Kimura Disease

A Clinicopathologic Study of 21 Cases

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Abstract: Kimura disease is a rare form of chronic inflammatory disorder involving subcutaneous tissue, predominantly in the head and neck region and frequently associated with regional lymphadenopathy and/or salivary gland involvement. This condition has a predilection for males of Asian descent and may clinically simulate a neoplasm. Kimura disease is sometimes confused with angiolymphoid hyperplasia with eosinophilia, which occurs in the superficial skin of the head and neck region. Although sporadic cases have been reported in non-Asians, there is no large, comprehensive study of Kimura disease in the United States. We report 21 cases with nodal involvement that, histologically, are consistent with Kimura disease. There were 18 males and 3 females (male/female ratio 6:1), 8 to 64 years of age (mean, 32 years), and included 7 Caucasians, 6 Blacks, 6 Asians, 1 Hispanic, and 1 Arabic. Anatomic sites of involvement included posterior auricular (n = 10), cervical (n = 6), inguinal (n = 3), and epitrochlear (n = 2) lymph nodes, with two patients having associated salivary gland involvement. Most (n = 16) cases had peripheral blood eosinophilia. Consistent histologic features were follicular hyperplasia, eosinophilic infiltrates, and proliferation of postcapillary venules. Follow-up data on 18 patients revealed that 13 were alive without disease (3 had recurrence), mean follow-up, 10.9 years; 4 were alive with disease (2 had a recurrence), mean follow-up, 8.8 years; and 1 died with disease (12.7 years). Kimura disease has been described more often in Asians, but it does occur in non-Asians with a similar clinicopathologic presentation. It is a distinctive entity with no known etiology. Kimura disease has characteristic histologic features that are important to recognize and can be used to differentiate it from hypersensitivity and drug reactions and infections.

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Kimura disease is a rare chronic inflammatory disorder of unknown etiology.[14] It presents as a deep, subcutaneous mass in the head and neck region and is frequently associated with regional lymphadenopathy or salivary gland involvement.[1,2,13,15,22,23] The disease was first described in the Chinese literature as "eosinophilic hyperplastic lymphogranuloma"[21] but became widely known as Kimura disease after Kimura et al reported similar cases under the title "on the unusual granulation combined with hyperplastic changes of lymphatic tissue."[20] Over the years, there has been considerable confusion between Kimura disease and angiolymphoid hyperplasia with eosinophilia (ALHE).[28,30,33] Indeed, a number of early reports used the terms Kimura disease and ALHE synonymously.[28,30] It is now thought, however, that the two diseases represent separate entities with distinctive clinic and histologic features.[2,9,11,22,32] Kimura disease is considered much more prevalent in young males of Asian lineage. The nodular lesions are deep-seated in subcutaneous tissue and clinically may mimic a neoplasm. One of the important clinicopathologic features is its frequent association with regional lymph node and/or major salivary glands involvement. Indeed, isolated lymphadenopathy might be the only initial presentation of Kimura disease.[22] Recognizing it as a distinctive reactive process is important, not only to avoid unnecessary treatment and patient anxiety but also to further studies of its etiology and pathogenesis. Although individual cases have been reported in the non-Asian population,[3,4,9,10,15,26] to the best of our knowledge in a review of the English literature (MEDLINE 1966–2003), there are no large, comprehensive studies of Kimura disease in the United States. It is our intention to present the clinical, laboratory, histology, and immunohistochemical findings of 21 patients with Kimura disease, with a special emphasis on its occurrence in non-Asian patients with a comparison of the clinical and histologic features in both populations.

The results will be presented in the context of a review of the pertinent English literature.

MATERIALS AND METHODS

The records of 139 patients with lesions diagnosed as "eosinophilic lymphadenitis," "eosinophilic lymphadenopathy," "ALHE," or "Kimura disease" were selected from the Hematopathology Registry at the Armed Forces Institute of Pathology between 1970 and 2002. Hematoxylin and eosin-stained slides from all cases were reviewed, and using strict morphologic criteria as described in earlier reports,[13,14] only 21 cases that were histologically consistent with Kimura disease were selected for inclusion. Fourteen cases were obtained from civilian sources, including university medical centers and foreign contributors, 5 cases from military hospitals, and 2 cases from Veterans Administration medical centers.

Materials within the Institute's files were supplemented by a review of the patient demographics (gender, age, race, ethnicity); symptoms and physical findings and duration at presentation; laboratory values (IgE values and peripheral blood eosinophilia); and past medical and surgical history. In addition, we reviewed radiographic, surgical pathology, and operative reports and obtained follow-up information by written questionnaires or direct communication with the treating physician(s) or the patient. Follow-up data, available for 18 patients, included information regarding disease location, presence of recurrent disease, treatment modalities used, and the current patient status. The three cases without follow-up included two foreign contributors and one case that was diagnosed recently. This clinical investigation was conducted in accordance and compliance with all statutes, directives, and guidelines of the Code of Federal Regulations, Title 45, Part 46, and the Department of Defense Directive 3216.2 relating to human subjects in research.

A complete workup for infectious agents was performed (on available material) and included the following stains or impregnations: Brown-Hopps, Brown-Brenn, Grocott Methenamine silver, Ziehl-Nielssen, and Warthin-Starry. Immunophenotypic analysis was performed in all cases with suitable material by a standardized Envision method using 4-μm-thick, formalin-fixed, paraffin-embedded sections. Table 1 documents the pertinent, commercially available immunohistochemical antibody panel used. The analysis was performed on a single representative block for each lesion. When required, proteolytic antigen retrieval was performed by predigestion for 3 minutes with 0.05% Protease VIII (Sigma Chemical Co., St. Louis, MO) in a 0.1 M phosphate buffer, pH of 7.8, at 37°C. Heat-induced epitope retrieval was performed, as required, by using formalin-fixed, paraffin-embedded tissue treated with a buffered citric acid solution, pH 6.0 (Citra, DakoCytomation Corporation, Carpinteria, CA), and heated for 20 minutes in a steamer. Following this, the sections were allowed to cool at room temperature in a citric acid buffer solution for 45 minutes before continuing the procedure. Standard positive controls were used throughout, with serum used as the negative control.

TABLE 1. Immunohistochemical Antibodies and Sources

Antibody	Dilution	Source	Pretreatment
CD20	1:250	DakoCytomation	None
CD3*	1:500	DakoCytomation	Pepsin
Kappa light chain*	1:10,000	DakoCytomation	Pepsin
Lambda light chain*	1:20,000	DakoCytomation	Pepsin
Bcl-2	1:100	DakoCytomation	Steam
CD21	1:100	DakoCytomation	Pepsin
p24	1:50	DakoCytomation	Steam
IgE	1:1000	DakoCytomation	None
LMP-EBV	1:500	DakoCytomation	Steam
CD68	1:100	DakoCytomation	Protease
S-100 protein*	1:400	DakoCytomation	Pepsin
Factor VIII RAg*	1:800	DakoCytomation	Protease

*Polyclonal antibody.

A review of publications in English (MEDLINE 1966–2003) was performed, with all cases reported as Kimura('s') disease were included in the review.

RESULTS

Clinical and Follow-up Data

A synopsis of the pertinent clinical features is listed in Table 2 and summarized in Table 3. There were 18 males and 3 females (male/female ratio 6:1). The ages ranged from 8 to 64 years (mean, 31 years). Among the 21 cases, 7 were Caucasians, 6 Blacks, 6 Asians, 1 Hispanic, and 1 Arabic. Except for case nos. 4, 7, and 12, all cases presented clinically as painless masses (14 were solitary lesions) in the posterior auricular (n = 10), cervical (n = 6), groin (n = 3), and epitrochlear (n = 2) regions. Case nos. 4 and 7 were described as "cyst,'' while case no. 12 was described clinically as a tick bite in a patient with cat contact. Regional lymphadenopathy was apparent clinically in 15 patients (71%). The patients had symptoms lasting from 1 to 48 months (mean, 8 months). At clinical presentation, peripheral blood eosinophilia was documented in 16 of 17 patients tested, while elevated IgE levels were detected in 8 of 9 patients tested. Follow-up was obtained in 18 (86%) patients and ranged from 1.2 to 33.3 years (mean, 10.3 years). All cases were treated by surgical excision, with 4 patients receiving a "wide-excision." Seven patients were also treated with corticosteroid therapy. A single patient received radiation therapy prior to corticosteroid treatment. As shown in Table 3, there is virtually no difference in the clinical findings between Asian and non-Asian patients. Of the 18 patients with follow-up, 13 were alive without evidence of disease, although 3 patients had developed a recurrence in the intercurrent period, followed for

TABLE 2. Clinical Features of Kimura Disease in 21 Cases

Patient No.	Age (yr)/ Gender/ Race	Clinical Presentation	Duration of Symptoms (mo)	Anatomic Location of Lymph Node	Size (cm)	Blood Eosinophilia	IgE Level	Outcome (Years of Follow-Up); Recurrence
1	13/M/B	Mass; chronic scalp eczema	8	Retroauricular	1.2	n/r	n/r	ANED (12.9)
2	10/M/C	Mass	4	Retroauricular	4.5	17%	Elevated	ANED (33.3); R×3
3	9/M/C	Mass	6	Retroauricular	2	2.2×10^9/L	Elevated	ANED (23)
4	21/M/S	"Cyst"	18	Retroauricular	2	n/r	n/r	LTF
5	37/M/B	Mass	12	Retroauricular	1.8	6.3×10^9/L	n/r	ANED (16.8)
6	64/M/C	Mass with pain	4	Epitrochlear	2.2	1×10^9/L	n/r	DWD (12.7): R*
7	13/M/C	Cystic mass, right		Retroauricular	1.8	Present	Elevated	ANED (6.5)
8	46/M/B	Enlarging mass	7	Mandible	1.6	2.2×10^9/L	Elevated	ANED (12.2)
9	37/F/B	Itchy mass	15	Epitrochlear	2.2	8.1×10^9/L	n/r	AWD (9.1)
10	23/M/C	Enlarging mass	4	Groin and cervical	2.5	7.1×10^9/L	6900 IU	AWD (8.4)
11	64/F/C	Mass	8	Submandibular	1.7	Normal	Normal	AWD (6.5); R
12	11/M/C	Tick bite and feline association	4	Retroauricular	1.6	Present	Elevated	ANED (6.4)
13	32/M/H	Mass	3	Groin	2.5	Present	n/r	ANED (2.8)
14	34/M/B	Mass	8	Neck	2.9	3.6×10^9/L	n/r	ANED (1.2)
15	43/F/B	Mass	3	Mastoid	n/r	n/r	n/r	LTF
16	53/M/A	Mass	2	Retroauricular and salivary gland	4.0	Marked	n/r	LTF
17	8.5/M/A	Mass, cat scratch 1 year prior	6	Cervical	6.5	2.9×10^9/L	5281 IU	ANED (9.3); R
18	9/M/A	Mass	6	Retroauricular	1.3	Present	Normal	AWD (7.2); R×3*
19	50/M/A	Mass	4	Parotid and retroauricular	2.2	3.6×10^9/L	2.2 mg/L	ANED (5.8)
20	22/M/A	Mass		Groin	1.6	n/r	n/r	ANED (5.8)
21	52/M/A	Mass	48	Supraclavicular	1.4	Present	n/r	ANED (5.3)

B, black; C, Caucasian; H, Hispanic; S, Arabic; A, Asian; ANED, alive, no evidence of disease; AWD, alive with disease; DWD: dead "with" disease but not "from" disease; R, recurrence; LTF, lost to follow-up; n/r, not reported.
*Contralateral side.

an average of 10.9 years; 4 patients were alive with disease, 2 of whom had developed recurrence, followed for an average of 8.8 years; and 1 patient had died with disease 12.7 years after initial presentation. This latter patient had a heart attack but had evidence of disease at the time of death. Therefore, he died "*with*" but not "*from*" disease.

Pathologic Findings

Macroscopic

The macroscopic specimens were mass lesions in all patients, including case nos. 4 and 7 described as "cysts" clinically, even though 5 patients (case nos. 1, 2, 10, 16, and 21) presented with multifocal masses (or lymph nodes) in proximate head and neck regions or involving both neck and groin areas. One patient (case no. 2) presented with bilateral retroauricular masses. Most (76%) presented with head and neck disease. The tumor masses ranged in maximum dimension from 1.2 to 6.5 cm, with an average of 2.5 cm.

Microscopic

The histologic features are listed and summarized in Table 4. While the nodal architecture was largely preserved, there were a few cases in which marked capsular fibrosis with

TABLE 3. Clinical Features: Summary of Kimura Disease

	Non-Asians (n = 15)	Asians (n = 6)
Age [range (yr)]	9–64	8.5–53
Age [average (yr)]	30	32
Females	3	0
Males	12	6
Anatomic site	7: retroauricular	3: retroauricular
	4: cervical	2: cervical
	2: epitrochlear	1: inguinal
	2: inguinal	
Parotid gland involvement	0	2
Duration of symptoms [mo (mean)]	7	12
Size (cm)	2.3	2.8
Peripheral blood eosinophilia	11 (of 12 tested)	5 (of 5 tested)
Elevated IgE levels	6 (of 7 tested)	2 (of 2 tested)
Follow-up data (in 18 patients)	9: ANED	4: ANED
	3: AWD	1: AWD
	1: DWD	2: Recurred
	3: recurred	

ANED, alive with no evidence of disease; AWD, alive with evidence of disease; DWD, dead with disease.

TABLE 4. Histologic Features: Summary of Kimura Disease

Histologic Features	Non-Asians (n = 15)	Asians (n = 6)	Total (n = 21)
Perinodal soft tissue involvement	12	6	18
Salivary gland involvement	0	2	2
Nodal architecture preserved	15	6	21
Follicular hyperplasia with well-formed mantle zones	15	6	21
Proteinaceous deposits in GC	14	6	20
Vascularization of GC	13	6	19
Necrosis of GC	4	1	5
Polykaryocytes	12	3	15
Eosinophils in GC	13	2	15
Eosinophilic folliculolysis	10	2	12
Eosinophilic microabscesses	15	6	21
Postcapillary venule proliferation	15	6	21
Stromal sclerosis	14	5	19
Perivenular sclerosis	15	6	21
Rare giant cell or small eosinophilic granuloma	4	1	5
IgE reticular staining in GC	13	5	18

GC, germinal center.

subcapsular sinus obliteration was seen (Fig. 1). Marked fibrosis was seen most frequently in advanced-stage disease. The inflammatory response extended into the perinodal soft tissue and/or subcutaneous soft tissue in most cases (n = 18). Characteristic features of Kimura disease included: prominent eosinophilic microabscesses (n = 21; Fig. 2); eosinophilic folliculolysis (n = 12; Fig. 3); germinal center necrosis (n = 5; Fig. 3); proteinaceous deposits in the germinal centers (n = 20; Fig. 4); eosinophilic infiltrates in the germinal centers (n = 15; Figs. 2, 3); vascularization of germinal centers (n = 19; Fig. 5); polykaryocytes within germinal centers and/or interfollicular areas (n = 15; Fig. 6); perivenular sclerosis (n = 21); and sclerosis (n = 19). All lymph nodes demonstrated the following features to a variable degree: follicular hyperplasia with reactive germinal centers and well-formed mantle zones; eosinophilic infiltrates in interfollicular areas, sinusoid, and perinodal soft tissue; and proliferation of postcapillary venules. Case nos. 16 and 19 contained parotid gland tissue, which demonstrated follicular lymphoid hyperplasia and periductal eosinophilic infiltrates. The acini were not affected. A few cases (n = 5) had small foci of discrete eosinophilic necrosis surrounded by epithelioid histiocytes or rare small clusters of giant cells (Fig. 7). A crystalline structure, resembling a Charcot-Leyden crystal, was noted within the cytoplasm of histiocytes in one case. The histologic features identified in the 15 non-Asian patients and 6 Asian patients were indistinguishable, as identified in summary Table 4.

Special Studies

Histochemical techniques (as described in Materials and Methods, above) failed to disclose any infectious agents. More specifically, special attention was given to the 5 cases that displayed giant cells or epithelioid histiocytes. The immunophenotypic findings in all tested cases supported the reactive nature of the lymphoid process. B and T cells were found in their normal nodal compartments. CD21 highlighted the follicular dendritic networks. Bcl-2 was negative in all germinal centers. Kappa and lambda light chains showed a polyclonal pattern. p24 immunoperoxidase staining for HIV was nonreactive in 15 cases tested. Germinal center deposition of IgE (Fig. 8) was noted in most cases (n = 18). Reactivity with LMP-EBV was identified focally in only 1 case.

DISCUSSION

Ever since the report by Kimura et al,[20] Kimura disease has been recognized as a distinct clinicopathologic entity.[1,2,9,22] Over the years, however, the disease has often been confused with ALHE, especially in the Western literature.[33] It was assumed the diseases were on a spectrum due to overlapping clinicopathologic features.[30] Clinically, both conditions present as soft tissue swellings that usually arise in the head and neck region with an indolent, prolonged clinical course. Microscopically, both processes show eosinophilic infiltrates and vascular proliferations. The confusion escalated by the introduction of an ever-expanding number of names applied to

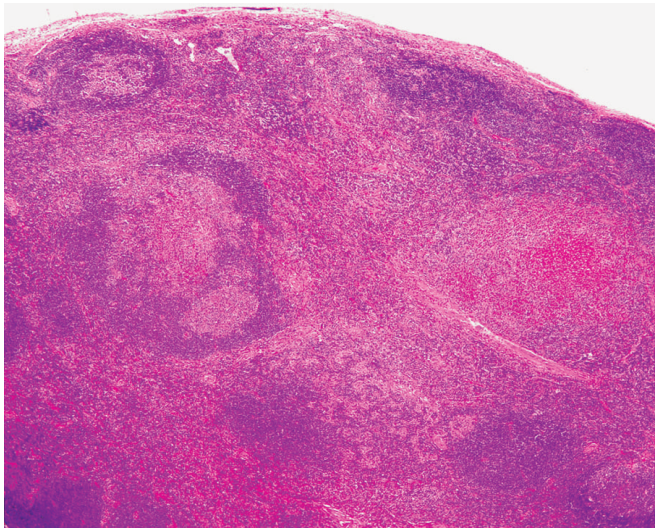

FIGURE 1. Focal fibrosis is noted separating hyperplastic germinal centers from areas of folliculolysis by an eosinophilic infiltrate.

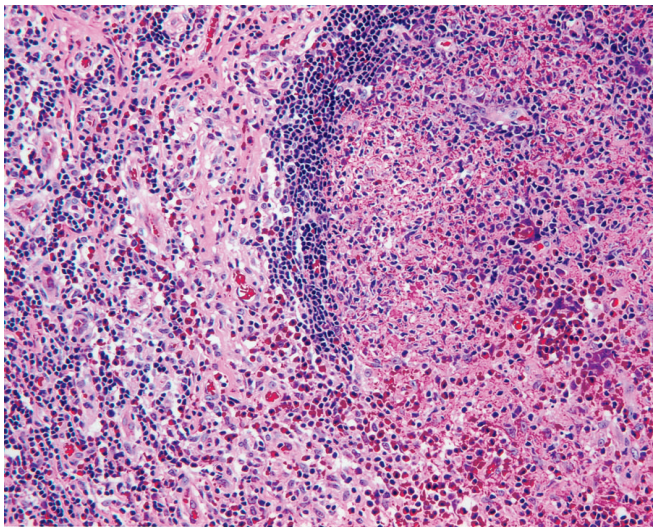

FIGURE 3. Germinal center necrosis with extensive folliculolysis. An eosinophilic infiltrate is noted.

both diseases, including eosinophilic granuloma, eosinophilic granuloma of lymph node and soft tissue, eosinophilic hyperplasic lymphogranuloma, eosinophilic lymphofollicular granuloma, eosinophilic lymphfolliculoid granuloma of the soft tissue,[11,24,35] atypical pyogenic granuloma, inflammatory angiomatous nodules, histiocytoid hemangioma, epithelioid hemangioma, subcutaneous angioblastic lymphoid hyperplasia with eosinophilia, and subcutaneous angiolymphoid hyperplasia with eosinophilia.[8,11] In 1979, the first good histologic dissection of the lesions was reported, in which Kimura disease was separated from ALHE, the latter classified under the group of histiocytoid hemangioma.[29] Others soon validated this separation with multiple comparative studies.[1,2,9,11,22,32] There are characteristic and distinctive clinicopathologic features despite a few similarities between the two diseases. In brief, Kimura disease occurs predominantly in Asians, with a male predilection. Patients invariably demonstrate a peripheral eosinophilia and elevated serum IgE levels. The solitary lesions are usually in the deep subcutaneous tissues, frequently associated with regional lymphadenopathy and salivary gland involvement. Curiously, although lymphadenopathy is common in Kimura disease, specific lymph nodes changes were

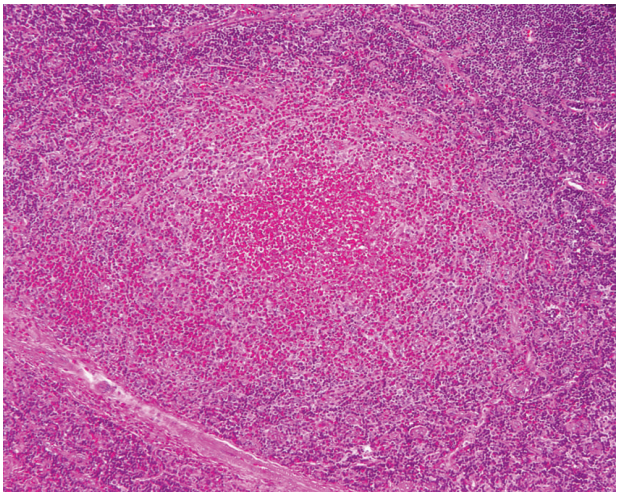

FIGURE 2. Prominent eosinophilic infiltrate with microabscess formation.

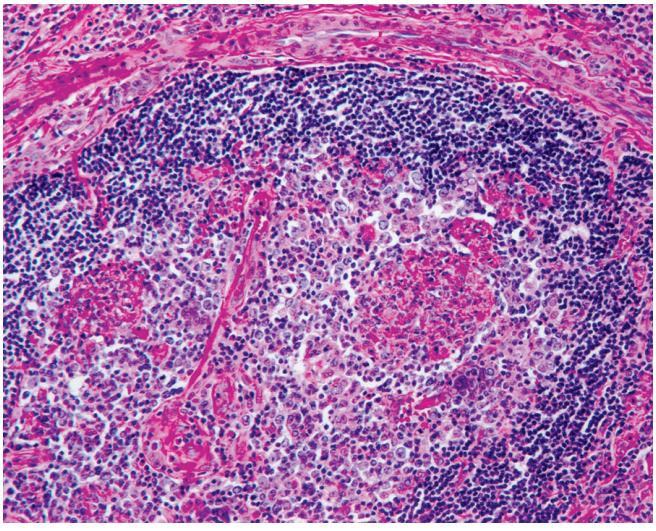

FIGURE 4. Perivascular fibrosis surrounds a germinal center with proteinaceous deposits and eosinophils.

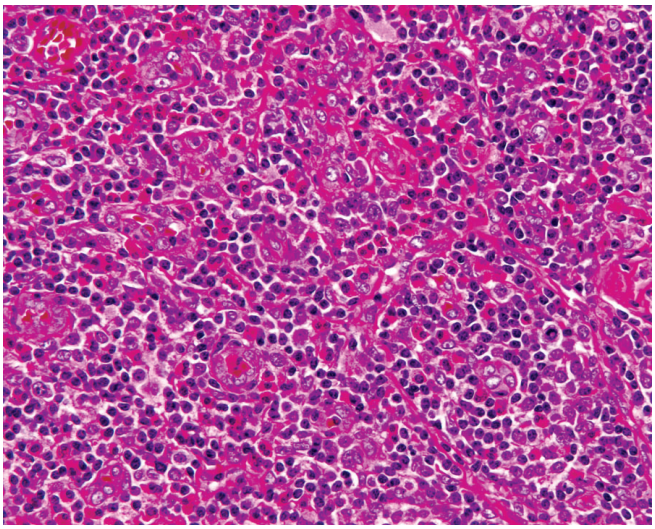

FIGURE 5. Increased vessels within the germinal center.

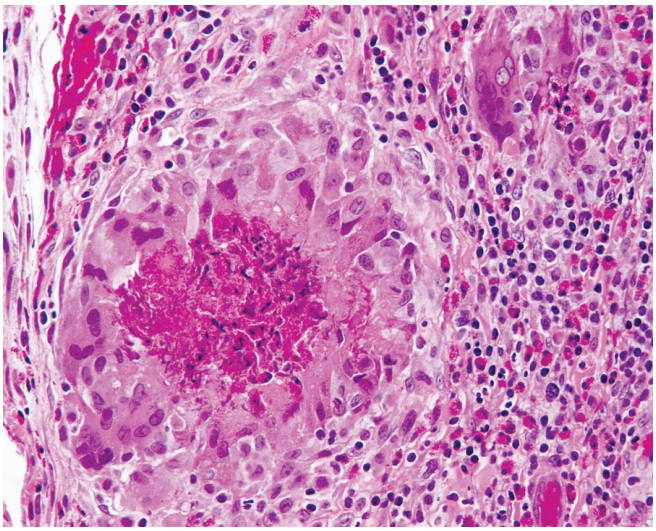

FIGURE 7. Eosinophilic necrosis surrounded by epithelioid histiocytes and giant cells in the subcapsular area.

not outlined until 1989.[13] By contrast, ALHE occurs in all racial groups with a slight female predominance. Patients present with small, superficial dermal papulonodules, frequently erythematous, accompanied by bleeding, pruritis, and tumor growth. Regional lymphadenopathy, serum eosinophilia, and elevated IgE levels are rare.[6] Histologically, Kimura disease usually has three components: cellular (inflammatory infiltrate including increased eosinophils and follicular hyperplasia), fibrocollagenous, and vascular (arborizing vascular proliferation of the postcapillary venule, although endothelial cells are usually flat and lack cytologic atypia or vacuolization). By comparison, the vascular proliferation is most significant in ALHE, forming aggregates or lobules comprised of plump endothelial cells with epithelioid or histiocytoid changes and frequently demonstrating cytologic atypia and vacuolization.[9,29] While the pathogenesis of both diseases is unknown, the presence of a T-cell receptor rearrangement in the inflammatory component of ALHE may suggest a T-cell lymphoproliferative disorder of a benign or low-grade malignant nature.[18]

The majority of patients with Kimura disease have been reported in Asian populations in China,[23,35] Taiwan,[22] Hong Kong,[1,13] and Japan.[32] Sporadic cases of Kimura disease have

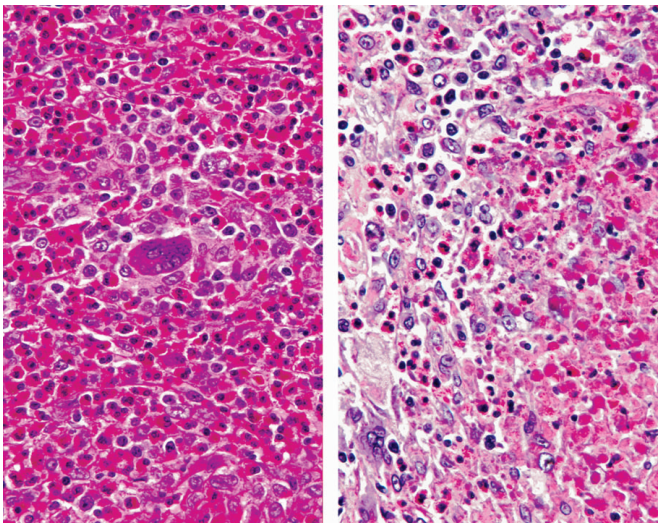

FIGURE 6. An eosinophilic microabscess with giant cell (left) often associated with necrosis and a prominent eosinophilic infiltrate within the germinal center (right).

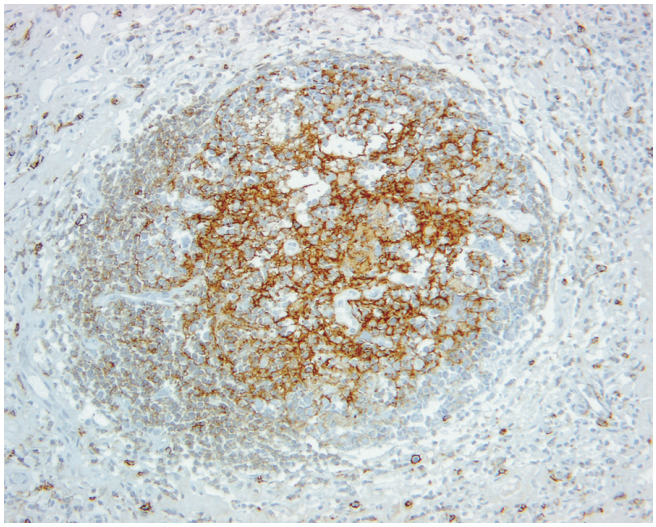

FIGURE 8. Immunohistochemical demonstration of IgE in the reticular network of a germinal center.

been described in other ethnic groups.[3,10,15,26] In this clinical series, we identified Kimura disease in 15 non-Asian patients, including Caucasians, Blacks, Hispanics, and Arabs, along with 6 patients of Asian descent. Most of our patients were young males, similar to previous reports. Whereas the majority of our cases (76%) and those reported in the literature occurred in the head and neck (76%), particularly infraauricular and retroauricular, orbit, eyelid, palate, and pharynx have also been reported, in addition to axilla, groin, and arm.[1,23] All of the cases in this clinical series demonstrated lymph node involvement, although a range of 32% to 100% has been reported.[1,2,13,22,23] Associated subcutaneous and/or dermal involvement occurred in many of our cases, similar to previous reports. We only identified salivary gland involvement in 2 patients, both of whom were Asian. The very low incidence of salivary gland involvement in non-Asian patients may be a legitimate finding, although given the referral nature of the AFIP, greater numbers would be needed to achieve statistical significance.

The seminal paper delineating the histologic features of the lymph nodes in Kimura disease[13] outlines constant, frequent, and rare histologic parameters. The constant features include preserved nodal architecture, florid germinal center hyperplasia, eosinophilic infiltration, and postcapillary venule proliferation. Frequent features include sclerosis, polykaryocytes, vascularization of the germinal centers, proteinaceous deposits in the germinal centers, necrosis of the germinal centers, eosinophilic abscess, and a reticular IgE deposition within germinal centers. Rarely, there may be progressive transformation of the germinal centers. Although nodal architecture is largely preserved in most cases, capsular fibrosis with subcapsular sinusoid obliteration and perinodal soft tissue involvement is frequently present. The stromal fibrosis appears to start from concentric perivenular fibrosis, a feature seen in nearly all cases. The fibrosis is similar to the fibrosis seen in subcutaneous lesions. Actually, trying to separate the late-stage "burned out" fibrotic lymph node from a lesion primarily arising from soft tissue may be quite difficult.[7] Despite this difficulty, the presence of fibrosis in general is a valuable feature in distinguishing Kimura disease from ALHE. Eosinophilic folliculolysis, a helpful feature in diagnosing Kimura disease, often coexists to some degree with eosinophilic deposits in the germinal center and germinal center necrosis.[13] In this clinical study, a few cases had infrequent small clusters of giant cells or small discrete eosinophilic necrosis with or without surrounding epithelioid histiocytes (Fig. 7). No true stellate necrosis was seen in the cases included for review, although this feature was prominent in many of the cases classified as "necrotizing lymphadenopathy with eosinophilia." The crystalline structure, resembling a Charcot-Leyden crystal, was noted within the cytoplasm of a number of histiocytes in one case, a unique finding, although perhaps alluded to by others when referring to phagocytosis of eosinophilic granules by tissue histiocytes.[1,9,17,22] We hypothesize that eosinophils infiltrate the germinal center, which undergoes folliculolysis, resulting in an eosinophilic necrosis with or without an associated epithelioid histiocytic reaction, suggesting a continuum along this histologic spectrum. This contention is further strengthened by a recent report in which eosinophilic epithelioid granulomatous reactions were produced by phagocytosis of the apoptotic eosinophils by macrophages.[12] While the histologic features for Asian groups are well described,[13] the findings are identical in either Asian or non-Asian patients in our study, proving that Kimura disease can develop in non-Asian patients.

None of the aforementioned individual histologic features is pathognomonic for Kimura disease as all may be seen in a variety of reactive and neoplastic processes. The differential diagnosis of Kimura disease is broad and includes Hodgkin lymphoma, angioimmunoblastic T-cell lymphoma, Langerhans cell histiocytosis, florid follicular hyperplasia, Castleman's disease, dermatopathic lymphadenopathy, ALHE, allergic granulomatosis of Churg and Strauss, lymphadenopathy of drug reactions, and parasitic lymphadenitis. In general, however, the separation of Kimura disease from neoplasms is not difficult when classic Reed-Sternberg cells and/or its variants, atypical lymphocytes, or Langerhans cells are identified and confirmed with appropriate immunohistochemical studies. The germinal center vascularization and vascular proliferation may be present in hyaline-vascular type Castleman's disease, but germinal centers are usually atrophic without eosinophilic infiltrates. Florid follicular hyperplasia may show many of the features of Kimura disease, including postcapillary venule proliferation, vascularization of germinal centers, polykaryocytes, and proteinaceous deposits in germinal centers. However, eosinophilic abscess, eosinophilic infiltrates in germinal centers, and folliculolysis are absent. Focal dermatopathic changes may be seen in Kimura disease, but the majority of features in Kimura disease are not seen in dermatopathic lymphadenopathy. Separation from ALHE has been discussed, although the vascular changes and fibrosis, along with serum studies, are most helpful. Kimura disease is often incorrectly included with drug reaction, hypersensitivity, and parasitic lymphadenopathy. Without specific or characteristic histologic changes in the latter conditions, except eosinophilic infiltrates and possible granuloma formation without reactive germinal centers, an infectious workup should be conducted in suspected cases of Kimura disease, particularly in those that demonstrate giant cells or epithelioid granuloma. Positive history of drug use (there was no history of drug/medication use in our patients) and detection of remnants of parasites (rare in the United States) by special stains will lead to a diagnosis of the drug reaction and parasitic infection, respectively.

Kimura disease is usually a localized process without systemic symptoms. Itchiness, urticaria, and chronic eczema have been reported in a few cases,[19,31] with scalp eczema identified in one of our patients. The most significant association is renal disease, which may develop before or concurrently with Kimura disease.[27,34] Interestingly, we identified a single patient who had a tick bite and feline association; however, the lymph node showed characteristic findings of Kimura disease, with negative special stains, and peripheral eosinophilia and elevated IgE level. We believe the insect bite and feline history are coincidental findings without a true relationship.

Although Kimura disease has now been accepted as a distinct benign reactive process, its etiology and pathogenesis remain unclear. An allergic reaction (parasite, virus, fungi, or toxin), trauma, and abnormal autoimmune reactions have all been postulated.[24] The presence of peripheral eosinophils, increased mast cells, and increased levels of IL5 and IgE suggests an abnormal T cell stimulation similar to a hypersensitivity-type reaction.[27] The prominent follicular hyperplasia suggested a possible human immunodeficiency and HHV-8 virus infection, but other researchers were unable to demonstrate such an association.[16] The significance of an EBV infection is unknown, although we found focal reactivity within the dendritic cells within the germinal centers in only a single case, similar to other authors.[25]

Kimura disease is a chronic disorder, with an indolent clinical course, frequently waxing and waning over time. Surgery is the mainstay of therapy, although regional or systemic corticosteroid therapy, cytotoxic therapy, and radiation have been used.[5,31] Recurrence after surgery or discontinued steroid treatment is common. As expected, since there is no difference in the histology for non-Asian patients, there is also no difference in the treatment.

In summary, we report the findings of 21 cases of Kimura disease. Our study confirmed that Kimura disease may develop in all ethnic groups with indistinguishable clinical and histologic features. Therefore, the diagnosis of Kimura disease can be made in non-Asian patients. Although Kimura disease is a rare disorder, it should be considered in the differential diagnosis of any lymph node demonstrating an eosinophilic infiltrate and prominent follicular hyperplasia. It is a distinctive clinicopathologic entity with characteristic histologic features and is important to separate from drug reactions, hypersensitivity, and infectious agents. With strict histologic criteria, we think a correct diagnosis can be achieved, especially when combined with pertinent clinical information and laboratory studies.

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