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Review Article

Ear, Nose and Throat Section

Kimura's Disease without Peripheral Eosinophilia: An Unusual and Challenging Case Simulating Venous Malformation on Imaging Studies- Case Report and Review of literature

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ABSTRACT

Kimura's Disease (KD) is a rare chronic inflammatory disorder presenting as multiple painless solitary subcutaneous nodules, predominantly in the head and neck region and frequently associated with regional lymphadenopathy and/or salivary gland involvement. Because of painless nature and indolent course, there is usually a delay in the patient's presentation. KD may radiologically mimic other chronic inflammatory conditions like tuberculosis, vascular malformations and neoplasms. Clinical correlation and histological evaluation along with elevated peripheral eosinophil and serum IgE level are considered important for confirmatory diagnosis. We report a case of painless swelling over right submandibular region extending to the right superficial parotid. The haematological reports were within normal limits. Ultrasound (USG), Magnetic Resonance Imaging (MRI) and Magnetic Resonance Angiogram (MRA) favoured a diagnosis of venous malformation. However, histopathological examination of excised lesion confirmed a diagnosis of KD. This case proves the possibility of the KD even in the absence of peripheral eosinophilia and/or elevated serum IgE level, and may mimic venous malformation on imaging studies. Therefore, KD must find a place in the differentials of solitary painless neck swelling even in the absence of peripheral eosinophilia and/or elevated IgE level.

Keywords: Angiolymphoid hyperplasia with eosinophilia, Immunoglobulin E, Subcutaneous nodule

CASE REPORT

An 18-year-old Indian male presented with a progressive swelling below right ear since nine years. History of present illness revealed no associated complaints like pain or itching over the swelling, dry mouth, weight loss or night sweating. Localized examination revealed a 5 x 3 cm, firm, non tender, partially mobile, subcutaneous nodule extending from right mandibular angle upto right parotid region [Table/Fig-1]. Overlying skin was normal. General physical examination showed no facial asymmetry, no cervical, axillary or inguinal lymphadenopathy and no hepatosplenomegaly.

Laboratory work up revealed a normal white blood cell count without eosinophilia (4%). Urine analysis and renal function test were within normal limits. Serum IgE level (59.30 IU/ml) and absolute peripheral eosinophil count (280/mm3) were normal.

USG with Doppler study showed a mixed echoic lesion over right side neck, 26x10x16 mm located superficially and extending superiorly over parotid gland. On Doppler study, the lesion appeared moderately vascular showing multiple tortuous arterial and venous channels. Arterial channels were also prominent and showed slightly high velocity and increased diastolic flow [Table/Fig-2]. On the basis of above mentioned USG findings, a diagnosis favouring arterio-venous malformation was reported by the radiologist and MRI along with MRA was planned next to get a more clear and detailed radiological information.

MRI revealed a soft tissue lesion in the right side of neck inferior to the superficial lobe of right parotid gland, measuring approximately 3.0x1.4x2.8 cm in maximum dimension. It was seen anterior to the sternoclenoid muscle abutting its anterior margin. The lesion was seen in close relation with the inferior pole of parotid with indistinct fat planes. It appeared hyperintense on T2 weighted images; hypointense on T1 weighted images [Table/Fig-3]. On post contrast dynamic angiogram, the lesion did not show enhancement in the arterial phase images/prominent arterial feeders. It showed progressive enhancement in delayed phase images with homogeneous enhancement. The lesion was draining into the external jugular vein [Table/Fig-4]. Mildly enlarged lymph nodes were seen in submandibular region, along the jugular chain bilaterally and submental region, largest measuring approximately 2.2x1.0 cm in size. The above MRI and MRA findings were consistent with venous malformation.

Surgical excision of the right subcutaneous mass and superficial parotidectomy was performed under general anaesthesia [Table/Fig-5]. The specimen measured approximately 7 cm in largest diameter, reddish brown in color, soft to firm in consistency, rough nodular with irregular borders [Table/Fig-6]. Postoperative recovery was good with no signs of facial nerve injury. Histological examination of surgical specimen with haematoxylin and eosin staining revealed salivary gland tissue showing lymphoid hyperplasia with germinal center formation [Table/Fig-7a], increase in number of blood vessels in the interfollicular area, some of which showed hyalinization [Table/Fig-7b] and eosinophilic infiltrate [Table/Fig-7c]. These histological features were consistent with Kimura's disease description.

The patient has been followed up in outpatient department and has been asymptomatic for the last one year without being on any medical management.

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review.

DISCUSSION

KD is a chronic disease with benign nature, and is rarely seen. KD is seen most commonly in the head and neck region, the

presentation is a deep subcutaneous mass with associated regional lymphadenopathy or salivary gland involvement. Peripheral eosinophilia and elevated IgE levels in the laboratory findings are most attributed to diagnosis of KD. To the best of our knowledge, only three cases of KD with normal serum eosinophil count or/and IgE levels have been reported worldwide and none reported from Indian subcontinent [1-3]. To the best of our knowledge, our's is the first reported case of KD from Indian subcontinent with normal serum eosinophil count and IgE levels. Additionally, KD mimicking venous malformation on imaging studies have been reported only once from Indian population [4], with our case being second.

KD was first described in China in 1937 and was later characterized by Kimura T et al., [5,6]. It is synonymous with eosinophilic granuloma, eosinophilic hyperplasia lymphogranuloma, eosinophilic lymphofollicular granuloma [7,8].

Although the disease can manifest at any age, most cases have been reported in second and third decades of life. The mean age being 31 years in a case series of patients from US [3]. In other case series of 54 Chinese patients, the mean age of the patients was 33.1 years [9]. The youngest age reported has been 15 months [10]. There is a male predominance, with six times as many males being affected than females [3]. Although it shown to have no racial predisposition in a case series of patients from US [3], majority of patients with KD have been reported from Asian populations in Japan [11], China [9,12], Taiwan [13] and Hong Kong [14]. Sporadic cases have been reported from other ethnic groups [15-18]. Uncommon in Indian natives, with only 20 cases reported from Indian population until 2013 [19]. Majority of cases reported in the literature occurred in the head and neck (76%) [3], in addition to buttock, axilla, groin, arm and femoral region [2,5,20-22].

No clear conclusions have been made about the exact cause and pathogenesis of KD; however various theories have been postulated. Although allergic, autoimmune, infective and neoplastic causes were proposed, no infective agent or allergen has been isolated so far in lesions of Kimura's disease [23]. Arthropod bites, Ebstein-Barr virus, Human herpes virus-8, Candida albicans and parasitic infection have been suggested [24-26]. KD in a haemodialysis patient has been reported once [27]. Immune reaction is thought to be the root of Kimura's disease and is supported by the presence of peripheral eosinophils, increased mast cells and increased levels of interleukin (IL)-5 and IgE, which imply an abnormal T cell stimulation [3,28].

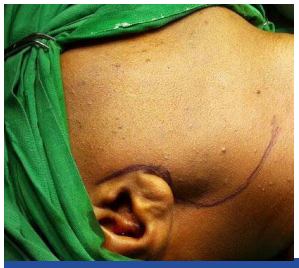
A total of 60% of cases of KD have associated renal involvement [29]. In those cases, the renal pathologies showed almost all types of glomerulonephritis [30,31]. In addition, association between KD and asthma, Raynaud phenomenon, Lichen amyloidosus, Ulcerative colitis, Temporal arteritis, erythroderma, eosinophilic myocarditis and eosinophilic panniculitis have also been reported [32-37].

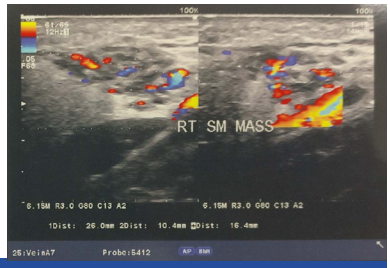
There is not fixed set of signs and symptoms associated with KD. Patients may present with a single or multiple subcutaneous nodules. These nodules are frequently pruritic and may also be painful in some cases. These nodules are slow growing. The diseases mimicking the findings of KD and may be confused with KD are Angiolymphoid Hyperplasia with Eosinophilia (ALHE), vascular malformations [38], pharyngeal pouch, tuberculous abscess, Castleman's disease, Hodgkin's lymphoma, Mikulicz's disease [39], nodal metastasis and reactive lymphadenopathy.

ALHE is most commonly confused with KD. These two disorders are sometimes known to occur in the same patient [40]. ALHE and KD were initially considered same entities by few authors. Rosai J et al., in 1979 eventually clarified this misconception, and KD and ALHE were established as two distinct entities [41]. The two diseases are differentiated on the basis of clinical, laboratory and histological findings [Table/Fig-8] [2,24].

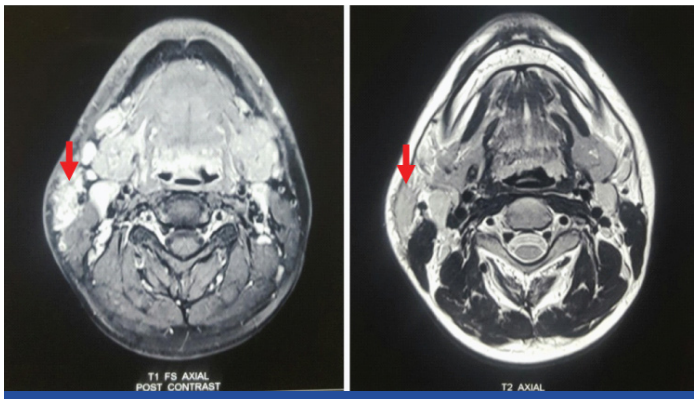
Diagnosis of KD can be difficult and misleading. Most consistent laboratory findings are elevated serum IgE level and peripheral eosinophilia. Absence of above laboratory findings, as in our case can lead to diagnostic dilemma. Only few cases of KD; three to our best knowledge have been reported with normal peripheral eosinophil and/or serum IgE levels. Yang T-H et al., reported KD of left side of neck with normal eosinophil and serum IgE levels [1]. Choi WJ et al., reported a KD occurring on the buttock of a five-year-old boy with normal peripheral eosinophil count while elevated serum IgE level (1,698 ng/ml) [2]. In a case series of patients from US [3], normal peripheral eosinophil level was documented in one out of 17 patients tested, while normal serum IgE level was detected in one out of nine patients tested. One study has shown a positive correlation between degree of blood eosinophilia and size of lesion and hence disease activity [42]. KD with high IgG-4 has also been reported [43]. Impaired renal function tests, leukocytosis, elevated ESR and C-reactive proteins are other possible laboratory findings.

Imaging studies can help in staging the extent and progression of disease, lymph node and parotid gland involvement and to rule

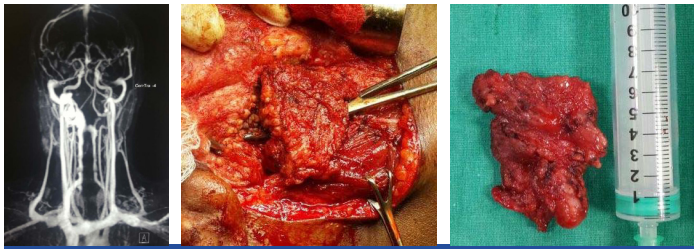




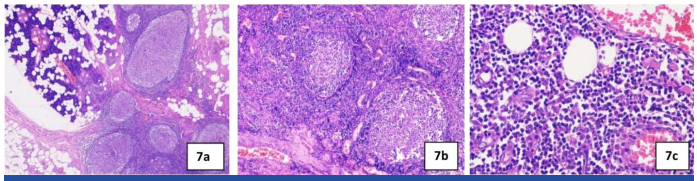
[Table/Fig-1]: Right subcutaneous swelling extending from angle of right mandible to right parotid region. **[Table/Fig-2]:** USG with Doppler study neck showing a superficially located mixed echoic lesion over right side neck and extending superiorly over parotid gland. The lesion appeared moderately vascular showing multiple tortuous arterial and venous channels on Doppler.



[Table/Fig-3]: MRI with T1 and T2 weighted image in axial view showing a right subcutaneous mass (marked by bold red arrows).



[Table/Fig-4]: MRA showing the lesion draining into external jugular vein.
[Table/Fig-5]: Intraoperative photograph of the lesion being excised.
[Table/Fig-6]: Excised surgical specimen.



[Table/Fig-7]: a) photomicrograph showing salivary gland tissue with lymphoid hyperplasia and germinal center formation (H&E 4x); 7b) photomicrograph showing increase in number of blood vessels in the interfollicular area, some of which shows hyalinization (H&E 10x); 7c) photomicrograph showing eosinophilic infiltrate (H&E 40x).

	Kimura's disease	ALHE
Age	2nd-4th decate	2rd-5th decate
ses	M>F	F>M
Demography	Japan, china, Korea	Any, mostly Caucasian
Location	Head & neck mostly	Various locations
Lymphadenopathy	Common	Uncommon
Peripheral eosinophilia	Usually present	Prsent in <10%
Serum IgE	Usually elevated	Usually normal
Serum ESR	Usually raised	Usually normal
Histology	Thin walled blood vessels with cubical endothelial lining	Hypertrophied and sometimes vacuolated endothelial cells with eosinophilic cytoplasm
Immunofluorescence	Heavy IgE deposit in germinal centers	Germinal centers lacks IgE deposit
Nephrepathy	Associated in 29-50% patients	No association

[Table/Fig-8]: Comparison between Kimura's disease and ALHE.

out other causes of neck masses. There is no strong consensus on characteristic imaging findings suggestive of KD. Park SW et al., reported specific intensity and signal changes in CT and MRI examination in lesions of KD [44] while Zhang R et al., showed no specific signal and intensity changes [45]. On radiological examination, KD mimics other chronic and neoplastic diseases. Yang T-H et al., reported a case of KD simulating Hodgkin's lymphoma on 18F-fluorodeoxyglucose positron emission tomography and computed tomography (18F FDG PET-CT) [1]. Rodrigues G et al., reported a doubtful pulsatile thigh swelling which was diffusely vascular on MR angiogram mimicking vascular malformation as in our case [4]. Therefore, diagnosis of KD cannot be based exclusively on imaging studies.

FNA is mostly inconclusive, or may yield a false diagnosis of reactive lymphadenitis [27] or chronic sialadenitis [46]. Both KD and ALHE cannot be differentiated cytologically [47].

Definitive diagnosis of KD is based on histological findings. Repeated biopsy might be required in uncertain cases if the histological findings are not typical for KD [48,49]. In 1989, Hui PK et al., gave histological classification features of KD as constant, frequent and rare [14]. Hyperplasia of germinal centers, intact nodal morphology, post-capillary venule proliferation and eosinophilic infiltrate are most constant histological features. Frequent findings include multinucleated giant cells, sclerosis, eosinophilic microabcessses, necrosis and vascularization of the germinal centers and florid proteinaceous material deposits in the germinal centers. The solitary rare feature is the progressive transformation of the germinal centers. Immunochemistry reveals the presence of IgE reticular network in germinal centers and IgE coated non-degranulated mast cells.

There is no gold standard treatment option and well defined treatment protocol for KD is yet to be established. However, treatment should aim to preserve function and aesthetics while preventing recurrences and long term sequels [50]. In asymptomatic cases, conservative observation is often adequate as lesions occasionally undergo spontaneous resolution. Surgical excision is considered as first line of treatment in symptomatic cases [28]; although recurrence (25%) is common [51]. Topical and systemic steroids are frequently used to prevent frequent relapse and in cases with concomitant nephrotic syndrome, but tumors may become refractory to treatment. Radiation therapy is useful to control lesions that are not responsive to steroids or with a relapse after surgery. Effective total dose is proved to be 20-30 Gy [52]. Recently, use of imatinib, cyclosporine, azathioprine, pentoxifylline and pranlukast has even been validated [35,50,53]. Antihistaminics like cetrizine [53] has been tried prior to corticosteroids for sparing the effects of systemic steroid in this disease. Successful use of photodynamic therapy in recurrence of KD after surgery has been reported [54].

The overall prognosis is good with no malignant transformation documented till date [13]; although, recurrences after all form of treatment are present. The recurrence of disease is affected by various factors, including disease duration, lesion diameter, blood eosinophil count, well-defined lesion boundaries, serum IgE levels and single or multiple lesions [55].

ABBREVIATIONS

KD: Kimura's disease

ALHE: Angiolymphoid hyperplasia with eosinophilia

IgE: Immunoglobulin E

USG: Ultrasonography

MRI: Magnetic resonance imaging

MRA: Magnetic resonance angiogram

CT: Computed tomography

18F FDG PET-CT: 18F-fluorodeoxyglucose positron emission tomography and computed tomography

FNA: Fine needle aspiration

IL: Interleukin

ESR: Erythrocyte sedimentation rate

IgG-4: Immunoglobulin G-4

Gy: Gray

CONCLUSION

KD is rare condition mostly seen in orientals and only few sporadic cases reported from Indian subcontinent. It can simulate venous malformation on imaging studies. Additionally, absence of peripheral eosinophilia can lead to a diagnostic dilemma. Histological diagnosis is only confirmatory.

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