CASE SERIES

Extra-nodal Kimura disease of head and neck region: A clinical perspective

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Abstract

Kimura's Disease (KD) is a rare, chronic inflammatory disorder of unknown etiology, potentially linked to dysfunctional immune responses or aberrant allergic reactions. It typically involves the head and neck, manifesting as subcutaneous nodules, often accompanied by regional lymphadenopathy, peripheral blood eosinophilia, and elevated serum IgE levels. While most commonly reported in young Asian males, cases in older individuals and females also occur. The definitive diagnosis is primarily based on histopathological examination of a biopsy specimen. Case series: This is cross-sectional observational study which reviewed 4 cases of extra-nodal KD, emphasizing its rarity and highlighting its presentation across different demographics. The patients presented with painless, slow-growing pre and post auricular swellings. Consistent findings included marked peripheral eosinophilia and imaging showed well-defined subcutaneous masses and reactive lymph nodes. Fine-needle aspiration cytology was non-specific. Histopathological evaluation of excised tissue confirmed KD, demonstrating characteristic hyperplastic lymphoid follicles with germinal centers, diffuse eosinophilic infiltration (including microabscesses), vascular proliferation, and fibrosis, correlating with the observed eosinophilia. These features aid in differentiating KD from similar conditions like angiolymphoid hyperplasia with eosinophilia. Treatment primarily involved surgical excision and systemic steroids were used for a recurrent case. Extra nodal KD is benign tumor yet can clinically and histologically mimic malignancy emphasizing the need for high clinical and pathological suspicion for accurate diagnosis and treatment.

Keywords: Kimura disease, head & neck, eosinophilia

Introduction

Kimura's Disease (KD) is a rare, chronic inflammatory disorder of unknown etiology. It was first described by Kimm and Szeto in 1937 as "eosinophilic hyperplastic lymphogranuloma" [1]. It gained prominence as KD following a report by Kimura and coworkers in 1948, which elaborated on an "unusual granulation combined with hyperplastic changes in lymphoid tissue" [2].

KD primarily involves the head and neck region specially in preauricular region, forehead or scalp and typically manifests as subcutaneous tumor-like nodules, often accompanied by regional lymphadenopathy, peripheral blood eosinophilia, and elevated serum Immunoglobulin E (IgE) levels [3].

Exact etiology remains elusive with possible theories considered are dysfunctional immune response, aberrant allergic response to viral, arthropod and tumor antigens. Presence of eosinophils, mast cells, interleukins and IgE suggest an abnormal T cell response to hypersensitivity type of reactions [4-5]. Association with autoimmunity and endocrine disorders have also been reported [3]. The exact prevalence of KD is not known. Most cases of this rare disease are reported in East and Southeast Asia, with a small number of cases reported in Europe. Male to female ratio ranges

from 3.5:1 to 9:1 in most series so far reported, with some exceptions. KD is usually seen in young adults during the third decade of life, with the median age being 28–32 years [6].

Morphologically KD is characterized by lymphoid follicles with germinal centers, marked eosinophilic infiltration, vascular proliferation, and fibrosis involving lymph nodes or extra nodal subcutaneous tissue. This research paper aimed to discuss the frequency and pathology of this rare disease.

Methods

This was a ten-year cross sectional observational study (2015 to 2025). Institutional ethical clearance was obtained from the Institutional Ethics Committee (SDMIEC/2023/517). Biopsy of confirmed cases (nodal/extra-nodal) of KD received in SDM College of Medical Sciences and hospital were noted from clinical records. Patient data were documented as demographic data (including age, gender etc), clinical presentation, haematological examination findings including haemoglobin, erythrocyte sedimentation rate, peripheral smear examination findings (and blood eosinophils levels), serum IgE levels, and Ultrasonography (USG) findings at the time of biopsy. The biopsy specimens obtained were processed as per standard operating procedure. The tissue sections were 4-6 microns thick and stained routinely with H&E. The H&E-stained slides were evaluated and correlated with serum IgE levels and blood eosinophil count.

Results

Considering KD is a rare entity, out of 11 KD encountered in present study, 4 were extra-nodal which are discussed here and remaining 7 cases of KD were in axillary and cervical lymphnodes.

Case 1: A 22-year-old male patient presented with a 10-year history of a gradually increasing swelling on the right side post auricular area. The swelling was painless with no other associated functional symptoms.

On examination: On local examination, an ill-defined swelling was palpated measuring about 6 cm × 5 cm, soft in consistency. Right level V discrete lymph nodes were enlarged. The skin over the swelling appeared normal with no signs of infection or inflammation. Fixation to the underlying structures was not present. Intraoral findings were unremarkable with no foci of infection. No other distant lymphadenopathy was elicited clinically.

Investigations: Haematological investigations revealed leucocyte count with normal limit with marked eosinophilia (46%) with all other peripheral blood findings within normal limits. High Resolution USG (HRUSG) of post auricular region showed a well-defined, lobulated, heterogenous solid, cystic, subcutaneous mass measuring 6 × 1.3 × 3.4 cm with minimal oedema. Numerous enlarged hypoechoic, level V discrete lymph nodes were seen with maintained USG morphology and raised vascularity suggestive of reactive change. Aspiration cytology revealed chronic inflammatory lesion.

Clinical diagnosis: The clinical differential diagnoses comprised a wide spectrum of conditions such as infected dermoid cyst or benign soft tissue lesion.

Treatment: Excision biopsy was performed and the specimen received on histopathological examination revealed KD.

Case 2: A 71 year female presented with a painless right preauricular swelling progressive in nature for last 6 years. The swelling was painless with no other associated functional symptoms.

On examination: On local examination a swelling was palpated measuring about 4 × 5cm, soft in consistency. The skin over the swelling appeared

normal with no signs of infection or inflammation. Fixation to the underlying structures was not present. Intraoral findings were unremarkable. No cervical lymphadenopathy was seen.

Investigations: Haematological investigations revealed leucocyte count within normal limits with marked eosinophilia (35%) with all other peripheral blood findings within normal limits. HRUSG showed a well-defined, lobulated, heterogenous solid subcutaneous mass measuring 4 × 4.2 × 4.8cm suggesting benign salivary neoplasm. Fine needle aspiration cytology was done and reported as chronic sialadenitis.

Clinical diagnosis: The clinical differential diagnoses were salivary benign neoplasm.

Treatment: Excision biopsy was performed and tumor diagnosed as KD.

Case 3: A 73 year female presented with a painless left postauricular swelling progressive in nature for last 1 year. The swelling was painless with no other associated functional symptoms.

On examination: On local examination a swelling was observed measuring about 3 × 3.5 cm, soft in consistency. The skin over the swelling and underlying tissue appeared normal with no signs of infection or inflammation.

Investigations: Haematological investigations revealed mild rise in leucocyte count with marked eosinophilia (38%) with all other peripheral blood findings within normal limits. HRUSG showed a well-defined, lobulated, heterogenous solid subcutaneous mass is seen measuring 3.2 × 2.8 × 2.9 cm. Fine needle aspiration cytology was done and reported as inflammatory lesion.

Clinical diagnosis: The clinical differential diagnoses was neurofibroma or schwannoma.

Treatment: Excision biopsy was performed and the specimen diagnosed as KD.

Case 4: A 56-year-old male patient presented with the complaint of right parotid swelling for the past 9 years which was insidious in onset and gradually progressive. He had history of left parotidectomy done 3 years back.

On examination: On examination 1 × 1 cm swelling was seen in the right preauricular area. It was firm in consistency. Scar noted on left preauricular area measuring 1.5cm in length.

Investigations: Haematological examination revealed eosinophilia with 58.7% eosinophils. HRUSG of right parotid showed a hypoechoic homogenous lesion measuring 2 × 1.8 × 1.5cm. CT done outside showed features suggestive of lymphoma sialadenitis. Fine needle aspiration of parotid swelling showed focal areas of micro abscesses with lympho-eosinophilic infiltrates. Diagnosis of chronic inflammatory lesion favouring KD was considered. On interrogation patient revealed left parotidectomy was diagnosed as KD.

Clinical diagnosis: A clinical diagnosis of recurrent KD was established.

Treatment: Excision of right parotid lesion was done and sent for histopathologic evaluation. As it was recurrent KD, the consulting hematologist treated the patient with systemic steroid therapy with a loading dose of 20 mg of prednisolone in divided doses with cetirizine for 4 months. There was good response to steroid therapy, and the lump started to regress >70% within 3 months which was confirmed by CT scan. Steroid dose was tapered. Short course of dexamethasone (60 mg) also started for a month.

Histopathological evaluation of all four excised tissue revealed similar morphology. (Figures 1, 2, 3 & 4)

Microscopy showed hyperplastic lymphoid follicles with prominent germinal centers with variable amount of fibrosis. Diffuse infiltration of eosinophils, histiocytes, plasma cells and mast cells were seen along with eosinophilic micro abscess formation destroying the follicles. Occasional multinucleated giant cells were also noted. Polykaryocyte were evident. Lymphoid folliculysis and follicular hyperplasia were evident, correlating with the hematological finding of eosinophilia. All the cases were diagnosed as KD.

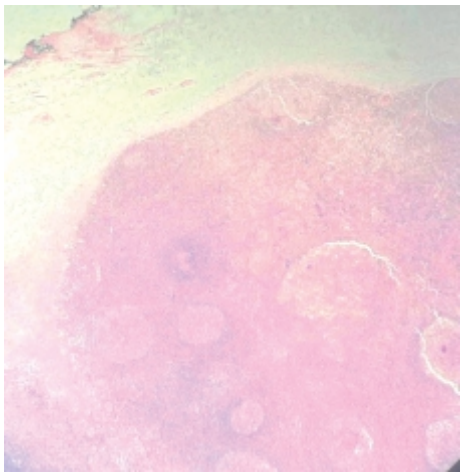

Figure 1: Scanner view H&E stain: Tissue displaying hyperplastic lymphoid follicles with prominent germinal centers with variable amount of fibrosis

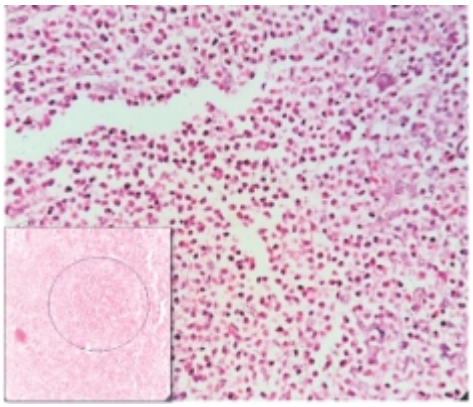

Figure 2: H&E stain High power displaying diffuse infiltration of eosinophils, histiocytes, plasma cells and mast cells seen along with eosinophilic micro abscess formation destroying the follicles (Inset). Occasional multinucleated giant cells were also noted

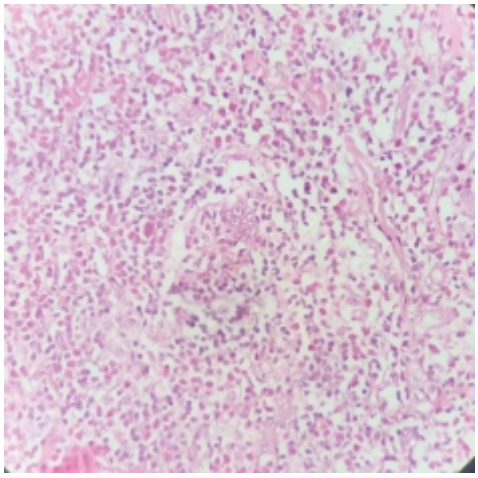

Figure 3: H&E stain High power displaying polykaryocyte in the follicles.

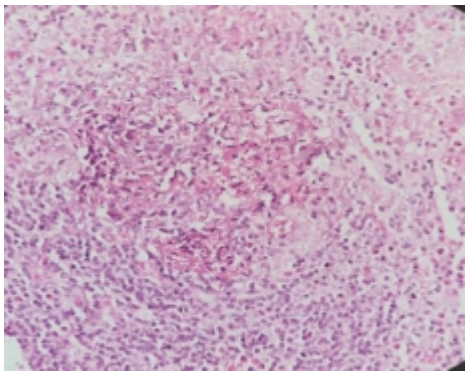

Figure 4: H&E stain High power displaying lymphoid folliculolysis

Discussion

KD is a chronic inflammatory disease of uncertain etiology and is proposed to be an immune response to unknown antigen. However, various theories in literature suggest dysfunctional immune response, aberrant allergic response to viral, arthropod and tumor antigens. Presence of eosinophils, mast cells, interleukins and IgE suggest an abnormal T cell response to hypersensitivity type of reactions. Association with autoimmunity and endocrine disorders have also been reported [3-5]. The cause of KD is still not well understood. Research has indicated that immunological imbalance related to IgE-mediated type 1 hypersensitivity and T Helper (Th)-2 cytokines significantly contribute to its pathogenesis, where tissue damage, allergies, infections, hormonal disorders, and autoimmunity may act as potential triggers. A crucial function of Th 2 cytokines in the development of KD is discussed in literature [6, 7]. Increased expression of Interleukin (IL)-4, IL-5, and IL-13 mRNA has been observed in the peripheral blood mononuclear cells of individuals with KD.

Immunohistochemical analysis of KD tissues showed heightened infiltration of IL-4C and IL-5C mast cells and T cells, along with increased levels of eotaxinC and C–C motif ligand 5 and mast cells, T cells, and activated eosinophils, reinforcing the prevalence of Th2 response. The disease's reactive characteristics are evident in the unique histopathologic patterns, including conspicuous follicular hyperplasia, dense eosinophilic and lymphoplasmacytic infiltration both intra and interfollicular, eosinophilic micro-abscesses (with or without Charcot-Leyden crystals), an abundance of small blood vessels, and marked stromal fibrosis. Lymphoproliferation is linked to the growth of postcapillary venules. The substitution of regular germinal centers with deposits of IgE or eosinophils, necrosis, and polykaryocytes (giant cells of the Warthin–Finkeldey type) may occur. In certain patients, the infiltration of nerve fibers by inflammation leads to skin irritation and itching [7]. The clinical presentations of KD described in the literature exhibit several consistent features, along with some variability.

Age and sex prediction

The literature suggests a predilection for young males of Asian descent. Study of 21 cases reported by Kung *et al.* (1984) included 18 male and 3 female patients with a mean age of onset of 28 years [1]. Similarly, study by Lee *et al.* (2022) with 23 Taiwanese patients showed a male predominance (16 males, 7 females) with a median age at diagnosis of 39 years [3]. A review of orofacial cases also noted a 94% male predominance by Iguchi et al. (1986) [8]. A case report by AlGhamdi *et al.* (2016) also emphasized that KD has no age or ethnicity limit, presenting a case of an 11-year-old Saudi boy [9]. Glibbery *et al.* (2018) reported a rare case in a 41-year-old Caucasian female [10]. Present study had 2 middle aged men affected with extranodal KD and 2 elderly females being affected by extranodal KD, which highlights that KD can occur in older individuals and females, although less commonly reported. These instances underscore the importance of considering KD even in atypical demographics.

Location of lesions

The head and neck region are the most frequently involved anatomical site in KD. Kung *et al*. (1984) found head and neck involvement in 23 out of 33 instances [1]. Lee *et al*. (2022) reported that 21 out of 23 patients presented with unilateral or bilateral head and neck masses [3]. In present study, 2 cases

had pre auricular and 2 cases post auricular swelling. These locations are consistent with the common presentation of KD. However, case series with an inguinal lymph node involvement by Punia *et al*. (2013) and Lee *et al*. (2022) reported cases with right flank and right arm lesions, indicating that KD can occur outside the head and neck, although less frequently [3, 11].

Nature of swelling

The lesions of KD are typically described as firm, painless, circumscribed subcutaneous masses. The painless nature and slow progression reported are characteristic of KD as was evident in present study. However, pruritus of the overlying skin has also been reported, which was not explicitly seen in present study. The size of the masses in the literature varies, ranging from 3-10 cm in the study by Kung *et al*. (1984) and 0.4 to 4.9 cm in maximal diameter in series by Lee *et al*. (2022) [1, 3]. Present cases had size variation from 1.8 to 5 cm.

Associated symptoms and findings

Regional lymphadenopathy is a common finding in KD. Kung *et al*. (1984) reported superficial regional lymph nodes affecting 14 of 21 patients. In present study the radiology revealed few discrete lymph nodes with reactive change. Peripheral blood eosinophilia and elevated serum IgE levels are considered typical laboratory findings. All cases in present study had significant eosinophilia of 46%, 35%, 38% and 58.7% respectively. These findings strongly support the diagnosis of KD and align with the literature, where eosinophil counts often range from mild to marked elevation. AlGhamdi *et al*. (2016) and Guimaraes *et al*. (2009) reported significantly elevated IgE level [7, 12]. While specific IgE levels were not provided in present cases but the presence of eosinophilia, a common association with elevated IgE in KD, further strengthens the clinical picture. Notably, the study by Lee et al. (2022) found increased eosinophils in 56.25% of patients and elevated IgE in 100% of the tested patients [3].

Key histological findings include:

Lymphoid follicles

These are hyperplastic with prominent germinal centers. The lymph node architecture is generally preserved. Extra nodal KD also displays hyperplastic lymphoid tissue.

Eosinophilic infiltrate

There is an intense infiltration of eosinophils, which can be focal or diffuse and may be massive in some lesions. Discrete foci of necrosis with eosinophils ("eosinophil abscesses" or eosinophilic microabscesses) are often present. Eosinophils may sometimes impinge on lymphoid follicles.

Vascular proliferation

There is proliferation of capillaries and small blood vessels, often with swollen endothelial cells. These are typically canalized vessels with flat endothelial cells, unlike the uncanalized masses with plump endothelial cells seen in Angiolymphoid Hyperplasia with Eosinophilia (ALHE). An increased amount of postcapillary venules is a constant feature. Hyalinization of sinusoidal vessels may be observed. Punia *et al*. (2013) illustrated vascular proliferation in their cases [11].

Fibrosis

Fibrosis surrounds the lesions, and fibrous bands may extend into the lesions as septa or outwards into adjacent structures, including lymph nodes. The fibrous tissue is variably cellular, with hyalinization being prominent in older lesions. Punia *et al*. (2013)

also reported areas of fibrosis in their cases [11]. Sparse plasma cells and histiocytes may be present, but giant cells, epithelioid cells, or granulomas are typically absent, which helps to distinguish KD from other inflammatory conditions. Immunochemical staining may reveal an IgE reticular network in germinal centers and IgE-coated non degranulated mast cells. Increased recruitment of IgG4+ plasma cells may be seen in some cases.

Other histological features

Occasional multinucleated giant cells were noted in present study, which can be seen in KD. Hyalinization of sinusoidal vessels with thick collagen bundles has also been described. The study by Lee *et al*. (2022) reported tissue eosinophilia (100%), florid follicular hyperplasia (78.26%), interstitial fibrosis (52.17%), lymphoplasmacytic infiltrates (48.82%), and increased small blood vessels (48.82%) as the most frequent histological features, which were concordant with present cases [4, 13,14].

Differential diagnosis

Besides ALHE, KD needs to be differentiated from other conditions presenting with head and neck masses and lymphadenopathy, including lymphoma, reactive lymphadenopathies, salivary gland tumors (benign and malignant), sarcoidosis, Kikuchi-Fujimoto disease, and infections (e.g., tuberculosis, fungal infections). The characteristic histological triad of lymphoid follicles with germinal centers, marked eosinophilic infiltration, and vascular proliferation is crucial for accurate diagnosis. The absence of granulomas, significant atypia, or malignant features helps to exclude other entities. In cases with atypical presentations, such as unusual location or association with panniculitis, careful pathological assessment is essential [13, 14].

Distinction from ALHE is critical

Clinically KD typically affects young Asian males with deeper subcutaneous nodules in the head and neck, often accompanied by lymphadenopathy, peripheral eosinophilia, and elevated IgE. ALHE, conversely, is more commonly found as superficial dermal nodules in middle-aged women, with less frequent lymphadenopathy and relatively lower eosinophilia and IgE levels [4].

Pathological differences

Histologically, KD shows well-developed lymphoid follicles with germinal centers, marked eosinophilic infiltration often forming microabscesses, vascular proliferation with canalized vessels and flat endothelial cells, and prominent fibrosis. ALHE is characterized by vascular proliferation with plump, atypical endothelial cells that may form solid masses without lumina, fewer lymphoid follicles often lacking germinal centers, variable eosinophilic infiltration without microabscesses, and less evident fibrosis [4].

Treatment and prognosis

There is no consensus on the optimal treatment for KD. Given its benign nature and the lack of malignant potential, the primary goals of treatment are to alleviate symptoms, reduce the size of lesions for cosmetic or functional reasons, and prevent recurrences [5, 7, 13, 15].

Surgical excision is often considered the first-line treatment for localized lesions. However, recurrences are common after surgical removal, occurring in a significant percentage of patients. Present cases were majorly managed surgically [5, 7]. Corticosteroids (topical, intralesional, or systemic) can effectively reduce the size of the nodules and alleviate symptoms. However, tumors may become refractory, and

long-term use is associated with side effects, with relapses often occurring upon discontinuation. AlGhamdi *et al*. (2016) showed temporary improvement with intravenous steroids and oral prednisone [9]. In present study one case was managed by steroids as there was history of recurrence.

Local radiation therapy has been used for recurrent or persistent lesions and has shown some success in achieving local control [10, 15]. Various other drugs like cyclosporine, interferon-alpha, thalidomide, leflunomide, intravenous immunoglobulins, antihistamines (e.g., cetirizine, loratidine), leukotriene receptor antagonists (e.g., pranlukast), imatinib, and omalizumab (anti-IgE antibody) have shown good response [15].

Conclusion

KD is a chronic inflammatory condition of unknown etiology; however, it is immune response to various antigenic stimuli. It does not increase the risk of malignancy but can clinically and histologically mimic malignancies. Histopathological examination of excision biopsy specimen with associated peripheral blood eosinophilia is the gold standard for diagnosis. High index of suspicion is warranted by the clinicians and pathologists to avoid misdiagnosis and unnecessary diagnostic and therapeutic modalities.

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