Kimura’s Disease: A Diagnostic Challenge

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ABSTRACT. Kimura’s disease is a rare inflammatory disorder of unknown cause, primarily seen in young Asian males. The disease is characterized by a triad of painless subcutaneous masses in the head or neck region, blood and tissue eosinophilia, and markedly elevated serum immunoglobulin E levels. We describe an 11-year-old Asian boy with Kimura’s disease who presented with a chronic left neck mass. The diagnosis was based on the characteristic histopathologic findings after surgical excision in conjunction with peripheral eosinophilia and elevated serum immunoglobulin E levels. Pediatricians in western countries should be aware of the clinical presentation of Kimura’s disease.

URL: http://www.pediatrics.org/cgi/content/full/110/3/e39; Kimura’s disease, eosinophilia, elevated immunoglobulin E level.

Kimura’s disease is a rare, chronic inflammatory disorder of unknown cause, primarily seen in young Asian males. The typical clinical presentation is characterized by a triad of painless unilateral cervical adenopathy or subcutaneous masses predominantly in the head or neck region, blood and tissue eosinophilia, and markedly elevated serum immunoglobulin E (IgE) levels. Descriptions of Kimura’s disease are limited in the English language pediatric literature. Early diagnosis of Kimura’s disease may spare the patient from potentially harmful and unnecessary invasive diagnostic procedures. We report a case of Kimura’s disease in a young Asian male and review the literature. The present report highlights the need for increased awareness by all pediatricians of this clinically impressive entity.

CASE REPORT

An 11-year-old Asian boy was referred to the pediatric otolaryngology service in September 2000 for evaluation of a left neck mass of 3 years’ duration. There was no history of pain, fever, night sweats, or weight loss. He was born in the United States of ethnic Chinese parents, and had traveled to Laos for a month at 4 years of age. On physical examination, he seemed well. A non-tender, nonfluctuant firm mass measuring 3 × 3 cm was palpable in the left anterior triangle of the neck, extending from the angle of the jaw to the left preauricular area. No warmth or redness was noted on the overlying skin. Neither axillary or inguinal lymphadenopathy nor hepatosplenomegaly was noted. The rest of the physical examination was normal.

Laboratory data included a hemoglobin of 13.1g/dL, platelet count of 387 × 10^9/L, and white cell count of 10.8 × 10^9/L; differential showed 26% eosinophils (2.81 × 10^9/L), 46% segmented neutrophils, 22% lymphocytes, and 6% monocytes. The erythrocyte sedimentation rate was 11 mm/hour. Results of serum electrolytes, liver function tests, albumin, blood urea nitrogen, and creatinine were normal. A chest radiograph and skeletal survey were unremarkable. A computed tomography (CT) scan of the neck showed a heterogeneous enhancing mass, anterior and adjacent to the left masseter muscle, bordered superiorly by the alveolar ridge of the mandible and inferiorly by the left submandibular gland. A chest CT scan was unremarkable. Neoplastic disease was the first diagnosis considered. Fine-needle aspiration biopsy of the mass showed an atypical lymphoid infiltrate, but the overall morphologic findings were considered nondiagnostic, and an open biopsy was recommended. In November 2000, the patient underwent an open biopsy of the left buccal space lymph node with excision of left cervical lymph nodes. Histopathology of the lymph nodes revealed a follicular lymphoid hyperplasia with intranodal and perinodal eosinophilic infiltrates and microabscesses (Fig 1). Immunohistochomical analysis was performed on paraffin sections, with antibodies against CD20 (L20), CD3, CD45 (LCA), CD15 (LeuM1), CD30, S100 protein, and CD1a. CD20 highlighted diffuse large follicular B-cells, CD3 and CD45 demonstrated numerous interfollicular T-cells, which were composed of an equal admixture of CD4-positive helper and CD8-positive cytotoxic T-cells, respectively. Additional stains for CD15, CD30, S100 protein, and CD1a were negative. In situ hybridization for Epstein Barr virus using an Epstein Barr virus-encoded RNA probe was negative. The overall staining pattern was nonspecific but consistent with a reactive process, and cultures and stains for bacteria, fungi, and mycobacteria were negative.

The mass enlarged painlessly during the next 6 months, necessitating readmission to the hospital in July 2001 for additional diagnostic evaluation. A repeat CT scan of the neck with contrast showed an increase in the pattern of heterogeneous enhancement and an increase in size of the mass overlying the left masseter muscle. The patient subsequently underwent a selective neck dissection to excise the left buccal space mass, including left superficial parotidectomy and excision of multiple lymph nodes involving the periparotid tissues. The inflammatory infiltrates involved the perinodal and periparotid adipose tissue and skeletal muscle. The salivary gland appeared morphologically unremarkable, without evidence of involvement. The tissue biopsy specimens showed similar histologic features as previously noted (Figs 1 and 2), although there was an increase in eosinophilic microabscesses impinging directly into reactive-appearing germinal centers, scattered multinucleated Warthin-Finkeldey cells, and a prominent vasculature within the extranodal soft tissues associated with lymphoid hyperplasia and sheets of eosinophils. The associated lymph nodes showed florid follicular hyperplasia, with focal eosinophilic microabscess formation within the paracortex and interfollicular region. Several germinal centers showed disruption by large aggregates and sheets of eosinophils. Stains and cultures were again negative for bacteria, fungi, and mycobacteria. At this point, clinical, histopathologic, and radiographic findings were...
carefully reviewed. A diagnosis of Kimura’s disease was made based on the clinical presentation, marked peripheral eosinophilia, and histopathologic findings. A serum IgE was obtained, which was markedly elevated at 1618 IU/mL (normal: 0–87 IU/mL), further supporting the diagnosis of Kimura’s disease. Renal function was normal, and there was no evidence of proteinuria.

**DISCUSSION**

Kimura’s disease was first described in China in 1937 by Kim and Szeto. However, the entity became more widely known as Kimura’s disease after a systematic description in 1948 by Kimura et al. Young and middle-aged Asian males of Chinese and Japanese origin are primarily affected. The disease typically presents with insidious onset of painless subcutaneous masses with adenopathy in the head and neck region. The disease usually involves subcutaneous tissues, lymph nodes (periauricular, axillary, and inguinal), parotid and submandibular salivary glands, and rarely, oral mucosa. Other unusual sites of involvement include the auricle, scalp, and orbit.

The clinical course of Kimura’s disease is generally benign and self-limited. Kimura’s disease may be complicated by renal involvement. Proteinuria may occur in 12% to 16% of cases. Nephrotic syndrome is the most common presentation; a wide spectrum of histologic lesions such as minimal change disease or mesangioproliferative glomerulonephritis, focal segmental glomerulosclerosis, membranous nephropathy, IgM nephropathy, and IgA nephropathy have been described. Our patient has normal renal function and no evidence of proteinuria. The lesions of Kimura’s disease usually precede or coincide with the development of renal disease; occasionally, Kimura’s disease may present with renal involve-
ment before the appearance of subcutaneous lesions leading to delayed diagnosis. The cause and pathogenesis of Kimura’s disease is unclear, although it might be a self-limited allergic or autoimmune response triggered by an unknown stimulus. It has been speculated that a viral or parasitic trigger may alter T-cell immunoregulation or induce an IgE-mediated type 1 hypersensitivity resulting in the release of eosinophilic cytokines. Immunohistochemical studies performed on skin, lymph nodes, and peripheral blood in Kimura’s disease have shown marked proliferation of human leukocyte antigen-DR CD4 cells. Activated CD4 cells of the Th2 phenotype can release cytokines such as granulocyte macrophage colony-stimulating factor and tumor necrosis factor-α, interleukin (IL)-4 and IL-5, which in turn may precipitate the high serum IgE and marked eosinophilia. Abundant expression of eosinophilic cytokines such as IL-4, IL-5, and IL-13 in peripheral blood mononuclear cells has been reported recently in a patient with Kimura’s disease. This suggests that these cytokines may have a role in pathogenesis. High levels of circulating eosinophilic cationic protein and major basic protein and high tissue IgE concentrations have also been found in the active stage of Kimura’s disease.

The pathology of Kimura’s disease is characterized by prominent germinal centers in involved lymph nodes containing cellular, vascular, and fibrous components. The cellular component consists of dense eosinophilic infiltrates in a background of abundant lymphocytes and plasma cells, eosinophilic microabscesses with central necrosis, Warthin-Finkeldey-type polykaryocytes, some degree of vascular proliferation of germinal centers, increased postcapillary venules in the paracortex, and sclerosis. Immunoperoxidase studies show IgE reticular network in germinal centers. The diagnosis of Kimura’s disease can be difficult. Clinicians and pathologists in western countries may be unfamiliar with the clinical presentation and pathology of this rare disease. Patients with Kimura’s disease are often extensively evaluated for other serious disorders, including neoplasia. Kimura’s disease can mimic other disorders such as Mikulicz’s disease, eosinophilic granuloma, malignant lymphoma, and salivary gland tumors. Laboratory tests often reveal peripheral eosinophilia and, if measured, elevated serum IgE levels. Imaging studies including CT and magnetic resonance imaging scans are useful to delineate the extent of the disease. Findings of intense contrast enhancement on CT scan and high TI- and T2-weighted signal intensities on magnetic resonance imaging in parotid glands and lymph nodes have been described. Biopsy is important to exclude malignant disorders. Kimura’s disease can also be confused with angiolymphoid hyperplasia with eosinophilia (ALHE). ALHE is a rare but distinctive vascular tumor typically presenting in women during early to mid-adult life. Lymphadenopathy is uncommon, and blood eosinophilia is noted in <10% of cases. Histologically, the presence of inflammation around medium-sized arteries or veins and evidence of vascular damage (florid fibrointimal proliferation and cuboidal to dome-shaped endothelial cells) are key features in differentiating ALHE from Kimura’s disease. Additional prominent morphologic features present in our case and characteristic of Kimura’s disease include the noncircumscribed inflammatory infiltrates within extranodal subcutaneous tissues and skeletal muscles associated with reactive germinal center formation and eosinophilic microabscesses. Blood vessels, although prominent, resemble those of the high endothelial venules of lymph nodes. The presence of reactive lymphadenopathy with similar-appearing inflammatory infiltrates is very common in Kimura’s disease. By contrast, ALHE is generally a well-circumscribed subcutaneous vascular neoplasm in which the vessel proliferation is more florid, and has very plump, epithelioid-appearing endothelial cells, which may even mimic glandular structures. Although the vascular tumor is associated with inflammatory infiltrates, the presence of reactive germinal centers and eosinophilic microabscess formation are uncommon features of ALHE, as is an associated reactive lymphadenopathy.

The treatment of Kimura’s disease is problematic. At initial presentation, surgical biopsy is the most frequent diagnostic procedure, and excision may be curative. However, recurrence is common. Localized initial regrowth can often be managed with surgical excision. Other therapeutic options, including radiation, systemic corticosteroids, cytotoxic agents, cyclosporin, and pentoxifylline, have all been tried with variable responses. Regrowth of the lesion is common after discontinuing such treatments. In addition, the risks from radiation and chronic steroid therapy pose limitations. Systemic steroids may be indicated in frequent relapses or cases complicated by nephrotic syndrome. Radiation may be considered in cases refractory to surgical and medical therapy, for recalcitrant and large tumors, or when surgery is not feasible.

The present case reiterates that Kimura’s disease may cause chronic neck masses in Asian children living in western nations, and highlights the need for awareness of Kimura’s disease by clinicians and pathologists to avoid unnecessary and potentially harmful investigations.

REFERENCES


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