A Case Report of Metastatic Carcinoma of the Gingiva

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A 67-year-old male was admitted to the Clinic of Oral and Maxillofacial Surgery II, Dental Hospital, Matsumoto Dental University, with a chief complaint of a painless swelling of the mandibular gingiva. Under a clinical diagnosis of an epulis of the gingiva, surgical excision was performed. The material was then diagnosed histopathologically as a poorly differentiated carcinoma. After reporting the biopsy results, we obtained important information that the patient had been tentatively diagnosed as having hepatocellular carcinoma by clinical examination. Therefore, the tumor was further examined immunohistochemically. The immunohistochemical examination used some useful markers for the diagnosis of hepatocellular carcinoma, i.e., CEA, EMA, α1-ACT, α1-AT, albumin, AFP, and CK 7, 8, 18, 19. The examination results were positive for many immunohistochemical profiles of hepatocellular carcinoma, although there was no so-called “hepatoid pattern” in the histopathological observation. Finally the gingival carcinoma was considered to be a poorly differentiated metastatic carcinoma that had originated from a “hepatocellular carcinoma”, as judged from our histopathological and immunohistochemical examinations. This was determined although the histopathological observation of the primary lesion in the liver was not carried out. No additional treatment was undertaken as according to the wishes of the family.

Key words: metastatic carcinoma, gingiva, hepatocellular carcinoma, immunohistochemistry

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Introduction
Metastatic neoplasms are rare in the oral and maxillofacial region. It is well known that the metastatic neoplasms in the oral and maxillofacial region account for only 1% or slightly more of all malignant neoplasms (1). The mandible is a commonly involved site, and the lesions are usually located in the premolar-molar region of the mandible. About 70% of the metastatic neoplasms reported occur in the fourth to seventh decades. Lung, breast, and kidney are the most common primary malignant neoplasms involved.

Hepatocellular carcinoma (HCC) is a most common malignant neoplasm. It does show a comparatively high incidence of metastasis, most frequently to areas within the liver, regional lymph nodes, or the lungs. Metastases to the oral region are very rare in the literature (2). According to published manuscripts, most cases of metastatic HCC of oral regions show typical histopathological patterns of HCC with a "so-called hepatoid pattern". We experienced an additional case of possible metastatic HCC of the gingiva, presenting no histopathological features, i.e., the so-called "hepatoid pattern". The following case report deals with the histopathological features, especially with immunohistochemical profiles.

Case Report
On April 16, 1997, a 67-year-old male was admitted to the Department of Oral and Maxillofacial Surgery II, with the chief complaint of the painless swelling of the left gingiva of the mandible. About 2 weeks earlier he had noticed a painless swelling on his gingiva. The swelling gradually enlarged, and so he was referred to a dental clinician, who in turn referred him to our Dental Hospital. Intraoral examination revealed that a soft tumor (25×27 mm in size) was present in the gingiva of his left mandible (Fig. 1). X-ray examination showed no

Fig. 1: Intraoral appearance showing a gingival tumor of the mandible
Fig. 2: Low-magnification view of the histopathological specimen (H-E: ×7.5)
Fig. 3: Granulomatous tissue with abundant capillaries (H-E: ×30)
Fig. 4: Neoplastic proliferating cell nests (H-E: ×30)
Fig. 5: Canalicular or trabecular pattern (H-E: ×100)
Fig. 6: Parenchymal cell nests and stromal tissue (H-E: ×150)
Fig. 7: Proliferating tumor cells showing evidence of strong cellular aryepia (H-E: ×300)
evidence of tumor resorption, but there were signs of resorption due to a chronic marginal periodontitis. Under a clinical diagnosis of an epulis, surgical excision of the tumor mass was performed on May 13, 1997. The surgical material had a glossy, reddish-brown surface and was 27×22 mm in size. The cut surface showed many lobular nodules.

The excised material was fixed in 10% neutral-buffered formalin solution and was embedded in paraffin. Sections were stained with hematoxylin-eosin (H-E). Histopathologically, the tumor mass was composed of capillary-rich fibrous granulation tissue covered with squamous epithelium, or in some areas with a fibrinous membrane showing ulceration (Fig. 2). The tumor mass was composed of fibro-granulomatous connective tissue with abundant capillaries, suggesting the diagnosis of an epulis granulomatosa (Fig. 3). In the mass, some solid tumor cell nests contained many proliferating cells containing round nuclei, granular and/or clear cytoplasm. The proliferating cells of the nests were often connected or surrounded by endothelial cells as stromal components (Figs. 4). Furthermore, some trabecular and canalicual patterns of proliferation were detected (Figs. 5). These proliferating tumor cells showed evidence of strong cellular atypia, i.e., polymorphism, hyperchromasia, and mitotic figures. (Figs. 6, 7). However there were no characteristic histopathological features observed in the H-E-stained specimens. Therefore, histopathologically, the resected material was diagnosed as a poorly differentiated carcinoma.

After reporting the biopsy results, we obtained information that the patient had been tentatively diagnosed as having hepatocellular carcinoma by clinical examination. His past history, in brief, was as follows: In December 1995, under the clinical diagnosis of alcoholic liver cirrhosis, a CT examination was performed at a general hospital. The result revealed a solid tumoral mass in the S8 area of the liver. The tumoral marker “PIVKAIL” was slightly elevated according to laboratory results. These clinical data strongly suggested “hepatocellular carcinoma”. Therefore, the attending physician recommended further examination and treatment. But the patient had been received no additional treatment, which was the wish of his family. He also had a ulceration of the stomach (a scar in his present condition) and multiple infarcts of the brain in his medical history.

According to the brief medical history mentioned above, the neoplasm was strongly suggested to be a metastatic hepatocellular carcinoma. Therefore, we performed careful histopathological examination of the neoplasm. However here were no more specific features, especially no so-called “hepatoid pattern”. Therefore we decided to conduct an immunohistochemical examination using antibodies against the following antigenic markers with source and dilution indicated: carcinoma-embryonic antigen (CEA), Dako, 1:300; epithelial membrane antigen (EMA), Dako 1:100, alpha-fetoprotein (AFP), Dako, 1:100; albumin, Dako, 1:200; alpha-1-antitrypsin (α-1-AT), Dako, 1:50; alpha-1-antichymotrypsin (α-1-ACT), Dako, 1:100; cytokeratin 8 (CK8), Dako, 1:5; cytokeratin 18 (CK18), Dako, 1:5; cytokeratin 7 (CK7), Dako, 1:5; and cytokeratin 19 (CK19), Dako, 1:5. Sections from paraffin blocks were mounted on silanized slides (Dako), and immunohistochemistry was performed using Universal LSAB Kit K0680 (Dako), with or without enzyme pretreatment with 0.05% trypsin (10 min.) or pretreatment by microwaving in a microwave oven with 6 M urea (5 min.×2 times) according to the method of Cattoretti et al. (3) or Harten et al.(4).

Immunohistochemically, almost all of the proliferating cells were negative for CEA, but there were a few positive cells in the large nests (Fig. 8); although strong positive staining was detected in the cytoplasm of neoplastic cells showing the canalicual pattern (Fig. 9). The EMA staining features showed nearly the same pattern; the positive staining was weak, especially in the cells of the canalicual pattern (Fig. 10). Alpha-fetoprotein (AFP), as a most useful marker in the differential diagnosis of HCC, was weakly positive only in some nests (Fig. 11), although it was absent in most of the tumor tissue. The immunohistochemical reaction for albumin was strongly positive in the cytoplasm of all of the neoplastic cells (Fig. 12). Furthermore, the immunoreactivities for α-1-AT and α-1-ACT were strong in most proliferating tumor cells (Fig. 13). As for the profiles of cytokeratins, CK 8 and 18 positive stainings were observed in the cells, especially in the periphery of the tumor cells (Fig. 14). Furthermore, CK 7 showed positive reactions (Fig. 15), although CK 19 showed weakly positive ones. The immunohistochemical examination results mentioned above are summarized in Table 1.

On June 14, 1997, the patient died of cerebral infarct. No autopsy was performed on him because after release from our Hospital, the patient was being consulted by his general physician.

Table 1: Results of immunohistochemistry

<table>
<thead>
<tr>
<th>Immunoreactivity</th>
<th>Remarks</th>
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<tbody>
<tr>
<td>CEA</td>
<td>negative: most of parts positive: canalicual pattern</td>
</tr>
<tr>
<td>EMA</td>
<td>weakly positive: canalicual pattern</td>
</tr>
<tr>
<td>AFP</td>
<td>negative: most of parts weakly positive: a few nests</td>
</tr>
<tr>
<td>α-1-AT</td>
<td>positive</td>
</tr>
<tr>
<td>α-1-AT</td>
<td>positive</td>
</tr>
<tr>
<td>Albumin</td>
<td>positive</td>
</tr>
<tr>
<td>CK-7</td>
<td>positive</td>
</tr>
<tr>
<td>CK-8</td>
<td>positive</td>
</tr>
<tr>
<td>CK-18</td>
<td>positive</td>
</tr>
<tr>
<td>CK-19</td>
<td>weakly positive</td>
</tr>
</tbody>
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*Pretreated by enzyme with 0.05% trypsin
**Pretreated by microwave-oven with 6-M-urea
Fig. 8: Some immunopositive reactions appearing in only a few cells in the large nests (CEA×150)
Fig. 9: Nearly all of the tumor cells with the canalicular pattern are immunopositive for CEA (×150)
Fig. 10: Some immunopositive cells showing the canalicular pattern (EMA×150)
Fig. 11: Weakly positive immunoreactivity (AFP×150)
Fig. 12: Strongly positive immunoreaction for albumin (×150)
Fig. 13: Cytoplasmic immunoreactivity presenting positive for α-1-AT (×150)
Fig. 14: Positive immuno-profile for hepatocyte cytokeratins 8 and 18 (CK8:×150)
Fig. 15: Positive immunoreaction for cytokeratin 7 (×150)
Discussion

Hepatocellular carcinoma (HCC) is one of the most common malignant neoplasms. Extrahepatic metastases are common, and the common sites are the lungs, breast, and kidney. Some cases of intraoral metastatic HCC were reported in the Japanese (5,6) and English (7-10) literature. The diagnosis of oral metastasis before recognition of the primary neoplasm is not so rare. Ashar et al. (1997) reviewed the collected cases of metastatic HCC in the oral regions, and found that in 19 out of 27 cases diagnosis of oral metastasis preceded that of the primary lesion (1). Their literature review revealed the mandibular angle and premolar region to be the most common metastatic sites. These sites may be related to the branching of the blood vessels within the bone or to local slowing of the blood flow, both of which would favor the fallout of neoplastic cells. Regarding our present case, the neoplasm appeared in a capillary-rich granulomatous epulis of the mandible. Therefore, we presume that the metastatic carcinoma may have spread to the gingiva from these vessels, although the histopathological examination of the primary lesion in the liver was not performed.

The histopathological examination showed that the neoplasm in the "epulis" was a poorly differentiated carcinoma, according to the above-mentioned findings. The immunohistochemical examination of some useful markers for the diagnosis of HCC, i.e., CEA, EMA, α-1-ACT, α-1-AT, albumin, AFP, and CK 7, 8, 18, 19, was undertaken to assess the possibility of a liver origin for this neoplasm. Strongly positive staining of cells in a canalicular pattern and negative results for most tumor cell nests for CEA, and an EMA reaction showing nearly the same pattern may suggest the tumor to have been a poorly differentiated carcinoma. As false-positive AFP staining was found only in some nests and all of the neoplastic cytoplasm was positive for albumin, the neoplasm is strongly suggested to be a metastatic HCC (1, 10). However, other neoplasms such as adenocarcinomas of the stomach and pancreas may demonstrate this antigen. Furthermore, the positive stainings indicating immunoreactivity for α-1-AT and α-1-ACT also are suggestive of HCC, although α-1-AT and α-1-ACT are quite non-specific for HCC.

According to the profiles of cytokeratins, CK 7, 8, 18, 19 are markers of simple epithelium; in particular CK 8 and 18 are found in the normal hepatocyte CK profile (11). However, a few reports indicated CK 8 and 18 to be present in some poorly differentiated neoplasms. In this present case, CK 8 and 18 positive stainings were observed in the cells. The CK profile also strongly suggests the tumor to be a metastatic HCC. Furthermore, the positive staining of CK 7 may suggest a little differentiation to the bile duct epithelium, although CK 19 showed weakly positive.

In conclusion, we consider that the tumor in the "epulis" may be a poorly differentiated metastatic carcinoma from a "hepatocellular carcinoma", judging from our histopathological and immunohistochemical examinations.

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References


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