Epithelioid Hemangioendothelioma of the Maxilla: Report of a Case and Literature Review

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We experienced a case of epithelioid hemangioendothelioma that occurred in the maxilla of a 50-year-old woman. The incidence of this disease is high in soft tissue and bones, and its development in the oral cavity has rarely been reported. The patient visited our hospital because of an asymptomatic tumor in the buccal-side gingiva. Under the diagnosis of oral benign tumor, we excised the lesion. Histopathologically, the tumor had multiple alveolar structures built up of spindle cells with egg-shaped nuclei. The alveolar structures had small lumina in their central part, and hemocyte components were observed in some of them. Immunohistochemically, the tumor cells were positive for Factor VIII related antigen. Electronmicroscopy revealed micropinocytotic vesicles and multivesicular bodies. On the basis of these findings, we made a diagnosis of epithelioid hemangioendothelioma. There are clinical and histological differences between epithelioid hemangioendothelioma of the oral cavity and the other site.

Key words: epithelioid hemangioendothelioma, oral cavity, maxilla, malignancy

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Introduction

Weiss and Enzinger first reported epithelioid hemangioendothelioma in 1982(1). Since then, there have been many reported cases of epithelioid hemangioendothelioma developing in soft tissue, bone, lung and liver. The incidence of this disease in the oral cavity, however, is quite low, with only 10 cases reported so far (2-9). Histologically, the tumorous endothelial cells build up microalveolar or funicular structures and form epithelioid lesions. Therefore, it is easy to confuse this vascular tumor with metastatic types.

We report an intraoral case of epithelioid hemangioendothelioma and discuss the malignancy of this disease.

Case report

A 50-years-old woman visited the department of Oral and Maxillofacial Surgery, Kanagawa Dental College Hospital, complaining of a painless lump in her gums, which she had noticed six months previously. The patient had a history of rheumatoid arthritis and hyperlipidemia. Physical examination revealed an elastic hard, hemispherical tumor measuring 10 × 12 mm in the buccal-side gingiva in the maxillary right canine and first premolar region. It was immovable but did not adhere to the mucous membrane. X-ray examination showed a unilocular radiolucent image, which extended down to the half root of the maxillary right canine, but there was no sclerosis in the lesion (Fig. 1). According to these findings, a pre-operative diagnosis of benign non-epithelial tumor was made, and partial maxillectomy after extracting the maxillary right lateral incisor and the second premolar was performed, involving the surrounded tissue.

Macroscopically, the resected tumor was well demarcated, but it showed expansion to the region from the alveolus to the buccal-side gingiva. The removed canine showed root resorption. The tumor measured 12 mm in diameter, and was encapsulated completely with connective tissue. The boundary between the tumor and the normal tissue was clear, and the tumor separated easily
Fig. 1: Dental radiograph showed unilocular radiolucent lesion approximately 10 mm in diameter, with resorption of the root of the maxillary right canine.

Fig. 2: The cross-section of the resected specimen. The cut surface was grayish white and a small hemorrhagic spot was observed in the central part. The tumor destroyed the maxillary buccal cortical bone.

Fig. 3: Histopathological findings of the tumor. (A,B) The tumor consisted of spindle cells with solid growth pattern and small nests. (C,D) Some of the tumor nests has small lumen and erythrocytes are observed. (E) Silver staining reveals cell cluster or aggregation of tumor cells. (F) Factor VII related antigen is positive for tumor cells. (Original magnification, A:×40, B,E:×200, C,D,F:×400)
from the surrounding bone. Cross sections of the dissected tissue were whitish-gray, and a small hemorrhagic spot was observed in the center (Fig. 2).

In order to prepare paraffin embedded sections for histopathologic study, the operation specimen was fixed in 10% formalin solution. The staining techniques adopted in this study included hematoxylin-eosin (HE) staining, periodic acid Shiff (PAS) staining, Alcian blue staining and silver staining. Labeled streptavidin biotin method was employed to perform immunological staining using antibodies to Factor VII related antigen, vimentin, S-100 protein, and alpha smooth muscle actin (DAKO, Tokyo, JAPAN). After performing double fixation in glutaraldehyde and osmic acid solution, we adopted regular techniques to process a part of the operation specimen into resin-embedded blocks for electronmicroscopy. Ultra-thin sections were prepared for uranyl acetate and lead citrate stainings.

**Pathological findings**

Microscopically, the tumor was composed of solid cell sheets, crowded solid nests with or without vascular formation, and cords of cells in a loose myxoid stroma. In solid cellular areas, spindle cells proliferated and vessels were formed by spindle cells, vacuolated or epithelioid endothelial cells with round or oval nuclei. There was a network of reticulin fibers, which divided the tumor tissue into small cell clusters or aggregations (Figs. 3A-E). The tumor cells had no PAS-positive or Alcian blue-positive material in their cytoplasm, but the myxoid stroma stained intensively with Alcian blue.

An immunohistochemical study with the antibodies to vimentin, Factor VII related antigen demonstrated that endothelial cells lining vascular channels, and vacuolated or epithelioid endothelial cells were positive for all these substances (Fig. 3F). These findings are suggestive of a tumor originating in vascular endothelial cells.

Ultrastructurally, the nuclei of the tumor cells were round, oval or occasionally irregular in shape, with infrequent nucleoli. The cytoplasm contained moderately-developed rough endoplasmic reticulum as well as numerous cytoplasmic granules and mitochondria. The granules contained vesicular bodies, vacuoles, granular materials and myelin-like figures. Typical Wibel-Palade body was not observed. A basal lamina partly surrounded some tumor cells, and numerous micropinocytotic vesicles were found in some tumor cells. At the junction between neighboring cells, interdigitation and desmosome were often present (Figs. 4A, 4B).

Taken together with the histological, immunohistochemical and ultrastructural features, the tumor was diagnosed as epithelioid hemangioendothelioma.

The patient's postoperative course was uneventful. Physical examination 9 years after resection revealed no evidence of recurrence.

**Discussion**

Many cases of epithelioid hemangioendothelioma have been reported since Weiss and Enzinger advocated a concept of this disease in 1982(1). It frequently occurs in soft tissue, bone, lung, and liver. However, the number of reported cases of epithelioid hemangioendothelioma developing in the head and neck is much smaller. The incidence of this disease in the oral cavity is so low that only 10 cases have been reported so far (2-9).

Ellis et al.(2) insisted on the need to discriminate epithelioid hemangioendothelioma from epithelioid hemangioma and Kimura's disease, and they mentioned the
If we can successfully confirm the findings characteristic of this disease, such as solid or funicular proliferation pattern of the epithelioid cells, cytoplasmic vacuoles and hyaloid or myxochondroid stroma, making a definite diagnosis should be relatively easy. In this case glomus tumor and meningioma have similar histologic characteristics and are worth being considered in making a diagnosis, although the latter disease may be excluded because of its location. We can easily distinguish epithelioid hemangioendothelioma from glomus tumor and meningioma by carrying out immunological staining using anti S-100 protein antibody or by confirming the absence of the characteristics of smooth muscle filament with electron microscope.

In the present case, electron microscopy disclosed no definite Weibel-Palade body, which indicates the known difficulty in detecting Weibel-Palade body in the tumor-ous vascular endothelial cells (5, 6). In the present study, the case proved to be a tumor derived from vascular endothelial cells because of the existence of basement membrane around the tumor cells and micropinocytotic vesicles characteristic of vascular endothelial cells and the positive findings of Factor VII related antigen in immunological staining.

The specific finding in this case was the existence of cytoplasmic myelin-like structure revealed by electron microscopy. Myelin-like structure is generally observed as a result of lipid accumulation in metabolic disease. The patient's past history of mild hyperlipidemia, however, bears no direct relation to the existence of myelin-like structure. Furthermore, there is no definite evidence linking myelin-like structure to the development of epithelioid hemangioendothelioma, and why such structure exists is not clearly explained.

Enzinger et al. (1) insisted on the need to recognize the histopathologic characteristics of this type of tumor and to distinguish it from tumor metastasized from other lesions, especially adenocarcinoma. The tumor cells observed in epithelioid hemangioendothelioma have abundant acidophilic cytoplasm and show various dyskaryotic levels. Generally, no definite alveolar structures are formed and a few scattered tumor cell groups, which are unrelated to the surrounding vessels, are commonly visualized.

Epithelioid hemangioendothelioma is clinically and histopathologically classified as a tumor of low grade malignancy (1, 2, 5, 7, 10). According to Enzinger et al. (1), 6 of the 41 reported cases of this disease developing in soft tissues showed metastases, and this tumor ranked in malignancy between hemangioma and angiosarcoma. Ellis et al. (2) reported 12 cases of epithelioid hemangioendothelioma developing in the head and neck, and they recognized metastases to related lymph nodes in two cases that occurred in the neck and submental areas.

The 11 cases of this disease developing in the oral cavity (Table 1, including the present case) (2-9) showed neither metastasis nor recurrence. Our patient has been doing well for 9 years postoperatively without showing any recurrence or metastasis. The histopathologic findings and the malignancy of intraoral epithelioid hemangioendothelioma seem to be slightly different from those obtained in the cases of this disease developing in various sites other than the oral cavity. Intraoral epithelioid hemangioendothelioma consists largely of spindle cells. Atypism was rarely observed, and tumor cells seemed to form the alveolar structure. Such differences are possi-

<table>
<thead>
<tr>
<th>No.</th>
<th>Age(years)</th>
<th>Site</th>
<th>Treatment</th>
<th>Outcome</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13/F</td>
<td>gingiva of maxilla</td>
<td>Excision</td>
<td>After 4 years, hemangiomia occurred discretely</td>
<td>Ellis et al. (2)</td>
</tr>
<tr>
<td>2</td>
<td>4/F</td>
<td>gingiva of mandible</td>
<td>Excision</td>
<td>no follow up</td>
<td>Ellis et al. (2)</td>
</tr>
<tr>
<td>3</td>
<td>4/M</td>
<td>gingiva of mandible</td>
<td>Excisional biopsy</td>
<td>9 months, free of disease</td>
<td>Aragio et al. (3)</td>
</tr>
<tr>
<td>4</td>
<td>25/F</td>
<td>the junction of the soft and hard palate</td>
<td>Excisional biopsy</td>
<td>21 months, free of disease</td>
<td>Moran et al. (4)</td>
</tr>
<tr>
<td>5</td>
<td>45/M</td>
<td>gingiva of maxilla</td>
<td>Wide enblock resection</td>
<td>12 months, free of disease</td>
<td>Marragi et al. (5)</td>
</tr>
<tr>
<td>6</td>
<td>36/F</td>
<td>tongue</td>
<td>Excisional biopsy</td>
<td>17 months, free of disease</td>
<td>Marragi et al. (5)</td>
</tr>
<tr>
<td>7</td>
<td>7/F</td>
<td>gingiva of mandible</td>
<td>Enblock resection</td>
<td>52 months, free of disease</td>
<td>Flatz et al. (6)</td>
</tr>
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<td>8</td>
<td>7/F</td>
<td>mandible</td>
<td>Enblock resection</td>
<td>6 years, free of disease</td>
<td>Hamakawa et al. (7)</td>
</tr>
<tr>
<td>9</td>
<td>18/F</td>
<td>buccal mucosa</td>
<td>Wide excision</td>
<td>2 years, free of disease</td>
<td>Orsini et al. (8)</td>
</tr>
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<td>10</td>
<td>44/M</td>
<td>mandible</td>
<td>Enblock resection</td>
<td>40 months, free of disease</td>
<td>Nosaka et al. (9)</td>
</tr>
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<td>11</td>
<td>50/F</td>
<td>maxilla</td>
<td>Enblock resection</td>
<td>9 years, free of disease</td>
<td>present case</td>
</tr>
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</table>
bly based on the difference in the background of the development site (soft tissue, lung, liver, and intramaxillary parts).

Recently, Weiss et al.(10) advocated using the term “malignant epithelioid hemangioendothelioma” because epithelioid hemangioendothelioma has a high frequency of metastasis or an aggressive course displaying atypical features. Accordingly, we propose adopting the term “benign epithelioid hemangioendothelioma” for the intraoral cases.

The results obtained in the present study can help make a differential diagnosis of epithelioid hemangioendothelioma in the oral cavity as compared with other sites. It is necessary, however, for us to further examine the malignancy of intraoral epithelioid hemangioendothelioma along with its histologic differences.

References

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