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ORIGINAL ARTICLE

Epithelioid hemangioendothelioma of the oral cavity

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OBJECTIVE: To investigate the clinicopathological characteristics and biologic behaviour of epithelioid hemangioendothelioma in the oral cavity.

MATERIALS AND METHODS: The clinical features and pathological findings of nine cases with intraoral epithelioid hemangioendothelioma were reviewed, including immunohistochemistry study.

RESULTS: This series comprised seven males and two females aged 6–53 years (mean 28 years). The sites of the tumour included the tongue ($n = 4$), lip ($n = 1$), the gingiva and alveoli of the maxilla ($n = 1$), the gingiva and alveoli of the mandible ($n = 1$), buccal mucosa ($n = 1$), and the floor of the mouth ($n = 1$). A painless solitary mass was the most common presentation and was found in eight cases. On pathology, the tumour grew in short strands, cords or nests of polygonal to slightly spindled epithelioid cells in fibro-myxoid stroma, with formation of intracytoplasmic lumina. Tumour cells were immunoreactive to CD34, FVIIIRAg, and vimentin. Focal-positive cytokeration were observed in three cases. Immunoreactivity for S-100 protein, epithelial membrane antigen (EMA) and human herpesvirus (HHV)-8 was negative in all cases. Two cases recurred after surgical excision, but no patient developed local or distant metastasis.

CONCLUSIONS: Wide local excision with long-term follow-up seems to be the treatment of choice for intraoral epithelioid hemangioendothelioma because of their unpredictable biological behaviour and recurrence potential.

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Keywords: vascular tumour; epithelioid hemangioendothelioma; oral cavity; pathology; immunohistochemistry

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Introduction

Epithelioid hemangioendothelioma (EHE) is an angiocentric vascular tumour with metastatic potential (Weiss and Bridge, 2002). Previous terminology used to describe this entity includes intravascular bronchioloalveolar tumour, angioglomoid tumour and myoid angioblastomatosis (Weiss and Bridge, 2002). The term 'epithelioid hemangioendothelioma' was originally described by Weiss and Enzinger (1982) to classify a vascular tumour with borderline biological properties intermediate between hemangioma and angiosarcoma. This tumour was described by WHO as an intermediate malignant neoplasm (Weiss and Bridge, 2002). Histologically, this tumour was typically composed of epithelioid endothelial cells arranged in short cords and nests, set in a distinctive fibro-myxoid stroma. Clinically, EHE can arise in soft tissues, viscera, skin and bone (Mentzel *et al*, 1997; Makhlouf *et al*, 1999). A few cases have been documented in the head and neck region including neck, thyroid gland, larynx and scalp (Weiss and Enzinger, 1982; Siddiqui *et al*, 1998; Pigadas *et al*, 2000; Amin *et al*, 2003). EHE are extremely rare in the oral cavity. In this study, we report nine additional cases, with further observation of the clinicopathological and immunohistochemical features of EHE in the oral cavity.

Patients and methods

We reviewed the recorded pathological slides of 484 vascular tumours from 1963 to 2003 in the Department of Oral Pathology, School and Hospital of Stomatology, Wuhan University. Nine cases of EHE in the oral cavity were pathologically diagnosed according to the latest WHO classification (Weiss and Bridge, 2002).

The clinical features were obtained by reviewing the medical records. Tumour size was based on the records or on the largest dimension from the clinical or gross measurement, or the microscopic slide.

The morphology was reviewed and examined from standard hematoxylin and eosin-stained sections, and

Table 1 Immunoreagents used in the analysis of epithelioid hemangioendothelioma of the oral cavity

Reagent	*Source*	*Dilution*	*No. cases studied*	*Positive cases*	*Quantitation of staining*[a]		
					< 25%	*25–75%*	*> 75%*
CD34 (Q Bend-10)	Santa Cruz, CA, USA	1:50	9	9	2	3	4
FVIII-RAg	Dako, CA, USA	1:400	9	8	4	4	0
Vimentin (V9)	Dako, CA, USA	1:200	9	8	0	5	3
SMA (1A4)	Santa Cruz, CA, USA	1:400	9	9	4	4	1
Keratin (AE1/AE3)	Dako, CA, USA	1:500	9	3	2	1	0
EMA (E29)	Dako, CA, USA	1:100	9	0			
S-100	Dako, CA, USA	1:100	9	0			
HHV-8 (KSHV)	Novocastra, Newcastle, UK	1:50	6	0			

[a]Proportion of positively stained cells.

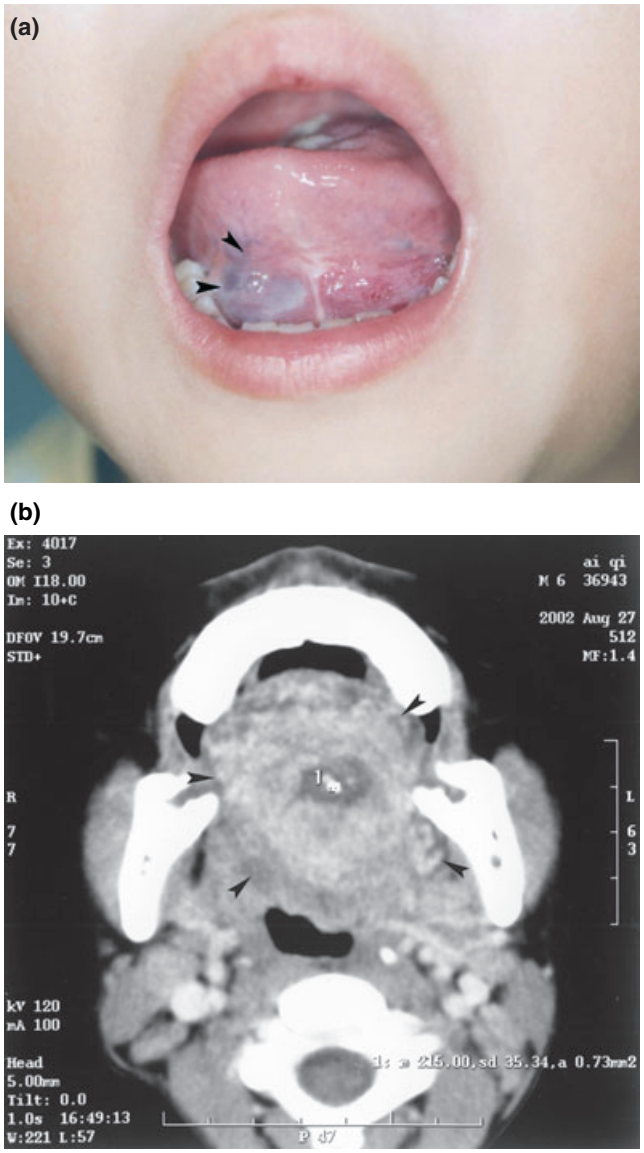

Figure 1 EHE of the floor of mouth in a 6-year-old boy. (**a**) Intraoral photo showing a blue-purplish nodule. (**b**) CT scan demonstrating an ill-defined solid lesion with heterogeneous contrasted image

immunohistochemistry was performed in all nine cases, using the avidin–biotin complex immunoperoxidase technique. The characteristics of the antibodies used are shown in Table 1. Follow-up information was obtained by reviewing medical records, interviewing patients or through telephonic or written communication with the patients.

Results

Clinical findings

The present series comprised seven males and two females, aged between 6 and 53 years (mean 28 years and median 21 years) at the time of presentation. The tumour was an incidental finding, of a painless oral mass, in seven patients (77.8%) (Figure 1a). Only two patients complained of spontaneous pain, including one who experienced limitation of tongue movement and fever. The mean duration prior to diagnosis was 4.5 months (ranging from 1 to 12 months). None of the 9 patients had a history of prior or concomitant malignancy, and of previous oral trauma.

The primary site of the lesion included the tongue (four patients), lip (one), gingiva and alveoli of the maxilla (one), gingiva and alveoli of the mandible (one), and buccal mucosa (one). One case presented with multiple anatomic sites including the floor of the mouth, right edge and dorsum of the tongue. The vascular lesions ranged in size from 0.5 to 7.2 cm in greatest dimension (median size 1.2 cm). Two lesions in the gingiva of the jaws were associated with tooth mobility. No local or distant metastasis was detected in all nine cases at diagnosis.

A computed tomography scan performed in one case revealed an ill-defined heterogeneous contrasted solid image, which appeared to radiate from the central vessels to the surrounding soft tissues (Figure 1b). Plain radiographs in two cases involving jaws demonstrated an ill-defined translucency.

Treatment and follow-up data

Initial surgical intervention for the nine patients consisted of a wide local excision ($n = 6$), *en bloc* resection ($n = 2$) and incisional biopsy ($n = 1$). A complete follow-up record was available for all patients. The tumour recurred in two patients after surgical excision, and they underwent wide local resection. One patient who had incisional biopsy and recurrence was referred to the oncology section, and was treated with radiation.

However, the lesion gradually continued to grow, but no metastasis was observed on a 2-year follow-up.

Pathological findings

Grossly, the tumours were firm and rubbery, most with a greyish-tan cut surface, and only one with hemorrhagic foci. The tumours had no capsule and grew with infiltrative margins (Figure 2a). The majority of tumours exhibited cords, strands, or a solid nest growth pattern within a collagenous and myxoid non-inflammatory stroma (Figure 2b). The tumour cells were epithelioid, rounded or slightly spindled in shape, with an eosinophilic cytoplasm. Nucleus was vesicular with an inconspicuous nucleolus. In all cases, tumour cells may demonstrate intracytoplasmic lumina, some containing red blood cells (Figure 2c). In five cases, the tumour also comprised spindle-shaped cells, covering from minor proportion up to 50% of the tumour cells (Figure 2d). In the majority of cases (five patients), no mitosis was identified, while three cases showed 2 mitoses/10 high power fields (HPF), and one case up to 4 mitoses/10 HPF. Nuclear atypia was graded as mild in one case, moderate in six cases, and marked in two cases. The neoplastic cells were dispersed in a fibrohyaline or myxoid stroma. Metaplastic cartilaginous or bone formation was not seen.

Immunohistochemical findings

Of the endothelial cell markers, CD34 was more frequently positive than FVIIIRAg. The epithelioid endothelial cells were immunoreactive for CD34 in all nine cases, whereby more than 50% of the cells showed cell membrane staining (Figure 3a). FVIIIRAg was expressed in eight of nine cases, to a much lesser extent than CD34, as in most cases, $< 50\%$ of the tumour cells demonstrated positive immunostaining (Figure 3b). α-smooth muscle actin (SMA) was expressed in all nine cases that were tested, and it highlighted a population of myopericytic cells intimately associated with the epithelioid endothelial cells (Figure 3c). The number of immunoreactive myopericytic cells varied: four cases showed focal reactive cells at the periphery of the lesion, four cases demonstrated moderately extensive reactivity in the middle and peripheral zones, and in one case the

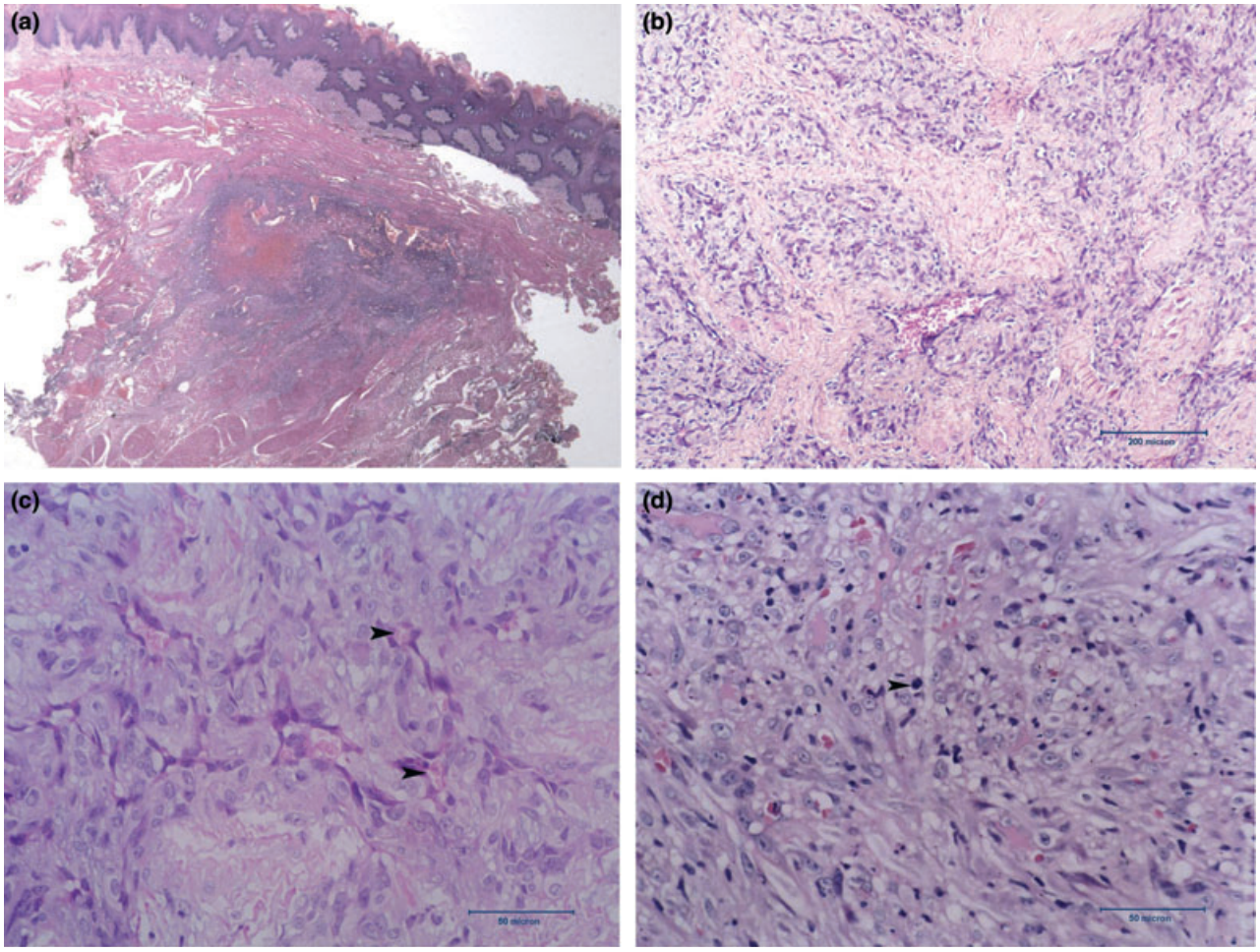

Figure 2 Histological features of EHE. (**a**) At low magnification, this tumour are non-encapsulated, with ill-defined margins, and infiltrating tongue muscles (Original magnification 0.8 × 2.0). (**b**) Tumour composed of nests or cords proliferating epithelioid endothelial cells. (**c**) Tumour cells with intracytoplasmic lumina with red blood cells (arrow). (**d**) Tumour composed of multiple spindle-shape epithelioid cells and mitosis (arrow) are easily found (H&E)

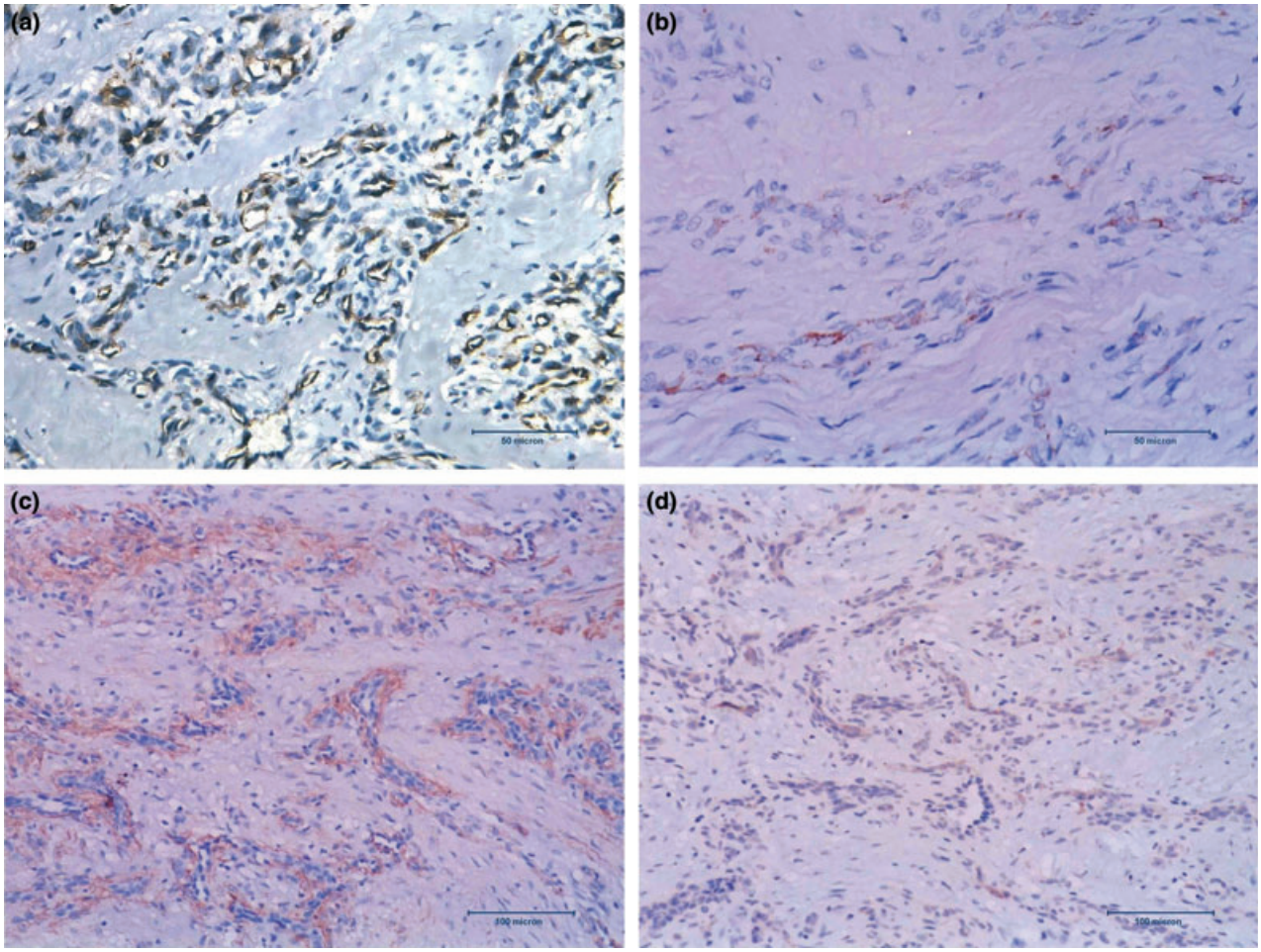

Figure 3 Immunohistochemical staining in EHE. (**a**) Nests of epithelioid tumour cells reactive to CD34. (**b**) Cords of neoplasm cells positive for FVIIIRAg. (**c**) Immunostaining for α-SMA of myopericytic layers surrounding tumour cells. (**d**) Focally tumour cells are positive for cytokeratin

reactivity was widespread throughout the entire lesion. Of the six cases tested, none of the tumour cells showed immunoreactivity to HHV-8 (KSHV).

Three of nine cases tested for the cytokeratins AE1/AE3 revealed scattered immunoreactive epithelioid endothelial cells (Figure 3d). The number of positive cells was typically small; only one case had keratin expression in >25% of the epithelioid endothelial cell population. Immunostains for vimentin were positive in eight of nine cases, and more than 50% of the tumour cells demonstrated positive immunostaining in six cases. None of the nine cases expressed epithelial membrane antigen (EMA), and S-100 protein.

Review of literature

Seventeen cases of intraoral EHE identified in the literature were reviewed with the nine patients in this series, and the clinical features of all 26 cases are summarized in Table 2. The mean age was 31 years, ranging from 4 to 76 years. There was no sex predilection with a female-to-male ratio of 1.2 to 1.0. The most commonly affected intraoral site was the gingival alveolar mucosa ($n = 9$) with five and four cases involving the mandible and the maxilla, respectively. Four cases arose intraosseously, including three in the mandible and one in the maxilla. The second most frequent location was the tongue ($n = 7$). Other less common sites included the buccal mucosa ($n = 2$), lip ($n = 2$), palate ($n = 1$), and floor of the mouth ($n = 1$). The tumour size ranged from 0.2 to 7.2 cm in maximum dimension. Most patients were asymptomatic, and only a few patients presented with pain or tenderness. Twenty-five of 26 patients presented as a solitary red-purplish mass, and only one with multiple nodules. All nine lesions arose from the gingival or alveolar mucosa leading to secondary erosion of the adjacent alveolar bone. Other clinical findings included tooth mobility ($n = 6$) and mucosal ulceration ($n = 2$). The radiographic appearance of the intraosseous lesions varied, ranging from a well- to ill-defined radiolucency with or without radiopaque foci. In most cases, an excisional biopsy was initially performed followed by wider excision or *en bloc* resection in the event of recurrence. Follow-up information was available for 22 cases with an average period of 32 months. In seven patients with local recurrence, wider excision or resection was performed with no further evidence of

Table 2 Clinical findings of reported epithelioid hemangioendothelioma of the oral cavity

Author (year)	*Age*	*Sex*[a]	*Location*	*History and examination*	*Follow-up*[b]
Wesley *et al* (1975)	18	F	Mandibular gingiva	Bone resorption	AND 2 years
Ellis and Kratochvil (1986)	13	F	Maxillary gingiva	Pink swelling, tooth mobility 4 years	AND 6 years
Ellis and Kratochvil (1986)	4	F	Mandibular gingiva	Tooth mobility, bone resorption	NA
Moran *et al* (1987)	25	F	Palate	1.0 cm nontender mass 1 year	AND 21 months
de Araujo *et al* (1987)	4	M	Mandibular gingiva	Ulcerated mass, tooth mobility 9 months	NA
Marrogi *et al* (1991)	45	M	Maxillary gingiva	1.5 cm erythmatous lesion	Rec 3,6 months
Marrogi *et al* (1991)	36	F	Tongue	Painful 0.2 cm nodule 2 months	AND 17 months
Flaitz *et al* (1995)	7	F	Mandibular gingiva	1.5 cm reddish nontender mass, tooth mobility, bone destruction	AND 52 months
Hamakawa *et al* (1999)	76	F	Anterior mandible	4.5 cm tenderness submucosal mass, bone destruction	AND 6 years
Orsini *et al* (2001)	18	F	Buccal mucosa	1.5 cm painless mass 7 months	Rec 9 months
Ramer *et al* (2001)	32	M	Maxilla	3.5 cm rock-hard mass	Rec 6 months
Molina Palma *et al* (2002)	65	F	Tongue	0.5 cm nontender mass 2 months	AND 21 months
Machalka *et al* (2003)	65	M	Mandible	Chin enlargement, tooth mobility	Rec 4.8 years
Anderson *et al* (2003)	18	F	Lower lip	Painless swelling 6 months	Rec 4 months
Chi *et al* (2005)	28	F	Maxillary gingiva	0.6 cm purple mass	AND 8 months
Chi *et al* (2005)	23	F	Mandible	2.0 cm bony destruction	NA
Uehara et al (2006)	72	M	Tongue	0.7 cm nontender mass 2 months	NA
Sun *et al* (this study)	12	M	Maxillary gingiva	3.0 cm ulcerated mass 3 months, bony destruction, tooth mobility	AND 6 months
Sun *et al* (this study)	53	M	Buccal mucosa	1.5 cm nontender mass 6 months	Rec 9 months
Sun *et al* (this study)	17	M	Tongue	0.5 cm mild tenderness mass 2 months	AND 18 months
Sun *et al* (this study)	52	F	Upper lip	2.0 cm purple mass for 1 year	AND 3 years
Sun *et al* (this study)	21	M	Tongue	0.5 cm reddish mass 2 months	AND 2 years
Sun *et al* (this study)	34	M	Tongue	1.0 cm rubbery mass 4 months	AND 6 years
Sun *et al* (this study)	11	M	Mandibular gingiva	2.0 cm painful mass 1 month, bony destruction, tooth mobility	AND 8 years
Sun *et al* (this study)	46	M	Tongue	1.2 cm reddish firm mass	Rec 4 months
Sun *et al* (this study)	6	M	Floor of mouth and tongue	7.0 cm painful reddish mass 6 months	AWD 2 years

M, male; F, female; NA, not available; AND, alive no disease; AWD, alive with disease; Rec, recurrence.

disease or metastasis on follow-up, and no patient died of intraoral EHE.

Discussion

Epithelioid hemangioendothelioma of the oral cavity has been infrequently reported. Clinically, the tumour occurred in nearly all age groups, ranged from the first to the seventh decade (Weiss and Bridge, 2002; Chi *et al*, 2005). Men and women were otherwise equally affected. The most common intraoral sites were the gingival alveolar mucosa and tongue (Chi *et al*, 2005). The clinical impression of oral EHE was nonspecific, and most frequently appeared as a benign painless mass, although on occasions the lesion was ulcerated. If the tumour was close to the jaws, bony destruction was often observed on radiographic examination (Wesley *et al*, 1975; Ellis and Kratochvil, 1986; de Araujo *et al*, 1987; Marrogi *et al*, 1991; Hamakawa *et al*, 1999; Ramer *et al*, 2001; Molina Palma *et al*, 2002; Chi *et al*, 2005). To our best knowledge, the present series reported the first case located in the floor of mouth and the largest of intraoral EHE. This tumour remains relatively rare, with a nonspecific clinical presentation. Hence a preoperative diagnosis based on clinical and radiographic findings is unlikely to be made, and the diagnosis relies on the pathology of the excised lesion.

Histologically, in contrast to cutaneous EHE, intraoral lesion rarely showed a marked propensity to spread along pre-existing blood vessels (Weiss and Bridge, 2002). The angiocentricity was observed in about 50% of the non-intraoral EHE cases, probably accounting for the high incidence of pain attributed to local ischaemia. An infiltrative growth with ill-defined tumour margins was much more common than circumscribed nodules (Ellis and Kratochvil, 1986; de Araujo *et al*, 1987; Hamakawa *et al*, 1999; Molina Palma *et al*, 2002). The tumour cells grew in short strands or solid nests, and assumed a plump epithelioid to a spindle shape with abundant pale eosinophilic cytoplasm (Weiss and Enzinger, 1982). The neoplastic cells may form a vascular lumina not only from a group of cells, but also from the intracytoplasmic luminal formation in a single cell. The presence of erythrocytes or lysed blood in the cytoplasmic vacuole indicates their endothelial nature (Weiss and Bridge, 2002). The stroma of EHE was distinctive for its varying proportion of collagenous hyaline and myxoid tissues. Most intraoral EHE appeared quite bland with little mitotic activity, but about a quarter of the cases showed atypical histologic features, with nuclear atypia, mitotic activity ($>1/10$ HPF), focal spindling of cells and necrosis, which conferred a more aggressive course to the tumour (Marrogi *et al*, 1991; Orsini *et al*, 2001). Weiss and Enzinger (1982) suggested that patients with metastases were those showing these atypical features.

Immunohistochemical evidence of an endothelial differentiation was an important criterion for the diagnosis of EHE. Immunoreactivity of tumour cells

for CD34, CD31, Fli-1 and FVIIIRAg were found in most reported cases of oral EHE (Chi *et al*, 2005). CD34 and Fli-1 were noted to be more sensitive and reliable markers than FVIIIRAg. However, the use of multiple vascular markers may be important, in cases with atypical features and heterogeneous expression of vascular antigens or malignant potential (Makhlouf *et al*, 1999; Weiss and Bridge, 2002). Immunoreactivity of EHE for cytokeratin was controversial. Previous studies demonstrated the co-expression of endothelial and epithelial markers in EHE of the bone. In our study, 33.3% of cases were positive for cytokeratin. The co-expression of endothelial marker and cytokine may complicate the differential diagnosis, and lead to the mistaken diagnosis of carcinoma for the unwary pathologist (Weiss and Enzinger, 1982). Expression of SMA in EHE was inconsistent in the previous reported cases (Weiss and Enzinger, 1982; Mentzel *et al*, 1997; Makhlouf *et al*, 1999; Chi *et al*, 2005). Mentzel *et al* (1997) reported positive immunostaining in five of their 11 cases. This study confirmed that SMA was expressed in all the nine cases examined, although such expression was focal, and seemingly by myopericytic cells. Makhlouf *et al* (1999) interpreted these cells as non-neoplastic myofibroblasts, involved in the formation of collagen matrix. While Kaposi's sarcoma showed distinctive morphology, and differentiated from EHE, the focal spindled tumour cells in EHE may raise the possibility of an association with Kaposi's lesion. However, the negative expression for HHV-8 or KSHV helped to exclude such consideration (Lai *et al*, 2001).

Pathologically, EHE should be differentiated from other vascular tumours showing epithelioid characteristics, including epithelioid angiosarcoma, epithelioid hemangioma, spindle cell hemangioma, kaposiform hemangioendothelioma (KHE) and epithelioid angiomatous nodule. Epitheloid angiosarcoma is an infiltrative, destructive vascular tumour, composed of pleomorphic cells, associated with numerous often atypical mitosis, and frequently with necrosis (Triantafillidou *et al*, 2002). While a few cases of EHE may show cellular atypia, this lesion does not show the degree of pleomorphism or atypical mitosis seen in epithelioid angiosarcoma. The head and neck region is of particular interest, being the typical location of epithelioid hemangiomas (Sun *et al*, 2006). Epithelioid hemangioma is a circumscribed lesion composed of well-formed, often immature vascular structures lined by plump endothelial cells, in which a large vesicular nucleus often protrudes into the lumina as a 'hobnail'. This lesion, also coined as angiolymphoid hyperplasia with eosinophilia, for its prominent inflammatory process permits its distinction from EHE. EHE should not be confused with spindle cell hemangioma (formerly spindle cell hemangioendothelioma), a benign lesion in older patients with a predilection for the limbs, and characterized by cavernous vascular spaces, with papillary structures, thrombi and phleboliths, associated with a focal solid spindled vascular tumour (Lai *et al*, 1991; Tosios *et al*, 1995). The tumour cells in kaposiform hemangioendothelioma may focally appear epithelioid with glomeruloid capillary proliferation, but this vascular tumour of infancy with a slit-like lumen is more reminiscent of Kaposi's sarcoma, which is distinct from EHE (Lai *et al*, 2001). Cutaneous epithelioid angiomatous nodule is a recently described vascular proliferation with distinct morphologic spectrum (Brenn and Fletcher, 2004). It is usually confined to the dermis with only infrequent extension into the superficial subcutaneous tissue and rarely in the submucosa. The lesion consistently presents with a unilobular pattern and without involvement of small muscular vessels. The spindle cells in synovial sarcoma are plump, and form solid masses with scanty vascular spaces or red blood cells, thus expressing that EMA can be differentiated from EHE (Bukachevsky *et al*, 1992). Finally, oral carcinoma, which is far more common than EHE, can be relatively easy to differentiate by its sheets of epithelial tumour cells, usually associated with significant pleomorphism, mitotic activity and keratin formation (Weiss and Enzinger, 1982).

With regard to therapy, wide local excision was therefore considered the treatment of choice and is probably curative in the majority of cases (Ellis and Kratochvil, 1986; Chi *et al*, 2005). The role of adjuvant chemotherapy, radiotherapy, and/or treatment with interferon-α-2 remains unclear. Radiotherapy alone was hardly ever effective because of the slow growth of the tumour cells. Although several chemotherapeutic regimens have been tried, the treatment was not curative. Mortality from the tumour varied greatly, depending on the organ affected and the propensity for multifocality (Weiss and Bridge, 2002). Reported mortality rates associated with EHEs in more common anatomic locations were as follows: 13% in soft tissue (Mentzel *et al*, 1997) and 35% in the liver (Makhlouf *et al*, 1999). Metastasis has been reported in approximately 20% of patients with soft tissue primaries and 25% with liver primaries. On review of the literature, the behaviour of intraoral EHEs appeared less aggressive than those arising from the soft tissues and bones. Among the intraoral cases of EHE reviewed, six cases exhibited local recurrence, and only one of these was associated with high-grade microscopic features (Machalka *et al*, 2003). None of the intraoral tumours resulted in metastasis or death from disease, which further set them apart from those primarily involving the soft tissues and bone. However, in view of their malignant potential, it appears that wide local excision with close clinical follow-up remains the appropriate management for intraoral EHEs.

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