without surgical intervention. He remained steroid free with no recurrence of neck swelling and had normal peripheral eosinophil counts for the past 9 months.

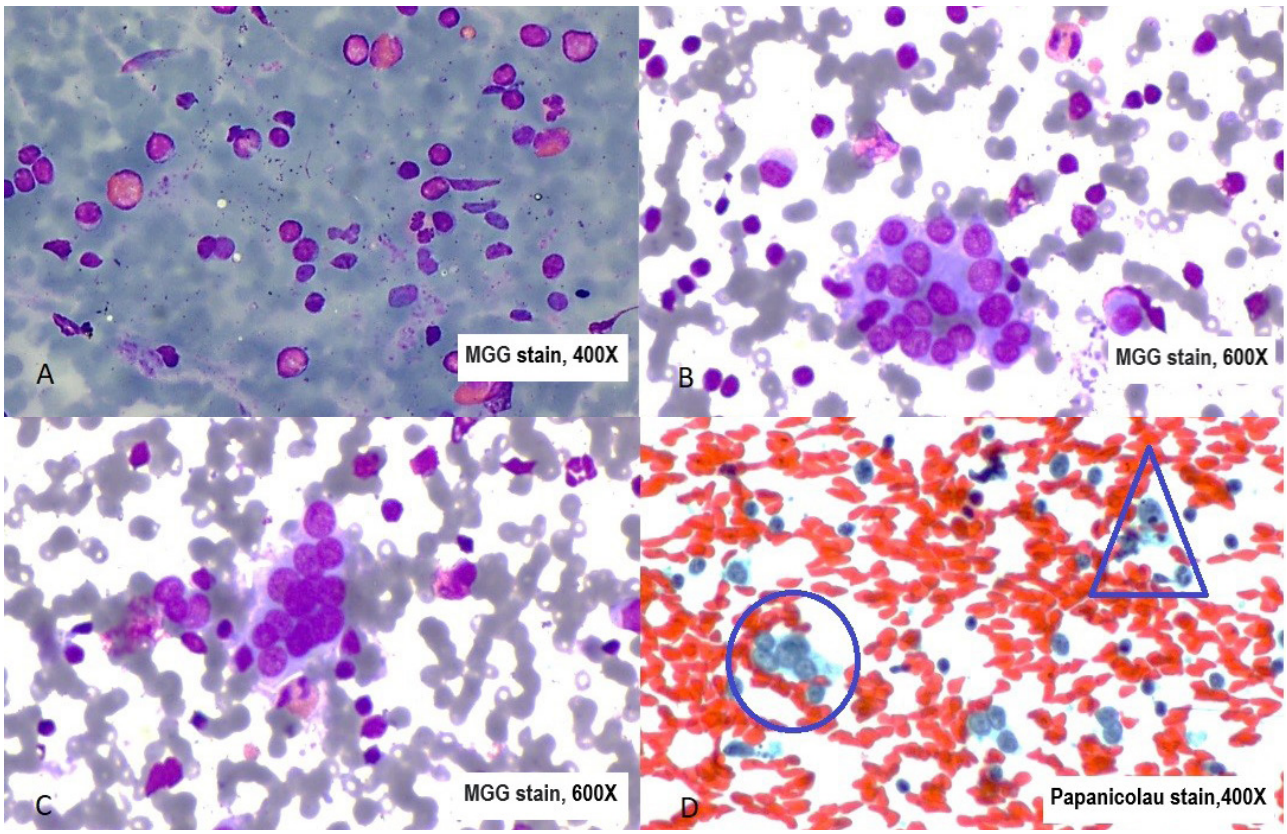

Fig. 2 (Case 3): **A**, Heterogenous population of lymphoid cells composed of mature lymphocytes and scattered eosinophils (Smear, MGG stain, 400X); **B**, Multinucleated giant cells with overlapping nuclear arrangement representing polykaryocytes (Smear, MGG stain, 600X); **C**, Another multinucleated giant cell seen in which the nuclei are arranged in grapevine-like structure which is the cytological description for polykaryocytes (Smear, MGG stain, 600X); **D**, Multinucleated giant cells (in the circle) with cells showing binucleation and tingible body macrophages (in the triangle) (Smear, Papanicolau stain,400X). MGG, May Grunwald Giemsa

Review of cases in the literature and hospital series

A review of the literature revealed 53 cases that have been reported in Malaysia. Together with the seven cases from our case series, a total of 60 cases were analysed. Details of the clinical characteristics, treatment modalities and clinical outcomes of each case are shown in Table 1.

Table 1: Clinical Characteristics, Treatment Modalities and Clinical Outcomes of 60 Patients with Kimura Disease in Malaysia

Author	Publication year	Cases	Age of onset/ Duration before diagnosis	Location of Mass and Size (cm x cm)	Treatment Modality	Recurrence (n) or Outcomes/ (Follow-up time)
Ayob Y (5)	1986	1	45y/ 1y	Ear lobule (5x6)	Surgery	-
		2	-	Cheek (6x6)	Surgery	-
		3	20y/ few weeks	Forehead (1.2x0.8)	Surgery	-
		4	47y/ 5m	Neck (4x3)	Surgery	-
		5	13y/ 3y	Parotid (7x6)	Surgery	-
		6	8y/ 7y	Parotid (10x10)	Surgery	-
Jayaram G *et al*. (6)	1995	1	21y/ 1y	R parotid (2x1.5)	-	-
		2	26y/ 1y	R parotid (6x3) L submandibular (1.5x1.3) L inguinal (1x0.5)	-	-
		3	40y/ 2y	L submandibular (2x3) L postauricular (1.5x1, 2x1) R inguinal (3x2)	-	-
Wong KT *et al*. (7)	1999	1	29y/ 6m	Forehead	-	-
		2	8y/ 6m	Neck	-	-
		3	22y/ 1y	Elbow	-	-
		4	42y/ 10y	Jaw	-	-
		5	15y/ 2m	Postauricular	-	-
		6	18y/ 5y	Jaw	-	-
		7	-	Postauricular, parotid and lymph node	-	-
		8	18y/ 5y	Parotid and lymph node	-	-
		9	39y/ 2y	Inguinal and cervical lymph node	-	-
Arshad AR (8)	2003	1	17y/ 1y	Parotid (3x4)	Surgery followed by steroid	-
		2	27y/ 3y	Parotid (5x5)	Surgery followed by steroid	-
		3	29y/ 1y	Parotid (9x9)	Surgery followed by steroid	-
		4	31y/ 1y	Parotid (9x9)	Surgery followed by steroid	-
		5	30y/ 2y	Parotid (6x6)	Surgery followed by steroid	-
		6	23y/ 20y	Parotid (10x10)	Surgery followed by steroid	-
		7	44y/ 2y	Parotid (9x9)	Surgery followed by steroid	-
		8	30y/ 3y	Parotid (5x5)	Surgery followed by steroid	-
Ismail F *et al.* (9)	2004	1	27y/ 10y	B parotids (6x5)	Refused surgery	

Table 1: Clinical Characteristics, Treatment Modalities and Clinical Outcomes of 60 Patients with Kimura Disease in Malaysia (continued)

Author	Publication year	Cases	Age of onset/ Duration before diagnosis	Location of Mass and Size (cm x cm)	Treatment Modality	Recurrence (n) or Outcomes/ (Follow-up time)
Abdul Rahman R *et al*. (10)	2005	1	56y/ 8m	R cheek (buccal) (2x2)	Surgery	-
		2	14y/ 1y 6m	R postauricular (3x4) Cervical lymph node	Surgery	No / (1 year) New swelling occurred at different location
Asma A *et al.* (11)	2005	1	10y/ 3y	R cervical (3x3)	Surgery	No / (3 years)
Shahrul H *et al*. (12)	2007	1	12y/ 15y	R postauricular (8x8) L postauricular (6x6)	Surgery followed by steroid	No
		2	-	L cervical	Surgery followed by steroid	No
		3	26y/ 3y	R pre and postauricular	Surgery followed by steroid	Yes (1), Recurred after defaulted treatment
Hafiz A *et al*. (13)	2010	1	24y/ 3y	L groin (28x18)	Combination steroid and surgery	No/ (7 years)
Ibrahim ZA *et al.* (14)	2011	1	1y/ 11y	R arm (4x3x3) R axilla lymph node	Surgery	No/ (6 months)
Othman SK *et al.* (15)	2011	1[b]	10y/ 30y	R cervical (2)[a] R postauricular (2x2)	Prednisolone 1mg/kg/day for nephrotic syndrome	No / (5 years 4 months)
Periasamy C *et al*. (16)	2012	1[b]	9y/ 2y	L postauricular (6x4) Cervical lymph node	Surgery	-
Ragu R *et al*. (17)	2014	1	25y/ 6y	R parotid (8x4)	Surgery	No/ (1 year)
Sia KJ *et al*. (18)	2014	1	49y/ 3y	R parotid (6)[a]	Surgery	No/ (2 years)
		2	38y/ 10m	L submandibular (3)[a]	Surgery	No/ (3 years)
		3	24y/ 6m	L parotid (3)[a]	Steroid (limited response) followed by surgery	No/ (8 years)
		4	15y/ 1y	R cervical (4.5)[a]	Surgery	Yes (1)/ (6 years)
		5	23y/ 6m	L postauricular (3.5)[a]	Surgery	No/ (4 years)
Azman MS *et al*. (19)	2017	1	17y/ 2m	R inferior orbital B cubital and inguinal	Steroid	Reduced R eye proptosis
Hashim HZ *et al.* (20)	2017	1	41y/ 6m	R submandibular (7x7)	Surgery	-
Gregory X *et al*. (21)	2018	1	50y/ 1m	B inguinal (Right: 4x4)	Surgery	No/ (6 months)
Aziz A *et al*. (22)	2018	1[b]	10y/ 5y	L postauricular (4x2) L cervical lymph node	Surgery	Yes (1)/ (1 year)
Zulkifli F *et al*. (23)	2019	1	14y/ 10y	L supraauricular (5x6) Cervical lymph node	Surgery	-
Ting SL *et al.* (24)	2020	1	32y/ 1y	L upper eye lid (lacrimal) (2x2) L preauricular	Surgery	No / (2 years)
		2	60y/ 1y	R upper eye lid (lacrimal) (1.5x2) R parotid	Surgery	No / (2 years)

Table 1: Clinical Characteristics, Treatment Modalities and Clinical Outcomes of 60 Patients with Kimura Disease in Malaysia (continued)

Author	Publication year	Cases	Age of onset/ Duration before diagnosis	Location of Mass and Size (cm x cm)	Treatment Modality	Recurrence (n) or Outcomes/ (Follow-up time)
Eh Dam VSK *et al.* (25)	2020	1	11y/ 5y	R parotid (13x13) Cervical lymph node	Combination steroid and surgery	-
Kamal NR *et al.* (26)	2020	1	48y/ 6m	R cheek (8x4x4)	Steroid and leflunomide	Reduced size in 1 month
Abdul Ghafar MH *et al*. (27)	2020	1	20y/ 13y	L parotid (12x10)	Combination steroid and surgery	-
Present study		1	11y/ 2y	R preauricular (2x1) R ear lobule (3x1)	First treatment: Surgery Second treatment: Steroid followed by azathioprine and cetirizine for recurrence Third treatment: Surgery 2 times	Yes (2) No reduction in size with second treatment (2 years and 6 months)
		2	10y/ 2y	L ear antihelix (3x2) L postauricular (5x3)	First treatment: Short course oral steroid and intralesional steroid injection Second treatment: Surgery 2 times Third treatment: Azathioprine for local recurrence post-surgery Fourth treatment: Surgery	Yes (2) ? unsatisfactory response with first treatment (unclear) No reduction in size with third treatment (3 years and 3 months)
		3[b]	16y/ 1m	L parotid (4x4) L cervical (2x2)	Prednisolone 1mg/kg/day for nephrotic syndrome	No/ (2 years)
		4	22y/ 5y	R submandibular (9x6)	Surgery	Yes (1)/ (8 months)
		5	10y/ 15y	L ear lobule (7x5) L parotid (10x6)	Surgery	No
		6	8y/ 10m	B postauricular (1.5x1.5)	Surgery	No/ (6 years and 1 month)
		7	12y/ 5m	B postauricular (R: 3x3)	Surgery	Yes (2)/ (2 years and 5 months) New swelling occurred at right upper cervical

[a]Diameter; [b]Renal involvement; B, Bilateral; R, Right; L, Left; y, years; m, months

Demographic and Clinical Characteristics

Table 2 shows a summary of the demographic and clinical characteristics of the patients. Among the 60 cases, 52 (86.7%) of them were men with a male:female ratio of 6.5:1. Majority were of the Malay ethnicity (77.1%), followed by Chinese (18.8%) and others (4.1%). Median age of onset was 22 years (IQR 12.5-31.5) with the youngest being a year old and the oldest at 60 years. Eighteen percent experienced the onset of a subcutaneous swelling at the age of 40 years old and above. Median duration between the onset of subcutaneous swelling and a diagnosis of Kimura disease was 2 years (IQR 0.8-5.0). The head and neck regions were the most frequent region involved (95%), including three cases of periorbital swelling. Thirteen percent of the patients also had swelling in other regions (five cases in the inguinal area and one each for cubital, groin, elbow, arm and axilla).

Peripheral eosinophilia was detected in 88.9% of the patients at presentation. Nephrotic syndrome was diagnosed in four patients (22.2%). Two cases of steroid sensitive nephrotic syndrome were diagnosed at 9 months (Case No. 3 in case series) and 30 years (15) after disease onset. One case each of steroid dependent (16) and steroid resistant (22) nephrotic syndrome were diagnosed at 7 and 3 years, respectively, before the onset of subcutaneous swelling.

Table 2: Demographic and clinical characteristics of Kimura Disease in Malaysia

Characteristics	No. of patients (%)
Gender (n=60)	
Male	52 (86.7)
Race (n=48)	
Malays	37 (77.1)
Chinese	9 (18.8)
Others	2 (4.1) (Iban, Bisaya)
Age of onset (year), median (IQR) (n=57)	22.0 (12.5-31.5)
Age of diagnosis (year), median (IQR) (n=60)	27.0 (16.0-40.8)
Duration before diagnosis (year), median (n=56)	2.0 (0.8-5.0)
Location of mass (n=60)	
Head and neck	57 (95.0)
Others	8 (13.3)
Presence of peripheral eosinophilia (n=36)	32 (88.9)
Renal involvement (n=18)	4 (22.2)

Treatment Modalities and Clinical Outcomes

Data on treatment modalities were available for 47 patients. Their first choice of treatment is summarised in Table 3, with surgery being the most common first choice. During follow up visits, nearly 95% underwent surgical excision. This is followed by the use of steroids in 44.7% of cases and immunosuppressive agents in 6.4% (two cases were on azathioprine and one on leflunomide). Local radiotherapy was not given for any patients.

Follow up data was available for 21 patients, from which the medium follow up period were 29 months (IQR 12-56), between a range of 6 to 96 months. Local recurrence was observed in 28.6% during follow up. With surgical excision, six (31.6%) out of 19 patients had at least one recurrence. There was no recurrence observed in two patients who were on high doses of steroids for their nephrotic syndrome. Recurrence was not observed during 7 years of follow up in a case with combination of surgery and steroids. Regression of a cheek swelling was observed after 1 month combination treatment of leflunomide and steroid medication. However, reduction in size of a recurred neck swelling was not observed in two patients who were treated with azathioprine.

Table 3: First choice of treatment modality given

Treatment modalities (n=47)	No. of patients (%)
Surgery	27 (57.5)
Steroid	5 (10.6)
Surgery and steroid	14 (29.8)
Immunosuppressive agent	0 (0.0)
Steroid and immunosuppressive agent	1 (2.1)

Discussion

A predominance of Kimura disease occurrence was demonstrated among Malaysian men with a median age of onset of 22 years. The presence of soft tissue swelling is the main presenting complaint, with head and neck being the most frequently involved regions. Peripheral eosinophilia was detected in 88.9% of cases at presentation. Nearly a quarter of the patients had renal involvements. Surgery was the commonest first choice of treatment, followed by a combination of surgery and steroid. Local recurrence was observed in one in every four patients with a median duration of follow up of 29 months.

The finding on males being the predominant gender in our study is similar to previous studies (28-31). Male predilection in Kimura disease is postulated to be influenced by the sex hormone and sex chromosome or the genetic factor, in the same understanding of female predilection in systemic lupus erythematosus and rheumatoid arthritis. More studies however are needed to confirm this hypothesis. Furthermore, the breakdown of ethnic groups in our study is consistent with the ethnicity

ratio in the local Malaysian population (32). This may illustrate no potential ethnicity tendency or predominance in Kimura disease among the Malaysian population.

Kimura disease usually occurs in young adults, especially during the third decade of age (1). Nevertheless, one notable finding from our study is the younger age of onset at 22 years old as compared to a cohort from Japan (26.2 years (31)) and two cohorts from China (27 years (30) and 44.5 years (28). This is potentially attributed to genetic differences among Asians. Furthermore, the interval duration between onset and diagnosis of Kimura disease in our patients was 2 years, which is similar to a study by Zhang and Jiao (30). Certainly, clinical characteristics of slow and progressive enlargement of subcutaneous swelling masses in Kimura disease may explain the late presentation and delay in seeking treatment. As for the presentation of symptoms, 95% of the patients had head and neck involvement, which is consistent with previous studies (28, 30, 33, 34). Hence, most patients usually first encountered an otorhinolaryngology surgeon, unless swelling occurred at other locations of the body. Majority of our patients also had peripheral eosinophilia at presentation.

Eosinophilia and elevated IgE levels are the hallmark characteristics of Kimura disease. It is postulated to be triggered by arthropod bites, or parasitic, candida and viral infection, T-cell immune-dysregulation, induction of IgE-mediated type 1 hypersensitivity, allergy and an association with autoimmune disease (1, 28, 35). However, the underlying pathogenesis is not well understood due to the rarity of the disease. Two of the patients in our study had a history of atopy and thus, IgE mediated type 1 hypersensitivity may help explain the pathophysiology that led to the presentation of peripheral eosinophilia.

Differential diagnosis of Kimura disease includes angiolymphoid hyperplasia with eosinophilia (ALHE), Hodgkin's lymphoma, Non-Hodgkin's lymphoma, angioimmunoblastic T-cell lymphoma, Langerhans cell histiocytosis, parasitic lymphadenitis, salivary gland diseases and many more (30, 36, 37). These diseases can be differentiated using histopathological examinations of the subcutaneous masses or affected salivary glands. Kimura disease on the other hand, has distinct and well described clinical histological features. Consistent with the histopathological findings of patient Case No. 1, Hui et al (38) had classified the salient pathological features into:

- Constant features, consisting of preserved nodal architecture, florid germinal centers, eosinophilic infiltration, increased postcapillary venules.
- Frequent features, marked by sclerosis, polykaryocytes in germinal centers and cortex, vascularisation of germinal centers, necrosis of germinal center, eosinophilic abscess, atrophic venules in sclerotic areas.
- Rare features, characterised by progressive transformation of germinal center.

Other notable features are the presence of IgE reticular network in the germinal center and IgE-coated non-degranulated mast cells.

Meanwhile, cytologic findings of polymorphous lymphoid population, a substantial number of interspersed eosinophils, fragments of collagenous tissues, presence of endothelial cells and Warthin-Finkeldey polykaryocytes are the commonest attributing features of Kimura disease (39). Warthin-Finkeldey polykaryocytes (described as multinucleated giant cells in grape-like clusters) however, has also been identified in conditions other than Kimura disease such as measles, reactive lymphoid hyperplasia and lymphoproliferative diseases, especially Hodgkin's lymphoma (38, 40, 41). Nevertheless, as seen in patient Case No. 3, the constellation of clinical presentations, cytological characteristics of FNAC, laboratory evidence of peripheral eosinophilia and elevated serum IgE confirm the diagnosis of Kimura disease without histopathological evidence (37, 39, 42).

Systemic diseases, especially renal involvements are widely associated with Kimura disease. The various renal pathological complications of this disease include membranous nephropathy, minimal change disease, mesangial proliferative glomerulonephritis, focal segmental glomerulosclerosis and IgM and IgA nephropathy (43, 44). Increased permeability of glomerular basement membrane by the various cytokines released from activated T-cells may explain the development of nephropathy in Kimura disease. Four patients in our cohort had nephrotic syndrome with variable responses to corticosteroid therapy. Although Kimura disease is a benign condition, some patients may develop end-stage renal disease (44). Other systemic diseases include cutaneous eosinophilic vasculitis (45), juvenile temporal arteritis (46), necrotizing eosinophilic vasculitis with peripheral arterial occlusive disease (47), and thromboembolism with variedly sized vessels (30). There was however, no reported cases of vasculitis or thrombosis from our reviews.

To date, there is no standardised treatment available for Kimura disease, due to disease rarity and lack of clinical studies of treatment options. Surgical excision alone, radiotherapy alone, a combination of surgical excision and radiotherapy, a combination of surgical excision and steroid, steroid alone and immunosuppressive agents are the currently available options with different levels of effectiveness. In addition, variable recurrence rates of up to 70% had been observed with different treatment modalities (28, 30).

A meta-analysis of 639 patients with Kimura disease was conducted to compare the effectiveness of treatment modalities between surgical excision alone, radiotherapy alone, and a combination of surgical and radiotherapy (48). The analysis showed that surgical excision alone and radiotherapy alone had higher rates of local recurrence (Relative Risk: 4.722 and 2.718 respectively), compared to a combination of surgical excision and postoperative low dose irradiation. The use of immunosuppressive agents

such as azathioprine (49), cyclosporin (49-54), tacrolimus (55, 56), methotrexate (57), mycophenolate mofetil (58, 59), leflunomide (60, 61), and cyclophosphamide (59, 62) have been reported but also with variable outcomes. Cetirizine (63), an anti-allergy, omalizumab (64), an anti-IgE therapy and mepolizumab (65), an anti-interleukin-5 have also been used to treat Kimura disease with favourable outcomes. Nevertheless, larger studies are required to confirm the efficacy and safety of these medications.

In our patient cohort, surgical excision (57.5%) and a combination of surgical excision and steroid (29.8%) were the main choices of treatment modalities. Local recurrence rate post-surgical excision alone was observed in about one-third of our patients. Similarly, a high local recurrence rate of 46-66% by post-surgical excision alone was reported in the literature (28, 30). High recurrence rate may be explained by several factors such as ill-defined boundaries (28, 66) of the swelling, diameter of the swelling (66), bilateral involvement (66), disease duration (66), eosinophil counts (66), smoking (67), systemic disease (67), choice of treatment such as surgery alone and surgery followed by oral steroid (28,67). In cases with local recurrence, surgery combined with postoperative radiotherapy might be a good option due to lower local recurrence rate (48). However, further study is needed to assess its efficacy in comparison with other treatment modalities.

To the best of our knowledge, this is the first report of Kimura disease based on cases in the literature in the Southeast Asia region, which is a complete review of published cases in Malaysia up to December 2020. Our analysis has clearly illustrated the clinical characteristics and outcomes of Kimura disease in this region. Limitations of our study include the limited availability of data from some reports on treatment, clinical outcomes and follow up duration. This limitation has led to a lower number of patients being analysed for the treatment and clinical outcome parameters.

Conclusion

Although demographic and clinical characteristics of Kimura disease in Malaysia were similar to reports from other Asian countries, a much younger age of disease onset was found among Malaysians. Early diagnosis can be made by correlations between clinical presentation, laboratory findings of peripheral eosinophilia, raised serum IgE and cyto-histopathological features. A high local recurrence rate of one in every four patients was observed despite the disease's benign nature. Thorough evaluation on the effectiveness of treatment strategies is needed to manage the high recurrences rate of Kimura disease in Malaysia.

Acknowledgement

We would like to thank the Director General of Ministry of Health, Malaysia for allowing us to publish this article.

Funding

This work received no specific grant from agency.

Competing interests

The authors have no conflict of interest to declare.

Ethics approval

Since this was a case series and a review, ethical approval was waived by Medical Research & Ethics Committee (MREC) Malaysia (NMRR-21-339-58522 S3 R1)

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