An extremely rare cause of generalized lymphadenopathy in children: Kimura's disease

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Kimura's disease, characterized by a triad of painless subcutaneous masses in the head and neck, prominent eosinophilia and markedly elevated immunoglobulin E levels, is an uncommon idiopathic, chronic inflammatory disease that usually affects young and middle-aged Asian males. Kimura's disease is known usually as a localized process and is an extremely rare cause of generalized lymphadenopathy in children. We report an eight-year-old Turkish boy with Kimura's disease who presented with generalized lymphadenopathy masquerading as malignant lymphoma.

Key words: Kimura's disease, generalized lymphadenopathy, children, immunoglobulin E, eosinophilia.

Kimura's disease is an uncommon idiopathic, chronic inflammatory disease that usually affects young and middle-aged Asian males. This benign condition is characterized by a triad of painless subcutaneous masses in the head and neck, prominent eosinophilia and markedly elevated immunoglobulin E (IgE) levels. The solitary lesions are usually in deep subcutaneous tissues, frequently associated with regional lymphadenopathy and salivary gland involvement, and clinically may mimic a neoplasm, including acute non-lymphocytic leukemia and Hodgkin disease and follicular lymphoma. Local or generalized pruritus and subacute or chronic dermatitis may occur[1,2]. Renal involvement, usually extramembranous glomerulonephritis, is found in up to 60% of patients, and proteinuria may occur in 12% to 16% of cases[3]. Reports of Kimura's disease are limited in the pediatric literature; therefore, pediatricians might not be familiar with this entity. We report a case with Kimura's disease who presented with generalized lymphadenopathy masquerading as malignant lymphoma.

Case Report

An eight-year-old Turkish boy was referred to our department for evaluation of cervical and axillary masses that had been growing for three weeks. Excluding the pruritus, he had no additional complaint related to the masses, and there was no history of fever, night sweats, or weight loss. Physical examination revealed a painless, nonfluctuant, immobile, soft rubbery mass at the right axillary region measuring 5x6 cm, and multiple masses were palpable at the right supraclavicular (2x3 cm), cervical (2 cm, 2 cm, 1 cm in diameter), and left posterior (2x3 cm) regions. The rest of the physical examination was normal. Laboratory findings included a hemoglobin level of 11.4 g/dl, platelet count of $344x10^9$/L, and white cell count of $12.5x10^9$/L; the differential showed 44% lymphocytes, 30% neutrophils, 20% eosinophils, and 6% monocytes. A peripheral blood smear showed mature eosinophils and no blasts. The erythrocyte sedimentation rate was 124 mm/hour. The C-reactive protein testing was 150 mg/L (normal: 0–5 mg/L). A urinalysis testing and serum electrolytes, calcium, urea nitrogen, creatinine, uric acid, glucose, albumin, lactate dehydrogenase, and liver enzyme levels were normal. A chest radiograph showed a superior mediastinal enlargement (Fig. 1). The tuberculosis skin test (PPD skin test) was negative. Presumptive diagnosis was

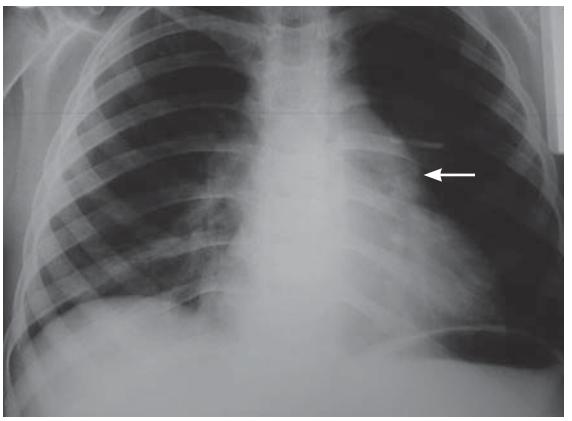

Fig. 1. A chest radiograph showed a superior mediastinal enlargement.

malignant lymphoma. A bone marrow aspirate showed hypercellular marrow with an excess of mature eosinophils and eosinophilic precursors with no abnormal cells (Fig. 2). An excision biopsy of the right inferior cervical lymph nodes was performed, which showed features suggestive of Kimura's disease. Eosinophilic infiltration and vascular proliferation were seen in microscopic examination (Fig. 3). The presence of leukocyte common antigen (LCA), CD20, CD3, CD79a, and CD31 were detected by immunohistochemical stains. F8 and CD34 were expressed in vessels.

With this pathological diagnosis, the literature was reviewed and laboratory data were re-evaluated. Total IgE level was markedly elevated at 18,345 IU/ml (normal: 0 – <150 IU/ml), while other serum immunoglobulins, including IgG, IgA and IgM, were normal. Serological tests for human immunodeficiency virus (HIV), *Toxoplasma gondii,* rubella, cytomegalovirus, *Fasciola hepatica, Toxocara canis* (IgG), and *Trypanosoma cruzi* were negative. Radioallergosorbent test (RAST) and stool examination for ova, cysts and parasites were negative. No urinary protein excretion was detected. A diagnosis of Kimura's disease was made based on the clinical presentation and laboratory and histopathologic findings. He was started on oral prednisolone at a dose of 60 mg/day, later tapered by 10 mg/week for 6 weeks. After one week of treatment, there was a significant decrease in the size of all masses as well as a reduction in peripheral eosinophils, and two weeks later he had completely improved. IgE levels fell to 3908 IU/ml gradually. The laboratory data were stable with 5 mg of prednisolone on alternate days and after one month, prednisolone was ceased. There was no recurrence at the 10-month follow-up.

Discussion

Kimura's disease was first described in China in 1937 as "eosinophilic hyperplastic lymphogranuloma" by Kimm and Szeto[4], but the definitive histopathological description was published by Kimura et al.[2] in 1948. The etiology of Kimura's disease is unknown. The disease is classified as a benign reactive process. Allergic reactions, infections and autoimmune reactions with an aberrant immune reaction have been suggested. Katagiri et al.[5] reported a finding of elevated mRNA levels of interleukin (IL)-4, IL-5 and IL-13 in patients with Kimura's disease[5]. The role of cytokines, especially IL-4, IL-5 and IL-13, has been a focus of attention in the regulation of IgE production by B cells required for Th2 lymphocyte differentiation[6]. IL-5 is a major cytokine for mature eosinophil activation and accelerates differentiation, proliferation and chemotaxis[7]. The disease typically presents with regional lymphadenopathy and painless subcutaneous swellings frequently localized in the head and neck regions, although Kimura's disease has also been described in different areas such as the groin, axilla, trunk, limbs, and oral cavity. Studies have described generalized lymphadenopathy rarely. Chen et

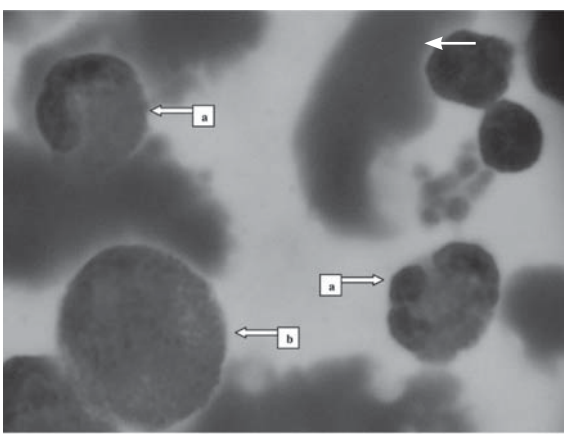

Fig. 2. A bone marrow aspirate showed hypercellular marrow with an excess of mature eosinophils (a) and eosinophilic precursors (b) with no abnormal cells.

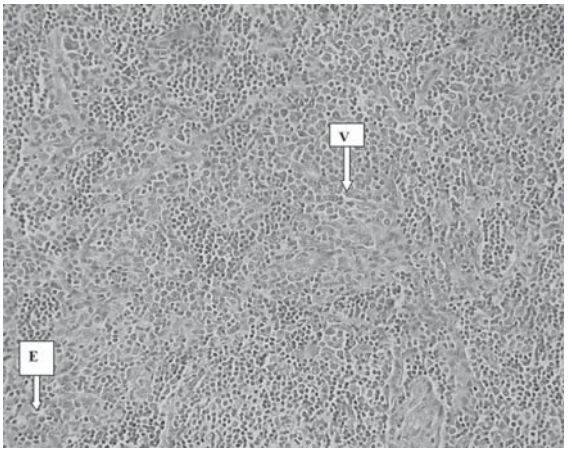

Fig. 3. Pathologic examination showed maintenance of nodal architecture with the presence of infiltrate of eosinophils (E) and vascular proliferation (V) (hematoxylin & eosin x400).

al.[8] described 21 cases with nodal involvement that was consistent with Kimura's disease histologically. There were 18 males (86%), 8 to 64 years of age (mean: 32 years). Most (76%) presented with head and neck disease. Five patients presented with multifocal masses (or lymph nodes), and only one of them had supraclavicular lymphadenopathy. Viswanatha[9] reported 18 children with Kimura's disease. The postauricular region was the commonest site of involvement (50%). Other sites were the lateral part of the neck (33.3%) and sub-mandibular (11.1%) and parotid (5.6%) regions. Supraclavicular lymphadenopathy and generalized lymphadenopathy were not determined by the authors. Thomas et al.[10] reported a three-year-old Indian boy with Kimura's disease who presented with generalized lymphadenopathy. Recently, Zhang et al.[11] described a 32-year-old Chinese man who presented with complaints of low-grade fever, cough and middle mediastinal mass with pleural effusion. The authors argued that he was the first case with Kimura's disease presenting with mediastinal mass. Indeed, Kimura's disease is known usually as a localized process without systemic symptoms excluding the renal involvement. Most diagnostic tests have focused on the locoregional involvement of this disorder. Kimura's disease was rarely considered as a differential diagnosis for a patient presenting with generalized lymphadenopathy. Due to the unexplained generalized lymphadenopathy (accompanying supraclavicular lymphadenopathy and mediastinal enlargement) and high erythrocyte sedimentation rate in our case, neoplastic disease, especially malignant lymphoma, was the first diagnosis considered. Therefore, bone marrow aspiration biopsy was performed urgently, and an excision biopsy of cervical lymph nodes was recommended. The differential diagnosis includes lymphoma, tumor metastases, and angiolymphoid hyperplasia with eosinophilia (ALHE). Lymphoma and tumor metastases were excluded with immunochemical stains. ALHE is considered to be a kind of endothelial neoplasm related to inflammatory stimulation. ALHE often affects middle-aged western women presenting with a superficial well-circumscribed mass without formation of lymphoid follicles and eosinophilic abscesses[12]. Patients with ALHE have normal IgE levels. The diagnosis of Kimura's disease should not be a problem when combined with results of the pathologic examination and markedly high levels of eosinophilia in peripheral blood and serum IgE.

There is no consensus on the management of Kimura's disease. Various treatment modalities have been tried with variable success, including surgical excision, radiotherapy, corticosteroids (intralesional and oral), pentoxifylline, cyclosporine, nonsteroidal anti-inflammatory drugs (NSAIDS), and oral retinoids[9-20]. The choice of treatment modalities should be individual. Recurrence is common with all the modalities of treatment. For the localized disease, complete surgical excision of the lesion(s) is the first-line therapy. However, complete excision may be difficult because it is infiltrative, and multiple sites are involved. Furthermore, recurrences have been reported, particularly after incomplete removal[11-13]. Local irradiation has also been shown to be effective in shrinking the lesion, but is not advocated in children[1-13]. The treatment of Kimura's disease has mainly involved the use of systemic corticosteroids. Systemic corticotherapy with prednisolone has been shown to reduce the size of the lesion. However, relapses are frequent after prednisone withdrawal. In cases complicated by renal involvement, treatment with steroids has been tried, with substantial success[9-13,20].

In conclusion, Kimura's disease with generalized lymphadenopathy can closely resemble that seen in neoplastic disorders such as lymphoma or metastatic lymphadenopathy. It should be taken into consideration as a differential diagnosis for a generalized lymphadenopathy, and pediatricians in western countries should be aware of the clinical presentation of Kimura's disease. The present report highlights the need for increased awareness of Kimura's disease by all pediatricians to avoid unnecessary and potentially harmful investigations such as bone marrow aspiration/biopsy and imaging studies.

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