Oral presentation of malignant mesothelioma

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We report a case of metastatic mesothelioma presenting as an oral metastasis in a 46-year-old patient. The patient presented with 2 polypoid lesions that appeared to be benign on the dorsum of the tongue. Excisional biopsy showed the presence of metastatic carcinoma that on further investigation proved to be mesothelioma.

The initial presentation of mesothelioma as an oral metastasis is not previously reported. This article highlights the importance of biopsy and histopathological diagnosis in presumed benign lesions and the role of the general dental practitioner in screening for oral neoplasms. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011; 111:e21-e26)

Any malignancy presenting in an unusual manner poses a diagnostic challenge. Although primary oral cancer is relatively common, metastases to the oral region are uncommon.\(^1,2\) Even when so diagnosed, it may be difficult to correctly identify the tumor’s origin.\(^2,3\) This situation may be particularly complex when a tumor, not classically associated with metastasis, is considered. This article highlights the case of a woman who presented with tongue metastases from malignant epithelioid mesothelioma. This pattern of presentation is not previously reported.

CLINICAL PRESENTATION

A 46-year-old, otherwise fit and well female patient, presented to her dental practitioner for a routine dental examination. The dentist noted a 10 × 5-mm firm nodular swelling on the left posterior dorsum of the tongue. The patient had been aware of the lump for 8 months but it had not caused any pain or discomfort. The dentist referred the patient to the Department of Oral Medicine at the Charles Clifford Dental Hospital for investigation and management. In the 2 weeks before being seen in the oral medicine clinic, a similar but smaller 3 × 3-mm lesion had developed 2.5 cm from the first lesion on the right dorso-lateral aspect of the tongue. She had a 29-pack-year smoking history but had stopped smoking 2 months earlier after a brief chest infection. Other than that, she had no significant past medical history and complained only of mild shortness of breath on marked exertion. She took no regular medications.

Extroral examination was unremarkable. Oral examination revealed 2 polypoid lesions on the dorsal surface of her tongue. One was a 10 mm diameter × 5 mm tall, firm, rounded, pink swelling on the left posterior dorsum of the tongue with a surface of normal lingual mucosa including filiform like papillae. The other lesion was very similar in appearance but smaller (3 mm diameter × 3 mm tall) on the right dorso-lateral aspect of the tongue. The macroscopic appearance was consistent with benign fibroepithelial polyps and be-
cause they were not regarded as anything out of the ordinary no clinical photos were taken.

DIFFERENTIAL DIAGNOSIS

The clinical appearance was most suggestive of a fibroepithelial polyp but within the differential diagnosis were other benign tumors of the oral mucosa including giant cell fibroma, lipoma, myxoma, neurofibroma, schwannoma, leiomyoma, and granular cell tumor, and because of the papillary surface, papilloma or verruciform xanthoma had to be considered although the papillae were closely similar to, and more suggestive of, the normal filiform papillae of the dorsal lingual mucosa. The lesions had no features to suggest a malignant process, including ulceration, induration, fixation to the deeper tissues, or associated lymphadenopathy. Furthermore, the dorsum of the tongue is a relatively uncommon site for presentation of malignant lesions. Therefore, excisional biopsy of the lesions was arranged to remove them for treatment purposes and to confirm the diagnosis histologically.

DIAGNOSIS

At low power (Fig. 1, A) the histology was superficially similar to that of a fibroepithelial polyp, but at high power (Fig. 1, B) histological examination revealed unremarkable stratified squamous epithelial tissue of the tongue with widespread infiltration of the underlying connective tissue by a mildly pleomorphic epithelioid neoplasm. The tumor was composed of bland epithelioid/cuboidal cells arranged in solid sheets and with some glandular-like areas. Eosinophilic cytoplasm and well-defined boundaries were noted. Minimal nuclear pleomorphism was present but scattered mitoses were seen. Immunohistochemistry using CK7, cytokeratin CAM5.2, CK19, AE1AE3, CA125, and EMA was positive with a moderate proliferation fraction of 20% (MIB1 immunohistology). No staining was seen with CD31, CD34, bcl2, GCDFP15, alpha actin, CK20, S100 protein, CDX2, CEA, ER, and TTF1. Although a primary head and neck adenocarcinoma could not be definitively excluded, it was felt that this was most likely to be a metastatic adenocarcinoma from outside the head and neck. The CA125 staining suggested that ovary and pancreas be excluded as possible primary sites.

Chest radiograph (Fig. 2, A), revealed a left-sided pleural effusion, pleural thickening, and mediastinal lymphadenopathy. Computed tomography (CT) scan of the chest, abdomen, and pelvis revealed nodular pleural thickening throughout the left hemithorax (Fig. 2, B), with mediastinal lymphadenopathy. No intrapulmonary lesions were identified although the left lower lobe was compressed by the pleural tumor, and a basal left pleural effusion was noted. No abnormalities were seen in the abdomen or pelvis. Careful clinical examination and a magnetic resonance imaging scan revealed no evidence of a head and neck primary. Breast examination and mammography were also normal. Serum tumor markers (CEA [carcinoembryonic antigen], CA19-9, and CA125) were not elevated. The pleural effusion, pleural thickening, and mediastinal lymphadenopathy seen on chest radiograph and CT thorax were in keeping with mesothelioma or a primary lung carcinoma with diffuse pleural (mesothelioma-like) spread.

An urgent referral was made to the thoracic oncology multidisciplinary team (MDT) and review of the original histology was undertaken. Further immunohistochemical studies showed strong positivity with calretinin (Fig. 3, A), CK5/6 (Fig. 3, B), HBME1, WT1, pan-keratin, and EMA antisera. Stains for carcinomaous antigens (BerEp4, AUA1) were negative. The appearances were judged to be in keeping with a metastatic mesothelioma of epithelioid, pseudo-glandular form.

MANAGEMENT

The diagnosis of mesothelioma raised questions as to whether the patient had had previous asbestos expo-
sure, as most mesotheliomas in the United Kingdom have such exposure. On further questioning, the patient could not recall any such event. However, from about the age of 15 she had worked for a period of about 8 years as a cleaner in old hospital and school buildings that may have contained asbestos. She gave no history of any household contacts with occupational exposure to asbestos.

Following MDT discussion, this patient commenced cisplatin and pemetrexed chemotherapy with palliative intent. She had a good radiological and symptomatic response to chemotherapy but approximately 6 months after completing treatment she developed a subcutaneous metastasis over her right posterior chest wall. This area received a single fraction of palliative radiotherapy with some flattening of the mass. Shortly after, she developed 3 small tongue lesions. The largest of these was in exactly the same position as the original lesion and similar in appearance (Fig. 4) but smaller (3-mm diameter) and with a smooth surface. All 3 of the tongue lesions were excised and the pathology again confirmed mesothelioma. She will soon be commencing retreatment with cisplatin and pemetrexed.

**DISCUSSION**

More than 90% of malignant oral tumors are primary squamous cell carcinomas. Metastases in the oral region are uncommon and represent only 1% of all malignant oral lesions. These lesions therefore often present a diagnostic challenge, as it must first be recognized that the lesion may originate from somewhere outside the oral region. Second, the site of origin of the primary lesion must be identified so that further investigation and treatment can be targeted appropriately. Interestingly, in 23% of patients, metastases in the oral region are the first sign of malignant disease at a distant
In the oral region, metastases to the jaw bones are more commonly reported than metastases to the oral soft tissues with a ratio of approximately 2:1. In the jaw bones, metastases are most often found in the molar areas. It has been suggested that hemopoietically active areas in the mandible may attract malignant cells. Among the oral soft tissues, the most commonly affected site of metastases is the attached gingivae (54% of all oral soft tissue metastases). One possible explanation might be that the rich capillary network in chronically inflamed gingivae trap malignant cells and the fragmented basement membranes of proliferating capillaries allow easier penetration by malignant cells than in more mature blood vessels. The second most common site of metastases to the oral soft tissues is the tongue (22.5% of cases), with the mobile tongue being more commonly involved than the nonmobile base or posterior border. The tongue is well vascularized and it has been postulated that this may provide a good setting for malignant cells.

Mesothelioma is a relatively uncommon disease with about 2000 new cases being diagnosed each year in the United Kingdom. The male:female ratio is 5.1:1.0. The disease most often involves the serosal surface of the pleura and less often involves the peritoneum. Mesothelioma is strongly associated with exposure to asbestos with a latent period of 20 to 40 years between exposure and development of the disease. It is important to note that exposure of occupants in buildings with asbestos-containing materials is generally not associated with increased asbestos fiber burden in the lung or an increase in mesothelioma; however, incidence studies of household contacts of asbestos workers who develop mesothelioma have shown that these patients often have pulmonary asbestos concentrations similar to occupationally exposed individuals. Mesothelioma classically shows either a sarcomatoid or epithelioid morphology, but mixed patterns exist often causing a delay in diagnosis. The most common presenting symptoms are shortness of breath or chest pain.

Although traditionally considered a localized disease, with distant metastases being an uncommon event, the potential for metastatic spread from mesothelioma is increasingly recognized. Indeed, the use of positron emission tomography–CT (PET-CT) scanning has demonstrated that between 4% and 24% of patients presenting with mesothelioma have metastatic disease not detected by routine clinical and conventional radiological evaluation.

The histological diagnosis of mesothelioma may be difficult by virtue of the histological pleomorphism these tumors exhibit and the limitations of the antibody tests available. There are more than 200 markers available that show variable specificity and sensitivity for mesothelioma. Conventionally, most pathology confirmation uses a panel of antisera. The original immunohistochemistry in this case focused on the lesion being a likely carcinoma, with the cytokeratin panel looking at the possibilities of oral, odontogenic, gastrointestinal, and female genital tract neoplasia. This was not unreasonable, given the site of the lesion, and age and sex of the patient. The possibility of alternate epithelial cell neoplasia (CD31/34 = vascular, GCDFP15 = skin adnexal/breast, actin = muscle, CK20 = large bowel, S100 protein = neural/melanocytic, CDX2 = bowel not otherwise specified (NOS), ER = breast, TTF1 = thyroid/lung) clearly gave no positive identification of the source of primary tumor. When, as a result of the imaging, mesothelioma entered the differential diagnosis, antibodies often positive with mesothelioma (calretinin, HBME1, WT1) were tested with positive results. By contrast, stains for carcinoma were negative, using BerEp4 and AU1 antisera. Thus, a final diagnosis of mesothelioma was reached.
Electron microscopy can show some mesothelial features (long slender microvilli) in well-differentiated epithelioid cases, but these features are not well developed in spindle mesotheliomas and have largely been replaced by immunohistology. However, ultrastructural features seen by electron microscopy that are typical of mesothelioma include cytoplasmic tonofilaments and long, sinuous, branching microvilli. In contrast, the microvilli of adenocarcinomas are relatively short, wide, and straight.

Lingual metastases from mesothelioma have previously been described, although these are a rare event. An English literature review revealed only 5 reported cases of metastases from mesothelioma to the tongue, all of which occurred in patients with a previous diagnosis of mesothelioma (Table I).

This case describes a very unusual presentation of mesothelioma with tongue metastases. The correct diagnosis allows the most appropriate chemotherapy to be administered to this young patient. This case highlights the importance of biopsy and histopathological diagnosis of presumed benign lesions and demonstrates the need to consider many sources of metastatic disease to the oral tissues. The diagnosis was facilitated by using a range of imaging modalities and serum antibodies. Metastatic mesothelioma should be considered when a metastatic epithelioid neoplasm is noted on biopsy because of its rising prevalence and the various histological patterns it can assume. The gap between asbestos exposure and mesothelioma induction must be appreciated. Furthermore, the role of the general dental practitioner in screening for oral neoplasms is demonstrated in this case.

**Table I.** Reported cases of tongue metastases in mesothelioma

<table>
<thead>
<tr>
<th>Age of patient at time of lingual metastasis, mo</th>
<th>Site of primary mesothelioma</th>
<th>Time from diagnosis to development of lingual metastasis, mo</th>
<th>Site of metastasis on tongue</th>
<th>No. of lingual lesions</th>
<th>Reference no.</th>
</tr>
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<tbody>
<tr>
<td>1 75 Male</td>
<td>Pleural</td>
<td>24</td>
<td>Right lateral</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>2 53 Male</td>
<td>Pleural</td>
<td>24</td>
<td>Right lateral</td>
<td>1</td>
<td>21</td>
</tr>
<tr>
<td>3 71 Male</td>
<td>Pleural</td>
<td>14</td>
<td>Right lateral</td>
<td>1</td>
<td>34</td>
</tr>
<tr>
<td>4 70 Male</td>
<td>Pleural</td>
<td>9</td>
<td>Left lateral</td>
<td>1</td>
<td>35</td>
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<tr>
<td>5 68 Male</td>
<td>Pleural</td>
<td>5</td>
<td>Anterior central</td>
<td>1</td>
<td>36</td>
</tr>
<tr>
<td>6 46 Female</td>
<td>Presenting feature</td>
<td></td>
<td>Left and right dorsum</td>
<td>2</td>
<td>Current report</td>
</tr>
</tbody>
</table>

**REFERENCES**

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