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CASE REPORT

Simultaneous tongue metastasis from malignant pleural mesothelioma: Case report and literature review

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Abstract

Malignant pleural mesothelioma (MPM) is a rare neoplasm of the serosal membranes. MPM usually manifests as local invasion, rarely with distant haematogenous metastases in different organs. Few cases of tongue metastasis have been documented. Here, we report the case of a 68-year-old man diagnosed with malignant pleural epithelioid mesothelioma together with a simultaneous tongue lesion, which was found to be metastatic malignant mesothelioma. Tongue metastasis from MPM is rare and the oral symptoms it causes could be an early sign of clinical manifestation. For patients with oral symptoms and a newly discovered tongue lesion, clinicians should be aware of the possibility of tongue metastasis and search for a primary malignancy.

Introduction

Malignant pleural mesothelioma (MPM) is a rare malignancy of the serosal membranes. In most cases, it is associated with asbestos exposure.[1] MPM usually manifests as local invasion, mostly in the lung, heart, pericardium, chest wall, and vertebrae. Distant metastasis of MPM is very uncommon. The reported metastatic sites include liver, lung, heart, brain, thyroid, adrenals, kidneys, pancreas, bone, soft tissue, skin and lymph nodes. Few cases of tongue metastasis have been previously documented. Here, we report a patient with MPM who presented with multiple unusual distant metastases, including tongue and muscle metastases.

Case report

A 68-year-old Chinese man came to our hospital with dyspnea and mild dysarthria which were found to be caused by a firm, submucosal mass in the posterior portion of his tongue. The patient had no history of any significant asbestos exposure in his working life. He reported a 20 pack-year history of tobacco use in the past but stated that he had not smoked cigarettes for 20 years. At the same time as the occurrence of the tongue lesion, multiple masses on the muscle of the bilateral upper limbs and jaw were also noted, but they were not biopsied. Chest computed tomography (CT) scan showed bilateral pleural effusion with pleural thickening (Fig 1) and CT scan of the oropharynx showed a low-density nodule in the right sublingual gland (Fig 2). Cytological examination of the pleural effusion fluid was highly suggestive of mesothelioma. A CT-guided biopsy of the mass in the left chest wall showed features consistent with malignant mesothelioma-epithelioid type (Fig 3a and b). Biopsy of the tongue lesion was consistent with the findings in the left chest wall (Fig 4a and b).

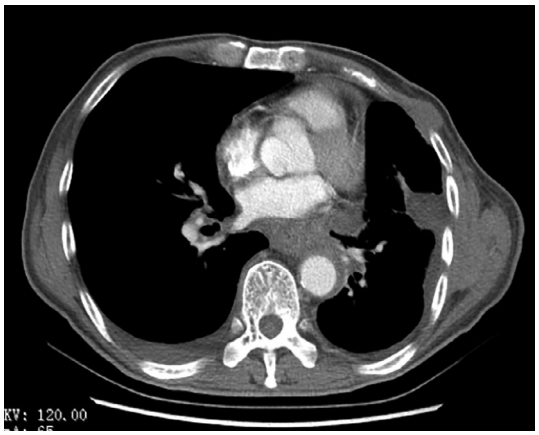

Figure 1 Computed tomography (CT) scan of the chest showed diffuse pleural thickening of the left hemithorax with mediastinal lymphadenopathy.

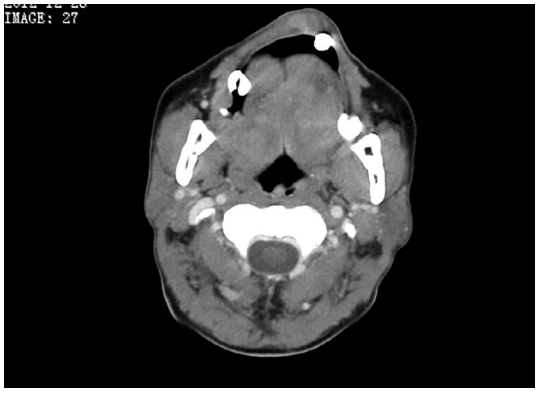

Figure 2 Computed tomography (CT) scan of the oropharynx showed low density nodule with fuzzy edges in the right sublingual gland, and the surface of the tongue was asymmetrical showing uneven enhancement.

Immunohistochemical stains were positive for calretinin (Figs 5a and 6a), cytokeratin 5/6, and WT-1 (Figs 5b and 6b) in both primary tumor and tongue metastasis, and negative for lung cancer markers TTF-1 and CEA. The patient achieved a partial response after five cycles of cisplatin and pemetrexed. However, he subsequently died of mesothelioma 17 months after the first manifestation on account of respiratory failure.

Discussion

Epidemiology and etiology

Most oral malignant tumors are primary squamous carcinoma and oral metastasis is uncommon. It is worth noting

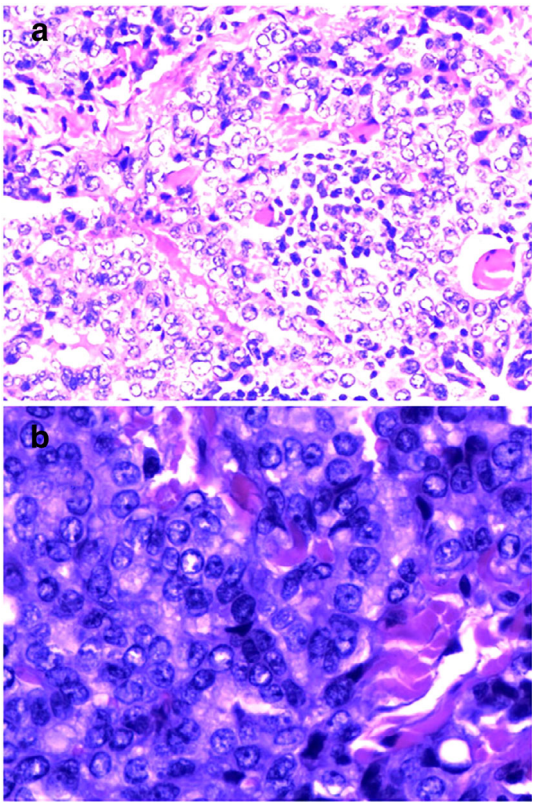

Figure 3 (**a**) Low power hematoxylin and eosin (H&E)-stained section showing cellular epithelioid infiltration (H&E, original magnification×10). (**b**) High power H&E section (H&E, original magnification×40).

that oral metastases could be the first sign of an undiscovered primary malignancy in 23% of patients. Major primary sites of oral metastases include lung, kidney, liver, and prostate for males, and breast, female genital organs, kidney, and colorectum for females. Jawbones, particularly the mandible, are more frequently affected than oral soft tissues (2:1). In oral soft tissues, the attached gingiva was the most commonly affected site (54%), followed by the tongue (22.5%). Tongue metastasis from mesothelioma has been reported to account for less than 3% of all oral metastatic malignancies.[2]

Most cases of mesothelioma are related to asbestos exposure. Asbestos consumption in China has increased steadily since the 1960s and is currently at half a million tonnes per year. Over a million people may be occupationally exposed, yet reliable disease statistics are unavailable.[3]

Histopathology

Histologically, mesothelioma is divided into epithelial, sarcomatous and mixed or biphasic subtypes. The epitheloid

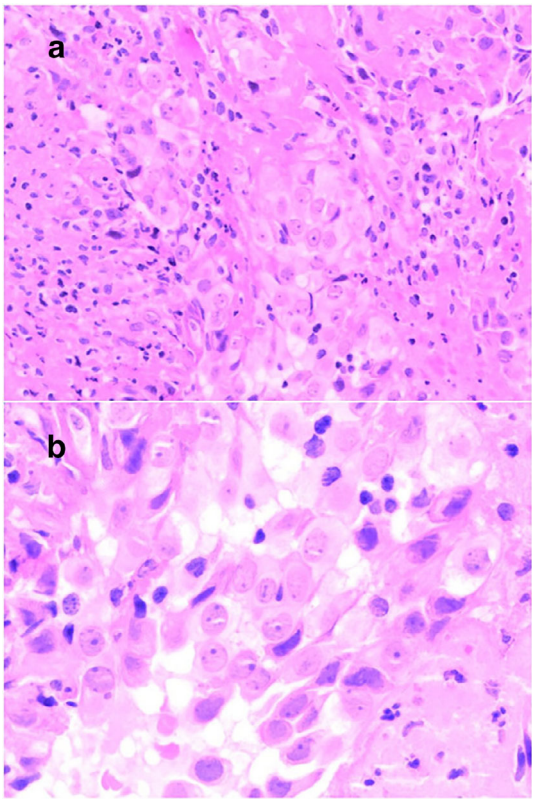

Figure 4 (**a**) Low power hematoxylin and eosin (H&E)-stained section of tongue metastasis (H&E, original magnification×10). (**b**) High power H&E section (H&E, original magnification×40).

type is the most commonly reported (60%), and the biphasic type of mesothelioma is only seen in 25% of patients. In several studies, patients with the epithelial type have been reported to have a significantly improved prognosis compared to those with the sarcomatous variant.[4] The relatively specific immunohistochemical reagents for mesothelioma include antibodies against calretinin,WT-1, cytokeratin 5/6 and vimentin.[5]

Treatment options

For local treatment, surgical resection could be performed on carefully selected patients, and pleurectomy/decortication (P/D) and extrapleural pneumonectomy (EPP) are the two main cytoreductive surgical procedures in MPM. An optimal treatment strategy remains controversial, mainly because it is disputed whether surgery improves long-term survival or whether survival benefit is best achieved with EPP or P/D within a multimodal regimen.[6–10] For early disease (confined to the pleural envelope, with no N2 lymph node involvement) with favorable histology (epithelioid) in low-risk patients (such as good performance status, absence of comorbidities), EPP may be the best

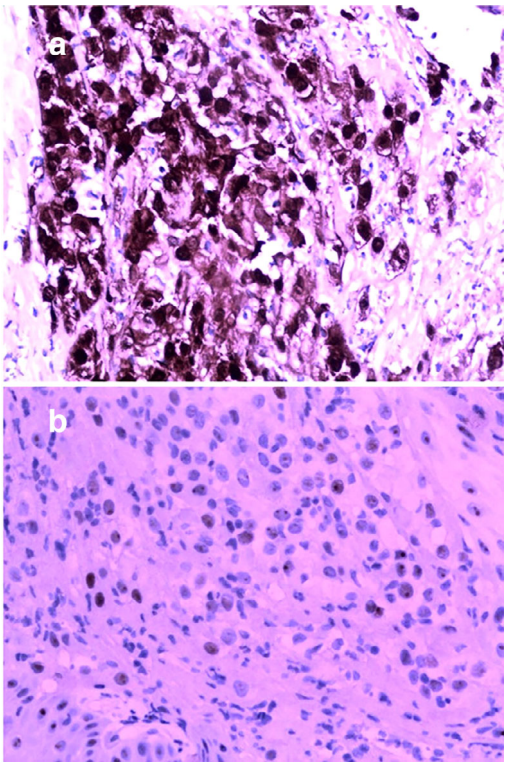

Figure 5 (**a**) Positive staining for calretinin in the primary tumor (original magnification×20). (**b**) Positive staining for WT-1 in the primary tumor (original magnification×20).

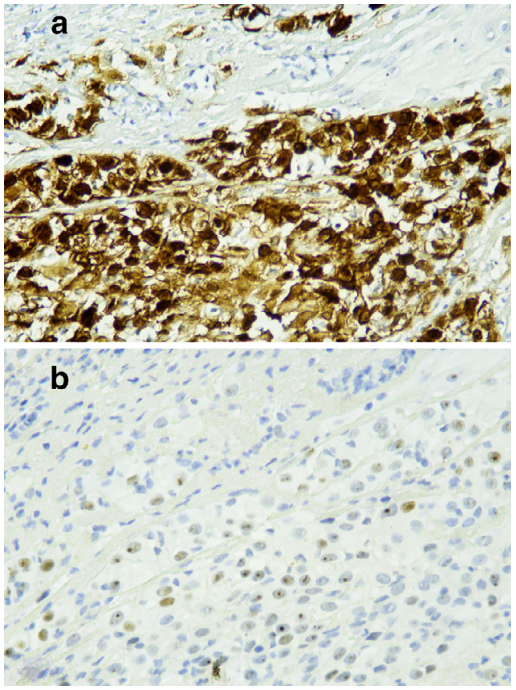

Figure 6 (**a**) Positive staining for calretinin in the tongue metastasis (original magnification×20). (**b**) Positive staining for WT-1 in tongue metastasis (original magnification×20).

Table 1 Summary of reported cases of malignant mesothelioma (MM) with tongue metastasis

Year of publication /Reference	Sex	Age at diagnosis	Asbestos exposure	Site and histopathology of primary MM	Site and histopathology of tongue metastasis	Time between diagnosis of primary MM and tongue metastasis	Treatment of tongue metastasis	Outcome after tongue metastasis
Kerpel & Freedman, 1993[29]	M	73 years	NM	Pleural/epithelioid type	2 cm firm submucosal swelling on the right ventral surface of the tongue/ epithelioid type	2 years	Adriamycin	Died of heart failure six months after tongue metastasis
Piatelli *et al.* 1999[30]	M	52 years	NM	Pleural/epithelioid type	Lesion on lateral tongue/ epithelioid type	2 years	Excision	Lost to follow-up
Zanconati *et al.* 2003[31]	M	71 years	NM	Pleural/epithelioid type	Bleeding and ulcerated nodular consolidation on the right dorsal lateral of tongue/ epithelioid type	14 months	Excision	Died three months after tongue metastasis
Tho & O'Rourke 2005[32]	M	70 years	+	Pleural/biphasic type	2 cm × 1 cm lesion on the left lateral tongue/biphasic type	9 months	No treatment	NM
Higginson *et al.* 2007[33]	M	69 years	NM	Pleural/epithelioid type	2.2 cm × 0.9 cm submucosal mass in muscle of the anterior tongue/ epithelioid type	5 months	Radiotherapy, 50 Gy in 20 fractions	Pleural and gluteal masses progressed after 26 months from the first diagnosis, but tongue mass remained stable
Hashitani *et al.* 2009[34]	F	59 years	+	Pleural/epithelioid type	0.5 cm × 0.5 cm nodule on the dorsal tongue/ epithelioid type	3 years	Excision	Died with multiple metastases one year later
Kirke *et al.* 2010[35]	M	71 years	+	Pleural/NM	3 cm right floor of mouth lesion with tongue involvement/poorly differentiated with "squamoid"	1 year	Excision and radical neck node dissection	Died 19 days after surgery because of aggressive disease and aspiration pneumonia
Murray *et al.* 2011[36]	F	46 years	NM	Pleural/epithelioid type	Two polypoid lesions: one was a 1 cm × 0.5 cm nodule on the left dorsal tongue, the other was a 0.3 cm × 0.3 cm nodule on the right dorsal lateral tongue/ epithelioid type	Tongue metastasis was initial presentation of mesothelioma	Chemotherapy of cisplatin and pemetrexed; excision of tongue leisions; palliative radiotherapy of chest metastasis	Alive with new subcutaneous metastasis of chest wall and three more small tongue leisions six months later
Vazquez *et al.* 2016[37]	M	35 years	–	Peritoneal MM of lower anterior abdomen/ well differentiated papillary pattern	3 cm mass in the anterior two-thirds of the tongue/NM	3 years	Radiotherapy, 50 Gy in 20 fractions	Lost to follow-up because of progressive deterioration over a few months, and died 5 years after primary diagnosis

+, present; –, absent; cm, centimeter; F, female; M, male; mm, millimeter; MM, malignant mesothelioma; NM, not mentioned.

option.[6,11–13] For advanced disease (local invasion, multiple lymph node metastasis), mixed histology, and/or high risk patients, pleurectomy/decortication may be a better choice.[14,15] Radiotherapy can provide effective local palliation in up to 50% of patients,[16] prevent chest wall recurrence and improve local control after pleurectomy or extrapleural pneumonectomy[17–20] with a high risk of radiation pneumonitis, myelitis, hepatitis, and myocarditis.

The current first-line systemic therapy for unresectable MPM is combination chemotherapy with pemetrexed and cisplatin. In 2003, Vogelzang and colleagues[21] reported the results of a phase III randomized clinical trial in 456 chemotherapy-naive patients with MPM, comparing treatment with pemetrexed and cisplatin with cisplatin monotherapy. Response rates were 41.3% in the pemetrexed/cisplatin arm versus 16.7% in the control arm ($P < 0.0001$). Median survival time in the pemetrexed/cisplatin arm was 12.1 months versus 9.3 months in the cisplatin-only arm ($P = 0.020$). Another randomized phase III study of cisplatin and raltitrexed in unresectable MPM showed similar increases in median survival.[22]

A multicenter phase 3 randomized trial[23] compared adding bevacizumab to cisplatin/pemetrexed (with maintenance bevacizumab) versus cisplatin/pemetrexed alone for patients with unresectable MPM who did not have bleeding or thrombosis. Overall survival was increased in the bevacizumab plus chemotherapy arm by 2.7 months when compared with chemotherapy alone (18.8 vs. 16.1 months; HR = 0.77; $P = 0.0167$). The NCCN panel recommends bevacizumab, cisplatin, and pemetrexed followed by maintenance bevacizumab for bevacizumab-eligible patients with unresectable MPM based on this trial. Recent data in CheckMate 743 showed dual checkpoint inhibition with nivolumab and ipilimumab is associated with prolonged OS relative to chemotherapy in treatment-naive patients with inoperable MPM.[24]

However, there is no current standard of care for second-line chemotherapy in MPM. The most commonly used second-line regimens include gemcitabine or other drugs with single-agent activity such as vinorelbine. Immunotherapy such as nivolumab ± ipilimumab[25,26] or pembrolizumab[27,28] provide hope for all patients with mesothelioma, and in the future may be combined with standard therapy in multimodality protocols.

Tongue metastasis from mesothelioma

The results of the literature search for cases of tongue metastasis from mesothelioma are summarized in Table 1. There were nine previously reported cases of malignant mesothelioma (MM) with tongue metastasis. The majority of patients were men, accounting for 78% (7/9). The median age at diagnosis was 69 years (range: 35–3 years). The primary lesions were predominantly epithelioid mesotheliomas (6/8) where primary type was stated, and other types included biphasic (1/8) and well differentiated papillary pattern (1/8). The median time between diagnosis of primary MM and tongue metastasis was 19 months (range: 5–36 months). Five patients underwent excision of the tongue metastasis and two patients received local radiotherapy, and the median survival time after tongue metastasis was more than six months (range: 19 days–5 years).

In conclusion, in our review of the literature, tongue metastasis from MPM was very uncommon. Systemic agents may be increasingly important in this disease. Attention should be paid to the study of prognostic factors, novel biomarkers, and genetic abnormalities. These might all be helpful in formulating an early diagnosis as well as in selecting a more accurately targeted treatment.

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Disclosure

All authors declare that they have no conflicts of interest.

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