Malignant mesothelioma metastatic to the oral region and latest topics (Review)

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Abstract. Malignant mesothelioma (MM) is a rare neoplasm with poor prognosis that usually develops after exposure to asbestos, and is characterised by aggressive local invasion and metastatic spread. While metastasis to the oral cavity is very rare, a total of 23 cases of MM metastasising to the oral cavity were identifed. Among those, the tongue was the most common site of metastasis (39.1%), and frequently involved the epithelioid MM cell type. Recent studies have elucidated the mechanisms underlying the development of MM. Chronic inflammation has been implicated in promoting MM growth and was shown to play a key role by driving the release of high mobility group box protein 1 following asbestos deposition. Inherited heterozygous germline mutations in the deubiquitylase BRCA-associated protein 1 were shown to increase the incidence of MM in some families. Infection by the simian virus 40 was also found to be associated with the occurrence of MM. Moreover, the increasing incidence rates of MM, together with its propensity to metastasise to the oral cavity, indicate that clinicians and pathologists should be highly aware of this disease. Furthermore, identification of novel serum biomarkers would enable better screening and treatment of MM, and improve the survival outcomes.

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Abbreviations: MM, malignant mesothelioma; BAP1, BRCA-associated protein-1; TNFα, tumor necrosis factor-α; CK, cytokeratin; HBME, human bone marrow endothelial cells; CEA, carcinoembryonic antigen; TTF-1, thyroid transcription factor 1; HM, human mesothelial cells; HMGB-1, high mobility group box protein 1; aCGH, array comparative genomic hybridisation; tNGS, targeted next-generation sequencing; NF2, neurofibromatosis type 2; SV 40, simian virus 40; WT1, Wilms' tumor 1; IGF-1, insulin-like growth factor-1

Key words: malignant mesothelioma, oral metastasis, high mobility group box protein 1, BRCA-associated protein-1

Contents

1. Introduction

Malignant mesothelioma (MM) is a rare tumor derived from the mesothelial cells lining the serosal surfaces of body cavities. There is currently no effective treatment for MM, and the majority of the patients succumb to the disease within 12-17 months post-diagnosis (1), as MM is resistant to most known treatment modalities (2). The majority of the MM variants have been reported to be associated with asbestos exposure (3,4). The incidence rates are higher among men compared with those among women (5:1), and most patients are aged 40-70 years at the time of diagnosis (5). Men exhibit a high association between the development of MM and exposure to asbestos, and they most commonly present with pleural MM. By contrast, MM in women is less likely to be associated with asbestos exposure (5). Similar to carcinoma, MM predominantly metastasises by direct invasion of adjacent tissue, in addition to lymphatic and haematogenous dissemination. Distant metastases are more common with the sarcomatous variant compared with other variants (6), whereas metastases to the oral cavity are rare. The aim of the present review was to assess the development of oral metastasis from MM and discuss the latest topics.

2. Clinical symptoms

MM affects the tissues surrounding the lungs, which are prone to inflammation caused by other agents, such as metallic ducts, gases, fumes and aerosols of biological agents; this may delay the correct diagnosis of MM by several months. Common

symptoms include pain in the chest or lower back, shortness of breath, cough, difficulty swallowing, hoarseness, swelling of the face and arms, presence of lumps under the chest skin and unexplained weight loss. In the majority of the patients, the symptoms persist for at least a few months before diagnosis. The findings on chest X-ray, computed tomography (CT) and positron emission tomography (PET)-CT examination generally include pleural thickening, exudation and pleural masses. The early stages of pleural MM are associated with multiple tumor nodules on the serosal and parietal surface of the viscera, which may merge at a later stage (5).

3. Aetiology

Asbestos fibres initiate mitosis in mesothelial cells, inducing multiple chromosomal abnormalities, such as those of chromosome 22 (7). To investigate the mechanism of inactivation of neurofibromatosis type 2 (*NF2*), a tumor suppressor gene implicated in MM, loss of heterozygosity analysis was performed with two microsatellite markers located in the vicinity of the *NF2* locus on chromosome band 22q12 (8). Of the 25 cell lines, 18 (72%) exhibited loss at one or both loci of *NF2*. All the cases exhibiting mutations and/or aberrant expression of *NF2* displayed allelic loss, suggesting that inactivation of *NF2* in MM occurs via a two-hit mechanism. Increased production of cytokines and growth factors and inactivation of tumor suppressor genes are associated with exposure to asbestos fibres.

It was previously suggested that alterations in the p53 and retinoblastoma (Rb) tumor suppressor pathways (9), and mutations in the *NF2* and *INK4a* tumor suppressor genes, are closely associated with the pathogenesis of MM (10,11). Moreover, asbestos enhances the proliferation of mesothelial cells in culture via the production of tumor necrosis factor-α (TNF-α), and induces second messenger signalling via the nuclear transcription factor NF-κB (12). Asbestos-induced carcinogenesis is linked to chronic inflammation. The deposition of a sufficient number of asbestos fibres is accompanied by the release of pro-inflammatory molecules from macrophages and mesothelial cells, particularly high mobility group box protein 1 (HMGB-1) and TNF-α.

Other studies suggest that non-asbestos-related mechanisms may contribute to the development of MM. For example, simian virus 40 (SV40) has been shown to induce MM in experimental animals (13). Furthermore, treatment of other cancers with radiotherapy or exposure to erionite fibres have also been shown to promote the development of MM (14). However, how MM is initiated in individuals who have not been exposed to asbestos or received radiotherapy treatment for other cancers remains elusive (14). The findings mentioned above indicate that genetic predisposition, radiotherapy and viral infection are co-factors that can, either alone or in combination with asbestos and erionite, initiate the development of MM (15).

4. Pathology

MM arises following malignant transformation of the mesothelial cells that form the pleura and visceral peritoneum. MM may also develop, albeit rarely, from the mesothelial cells that line the pericardium and testicular sheath membrane. These mesothelial cells are undifferentiated and, hence, possess differentiation potential. Therefore, MM cells exhibit various morphologies, such as the epithelial-like, spindle-shaped cell (sarcomatoid or fibrotic MM) or biphasic variants (16), which are rare and may be misdiagnosed during routine pathological examination, such as synovial sarcoma and small-cell carcinoma. Histologically, epithelioid MM is less invasive compared with the spindle-shaped cell variants (16). The biphasic variants generally behave according to their main histological component, and fibrotic MM tends to be more malignant (16). Bueno *et al* (17) reported that recurrent gene fusions and splice alterations are frequent mechanisms underlying the inactivation of *NF2*, BRCA-associated protein 1 (*BAP1*) and the histone methyltransferase SET domain containing 2 (*SETD2*). Furthermore, with integrated analyses, Bueno *et al* identified alterations in the Hippo, mammalian target of rapamycin, histone methylation, RNA helicase and p53 signalling pathways in MM.

Despite identifying these alterations, patients with MM are often misdiagnosed. As reviewed by a thoracic pathologist in France, only 67% of the cases were initially diagnosed as MM (18). Additionally, the spindle-shaped cell variant is difficult to diagnose, although immunohistochemistry (IHC) may improve the diagnostic accuracy. Cellular proteins, such as calretinin and Wilms' tumor 1 (WT1), serve as positive markers for MM, along with thyroid transcription factor 1 (TTF-1), p63, epithelial glycoprotein 2 and carcinoembryonic antigen (CEA), which may help distinguish most other carcinomas from MM. WT1 is considered as a specific marker for MM, and tumor cells displaying nuclear staining for WT1 and calretinin, together with strong membranous staining for cytokeratin (CK) CAM5.2, have been characterised as MM cells (19,20).

5. Immunohistochemical characteristics

Studies suggest that the use of antibodies with appropriate negative and positive controls may improve the accuracy of MM diagnosis (21-28). Normal mesothelial cells express low molecular weight CKs and vimentin; hence, tumors expressing both types of intermediate filaments may have a mesothelial origin. The most sensitive antibodies for identifying pulmonary adenocarcinoma are MOC-31 and BG8 (both 93%), while the most specific are monoclonal antibodies against CEA (97%) and TTF-1 (100%). Furthermore, antibodies against CK5/6 (83%) and human bone marrow endothelial cells (HBME-1) (85%) are useful for the identification of epithelioid MM. However, none of these antibodies can differentiate between pulmonary adenocarcinoma and MM on their own. Therefore, the use of a combination of highly sensitive and specific antibodies is recommended (21).

All MM variants have been shown to express glucose transporter 1 (GLUT-1). GLUT-1 is absent during reactive mesothelial proliferation, which is associated with hyperplasia and neoplasia. Thus, GLUT-1 may allow distinguishing reactive mesothelial nodules from MM (22,23).

The majority of MMs exhibit positive staining for keratin markers (AE1/AE3, CK5/6, CK7, CK19 and CAM 5.3) (24), among which CK 5/6 is the most useful for the diagnosis of MM. Furthermore, MMs generally stain positive for epithelial membrane antigen and vimentin (25).

Calretinin is expressed in neuronal tissues, and often shows a helix-loop-helix domain structure expressed in the epithelioid MM variant (26). While both cytoplasmic and nuclear staining of calretinin may be observed, nuclear staining confirms MM (25). WT1 is expressed in normal mesothelial cells and shows nuclear positivity in most cases of epithelioid MM (20,23). Anti-HBME-1, an antibody that recognises normal and malignant epithelioid mesothelial cell antigens, may stain positive for another protein, mesothelin, in the microvilli (27,28). Antibodies against two or more epithelial markers generally allow identification of carcinomas, such as monoclonal and polyclonal anti-CEA, Ber-EP4, B72.3, CD15, MOC-31, TTF-1, BG8 and others, and two or more mesothelial markers, such as CK-5/6, calretinin, HBME-1, thrombomodulin, WT1, mesothelin, D2-40 and podoplanin, confirm the diagnosis of MM (25). CEA and TTF-1 serve as negative markers (23). Sarcomatoid MM stains positive for CK and vimentin, and few cases are positive for calretinin (25). Moreover, all types of MM are negative for neutral mucin on IHC.

Serum biomarkers are extensively used for the screening and identification of MM patients with known exposure to asbestos (28,29). Furthermore, measuring the serum levels of osteopontin and megakaryocyte potentiating factor may serve as a non-invasive method for assessing the response of patients to treatment (28).

6. Oral metastases from pleural MM

A comprehensive search for MMs that metastasise to the oral cavity was performed using the PubMed database and combinations of 'mesothelioma', 'metastatic' and 'oral' as the search terms. The reference lists of the related publications were also manually reviewed. The outcome of the literature search for cases of oral metastasis is summarised in Table I (30-50). A total of 23 cases of MM were metastatic to the oral cavity, and 11 cases were reported in different contexts on two occasions. Furthermore, 19 patients were men and the ratio of men to women was 4.8:1. The mean age at diagnosis was 61.7 years (range, 35-75 years). One patient (case 14) whose oral metastatic lesions were the first evidence of MM (43) was ultimately diagnosed with pleural MM. Furthermore, 9 of the 23 studies presented patients with tumor metastasis to the tongue (39.1%), most of which were of the epithelioid type. The epitheloid type is the most common variant of diffuse MM, and is also frequently observed in oral metastases. While these data may aid with diagnosis, it is necessary to differentiate MM from squamous cell carcinoma, which accounts for the majority of primary oral malignant lesions. A possible explanation for the frequent metastases to the tongue may be the rich capillary network, particularly where the fragmented basement membranes of proliferating capillaries allow easier penetration by malignant cells compared with mature blood vessels. Additionally, the tongue is well vascularised and it has been hypothesized that this may create favourable conditions for the establishment of the malignant cells (19). Moreover, Piattelli *et al* (32) suggested that the tongue may be the preferred site due to the abundant blood supply present in its posterior third. Thus, given the posterior location of the lesions, the symptoms may be vague and the lesions may be difficult to identify and palpate.

The sarcomatoid variant of MM was identified in 3 cases, and was located at the mandibular region. Piattelli *et al* (32) reported that sarcomatous type tumors tend to metastasise haematogenously, similar to sarcoma, to the small intestine, axillary lymph nodes, mediastinal lymph nodes and mandible. Moreover, the haematopoietic areas in the mandible favour early deposition of tumor cells. Additionally, the bones with red marrow are common sites for metastatic adhesion, and red marrow is usually found in the posterior part of the mandible. Consistently, 3 of the cases of sarcomatoid MM presented herein involved the posterior part of the mandible. In such cases, it is difficult to distinguish inflammation and osteomyelitis from metastatic lesions. When a patient presents with a highly metastatic neoplasm in any organ, careful examination of the jaws should also be considered.

The diagnosis of primary MM is established based on the combination of clinical, imaging (CT, magnetic resonance imaging and PET-CT) and histopathological characteristics. The diagnosis of secondary MM in the oral region may be confirmed more readily in cases with a known history of primary MM. However, it may still be difficult to diagnose this disease, and it may be necessary to refer to the location and symptoms of the lesion, as described above. Additionally, both the primary and metastatic lesions of MM can be confirmed by immunostaining. The use of at least 2 positive (e.g., calretinin and WT1) and 2 negative MM markers (e.g., CEA and TTF1), along with a broad-spectrum CK as an initial screening panel, is recommended for confirmation (24,27). The results of immunostaining for all markers are summarised in Table I. The IHC markers used to distinguish between oral squamous cell carcinoma and MM are listed in Table II.

The optimal method for treating tumors metastasising to the oral cavity has yet to be established. Moreover, considering the aggressive nature of MM and its poor prognosis, the treatment for metastasis must be determined based on holistic assessment of the invasiveness and residual functional disruption after surgery, length of survival and quality of life (QoL). Therefore, an accurate diagnosis is crucial for avoiding unnecessary aggressive surgery and preserving the QoL of the patients.

7. Asbestos and MM

Epidemiological and experimental studies that have primarily focused on asbestos fibre research over the past several decades, indicate a strong association between exposure to asbestos fibres and the occurrence of MM (3,51). Asbestos is a collective term referring to several types of mineral fibres that were used industrially in the 1970s (52). Several fibres have been shown to act as carcinogens, and their use has been largely unrestricted (53). The precise mechanism remains to be elucidated, although the role of chronic inflammation in promoting asbestos-induced carcinogenesis has been established (54). Two human MM cell lines were used to generate a SCID mouse xenograft model to assess the time-dependent patterns of inflammation and tumor formation (54). Inoculation of MM cells into the mice resulted in increased levels of interleukin (IL)-6, IL-8, basic fibroblast growth factor and vascular ndothelial growth factor. Furthermore, cytokine production was confirmed by an increase in neutrophil levels. These results

Table I. Details of reported cases of malignant mesothelioma metastastic to the oral region.

Case no.	First author	Sex	Age at diagnosis (years)	Oral site	Histopathology of metastasis	Immunopathology (+)	Immunopathology (-)	(Refs.)
1	Kerpel	M	73	2x2-cm submucosal mass of ventral tongue	Epithelioid with glandular areas	Cytokeratin	Vimentin, CEA, B72.3	(30)
2	Kerpel	M	45	Mass on lower gingiva with assosiated bone loss of the mandible	Epithelioid with glandular areas	Cytokeratin, focally vimentin	Leu-M1, CEA, B72.3	(30)
3	Sproat	M	48	Mandibular alveolus	Sarcomatoid	Vimentin, focally cytokeratin (CAM5.2)	CEA, EMA	(31)
4	Piattelli	M	52	Lesion on lateral tongue	Epithelioid	Vimentin, cytokeratin	CEA, B72.3, Leu-M1	(32)
5	Garcia-Reija	M	63	Lower gingiva	Epithelioid with glandular areas	Vimentin	Not stated	(33)
6	Cassarino	M	64	0.8x0.7-cm ulcerated nodule of the upper lip	Epithelioid with glandular areas	Cytokeratins (AE1/3,CK19), HBME-1	CEA, BER-EP4, B72.3, Leu-M1	(34)
7	Zanconati	M	71	Ulcerated mass on dorsolateral tongue	Epithelioid	Keratins, EMA, vimentin, thrombomodulin, calretinin	Not stated	(35)
8	Soyuer	F	50	0.8-cm mass in the buccal mucosa	Not stated	Cytokeratin cocktail, CEA, Leu-M1, B72.3, EMA, calretinin, vimentin	Not stated	(36)
9	Terakado	M	53	Periapical radiolucency associated with mandibular third molar	Sarcomatoid	Vimentin, cytokeratin-AE1/3	CD34, CK10, BER-EP4	(37)
10	Tho	M	70	2x1-cm lession on lateral tongue	Biphasic	Calretinin, mesothelin, CK5	CEA, TTF-1, thrombomodulin	(38)
11	Higginson	M	69	2.2x0.9-cm submucosal mass in floor of mouth with involvement of the tongue	Epithelioid	Calretinin, CK5/6, AE1/3, CD15	BER-EP4, mucicarmine	(39)
12	Hashitani	F	59	0.5x0.5-cm nodule on dorsal tongue	Epithelioid with glandular areas	CK5/6, AE1/3, EMA, calretinin, HBME-1, mesothelin, TTF-1	Not stated	(40)
13	Kirke	M	71	3-cm submucosal mass in floor of mouth with involvement of the tongue	Poorly differentiated with squamoid cells	MNF116 keratin, EMA, CK5, calretinin	Not stated	(41)
14	Murray	F	46	1x0.5-cm nodule on dorsal tongue	Epithelioid with glandular areas	CK7, CK19, AE1/3, CA125, EMA	CD31, CD34, Bcl2, GCDFP15, alpha actin, CK20, S100, CDX2, CEA, ER, TTF-1	(42)

Table I. Continued.

Case no.	First author	Sex	Age at diagnosis (years)	Oral site	Histopathology of metastasis	Immunopathology (+)	Immunopathology (-)	(Refs.)
15	Sinon	M	65	0.8-cm submucosal mass in buccal mucosa	Epithelioid with pseudoglandular areas	CK5/6, CK7, CK19, CAM5.2, EMA, calretinin, WT1	Not stated	(43)
16	Billè	F	68	Mandibular alveolus	Sarcomatoid	WT1, calretinin	Claudin-4, BER-EP-4	(44)
17	Arslan	M	59	Retromolar trigone area	Epithelioid	Calretinin	Not stated	(45)
18	Ohnishi	M	62	3x2.5-cm mass in maxillary gingiva	Epithelioid	Vimentin, focally cytokeratin	CEA, EMA	(46)
19	Moser	M	75	1.5-cm mass in lower right molar gingiva	Epithelioid	Calretinin, CK5/6	BER-EP4	(47)
20	Sawaki	M	75	3.8x2-cm mass in upper gingiva	Epithelioid	Vimentin, focally keratin AE1/3	CEA, LCA, CD3, CD20, CD79, S-100, HMB-45	(48)
21	Vazquez	M	66	3-cm mass in the anterior 2/3 of the tongue	Epithelioid	Not stated	Not stated	(49)
22	Arslan	M	59	Retromolar trigone area	Epithelioid	Calretinin	Not stated	(45)
23	Tanaka	M	66	0.5-cm mass in the left buccal gingiva of the maxilla	Epithelioid	Calretinin, thrombomodulin, CAM5.2	MOC31, BER-EP4, TTF-1	(50)

CK, cytokeratin; EMA, epithelial membrane antigen; CEA, carcinoembryonic antigen; LCA, leukocyte common antigen; TTF-1, thyroid transcription factor 1; HMB-45, human melanoma black 45; WT1, Wilms' tumor 1; HBME-1, Hector Battifora mesothelial epitope-1; ER, estrogen receptor; BER-EP4, anti-human epithelial antigen; GCDFP15, gross cystic disease fluid protein-15.

Table II. Summary of immunohistochemical markers useful for distinguishing between MM and OSCC.

Marker	MM	OSCC
CK20	-	+
CEA	-	+
Vimentin	+	-
Calretinin	+	-
HBME-1	+	-

MM, malignant mesothelioma; OSCC, oral squamous cell carcinoma CK, cytokeratin; CEA, carcinoembryonic antigen; HBME-1, Hector Battifora mesothelial epitope-1.

indicate that the development of MM is dependent on inflammation and cytokine production. Furthermore, the exposure of human mesothelial (HM) cells, derived from pleural effusion of non-malignant patients, to asbestos induced necrotic cell death along with release of HMGB-1. This result suggests that asbestos-induced inflammation promotes mesothelial cell transformation (12,55). HMGB-1, a danger-associated molecular pattern (DAMP) molecule, which is normally present in the nucleus, mediates the initiation of asbestos-induced MM. HMGB-1 acts as a non-histone chromatin-binding protein that regulates nucleosome organisation and chromatin structure. As a DAMP, HMGB-1 is either released upon necrosis of HM cells, or secreted by immune cells or cancer cells, and initiates inflammation in response to asbestos. Moreover, asbestos persists in the body over a prolonged time period, initiating a chain reaction of chronic cell death and inflammation that promotes the development of MM (56). Thus, HMGB-1 acts as an important factor in the onset and maintenance of chronic inflammation causing MM cell proliferation. Additionally, high levels of HMGB-1 may be found in the serum of patients with MM and those exposed to asbestos. Furthermore, hyperacetylation of HMGB-1 is associated with its release by inflammatory cells. Comparative analysis suggests that the levels of HMGB-1 and fibrin-3 may allow distinguishing between patients with MM and those with other causes of pleural effusion. Taken together, these observations suggest that analysing acetylated HMGB-1 levels may enable selective identification of patients with MM and those exposed to asbestos (57).

8. BAP1 and MM

Erionite was shown to cause MM and death in >50% of the Turkish population exposed, strengthening the gene x environment hypothesis (58,59). Furthermore, certain American families were also found to be susceptible to MM, despite not being exposed to asbestos. The analysis suggested that these individuals carried germline mutations in *BAP1*, which also increased the risk of uveal melanoma or other carcinomas, such as renal cell carcinoma, basal cell carcinoma and lung adenocarcinoma, as well as that of MM, the risk of which increased further upon exposure to asbestos (60). These results may provide a basis for identifying individuals at higher risk of developing MM and improve diagnosis and treatment. Carriers of the *BAP1* germline mutation exhibit early onset of characteristic benign melanocytic BAP1-mutated atypical intradermal tumors (61,62). Moreover, families with the *BAP1* germline mutation present early in life with a novel cancer syndrome characterised by benign melanocytic skin tumors, and are at a higher risk of later developing MM, uveal melanoma, cutaneous melanoma, as well as other cancers (61). Furthermore, similar to other cancers, somatic mutations in *BAP1* occur in >60% of sporadic MM cases, suggesting *BAP1* to be one of the most commonly mutated genes in MM (63), regardless of the ethnic background or other clinical characteristics. IHC is considered to be an easily accessible and reliable method for detecting BAP1 status in MM biopsies.

Yoshikawa *et al* (64) have screened the genetic changes of chromosome 3p21 in 33 cases of MM using high-density array comparative genomic hybridisation (aCGH) and targeted next-generation sequencing (tNGS). The analysis identified recurrent biallelic genomic deletions in 46 genes on 3p21, where many deletions were distant and alternated with normal DNA segments as observed in chromothripsis, although independent deletion events may occur sequentially. Furthermore, mutations in *BAP1*, along with those in *SETD2, PBRM1* and *SMARCC1*, were found to be frequent in MM. Moreover, that study provided the basis for the use of high-density aCGH and tNGS for precise estimation of the frequency and variety of inactivated genes in human cancers.

9. SV40 and MM

A study conducted in 1994 indicated that >60% of the MM samples carried SV40 DNA and expressed the SV40 large T (tumor) antigen. However, the percentage of positive samples ranged between 6 and 83%, which may be attributed to technical and geographical differences. For example, the presence of infectious SV40 in the polio vaccine administered to children in the former Soviet Union and other affected countries has been reported (65). However, according to the National Academy of Sciences Medical Research Institute, the evidence obtained were inadequate to firmly establish or exclude a causal association between the SV40-containing polio vaccine and cancer incidence. Furthermore, mechanical and animal experiments in HM cells support the role of SV40 and cofactors, such as asbestos fibres, to the pathogenesis of several cases of MM (66). Additionally, the lack of late viral gene expression may help SV40-transformed mesothelial cells to escape immune surveilance. Suppression of late viral gene products is considered to be an important step in viral carcinogenesis. Furthermore, when cells expressing p53 are infected with a DNA tumor virus, p53 binds to a viral tumor antigen (Tag). This Tag-p53 complex then binds to the insulin-like growth factor-1 (IGF-I) promoter with pRb and p300, and regulates transcription of the *IGF-I* gene to increase the expression of the IGF-1 receptor. The SV40 T antigen binds to and activates the IGF-1 receptor, thereby promoting tumor cell proliferation (67).

10. Conclusion

Based on the currently available information, the detailed mechanism underlying *BAP1*-induced carcinogenesis is

expected to be elucidated in the near future. This may provide the opportunity to treat MM by inhibiting the components involved in the gene-environment interactions. A similar analysis of *HMGB-1* or other biomarkers may allow stratification of asbestos-exposed patients at high risk and improve diagnosis and treatment. Moreover, genetic or biochemical tests for biomarker identification may also be of value in the treatment of MM patients with oral metastases. Our research group has focused on various aspects of MM, such as assessment of *HMGB-1* and other biomarkers, identification of patients exposed to asbestos, and devising tests to identify patients with MM during the course of disease progression.

The predictions for occurrence of MM vary worldwide, with declining rates in France and the US, constant rates in Australia, and unclear in the UK (68,69). Furthermore, considering the latency period, precautionary measures to avoid exposure to asbestos may be effective in reducing the incidence of MM, particularly in the US (70). However, it is also predicted that the global incidence of MM may continue to increase, given the widespread exposure to asbestos in certain developing countries (71). Moreover, oral metastases from MM should also follow this trend and, although rare, may warrant differential diagnosis of the disease. Although a known previous diagnosis of MM may help oral cancer pathologists, precise diagnosis using histological and immunohistochemical analysis is recommended, in order to ensure avoiding unnecessary over treatment and improving the overall survival and QoL of the patients.

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Authors' contributions

YO and TF designed the review. TS, MW, HK and TM were involved in the collection and collation of references. YO wrote, reviewed and edited the manuscript. MN critically revised the manuscript for intellectual content. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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