KIMURA'S Disease – An E[X]clusive Condition

Prashanthi Gurram, Saravanan Chandran, Priyadarshini Parthasarathy, Magesh Karuppur Thiagarajan, Karthik Ramakrishnan
Department of Oral and Maxillofacial Surgery, SRM Kattankulathur Dental College and Hospital, SRM University, Kancheepuram, Tamil Nadu, India

Abstract

Kimura's disease is a rare autoimmune disease of unrecognized etiology. Due to its unspecific clinical presentation and laboratory studies, Kimura's is a diagnosis of exclusion . A systematic multidisciplinary approach is mandatory to rule out the other common causes of cervicofacial lymphadenopathy. A thorough Histopathological examination including immunohistochemical analysis along with the presence of specific biochemical markers, including raised Absolute eosinophilic count is necessary to conclude the diagnosis as Kimura's Disease. In this article we present a case of a middle aged Asian woman with cervicofacial lymphadenopathy with no associated illness. The above described protocol of clinical, radiological and histolopathological investigations was followed before establishing the final diagnosis of Kimura's. The review of literature on contemporary management and prognosis is discussed.

Keywords: Cervicofacial lymphadenopathy, immunohistochemistry, Kimura's disease

Introduction

Cervicofacial lymphadenopathy refers to an abnormal change in the size, number, or consistency of lymph nodes in the head and neck region. The human body contains about 600 lymph nodes. The submandibular, axillary, or inguinal regions may be palpable in healthy individuals too. Diagnosis of lymphadenopathy can be usually arrived with comprehensive history and complete physical examination. Additional definitive tests may have to be performed for confirmation of specific systemic illness.

In the head and neck region, a good clinical examination can often lead to a final diagnosis. A palpable lymph node of size more than 1 cm diameter is usually considered abnormal. Pain or tenderness and a softer node are due to the stretch of the lymph node capsule due to inflammation or infection. Stony hard consistency is usually a sign of malignancy. Firm rubbery nodes may suggest lymphoma.

In unexplained localized lymphadenopathy with no demonstrable clinical lesion, a 3–4-week observation period may be prudent. In case of persistent localized or generalized lymphadenopathy, a systematic clinical and radiological evaluation is mandatory. Ultrasonography, magnetic resonance imaging (MRI), and computed tomography (CT) contrast are invaluable. However, definitive diagnosis is made through fine needle aspiration cytology (FNAC), excisional biopsies, and immunohistochemical analysis.[1]

We present one such case here with unexplained unilateral lymphadenopathy of the infraorbital and submandibular regions with no demonstrable precipitating lesion. A thorough systemic examination ruled out any other regional nodal involvement. Initial biopsy results proved to be nonconclusive suggesting reactive changes. However, immunohistochemistry studies confirmed the diagnosis as Kimura's disease – a rare autoimmune disease.

Case Report

A 41-year-old Asian female patient reported to the Department of Oral and Maxillofacial Surgery with a 4-month history of a gradually increasing swelling on the right side of the face. The swelling was largely painless with no other associated functional symptoms. On local examination, a diffuse swelling was observed measuring about 6 cm × 5 cm on the

Address for correspondence: Dr. Prashanthi Gurram, SRM Kattankulathur Dental College and Hospital, SRM University, Kattankulathur, Kancheepuram - 603 203, Tamil Nadu, India.
E-mail: drprashanthig@yahoo.com

Access this article online

Quick Response Code:

Website: www.amsjournal.com

DOI: 10.4103/ams.ams_159_17

How to cite this article: Gurram P, Chandran S, Parthasarathy P, Thiagarajan MK, Ramakrishnan K. KIMURA'S disease – An E[X]clusive condition. Ann Maxillofac Surg 2019;9:183-7.

right side infraorbital region with regional lymphadenitis of the submandibular region of that side. The skin over the swelling appeared normal with no signs of infection or inflammation [Figure 1 (a and b)]. The lump was diffuse, firm, and mildly tender. Fixation to the underlying structures was not present. Intraoral findings were unremarkable with no foci of infection. No other distant lymphadenopathy was elicited clinically. All her hematological investigation parameters were within normal limits. Chest X-ray confirmed the absence of any pathology including hilar lymphadenopathy. The clinical differential diagnosis comprised a wide spectrum of conditions such as lymphoma, fibrosarcoma, and neuroma.

MRI scan of the head and neck showed a homogeneously enhancing infiltrative lesion seen involving the premaxillary space, buccal space, retromolar trigone, and lateral pterygoid in the masticator space on the right side. There was no significant bony destruction. Multiple enhancing solid lymph nodes were seen in the right submandibular, upper deep jugular group and the left submandibular group, largest measuring 18 mm × 12 mm in the right submandibular region. MRI report gave a differential diagnosis of neurofibroma [Figure 2].

FNAC was performed initially, but the result was inconclusive. Therefore, we proceeded with examination under anesthesia and biopsy. The incisional biopsy report suggested a nonspecific type of lymphoid hyperplasia. Hence, definitive surgery was planned with complete excision of the lesion. Intraoperatively, it was observed that the mass was well defined, capsulated, and firm. The histopathology showed dense fibrous connective tissue with some areas exhibiting sheets of numerous small well-differentiated lymphocytes interspersed along with reactive lymphoblasts that were infiltrating into the muscle tissue, blood vessels, and nerves, and in few areas, it formed germinal centers. Mixed type of inflammatory cells including plasma cells and macrophages were seen. The final histopathology report confirmed the diagnosis as reactive lymphoid hyperplasia with no evidence of malignancy.

Additional immunohistochemistry studies were performed to arrive at a more definitive diagnosis. It showed positivity for CD4, CD5, CD3, and CD20 and positivity for both kappa and lambda. This strongly suggested a pathology of inflammatory origin, ruling out malignancy. The patient was kept under close observation.

One year later, the patient reported with a recurrent swelling in relation to the right submandibular region. FNAC was performed again, this time from submandibular region. The cellular smear studies showed sheets of centrocytes, centroblasts, lymphocytes with epithelioid granulomas composed of round-to-oval cells with abundant cytoplasm, and sole-shaped nucleus admixed with necrosis and fibrous tissue suggesting granulomatous lymphadenitis.

In view of the earlier histopathological studies being inconclusive, persistent swelling, and FNAC showing granulomatous changes, we opted for a multidisciplinary approach to rule out other granulomatous diseases such as atypical tuberculosis and sarcoidosis. Fresh CT contrast studies were obtained. CT report suggested a diffusely enhancing soft tissue density lesion in the right buccal region involving upper and lower gingivobuccal space and retromandibular space. The region was closely abutting the right side of the mandible and obliterating the fat plane in the masticator space [Figure 3 (a and b)]. Multiple enlarged lymph nodes were noted in the submandibular region and the upper deep cervical regions, the largest size being 2.1 cm in the submandibular region.

Lymph node biopsy was performed under general anesthesia, through a right submandibular approach. Intraoperatively, two huge solid lymph nodes, well encapsulated and firm in consistency, were removed [Figure 4]. The samples were sent for both histopathological studies and for microbiological tests. The culture test was negative for mycobacterium. The histopathology report this time suggested lymph nodes with multiple predominant follicles with prominent germinal centers with extensive fibrosis and inflammatory cells including multinucleated giant cells. Amidst these proliferating capillaries, prominent endothelial cells were evident. Based on the histopathology report, the patient was evaluated for serum immunoglobulin E (IgE) levels, peripheral eosinophils, and absolute eosinophilic count to rule out Kimura's disease. The IgE levels in this patient were considerably increased with 417 IU (reference value: <180 IU), absolute eosinophil count was marginally elevated with 445/cumm (reference value: <350/cumm), and differential count of eosinophils was 5%. The diagnosis of Kimura's disease was confirmed thereafter.

Based on the available scientific evidence, the immunologist suggested that the patient is started on systemic steroid therapy with a loading dose of 60 mg of prednisolone in divided doses for 3 months. There was good response to steroid therapy, and the lump started to regress within 3 months which was confirmed by CT scan. Steroid dose was tapered to 2.5 mg OD over a period of 6 months. Complete remission of the lesion is observed for the past 18 months, and the patient is on a maintenance dose of 2.5 mg of oral prednisolone.

Discussion

Kimura's disease is a rare chronic inflammatory disorder of unknown etiology. It is postulated to be an unusual immune reaction to an unknown antigenic stimulus. It is a rare entity in the Caucasian population and endemic in Asia with only about 200 reported cases worldwide. It occurs in the second to fourth decades of life mostly in males (70%–80%).[2] The clinical picture is usually painless, sometimes disfiguring subcutaneous nodules predominantly in the head-and-neck region. It is accompanied by raised serum eosinophilic counts and elevated IgE levels.[2-4] It may mimic neoplasm, and early diagnosis could spare the patient from unnecessary anguish and multiple interventions.

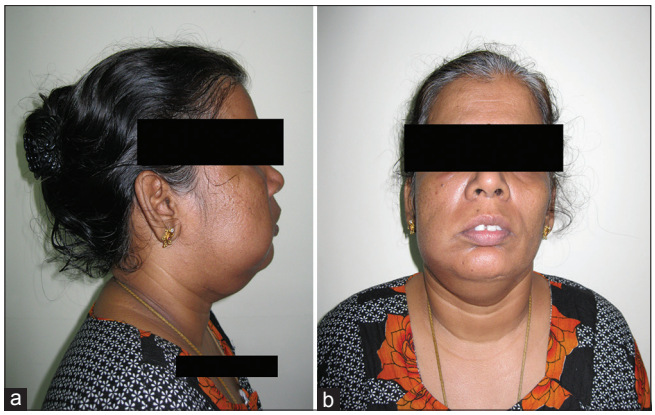

Figure 1: (a and b) Diffuse swelling over the right submandibular region

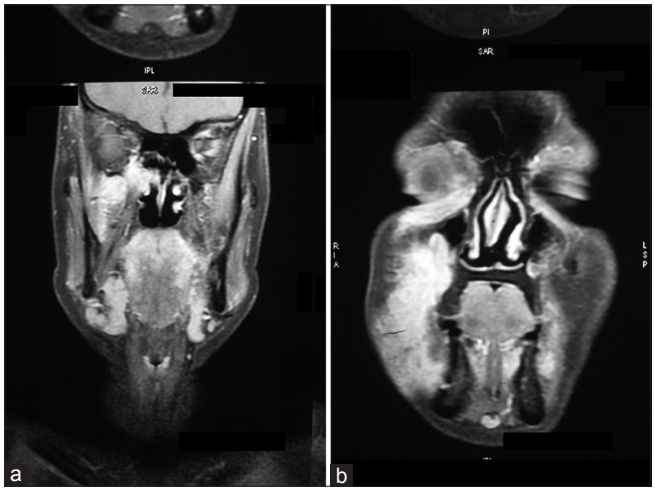

Figure 3: (a and b) Computed tomography contrast showing lesion over the right buccal space region

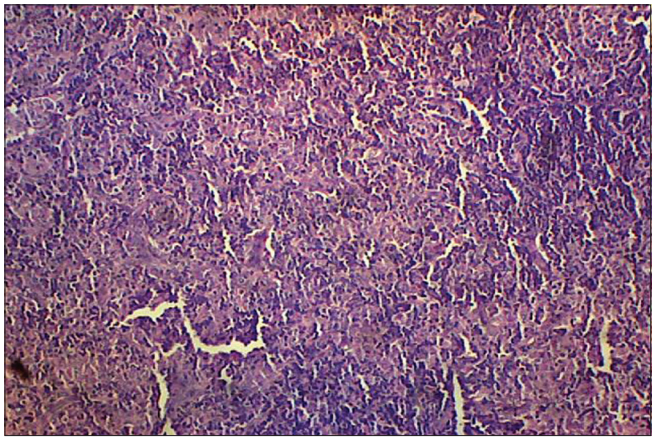

Figure 5: Low-power view shows few germinal centers with areas of necrosis

Kimura was first described in the Chinese literature by HT Kimm and C Szeto (1937). The histological description was published by Kimura *et al*. in 1948, and hence, the disease has borne his name. The commonly involved nodes are the parotid glands, epitrochlear, axillary, and inguinal nodes.

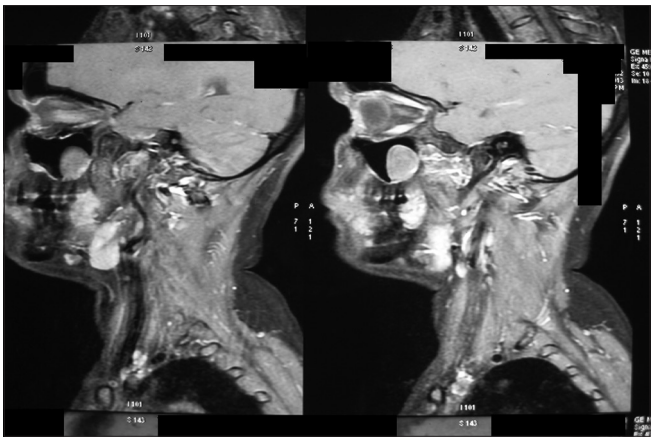

Figure 2: Magnetic resonance imaging scan showing lesion over the right premaxillary region

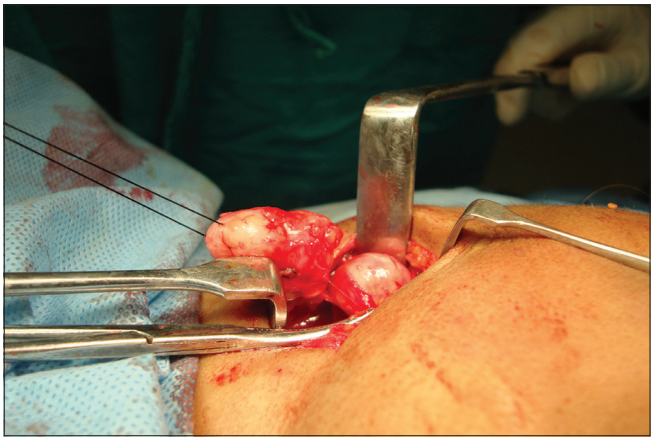

Figure 4: Two huge well-encapsulated solid lymph nodes

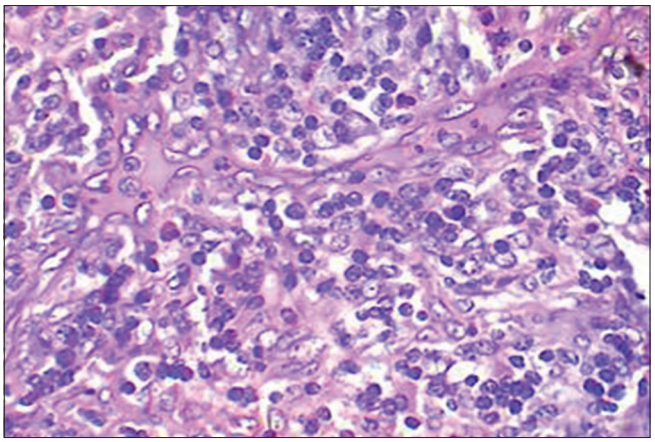

Figure 6: High-power view shows infiltration of eosinophils, lymphocytes, and plasma cells surrounding the endothelial-lined blood vessels

Pruritus and dermatitis may also be present. Rarely, it may involve the kidneys, orbits, ears, and nerves too.[3-6] Renal involvement results in nephrotic syndrome in 60% of the patients where the frequency is much more in comparison to the general population.[6-9] Widespread disseminated intravascular thrombosis is also reported in literature, affecting mesenteric

and renal veins (thrombotic storm). The etiology is thought to be an abnormal immune response to an unknown antigenic stimulus.[2,3] Persisting antigenic stimulus following anthropoid bite and parasitic or candidial infection are also suspected causes.[2] Our patient was a female in her forties with no relevant social history of insect bite, previous allergies, or drug-related adverse effects. There was no lymphadenopathy in any other part of the body. Her renal function was normal.

Histologically, our case showed both lymph node involvement and the extranodal tissue showing marked follicular lymphoid hyperplasia with heavy eosinophilic infiltrate. The lymphoid follicles showed prominent germinal centers with vascularization [Figure 5]. The interfollicular zone showed infiltration of small lymphocytes, plasma cells, eosinophils, and mast cells. High endothelial venules were increased [Figure 6]. Some cases of Kimura's disease may also show eosinophil abscess formation, eosinophilic follicle lysis, or the presence of scattered polykaryocytes, and perivenular sclerosis in later stage of the disease.[2,3,6,10,11] However, these findings were not present in our case.

With heavy eosinophilic infiltration, other differential diagnoses include classical Hodgkin lymphoma, Langerhan's cell histiocytosis, T-cell lymphoma, parasitic infestation, allergy, or drug reactions. In the above case, lymph node architecture was preserved. Characteristic cells were absent, for example, absence of Reed–Sternberg cells excluded Hodgkin's disease and the absence of compact clusters of Langerhans cells with grooved nuclei excluded Langerhans cell histiocytosis.[3,6,10,11] Immunohistochemistry was performed, and it showed positivity for CD4, CD5, CD3, and CD20 and positivity for both monoclonal antibodies kappa and lambda. Hence, malignancy was ruled out. The absence of giant cells, necrotic foci, and organization of inflammatory component in a florid pattern of lymphoid follicles ruled out granulomatous conditions, allergic, parasitic, and drug reactions. Although atypical histiocytosis X can present with subcutaneous masses, the diagnosis is made by finding the characteristic abnormal histiocytes and detecting CD1A marker.[3,10]

In the past, Kimura's disease was confused with epithelioid hemangioma (angiolymphoid hyperplasia with eosinophilia [ALHE]). ALHE occurs predominantly in the skin as compared to Kimura's disease which occurs as subcutaneous lesions. Both are characterized by heavy eosinophilic infiltration, vascular proliferation, and predilection for head and neck region.[6,10,11] However, angiolymphoid hyperplasia has nuclei of varied size and shape and hemosiderin deposits. Furthermore, the endothelial lining is more than one cell thick. This suggests that ALHE is neoplastic in origin, whereas Kimura's disease is an immune-mediated disorder.[3,10,12,13]

Kimura's disease can be distinguished from other diseases with tissue eosinophilia in that there must be florid-reactive follicular hyperplasia, accompanied by characteristic germinal center changes as described above.[11]

Treatment of Kimura's disease is not codified. Surgical excision is the first line of treatment. Systemic corticosteroids with prednisone have been indicated for relapse cases, but the risk of relapse when steroid treatment is withdrawn has also been observed. When both surgical and medical management fails, radiation has also been suggested to be effective (total dose of 20–30 Gy). Irradiation can be considered an alternative to steroid therapy in view of the side effects caused by steroids. Other treatment modalities include intralesional administration of steroids, cytotoxic agents, and electrodesiccation. All transretinoic acid with low-dose prednisone has also shown remission in one case. Pranlukast, a leukotriene receptor antagonist, and cetirizine, a H1 receptor blocker, were also effective in inducing clinical remission in a few cases.[3,6,10,14-16]

Conclusion

Any persistent lesion or lump causes significant anxiety to both the patient and the clinician alike. Cervicofacial lymphadenitis though being a very common condition has a wide spectrum of etiopathogenesis. To go about a methodical approach is of prime importance not only to minimize the risk of missing the common conditions but also to consider other rare possibilities. We present one such case of Kimura's disease – an uncommon autoimmune condition of unknown etiology in the cervicofacial region.

The diagnosis was arrived after a process of exclusion in which common causes of lymphadenitis including malignancy were ruled out. Immunohistochemical analysis finally helped confirm the disease which revealed elevated IgE levels and tissue eosinophilia. Based on the available scientific evidence, the patient was started on medical management with good response. Although currently on remission, a large case series is necessary to know the possible outcome and long-term prognosis of Kimura's disease.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Ferrer R. Lymphadenopahty: Differential diagnosis and evaluation. Am Fam Phys 1998;58:1313-20.
2. Larroche C. Kimura's Disease. Orphanet Encyclopedia; February, 2005.
3. Kumar V, Salini, Haridas S. Kimura's disease: An uncommon cause of lymphadenopathy. Indian J Med Paediatr Oncol 2010;31:89-90.
4. Kuo TT, Shih LY, Chan HL. Kimura's disease. Involvement of regional

lymph nodes and distinction from angiolymphoid hyperplasia with eosinophilia. Am J Surg Pathol 1988;12:843-54.
5. Kung IT, Gibson JB, Bannatyne PM. Kimura's disease: A clinico-pathological study of 21 cases and its distinction from angiolymphoid hyperplasia with eosinophilia. Pathology 1984;16:39-44.
6. Guimaraes CS, Levy NM, Sapadin A, Vidal C. Kimuras disease. Case Reports Med. 2009; Article ID:424053. [doi.10.1155/2009/424053].
7. Chan TM, Chan PC, Chan KW, Cheng IK. IgM nephropathy in a patient with Kimura's disease. Nephron 1991;58:489-90.
8. Akosa AB, Sherif A, Maidment CG. Kimura's disease and membranous nephropathy. Nephron 1991;58:472-4.
9. Rajpoot DK, Pahl M, Clark J. Nephrotic syndrome associated with Kimura disease. Pediatr Nephrol 2000;14:486-8.
10. Jani A, Coulson M. Kimura's disease. A typical case of a rare disorder. West J Med 1997;166:142-4.
11. Barnes L. Hematolymhoid leison of head and neck. In: Chan AC Chan JK, editors. Surgical Pathology of Head and Neck. 3rd ed., Vol. 2. New York: Informa Healthcare; 2009. p. 1016-8.
12. Hui PK, Chan JK, Ng CS, Kung IT, Gwi E. Lymphadenopathy of Kimura's disease. Am J Surg Pathol 1989;13:177-86.
13. Chow LT, Yuen RW, Tsui WM, Ma TK, Chow WH, Chan SK, *et al*. Cytologic features of Kimura's disease in fine-needle aspirates. A study of eight cases. Am J Clin Pathol 1994;102:316-21.
14. Boulanger E, Gachot B, Verkarre V, Valensi F, Brousse N, Hermine O, *et al.* All-trans-retinoic acid in the treatment of Kimura's disease. Am J Hematol 2002;71:66.
15. Itami J, Arimizu N, Miyoshi T, Ogata H, Miura K. Radiation therapy in Kimura's disease. Acta Oncol 1989;28:511-4.
16. Larroche C, Bletry O. Kimura's Disease. Orphanet Encyclopedia; February, 2005. Available from: http://www.orpha.net/data/patho/GB/uk-kimura.pdf. [Last accessed on 2019 Jun 3].