Kimura Disease: 2 Case Reports and a Literature Review

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Kimura disease (KD) is a chronic inflammatory soft-tissue disorder often presenting as swollen soft tissue or enlarged lymph nodes. KD is rare, and most reported cases have involved Asians. The pathogenesis is poorly understood, and treatments are unsatisfactory. KD is associated with allergic conditions such as asthma, rhinitis, and eczema. We present the cases of 2 patients treated for chronic endogenous eczema and KD in our dermatology clinic.

Kimura disease (KD) is a rare chronic inflammatory soft-tissue disorder of unknown cause. In KD, lymphoid and angiomatous tissue proliferations are accompanied by lymphadenopathy, peripheral blood eosinophilia, and raised levels of immunoglobulin E (IgE). Most reported cases have involved Asians, as do the 2 cases we present.

Case Reports

Patient 1—In 1985, a 34-year-old Chinese woman with chronic eczema presented with a soft-tissue lump on the medial aspect of the left elbow. The lump was excised, and recovery was uneventful. The diagnosis was not made known to the patient, and she was lost to follow-up.

In 1987, the patient presented with a 4-cm mass in the left groin. An excisional biopsy was performed, and a diagnosis of angiolymphoid hyperplasia with eosinophilia (ALHE) was made.

In 1990, the patient developed a similar lesion in the right thigh; in 1993, she presented with a second nodule in the left elbow. Surgery was performed on both lesions. The recurrent nodule and the left median nerve seemed to be completely enmeshed; an incisional biopsy of the recurrent nodule was performed, and the nerve was preserved.

All the biopsy specimens from the various sites (except the 1985 specimen, which was lost) had similar histologic features consistent with KD. The multiple lymphoid follicles exhibited vascularization, necrosis, and eosinophilic infiltration of germinal centers; the stroma between the follicles was richly vascularized and infiltrated by numerous eosinophils, with scattered collections forming eosinophilic abscesses. In addition, the vessels were lined by endothelial cells lacking epithelioid features.

Patient 2—A 46-year-old Chinese man reported a history of eczema, asthma, and allergic rhinitis dating back to childhood. He told of an asymptomatic neck lump that had been excised when he was 16 years old—the diagnosis had not been made known to him—and of the discovery then that he had peripheral blood eosinophilia. Soon after the excision, he had noticed a (slow-growing) swelling on each arm, but only now did he decide to have another examination.

Both arms had extensive dry eczema. Each of the 2 soft-tissue swellings was firm, nontender, bilateral, and 10 cm in diameter (Figure 1). No other swellings were noted. Lymphadenopathy and organomegaly were not present. The patient's eosinophil count was above normal (29.6%), and his IgE level was markedly raised (5000 IU/mL; reference range, 5–100 IU/mL).

An incisional biopsy of the left-arm swelling was performed; results of a hematoxylin and eosin (H&E) stain showed an aggregate of lymphoid cells forming germinal centers in the specimen (Figure 2). Anastomosing vessels with proliferative endothelium entered the lymphoid aggregate, and the stroma had an intense eosinophilic infiltrate (Figure 3). The histologic features were those of KD.

Comment

KD was first described in 1937 in China (Kim and Szeto[1] reported 7 cases of eosinophilic hyperplastic lymphogranuloma). The common term *Kimura disease* was coined in 1948; Kimura et al[2] used it in describing "an unusual granulation combined with hyperplastic changes of lymphatic tissue." Since then, several hundred cases (mainly among young Asian men[3-5]) have been reported under various names—*angiolymphoid hyperplasia with eosinophilia*,

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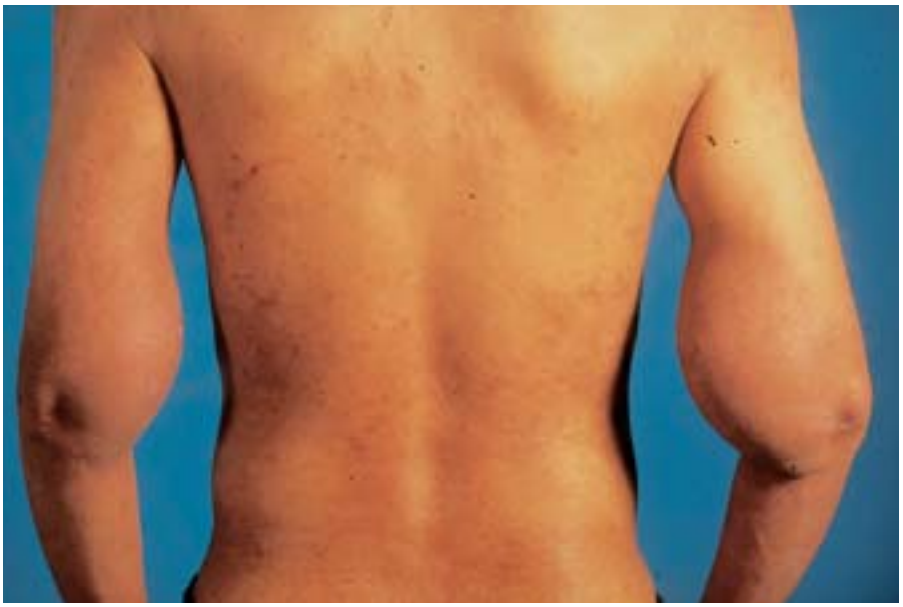

Figure 1. Firm, nontender, bilateral soft-tissue swellings on the upper arms.

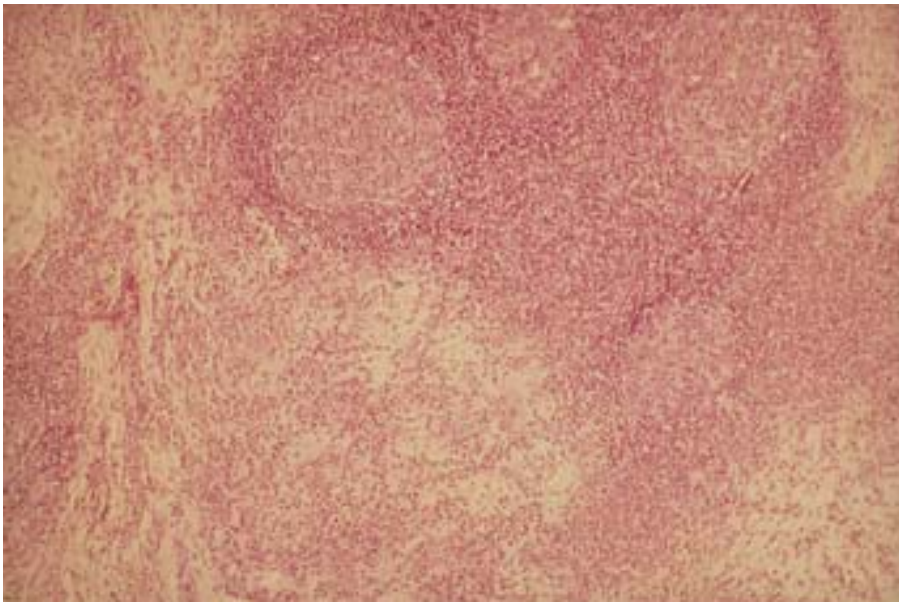

Figure 2. Aggregates of lymphoid cells forming germinal centers (H&E, original magnification ×20).

eosinophilic granuloma of soft tissue, *eosinophilic lymphofolliculosis*, *eosinophilic lymphogranular granuloma*, and *eosinophilic lymphoid granuloma*.

The site most frequently affected by KD is the head-and-neck region (70%),[3] with involvement of the subcutaneous tissue, parotid glands, and lymph nodes. The usually slow-growing KD lesion is either a large deep-seated soft-tissue swelling or multiple bilateral nodules; in either case, it does not produce any significant change in the overlying skin. Because the lesion is commonly symptomless, some patients may decide to ignore it. Sites affected less often include the groin (15%), extremities (12%), and trunk (3%); rare sites of involvement include the kidneys,[6] orbits,[7] ears (external),[8] spermatic cord,[9] and median nerve.[10]

Several findings are associated with KD. Regional lymphadenopathy occurs at some stage of the disorder in 66% of patients.[3,11] Peripheral blood eosinophilia is often reported; it was present in all KD cases in a large series of Japanese patients.[12] KD and raised levels of IgE are often associated.[13] Renal disease occurs more often in patients with KD than in the general population. Among a series of 175 Japanese patients with KD, 13 (7%) also had nephrotic syndrome, and 8 (5%) also had proteinuria.[14] Asthma and Löffler syndrome also have been reported as occurring with KD.[15] Both

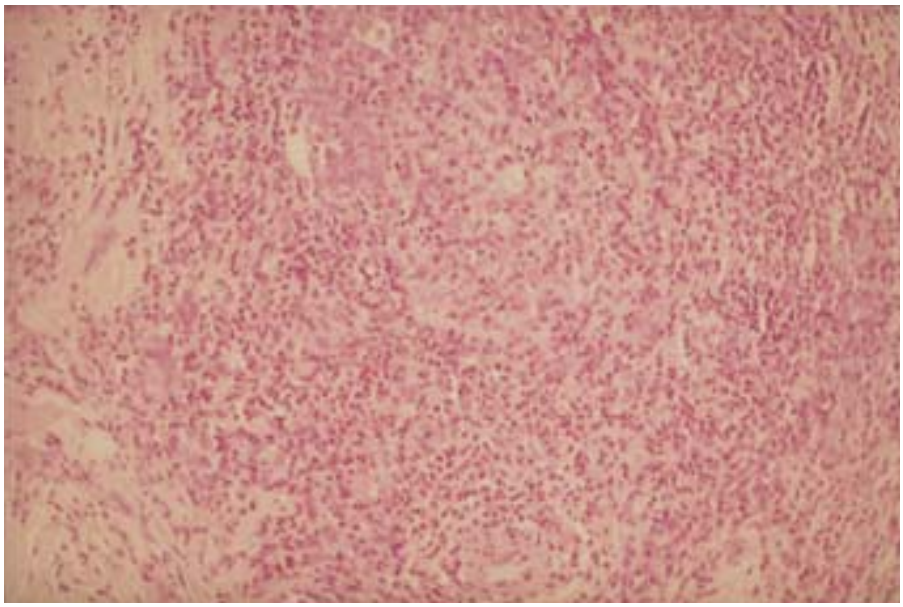

Figure 3. An intense eosinophilic infiltrate in the stroma (H&E, original magnification ×100).

KD and Sézary syndrome (with raised levels of IgE and blood eosinophilia) are more likely to occur with atopic dermatitis,[16,17] but KD is not known to develop into Sézary syndrome.

Histologically, KD is characterized by dense fibrosis, lymphoid infiltration with reactive follicles, and a mixed inflammatory cell infiltrate with numerous eosinophils,[11] all of which can develop in subcutaneous tissue, salivary glands, and lymph nodes. Some authors view KD as having 3 components—cellular, fibrocollagenous, and vascular.[18] The conspicuous feature of the cellular component is distinct lymphoid follicles, consisting mainly of lymphocytes. The fibrocollagenous component is formed by the infiltrate with numerous eosinophils, and eosinophilic microabscesses are common; mast cells and plasma cells also abound; fibrosis is a constant, even in young lesions. The vascular component consists of proliferating and swollen endothelial cells, but these do not have atypical nuclei or abundant eosinophilic cytoplasm; salivary glands are frequently involved (they experience parenchymal atrophy and fibrosis); regional lymph nodes, usually enlarged, experience follicular hyperplasia with increases in eosinophils with or without fibrosis.

KD is sometimes confused with ALHE. Wells and Whimster[19] published the first report on a condition resembling KD and designated it *subcutaneous ALHE*. In the 1980s, considerable controversy arose about the relation between KD and ALHE. Some authors believed that both conditions are variants of histiocytoid hemangioma,[20,21] whereas others suggested that KD and ALHE are different disorders.[3,22,23] In a study involving 4 cases of KD and 22 cases of ALHE, Helander et al[24] concluded that KD has relatively uniform clinical and histologic features, whereas ALHE has a broader spectrum of features. Chun and Ji[11] also noted distinct clinical differences between the disorders (Table). In ALHE, the blood vessels range from well-formed mature vessels to poorly formed uncanalized vessels. Cytologically, the endothelial cells vary, in different areas of the section, from markedly atypical cobblestonelike "histiocytoid" cells to plump but not irregular pale-stained cells and dark endothelial cells. Regarding intracytoplasmic vacuolation, the endothelial cells vary in having multiple marked vacuoles to no vacuoles; the degree of eosinophil infiltration in tissues taken from different sites of the same patient varies from minimal to moderate; and the depth of eosinophil infiltration differs from case to case depending on the involvement of the papillary dermis, the reticular dermis, and the panniculus in various combinations. In KD, in contrast, the infiltration is usually deep; marked lymphoid follicles develop; and the organization of the lymphoid infiltrate ranges from a diffuse pattern, through nodular aggregates with germinal centers, to well-formed lymphoid follicles (Table).

The etiology of KD remains unknown. The consistent finding of peripheral blood eosinophilia and raised levels of IgE, together with the occasional association of KD with immunologically mediated renal disease, suggests an allergic or autoimmune

Clinical[11,22] and Histologic[22] Differences Between Kimura Disease and Angiolymphoid Hyperplasia With Eosinophilia

Characteristic	Kimura Disease	Angiolymphoid Hyperplasia With Eosinophilia
Clinical		
Race	Asian	Any
Sex	Male	Male and female
Age	20–40 y	All ages
Morphology	Subcutaneous mass	Dermal papulonodules
Infiltration	Deep	Superficial
Overlying skin	Normal	Erythematous or brown
Sites	Head and neck	Multiple
Lymphadenopathy	Always	Rare
Blood eosinophilia	Mild to moderate	Moderate to marked
Glomerulonephritis	Occasional	Rare
Histologic		
Infiltration	Subcutaneous, muscle	Subcutaneous, dermis
Infiltrate	Nodular	More diffuse
Germinal centers	Always	Uncommon
Fibrosis	Usually marked	Mild
Eosinophilia	Massive	Mild to moderate
Edema	Often marked	Minimal
Blood vessels	Well-formed	Variable
Endothelial cytology	Occasionally atypical	Often atypical

process. Morphologic and immunologic analyses of renal disease associated with nephrotic syndrome and the presence of IgE in the renal glomeruli suggest the possibility of a relation between raised levels of IgE and renal disease in KD.[14,22,25] Occasional associations with atopic disorders such as bronchial asthma,[26] allergic rhinitis,[16,27] and atopic dermatitis[28] have been reported, but establishing causality in such cases is difficult.

Surgical resection, radiotherapy, systemic steroid therapy, and conservative management have all proved to be unsatisfactory treatments for KD. After surgical resection and variable follow-up time, the KD lesion tends to recur in as much as one fourth of patients.[3] Also, complete surgical removal of a head or neck lesion may be difficult given the subsequent facial reconstruction needed and the danger of neurologic deficit; radiotherapy combined with use of an immunosuppressive agent may be more effective in such cases.[29] Radiotherapy is used with residual and recurrent KD lesions in postsurgical cases—it provided local control in 74% of treated lesions,[30] and the rerecurrence rate after radiotherapy was 11%[31]—but it is not used as monotherapy for KD. In 2 patients with associated nephrotic syndrome, subcutaneous KD lesions subsided during systemic steroid therapy but recurred immediately after therapy was discontinued.[6] Given this temporary effect, immunosuppression with systemic steroids is not used as monotherapy for KD. Steroid therapy is useful, however, in initial surgical treatment of KD tumors—steroids are used to shrink a tumor in preparation for surgery, particularly surgery in the head-and-neck region.[32]

In general, most experts treating a KD lesion advocate surgical resection and, if necessary, either reresection or radiotherapy.

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