Clinicopathologic study of parotid involvement in 21 cases of eosinophilic hyperplastic lymphogranuloma (Kimura’s disease)

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Objective. To investigate the clinicopathologic features of eosinophilic hyperplastic lymphogranuloma (Kimura’s disease) in the parotid gland.

Study design. The hematoxylin and eosin sections and clinical data of 60 patients with eosinophilic hyperplastic lymphogranuloma (Kimura’s disease), including with parotid involvement, were reviewed.

Results. Of 60 cases of eosinophilic hyperplastic lymphogranuloma (average age, 42 years; average disease duration, 5.8 years), 35 cases (58%) were clinically seen to involve swelling of the parotid region. Parotid specimens were available in 21 cases and showed different microscopic changes. In mildly affected parotid samples, the histological features included infiltration of lymphocytes and eosinophils around the ducts of the interlobular connective tissue. In the moderately involved glands, the infiltrated area was enlarged and contained lymphoid follicles, resulting in adjacent acinar atrophy that was particularly obvious around the salivary ducts. In severe lesions, most acini were lost and only a few ducts remained. All cases with parotid involvement showed more severe pathological changes in the subcutaneous connective tissues and/or local lymph nodes. The parotid lesions often surrounded a central intraglandular lymph node with characteristic features of the disease; however, the salivary parenchyma was left alone. Nerve fibers affected by inflammatory lymphocytes and eosinophils were seen in 38/60 (63%) cases of eosinophilic hyperplastic lymphogranuloma (Kimura’s disease) examined in this study.

Conclusions. Eosinophilic hyperplastic lymphogranuloma (Kimura’s disease) does not show primary parotid involvement; instead, pathological changes in the parotid gland are a result of disease spread from the intraparotid lymph nodes and adjacent soft tissues. In addition, our observations suggest that the pruritus often associated with the disease may be due to nerve infiltration by lymphocytes and eosinophils. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006;102:651-8)

Eosinophilic hyperplastic lymphogranuloma (EHLG, Kimura’s disease, eosinophilic lymphofolliculoid granuloma, eosinophilic granuloma) is an inflammatory disorder of unknown etiology that tends to occur among Asians such as the Chinese and Japanese. Recent study has shown that EHLG occasionally shows a clonal proliferation of T cells.¹ The disease commonly involves the head and neck region of young and middle-aged individuals.²-⁶ Previous studies have noted that parotid tissues are often involved in EHLG,⁷-¹¹ and clinicians may misdiagnose this disease as a salivary gland swelling or even as a malignancy. However, little is known about the precise clinicopathologic features of the parotid involvement in EHLG. We retrospectively studied the clinicopathologic manifestations in 60 cases of EHLG to reveal further insight of clinicopathologic features of this disease of the parotid gland.

MATERIALS AND METHODS

This study includes 60 patients diagnosed as EHLG at the Peking University School of Stomatology between 1983 and 2003. The pathologic diagnosis was made according to the criteria proposed by Hui et al.¹² Clinical data such as age, affected locations, disease course, symptoms, and clinical findings were reviewed. Histopathologic sections from postoperative or biopsy tissues from the 60 patients were reviewed for histopathologic changes, including location, lesional severity, and intraglandular lymph nodes, and their relationships to the surrounding parotid parenchyma and subcutaneous connective tissues. Histopathologic changes confined to parotid gland tissues are graded as mild, moderate, and severe according to the following criteria: (1) mild: there are only some lymphocytes and eosinophils in the interlob-
Table 1. Clinical features of 60 cases of Kimura’s disease

<table>
<thead>
<tr>
<th>Location</th>
<th>No. of patients</th>
<th>Male</th>
<th>Female</th>
<th>Swelling</th>
<th>Pruritus</th>
<th>Melanin pigmentaion</th>
<th>Coarse skin</th>
<th>Peripheral blood eosinophilia*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parotid gland</td>
<td>35</td>
<td>32 (91%)</td>
<td>3 (9%)</td>
<td>35</td>
<td>20 (57%)</td>
<td>9 (26%)</td>
<td>7 (20%)</td>
<td>17/21 (81%)</td>
</tr>
<tr>
<td>Submandibular</td>
<td>12</td>
<td>10 (83%)</td>
<td>2 (17%)</td>
<td>12</td>
<td>3 (25%)</td>
<td>0</td>
<td>0</td>
<td>2/3 (67%)</td>
</tr>
<tr>
<td>Cheek</td>
<td>7</td>
<td>5 (71%)</td>
<td>2 (29%)</td>
<td>7</td>
<td>2 (29%)</td>
<td>0</td>
<td>0</td>
<td>1/4 (25%)</td>
</tr>
<tr>
<td>Other sites†</td>
<td>6</td>
<td>4 (67%)</td>
<td>2 (33%)</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>51 (85%)</td>
<td>9 (15%)</td>
<td>60 (100%)</td>
<td>25 (42%)</td>
<td>9 (15%)</td>
<td>8 (13%)</td>
<td>21/26 (81%)</td>
</tr>
</tbody>
</table>

*Data were available in 26 cases. Number on the left indicates cases with eosinophilia; number on the right indicates number of cases examined.
†Three cases were submental, 2 cases in the lip, and 1 case in the neck.
‡The data was available in 26 cases.

ular connective tissues, without fibrous hyperplasia and acinus atrophy; (2) moderate: there is extensive infiltration of eosinophils and lymphocytes with lymphoid follicle formation and adjacent acinus atrophy, but without fibrous hyperplasia; and (3) severe: there is extensive acinus atrophy and fibrosis, besides infiltration of lymphocytes and eosinophils. Histopathologic changes are also correlated with clinical manifestations.

RESULTS

Of the 60 patients pathologically diagnosed as EHLG, 9 were female and 51 were male, with a female to male ratio of 1:5.7. The youngest patient was 3 years old, and the oldest was 68 years old (average age, 36.4 years). The disease course ranged from 20 days to 26 years, with an average of 4.9 years. Among the 60 patients, 35 (58%) were clinically diagnosed as parotid swelling. Most of them showed tumefaction of the parotid gland. When pathological sections of the 60 patients were reviewed, 21 (35%) were found to include parotid tissues and showed involvement of them; the average age of these patients was 42 years (2 females and 19 males). The clinical features of the 60 patients are summarized in the Table. Swelling and pruritus of the parotid region were the main complaints. Melanin pigmentation and coarseness of the skin were the main clinical signs (Fig. 1).

In terms of macroscopic appearance, the surgical specimens often consisted of subcutaneous tissues with or without portions of the neighboring salivary glands. The subcutaneous tissues were not well circumscribed. The texture differed widely, and specimens ranged in color from grayish to yellowish-white when sectioned. Some areas were darker in color and slightly nodular. The salivary gland tissue was often easily distinguished from neighboring soft tissues except for those glands involved by the disease, in which case the gland tissue was adherent to the subcutaneous connective tissue. Some samples included lymph nodes of different sizes, numbers, and colors, ranging from dark red to brown.

Fig. 1. Parotid region swelling with melanin pigmentation in an EHLG.

In terms of microscopic appearance, the disease involved mainly the subcutaneous soft tissue and lymph nodes. The most prominent microscopic features were lymphoid tissue hyperplasia, with lymphoid nodules containing germinal centers, which were scattered or aggregated in the subcutaneous tissues. The involved lymph nodes were enlarged and had increased numbers of follicles with germinal centers (Fig. 2) that contained eosinophilic infiltrates of various degrees. Vascularization and necrosis were also seen in these germinal centers. The eosinophils infiltrated throughout the lesions, sometimes associated with eosinophilic microabscesses in the connective tissue or within the lymphoid follicle. The number of capillary vessels increased with endothelial cell swelling similar to those in postcapillary venules but without atypical nuclei and eosinophilic cytoplasm. Intravascular eosinophils were common. Infiltration of plasma cells and neutrophils was also common in the lesions. Eosinophils could even be seen near or within the neural fibers (Fig. 3).

When the parotid gland was involved, the majority of diseased tissue was seen in the intraparotid lymph
nodes. The lesion severity tended to vary across the different areas of the gland parenchyma. It was highly unusual for the entire gland to be affected. The most severe and typical parotid lesions were usually located in the lobules near the lymph nodes or adjacent to subcutaneous connective lesions. The gland lobules
distant from the diseased nodes were usually totally free of pathological changes (Figs. 2 and 4). In the severe cases, the diseased tissue was seen either in the intraparotid lymph nodes or in the adjacent subcutaneous connective tissues. The involved glandular tissues showed changes similar to those seen in the subcutaneous or connective tissues. Besides focal or scattered eosinophil infiltration and lymph follicle formation (Fig. 5), the prominent changes were extensive acinus atrophy and periductal fibrosis (Fig. 6). Duct epithelial squamous cell metaplasia was also noted in the most severe cases. In the moderate involvement cases, there was extensive infiltration of eosinophils and lymphocytes in the interlobular connective tissues, with lymphoid follicle formation. The adjacent acini began to atrophy, but not as extensively as in the severe cases. Fibrosis and squamous metaplasia were not obvious. In cases with mild lesions, only some infiltration of lymphocytes and eosinophils into the interlobular connective tissues were found, mainly next to the salivary ducts (Fig. 7) and without lymph follicle formation. Eosinophils were often seen in the dilated blood vessels in the interlobular connective tissues. Whatever severe, moderate, or mild parotid involvement there was, there were more definitive and severe affected adjacent connective tissues and/or lymph nodal tissues, and this was the precondition, especially for mild and moderate parotid involvement. That is, the connective tissue and lymph nodes showed more severe disease than did the adjacent salivary parenchyma, where the lesions in the salivary gland were often mild or even nonexistent. In cases where the diseased tissue outside the parotid capsule was significant, the salivary gland tissues within the parotid capsule often showed only mild changes, even though there was only a thin capsule between the gland and the diseased tissues (Fig. 8).

DISCUSSION

Clinically, EHLG often presents as a swelling in the parotid or submandibular region, most often involving the parotid gland. Among the 60 patients with EHLG examined in this study, 35 (58%) clinically showed tumefaction of the parotid gland. Other important clinical manifestations, which may indicate the diagnosis of EHLG, included skin pruritus (57%), melanin pigmentation (26%), and coarseness (20%) of the skin overlying the parotid region. Peripheral blood eosinophilia was seen in most of the patients (81%).

Microscopically, 21 patients showed different degrees of parotid gland involvement. In fact, the actual cases of salivary gland involvement may exceed this number, due to insufficiency of the biopsy or surgical specimens. Submandibular gland involvement was noted in 3 patients, and minor salivary gland involvement was also occasionally seen, perhaps due to spreading of the primary lesion. The microscopic appearances are similar to those in the parotid gland.
EHLG mainly develops in the subcutaneous connective tissue and lymph nodes of the head and neck regions. There have been many studies on the pathological characteristics of this disease. However, few previous studies have systematically investigated the histopathologic changes in parotid glands affected by EHLG. Tham et al. pointed out that salivary gland lesions might be from the extension of EHLG in the lymph nodes around the parotid gland. In this study, all cases of salivary gland involvement were accompanied by neighboring connective tissue changes. The lesions are more severe in the connective tissues than in the parotid gland. When intraglandular lymph nodes show typical features of EHLG, adjacent salivary gland tissues often have similar changes, whereas the glandular parenchyma distant from the lymphadenopathy is often histologically normal. These observations indicate that the pathological changes in the parotid gland are resulting from lesions in the intraparotid lymph nodes or...
adjacent subcutaneous connective tissues. The clinical swelling of the parotid region might then be mainly due to disease infiltration and edema in the subcutaneous connective tissues of the parotid region.

EHLG may intrude into the parotid parenchyma via two possible pathways: through adjacent soft tissues and through the intraglandular lymph nodes. We found significant lesional change in the connective tissue outside the parotid capsule, whereas the salivary gland tissues within the capsule often showed much milder lesions. These observations indicate that the parotid capsule functions as a biologic barrier between the gland and the soft tissues outside the salivary gland.

According to the results of this study, the parotid lesion initially presents as lymphocyte and eosinophil infiltration into the interlobular connective tissue. At the beginning, only a few lesional cells are distributed around excretory ducts. As the lesion intensifies, it extends into the intralobular connective tissues, mainly as lymphocytic and eosinophil infla-
tration around the ducts. Adjacent acini gradually become atrophic as the lesion advances, leaving the ducts with corresponding increases in the surrounding collagen fibers. Squamous cell metaplasia is also sometimes seen. In the most severe cases, the lesion might spread throughout sever al lobules. Because the involvement is often partial, some glandular tissues still exhibit normal structure in most cases. In fact, none of the examined patients suffered from xerostomia.

Besides the tumefaction, the patients usually complained of itchy, coarse, and pigmented skin in the area affected by EHLG. We postulated that the inflammatory cells observed microscopically, such as eosinophils, might release certain cytokines and neurotransmitters, leading to the noted skin irritations and occasionally infiltrated neural fibers.

EHLG typically presents as large subcutaneous masses characterized by a deep inflammatory infiltration with vascular proliferation, and well-developed subcutaneous germinal centers. Associated lymph nodes and parotid gland involvement with fibrosis and edema are also common features. It is often accompanied by peripheral eosinophilia and an increased serum IgE level. According to these features plus clinical manifestations such as skin pruritus, melanin pigmentation, and coarseness, a diagnosis of EHLG can be made. Although EHLG and angiolymphoid hyperplasia with eosinophilia share some similarities both clinically and pathologically, angiolymphoid hyperplasia with eosinophilia, showing prominent epithelial endothelia cells not seen in EHLG, is characterized by superficial papules or nodules with no lymphadenopathy and is less frequently accompanied by peripheral eosinophilia and parotid involvement.52 Lymphoplasmacytic sialadenitis with eosinophils and periductal fibrosis24 and follicular lymphoma with fibrosis25 may also involve major salivary glands and should be differentiated from EHLG with salivary gland involvement. Other diseases that should be considered in the differential diagnosis from EHLG are Hodgkin’s lymphoma, non-Hodgkin’s lymphoma such as angioimmunoblastic T-cell lymphoma, Langherans cell histiocytosis, various lymphadenopathies, Churg-Strauss disease, drug reaction, and parasitic infection.

The authors are grateful to Dr. Lan Su and Dr. Kuilhua Zhang for the revision of this manuscript.

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