A Clinicopathological Study of Kimura's Disease and Epithelioid Hemangioma

Hee Jeong Ahn and Kwang-Gil Lee

The clinicopathological features of 9 cases of Kimura's disease and 5 cases of epithelioid hemangioma (EH) were reviewed. Patients with Kimura's disease presented with multiple or solitary large tumors occurring in the thigh, arms as well as parotid gland. Histologically, the lesions were characterized by numerous lymphoid follicles with proliferation of post-capillary venules lined by plump endothelium and a marked eosinophilic infiltration. Patients with EH were older than those with Kimura's disease and presented papular nodular lesions, less than 1cm in size. Microscopically, there was proliferation of blood vessels lined by epithelioid endothelium with infiltration by lymphocytes and eosinophils. Although there may occasionally be clinicopathological overlap between Kimura's disease and EH, we consider that these two disorders can be recognized as separate entities.

Key Words: Kimura's disease, epithelioid hemangioma, angiolymphoid hyperplasia with eosinophilia

Kimura's disease is a chronic inflammatory disease of unknown etiology considered by Kimura et al. (1948) as "abnormal granuloma with proliferation of lymphoid tissue". More than 100 cases of this condition were cited in the Japanese literature during the following decade, and Lizuka (1959) coined the term "Kimura's disease" for his cases. Other similar cases were reported in Asian and western literature under the name of 'eosinophilic lympho-folliculosis of the skin' (Kawada 1966), 'pseudo- or atypical pyogenic granuloma' (Wilson-Jones and Bleeheen 1969), and 'nodular angioblastic hyperplasia with eosinophilia and lymphofolliculosis' (Bendel 1977). The disease occurs as tumor-like nodules in the subcutaneous tissue of the head and neck, antecubital fossa, inguinal region, and the parotid gland. It is frequently associated with regional lymphadenopathy, peripheral blood eosinophilia and sometimes elevated IgE levels.

Microscopically, Kimura's disease is characterized by proliferation of blood vessels lined by plump endothelial cells, surrounded by a moderate to severe inflammatory cell infiltrate composed predominantly of eosinophils and lymphoid follicles.

'Subcutaneous angiolymphoid hyperplasia with eosinophilia (ALHE) was first reported by Wells and Whimster (1969). They described nine patients who had histories of chronic cutaneous and subcutaneous nodules located in the head and neck regions. The lesion was characterized by exuberant proliferation of capillaries, massive eosinophilic infiltration, and lymphohreticular hyperplasia. They considered that the ALHE was identical to Kimura's disease. Articles thereafter have continued to report cases of ALHE and Kimura's disease as the same disease entity (Kandil 1970; Mehregan and Shapiro 1971; Reed and Terazakis 1972; Kimm et al. 1975; Henry and Burnett 1978; Song and Kang 1983). But Rosai et al. (1979) believed that ALHE and Kimura's disease represented two separate entities, because the endothelial cells of Kimura's disease did not exhibit the 'histiocytoid' nature seen in histiocytoid hemangiomas including ALHE (Castro and Winkelmann 1974; Burrall et al. 1982), although the vessels were numerous and hyperplastic. The term "epithelioid hemangioma" was first proposed by Enzinger and Weiss (1983) as a synonym for ALHE, and they felt that Kimura's disease and epithelioid hemangioma probably represented different entities. Subsequently, Googe et al. (1987) and Urabe et al. (1987) commented that the two disorders were sufficiently different to warrant their recognition as two distinct entities.

In this report, we reviewed 14 cases diagnosed as Kimura's disease and ALHE to study whether or not
the two disorders are sufficiently different to classify them as separate entities.

MATERIALS AND METHODS

Five cases of ALHE (epithelioid hemangioendothelioma) and nine cases of Kimura's disease were selected from the records of the Department of Pathology, Yonsei University College of Medicine. The clinical histories were reviewed.

All paraffin blocks were recut and stained with hematoxylin and eosin. Special stains used included silver impregnation for reticulin, Masson's trichrome and Weigert-van Gieson for collagen, Victoria blue for elastin, and toluidine blue stain for mast cells.

RESULTS

Clinical Features

Clinical data on patients with Kimura's disease are summarized in Table 1. Included were eight men and one woman whose ages ranging from 14 to 53 years, with a mean of 32 years. The duration of the disease ranged from 1 to 15 years, with a mean of 7.4 years. Four of the lesions were found in the parotid gland, and two in the thigh. The other three cases occurred in the arm and cheek, neck, and elbow. The lesions presented as a single mass in five cases and as multiple lesions in four cases. The size of the lesion ranged from 2.4 to 16.0 cm in diameter, with a mean of 5.6 cm. Regional lymphadenopathy was noted in five patients (55.6%), and peripheral blood eosinophilia above 10% was recorded in six patients (66.7%).

Clinical data on patients with epithelioid hemangioendothelioma are summarized in Table 2. They included four men and a woman ranging from 34 to 58 years of age with a mean of 48.2 years. The duration of the lesion was 3 to 6 months. The anatomic distribution included the scalp, face, preauricular area, ear, and thigh. The lesions appeared as papules and/or nodules ranging from 0.3 to 1 cm in size. Peripheral eosinophilia was present in one case (case 4) and regional lymphadenopathy was not evident in any case.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Location</th>
<th>No. of lesions</th>
<th>Size (cm)</th>
<th>Duration (yrs)</th>
<th>Lymphadenopathy</th>
<th>Peripheral eosinophilia</th>
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<td></td>
<td>Parotid</td>
<td>3</td>
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<td>7</td>
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<td>+ (16%)</td>
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<td>2</td>
<td>40/M</td>
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<td>Cheek, arm</td>
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<td>4</td>
<td>10</td>
<td>NG</td>
<td>+ (5.1%)</td>
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<td>Parotid</td>
<td>1</td>
<td>7</td>
<td>9</td>
<td>+</td>
<td>-</td>
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<tr>
<td>4</td>
<td>32/M</td>
<td></td>
<td>Parotid</td>
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<td>5</td>
<td>3</td>
<td>+</td>
<td>+ (10.9%)</td>
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<tr>
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<td>28/M</td>
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<td>3.5</td>
<td>3</td>
<td>+</td>
<td>-</td>
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<tr>
<td>6</td>
<td>19/M</td>
<td></td>
<td>Thigh</td>
<td>2</td>
<td>16, 11</td>
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<tr>
<td>7</td>
<td>53/M</td>
<td></td>
<td>Neck</td>
<td>1</td>
<td>4</td>
<td>15</td>
<td>-</td>
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<tr>
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<td>52/M</td>
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<td>7</td>
<td>15</td>
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<td>+ (61%)</td>
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<tr>
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<td>Elbow</td>
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<td>4</td>
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<td>+ (32%)</td>
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No.: number, NG: not given, +: present, -: absent

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<tr>
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<th>Sex</th>
<th>Location</th>
<th>Size (cm)</th>
<th>Duration (months)</th>
<th>Gross finding</th>
<th>Peripheral eosinophilia</th>
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<td>Preauricular area</td>
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<td>Multiple papules &amp; nodules</td>
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<td>34/M</td>
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<td>Ear</td>
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<td>3</td>
<td>Multiple papules &amp; nodules</td>
<td>-</td>
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<td></td>
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<td>NG</td>
<td>Single nodule</td>
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<td>Scalp &amp; temporal area</td>
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<td>6</td>
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<td>NG</td>
<td>NG</td>
<td>Single nodule</td>
<td>NG</td>
</tr>
</tbody>
</table>

NG: not given, +: present, -: absent
Microscopic Findings

Kimura's disease: The lesions were well-defined, not encapsulated and composed of three major components: the inflammatory, vascular and fibrous. The inflammatory component was most prominent. Virtually the entire lesion was infiltrated by inflammatory cells composed mainly of lymphocytes and eosinophils, the latter sometimes forming eosinophilic microabscesses. Other constituents included plasma cells and mast cells. In all cases, there were numerous lymphoid follicles with germinal centers (Fig. 1A). The eosinophilic infiltrate in some areas appeared to cuff small- and medium-sized blood vessels without evidence of vasculitis (Fig. 1B). In some

Fig. 1. Kimura's disease. (A) Massive inflammatory infiltrate forming lymphoid follicles (H & E, x40). (B) Proliferation of irregular vascular channels lined by plump endothelial cells. The inflammatory cells are predominantly eosinophils and lymphocytes (H & E, x200).

Fig. 2. Kimura's disease. (A) The old lesion (case 7) showing dense collagenous fibrosis with infiltration by many plasma cells (H & E, x200). (B) A blood vessel lamellated by collagen fibers (Masson's trichrome, x400).
of the older lesions, the germinal centers appeared degenerated and contained amorphous, eosinophilic, hyaline material.

The vascular component was composed of a proliferation of capillaries and post-capillary venules lined by plump or flattened endothelial cells, located in the interfollicular areas of the lesion. The vessels were relatively uniform in size. The fibrous component consisted of interstitial fibrosis (Fig. 2A) was composed of reticulin and collagenous fibers. This component was severe in three cases, in which hyalinization was also seen. Perivascular lamellation of collagen fibers was another frequent characteristic finding (Fig. 2B).

**Epithelioid hemangioma**: Four lesions were located in the dermis and were relatively well-circumscribed. The lesions consisted of a proliferation of small to medium-sized blood vessels surrounded by an inflammatory infiltrate composed predominantly of lymphocytes and eosinophils as well as some plasma cells and mast cells. The vessels were lined by epithelioid-appearing endothelial cells having enlarged round nuclei and abundant eosinophilic or clear cytoplasm. Some vessels showed luminal obliteration by proliferating epithelioid endothelium (Fig. 3A); in one case, intracytoplasmic vacuoles representing a primitive vascular lumen were demonstrated (Fig. 3B). The vessels in the periphery of the lesion, however, were lined by plump or flattened endothelium without epithelioid features. Occasionally, blood vessels were lined by hobnail- or scallop-shaped endothelial cells.

The severity of inflammatory infiltrate was less than that of Kimura’s disease, but its composition was similar. Fibrosis was minimal and mostly perivascular. In the interstitium it consisted of mainly reticular fibers rather than the thick collagen fibers which were seen in Kimura’s disease.

One case which occurred in the thigh in a 48-year-old woman demonstrated histological features that bordered between Kimura’s disease and EH. This lesion was located in the subcutaneous fat and its margin was ill-defined. This case demonstrated all the features of Kimura’s disease including interstitial collagenous fibrosis, lymphoid follicles and a severe inflammatory infiltrate composed of many eosinophils, lymphocytes, mast cells and plasma cells (Fig. 4A). In addition, there was also a proliferation of small blood vessels having the obviously epithelioid endothelium (Fig. 4B), a histologic hallmark of EH.

**DISCUSSION**

Kimura’s disease was first described in China by Kimm and Szeto (1937), initially called “eosinophilic hyperplastic lymphogranuloma”. This condition was more widely known as Kimura’s disease after Kimura et al. (1948) reported similar cases in Japan. Our cases of Kimura’s disease showed typical clinical and histologic findings of reports from Japan (Iizuka 1959; Kawada 1966). Kimura himself compared his two
Fig. 4. Epithelioid hemangioma with predominant histologic features of Kimura’s disease (case 5). (A) The marked inflammatory infiltrate with a lymphoid follicle in the subcutaneous tissue (H & E, ×100). (B) Proliferating blood vessels lined by epithelioid endothelial cells with vacuoles in some of them. The background inflammatory cells are predominantly eosinophils (H & E, ×400).

reported cases to Mickulicz’s disease, commenting on the lymphocytic and granulomatous appearance of the lesions, but making no mention of vascular proliferation as part of the neoplastic process (Kimura et al. 1948). It is thought that the vascular proliferation was ignored by Kimura because of the similarity of proliferating vessels to the post-capillary venules of the interfollicular regions of usual reactive hyperplasia. The “EH” has been used to describe an entity similar to ALHE. ALHE was first reported by Wells and Whimster (1969) in the English literature. Shortly thereafter, Wilson-Jones and Bleeheen (1969) and Wilson-Jones and Marks (1970) reported other similar groups of patients. These cases represented one entity and the
slightly varied microscopic descriptions might be related to different stages of disease development or different host responses. In previously reported cases, EH presented in the dermis or subcutaneous tissue. Olsen and Helwig (1985) commented on the large vessels showing intravascular endothelial proliferation and cutaneous arteriovenous(AV) shunts in their analysis of 116 patients. Moesner et al. (1981) and Urabe et al. (1987) demonstrated an AV fistula and related this feature to the pathogenesis of EH. In our series, all cases of EH were the dermal type, in which the lesions were restricted in the dermis and the inflammatory infiltrate was not prominent. In two cases (case 3 and 4), the inflammatory infiltrates were almost absent. AV shunt or AV fistula was not demonstrated.

The comparative histologic features of the two diseases are summarized in Table 3. Clinically, the lesions of EH were smaller than those of Kimura’s disease, and the duration was shorter. One patient with EH had peripheral eosinophilia (19.3%), which was present in 6 cases out of 9 patients (6.7%) with Kimura’s disease. Histologically, EH is characterized by proliferation of small-to-medium-sized blood vessels lined by endothelial, atypical endothelial cells. In contrast, the proliferating blood vessels in Kimura’s disease are mostly post-capillary venules lined by plump or flat endothelial cells, surrounded by a heavier inflammatory infiltrate including many well-formed lymphoid follicles. Interstitial collagenous fibrosis was noted only in Kimura’s disease.

The relationship of EH to Kimura’s disease remains uncertain. Since Wells and Whimster (1969) proposed that Kimura’s disease and ALHE represented different parts of the same disease spectrum, the majority of opinion has adopted this viewpoint. Rosai et al. (1979), Enzinger and Weiss (1983), and Urabe et al. (1987), however, argued this concept and highlighted clinical and histologic differences.

In this study, a case of EH demonstrated borderline histologic features of both EH and Kimura’s disease. Similarities to Kimura’s disease included a marked inflammatory infiltrate, interstitial collagenous fibrosis, and occurrence in the thigh. This case was included in the spectrum of EH because of the epithelioid appearance of the endothelium of proliferating blood vessels. This is in compliance with the opinion of recent articles (Rosi et al. 1979; Enzinger and Weiss 1983; Urabe et al. 1987) which assert that the epithelioid endothelial cell was the most significant discriminating feature between these diseases. However, the clinical and other morphological features of EH also separate it from Kimura’s disease.
In EH, the disease is of shorter duration, the lesion is smaller, and there is no lymphadenopathy. Accordingly, we consider these two diseases as separate entities. However, they may share similar etiologies in light of clinical and histological features.

**REFERENCES**


Burraill BA, Barr RJ, King DF: Cutaneous histiocytoid hemangioma. *Arch Dermatol* 118:166-170, 1982


Kandil E: Dermal angiolymphoid hyperplasia with eosinophilia versus pseudopogenic granuloma. *Br J Dermatol* 83:405-408, 1970


Reed RJ, Terazakis N: Subcutaneous angioblastic lymphoid hyperplasia with eosinophilia (Kimura’s disease). *Cancer* 29:489-497, 1972

Rosai J, Gold J, Landry R: The histiocytoid hemangiomas: a unifying concept embracing several previously described entities of skin, soft tissue, large vessels, bone, and heart. *Hum Pathol* 10:707-730, 1979


