

Kimura's disease: Report of a pediatric case in the United States

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A 14-year-old male adolescent is described with a 6-year history of active lymphadenopathy, skin rash, peripheral blood eosinophilia, and markedly elevated serum-IgE level. Complete histopathologic and immunologic evaluations established the diagnosis of Kimura's disease as first described in Japan. Because of its relative infrequency and varied features, this disorder can be difficult to diagnose when it is encountered in the United States. (J ALLERGY CLIN IMMUNOL 73:561, 1984.)

KD was first described as a clinicopathologic entity in 1948 in Japan.¹ Since then a number of reports from Japan and China have documented its major clinical features as subcutaneous or dermal tumors and/or enlarged lymph nodes in association with peripheral blood eosinophilia.²⁻⁶ Although the etiology is unknown, the tumors and lymph nodes have a specific histopathologic appearance. A related condition, ALH, was first described in the English literature in 1969,⁷ and numerous subsequent reports have followed.⁸ The patient reported in this article has the features of KD as described in the Oriental literature and is presented to familiarize clinicians and pathologists in this country with this unusual disorder.

Case report

The patient, a 14-year-old black male adolescent, was first observed at age 10 yr for evaluation of regional lymphadenopathy and chronic dermatitis. Nontender lymphadenopathy had been present in the left groin area for 3 yr and in the left cubital area for 4 mo. The dermatitis was moderately pruritic and had preceded the lymphadenopathy by several years. General health was excellent. There was no history of foreign travel and, except for a younger male sibling with asthma and allergic rhinitis, family history was unremarkable.

Positive physical findings were limited to the skin and

Abbreviations used

KD:	Kimura's disease
ALH:	Angiolymphoid hyperplasia
CBC:	Complete blood count
WBC:	White blood count

regional lymph nodes. A pruritic rash consisting of discrete papules (1 to 2 mm in diameter) was distributed randomly over the flexor and extensor surfaces of the forearms and lower legs and over the anterior trunk. At areas of excoriation, there was both hyper- and hypopigmentation and, in some areas, slight lichenification. There was a firm, mobile, and nontender aggregate of left femoral and inguinal lymph nodes that measured 4.5 by 6.0 cm. A left epitrochlear node measured 4.5 by 2.0 cm. There was no other significant lymphadenopathy.

The following diagnostic studies were normal or negative: serum calcium, total protein, albumin, and immunoglobulins (IgG 1317 mg/dl, IgM 53 mg/dl, IgA 145 mg/dl); mono spot test; tuberculin skin test; serology titers (brucellosis, tularemia, psittacosis, histoplasmosis, toxoplasmosis, and filariasis); and chest roentgenogram. Stool examination for ova and parasites was negative. A CBC was normal except for a peripheral eosinophil count of 16% (total WBC 7500 cells/mm³). For diagnostic purposes, the left epitrochlear lymph node was removed surgically. All cultures and stains for infection (mycobacterial, bacterial, and fungal) were negative, and there was no evidence of malignancy (see below).

During the next 4 yr, the patient remained in good general health, but the regional lymphadenopathy increased. Examination at age 12 yr revealed the following aggregates of lymph nodes: left femoral 4.5 by 4.5 cm, left inguinal 2.0 by 2.0 cm (with four slightly smaller surrounding nodes); right femoral 7.5 by 5.0 cm; right inguinal 4.0 by 2.0 cm;

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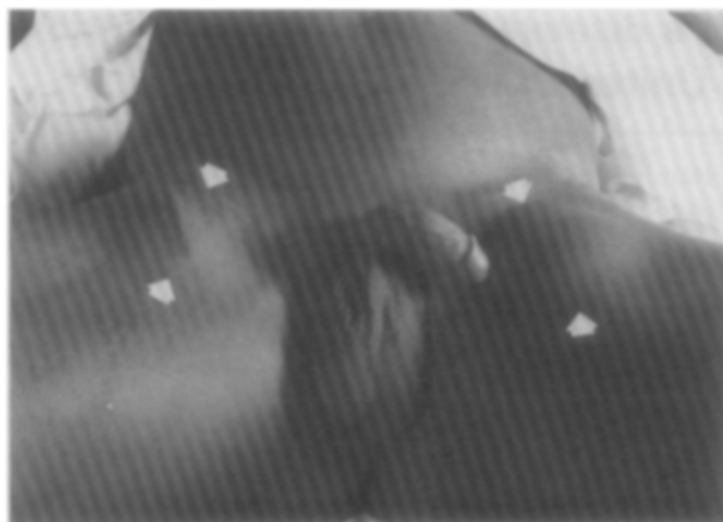


FIG. 1. Bilateral inguinal lymphadenopathy. The smooth, confluent masses of regional lymph nodes are obvious.

right epitrochlear 3.5 by 2.0 cm. The dermatitis was unchanged. CBC was again normal except for a peripheral eosinophil count of 35% (total WBC 9300 cells/mm³). At age 12 yr, a punch biopsy of a typical papule on the left leg and an excisional biopsy on the main aggregate of right femoral nodes were performed (see below). At age 14 yr, he continued to have active dermatitis, lymphadenopathy (Fig. 1), and peripheral blood eosinophilia. A battery of epidermal (prick) skin tests to 40 local pollens, molds, animal danders, house dust, house dust mite, and foods was entirely negative with a positive histamine (5 mm wheal) and negative control.

SPECIAL LABORATORY STUDIES

Immunologic blood evaluation

Total serum IgE was 32,000 U/ml. Serum RAST testing resulted in 1+ (on a scale of 1 to 10) or negative reactions to all allergens tested including oak tree, short ragweed, house dust mite, *Monilia*, egg white, and milk lactoglobulin.

Immunologic typing of peripheral blood lymphocytes demonstrated 64% E-rosetting cells (T cells), 48% reacting with monoclonal antihelper/inducer T cell antibodies, 12% reacting with antisuppressor/cytotoxic monoclonal antibodies, 11% demonstrating surface gamma immunoglobulin chains, 10% mu chains, 9% delta chains, 5% alpha chains, 4% epsilon chains, 12% kappa light chains, and 19% lambda light chains. All of these values are within the normal range except for the proportion of IgE-bearing lymphocytes that is elevated above the normal range of $1.4 \pm 0.5\%$.⁹

Neutrophil chemotaxis was performed by modification of the method of Nelson, et al.¹⁰ The patient's neutrophils responded to the chemotactant

substances regardless of the culture conditions used. The patient's serum supported chemotaxis of control neutrophils.

Light microscopic lymph node evaluation

The epitrochlear lymph node removed in 1978 and the femoral lymph node removed in 1981 had virtually identical morphologic abnormalities. There was marked follicular hyperplasia with variably sized and shaped follicles containing a polymorphous spectrum of follicular center cells, occasional mitotic figures, and scattered histiocytes, some with tingible bodies (Fig. 2). Within interfollicular, paracortical, and medullary areas were focally variable, vascular hyperplasia and eosinophil-rich inflammation, often present together. In areas having vascular hyperplasia, there were numerous small vessels lined by plump endothelial cells with large vesicular nuclei frequently containing prominent nucleoli. Most of these small vessels had associated pericytes and the morphology of postcapillary venules. Foci of inflammation contained numerous eosinophils admixed with mononuclear phagocytes and lymphoid cells (Fig. 3). In some foci, many histiocytes with abundant acidophilic cytoplasm produced a granulomatous appearance. Giemsa and Toluidine blue stains revealed mast cells scattered throughout the lymphoid tissue. Occasional foci of inflammation contained irregular areas of liquefactive necrosis with nuclear debris. Periodic acid-Schiff, Gomori methenamine silver, Brown-Brenn, Giemsa, Goodpasture, Ziehl-Neelsen, and Auramine-Rhodamine stains revealed no microorganisms within the lymph node tissue.

Wright-stained lymph node-touch preparations

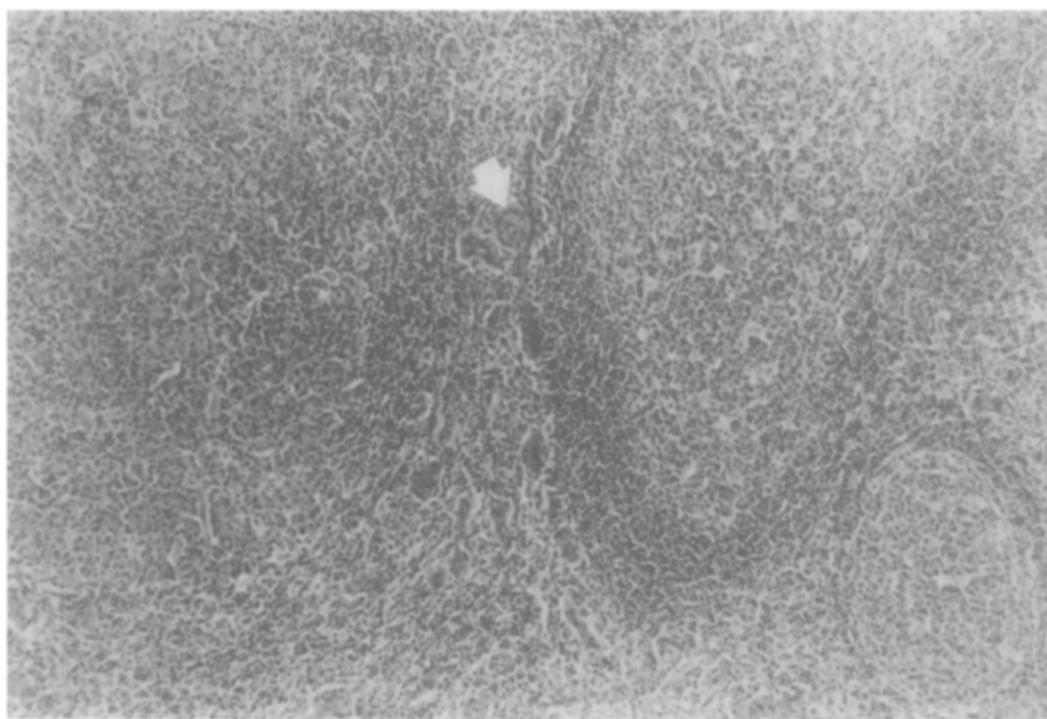


FIG. 2. Photomicrograph of the femoral lymph node removed in 1981 demonstrating two follicles with large germinal centers *right*, and *left*, area rich in eosinophils and having numerous small vessels with plump endothelium (*arrow*). (Hematoxylin and eosin; magnification $\times 100$.)

demonstrated a predominance of small, medium, and blastically transformed lymphocytes admixed with numerous eosinophils. There were also scattered mast cells and mononuclear phagocytes often containing tingible bodies.

The skin biopsy specimen obtained in 1981 demonstrated only nonspecific chronic dermatitis with hyperkeratosis and slight perivascular chronic inflammatory cell infiltration.

Immunologic lymph node evaluation

Frozen sections of the right femoral lymph node removed in 1981 were evaluated by immunofluorescence microscopy after staining with fluoresceinated goat antibodies specific for human gamma, mu, alpha, delta, epsilon, kappa, and lambda immunoglobulin chains (Meloy Laboratories, Springfield, Va.). The most substantial staining was in the germinal centers where, on a scale of 0 to 4+, there was 4+ staining for IgE, 3+ for IgM, 1+ for IgG, 0 for IgA and IgD, 4+ for kappa light chains, and 3+ for lambda light chains. This intense staining of germinal centers with anti-IgE is very rare in usual hyperplastic lymph node specimens. In the extrafollicular tissue, there were a few scattered plasma cells with cytoplasmic IgE, IgA, or IgM.

Frozen sections of the femoral lymph node were

also evaluated by biotin-avidin-peroxidase immunoenzyme microscopy by use of monoclonal antibodies specific for suppressor T-lymphocytes, helper T-lymphocytes, monocytes, and thymocytes (Becton-Dickinson, Sunnyvale, Calif.), and antibodies specific for factor VIII-related antigen and lysozyme (Dako Corporation, Santa Barbara, Calif.). The extrafollicular tissue was rich in T-lymphocytes with T-helper cells predominantly over T-suppressor cells. Scattered monocytes were present, but no cells reacted with antithymocytes antibodies. This distribution of lymphocyte subsets and monocytes is what is usually seen in surgically removed lymph nodes. The numerous endothelial cells bound the factor VIII-related antigen antibodies. The infiltrating eosinophils stained intensely with the antilysozyme antiserum (Fig. 3, B).

Viable cell suspensions isolated from the femoral lymph node by mechanical disruption and density gradient centrifugation were evaluated for lymphoid subset distribution. Thirty-two percent of cells formed rosettes with sheep red blood cells (T-lymphocytes) and had the morphology of predominantly small lymphocytes on Wright-stained preparations. Monoclonal antibodies to T-lymphocyte subsets showed that most T cells had a helper-T cell rather than suppressor-T cell antigen phenotype. Antibodies specific for immunoglobulin heavy or light chains

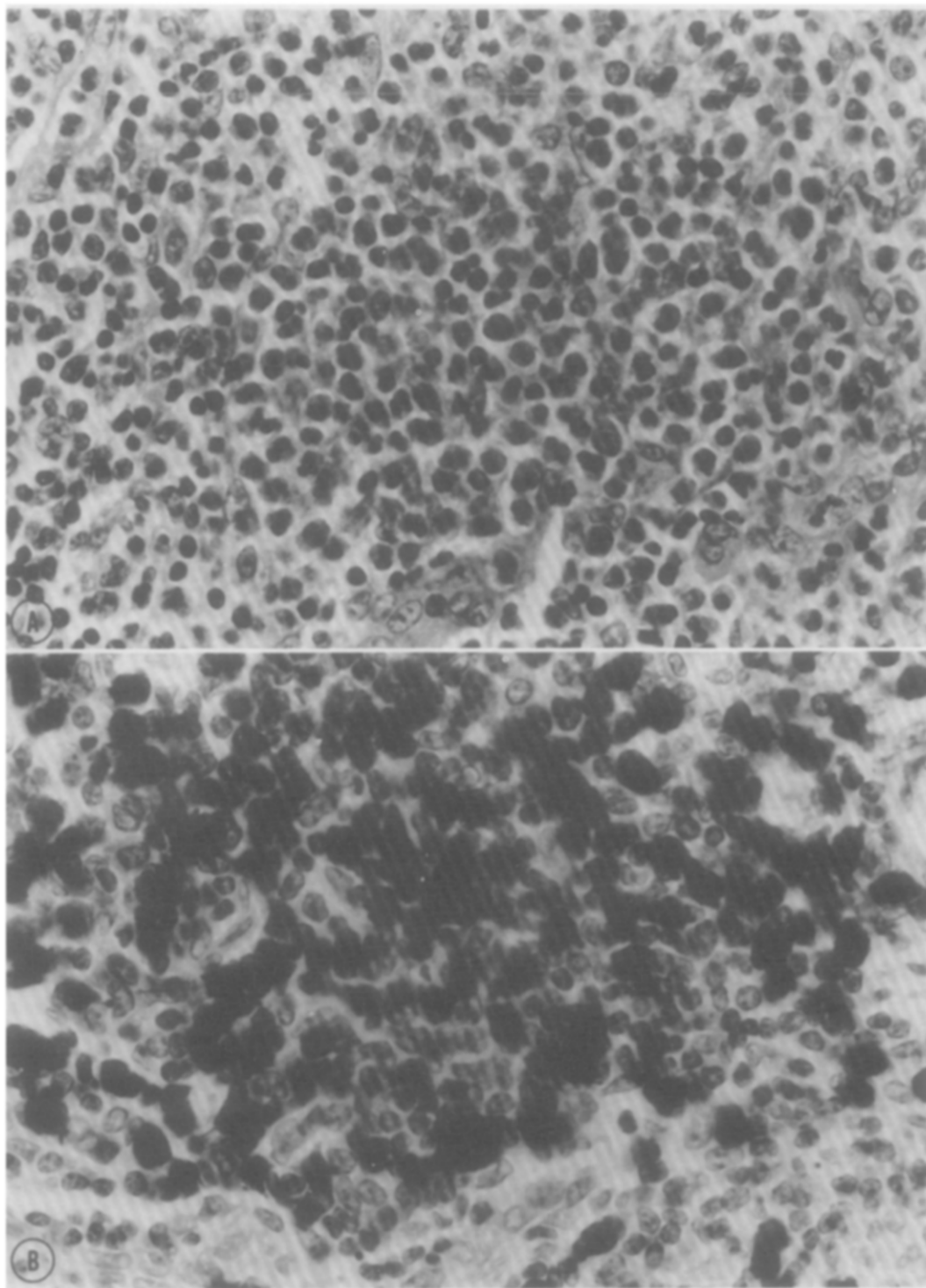


FIG. 3. A, Photomicrographs of eosinophil-rich area of femoral lymph node stained with hematoxylin and eosin. **B,** Stained by biotin-avidin-peroxidase immunoenzyme technique by use of antilysozyme to better illustrate the numerous eosinophils. (Magnification $\times 650$.)

demonstrated surface membrane immunofluorescence of 22% of cells with antikappa, 17% with antilambda, 14% with antigamma, 12% with antimu and less than 1% with antialpha. Antiepsilon antibodies were not tested against cells in suspension. This distribution of lymphocyte markers is within the expected range for surgically removed lymph nodes.

DISCUSSION

Patients with KD present with subcutaneous or dermal masses and/or enlargement of regional lymph nodes. The involved tissues are soft, painless, and unless primarily involving the dermis, usually not adherent to overlying skin. Distribution of involved masses or lymph nodes is most common on the head and neck (including the salivary glands) and in the axillary, cubital, or inguinal areas. The extent of involvement in individual patients ranges from a solitary mass on the scalp to generalized disease in lymph nodes at separate anatomic sites. Involved tissues may range in size from pea-sized nodules to aggregate masses as large as an adult fist. Pruritus, either generalized or at the site of involved tissues, is a common complaint.¹¹ Onset is insidious and occurs most often in young male men in the first or second decades. The main ancillary laboratory finding is peripheral eosinophilia, and some cases have had markedly elevated IgE levels on being measured.² The general health of patients is good, and there are no reports of the development of malignant changes. The etiology of KD is unknown, but some authors believe it is a manifestation of an atopic state.² Various treatment modalities (surgical or laser excision, irradiation, systemic corticosteroid administration) have been used and are directed toward the removal or reduction of individual masses.¹² Although spontaneous resolution is reported, the disease may remain active for years with indolent enlargement of the tissues, persistent eosinophilia, and pruritus.

In contrast, while patients with ALH may present with similar types of subcutaneous and dermal lesions, the location is almost always on the head and neck area.⁷⁻⁸ Often, there is only one discrete soft tissue mass which can be removed completely. Involvement of regional lymph nodes may or may not be present. Onset usually occurs in the adult years, and the condition is found more often in female adults. The peripheral eosinophil count is usually normal. The tissue changes in ALH are similar to those found in KD. However, Roasi et al.¹³ after comparing tissue slides from a series of Japanese patients with KD to slides from American cases of ALH, concluded that the two processes could be dif-

ferentiated histologically. Other authors note the clinical and pathologic similarities between KD and ALH and suggest that the two conditions be considered as part of the same clinical entity.¹⁴

The patient in our study has the typical clinical and laboratory features of KD as described in Japan. He is a young male adolescent with onset in the first decade, and although his disease has been active for 6 yr, his general health remains excellent. The involvement of tissues in separate anatomic areas of the body (specifically the inguinal and cubital areas), the persistence of peripheral blood eosinophilia, and the marked elevation of the serum-IgE level are all consistent with Oriental descriptions. Histologically, the marked lymphoid follicular hyperplasia with conspicuous IgE, tissue eosinophilia, mast cell hyperplasia, and vascular proliferation observed in the lymph nodes of this patient are all features that have been recognized in patients with KD.^{2, 5, 12} With the increased IgE in serum and within germinal centers, the elevated proportion of peripheral lymphocytes bearing surface IgE is not surprising. This patient differs from the majority of Oriental patients in that his soft tissue lesions involve the skin and the associated regional lymph nodes instead of forming discrete soft tissue tumors. However, patients without soft tissue tumors but with involved lymph nodes have been previously reported and constitute as a definite subgroup of KD patients.^{2, 4, 6} The finding of an extensive and chronic papular dermatitis is not previously described in patients with KD. Although the etiology of the dermatitis in this patient remains obscure, the anatomic proximity to the enlarged lymph nodes suggests a relationship.

The significance of the markedly elevated serum-IgE level is unknown. In addition to atopic diseases, elevated IgE levels also have been found in certain immunodeficiency disorders,¹⁵ parasitic infections,¹⁶ and atopic dermatitis.¹⁷ Increased numbers of IgE-bearing lymphocytes in the blood also have been found in patients with atopic diseases.⁹ Buckley et al.¹⁸ have described a syndrome of hyperimmunoglobulinemia E, chronic dermatitis, and recurrent infection. Although our patient exhibits some of these features, there is no evidence for increased susceptibility to infection. In a series of KD patients with elevated IgE levels, Takenaka et al.² postulated an allergic sensitivity to *Candida albicans* as the cause of the KD. Unlike Takenaka's patients, neither RAST nor skin testing of this patient demonstrated IgE antibody to *C. albicans*.

This patient presented problems in diagnosis because clinicians and pathologists involved with the

case were not familiar with KD. Initial diagnostic efforts were directed toward excluding malignancy and infection. As studies failed to establish a definitive diagnosis, descriptive diagnosis such as "atypical atopic dermatitis with lymphadenopathy" and "reactive lymphadenitis with eosinophilia" were used. Finally, a literature search for cases with similar features led to reports of KD. Establishing the correct diagnosis in cases of KD is important because the clinical course of an individual patient can be predicted and treatment alternatives evaluated in the context of previous published cases. This is particularly true because of concerns about the development of malignancy in patients with progressively enlarging soft tissue masses. Patients and their physicians are reassured by the knowledge that KD is not associated with malignant changes.

Currently, the main symptom in this patient is pruritus associated with his generalized dermatitis. This has been controlled with topical applications of 1% hydrocortisone cream. The lymphadenopathy is not painful and is not causing discomfort. Therefore no specific therapeutic effort has been directed toward arresting the process. Obviously, definitive management in cases like this must await further research into pathogenesis.

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