

**ORAL PRESENTATION OF EPITHELIOID ANGIOSARCOMA
WITH FIRST SIGN IN THE SCAPULA :
REPORT OF A CASE AND REVIEW OF THE LITERATURE**

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(Received March 1, 2005, accepted June 8, 2005)

Abstract : Occurrence of a primary or metastatic angiosarcoma in the oral cavity is extremely rare. The term “epithelioid angiosarcoma” (EA) has been used to designate a morphological variant of angiosarcoma characterized by poorly differentiated epithelial-like cells arranged in carcinoma-like fashion, but which still forms identifiable vascular channels. To our knowledge, EA in the oral region is extremely rare. Only two previous instances of EA in the maxilla have been reported. We present an additional oral case of EA in a 71-year-old man. Histology of the initial oral biopsy revealed suspicion of un-differentiated carcinoma. In order to confirm the diagnosis, immunohistochemical examinations were performed. The final diagnosis was EA. The patient died of multiple metastases shortly after the final diagnosis, implying an aggressive clinical course. This case showed that it was essential to use the vascular markers, such as FVIII-Rag and CD34, for a correct histological diagnosis of EA. The oral EA described here almost certainly represents a metastatic focus, rather than the primary site of tumor origin. This is because clinical history of EAs appears to arise in deep, rather than in more superficial tissues.

Key words : epithelioid angiosarcoma (EA), oral cavity, immunohistochemical examination

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INTRODUCTION

Angiosarcoma is a rare tumor of vascular endothelium. Occurrence of a primary or metastatic angiosarcoma in the oral cavity is uncommon^{1,2,3}. The term "epithelioid angiosarcoma" has been used to designate a morphological variant of angiosarcoma characterized by poorly differentiated epithelial-like cells arranged in carcinoma-like fashion, but which still forms identifiable vascular channels⁴. This type of tumor has been described, although infrequently, in a variety of sites. To our knowledge, epithelioid angiosarcoma (EA) in the oral region is extremely rare. Only two previous instances of EA in the maxilla have been reported^{5,6}. In this paper, we present an additional case of EA in the oral region in a man in his seventh decade. His first sign was in the right scapular region. He died of multiple metastases shortly after the final diagnosis, implying an aggressive clinical course. Also this case emphasizes the importance of careful immunohistochemical examina-

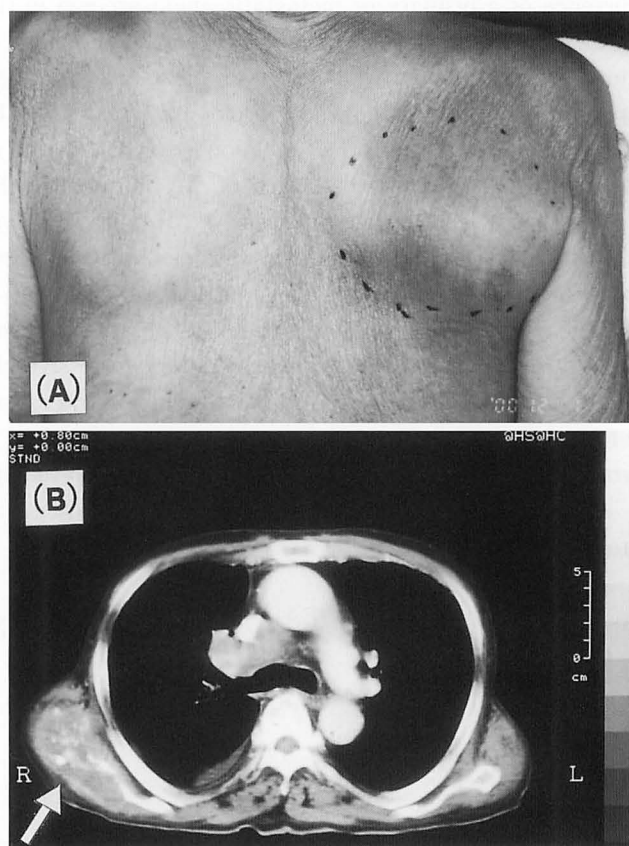


Fig. 1. (A) Large expansile mass of the right scapular area at initial presentation (circumscribed by dotted line). (B) CT scans showing an expansile osteolytic lesion of the right scapula (arrow).

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CASE REPORT

A 71-year-old man was referred to the Department of Orthopedic Surgery, Fukushima Medical University in 2000 from the primary physician for treatment of severe pain and a swelling in the right scapular region, which he had noticed about 2 months earlier. His severe pain had been controlled by painkiller. Physical examination revealed a hard mass, approximately 7 cm in diameter, with ill-defined border in the right scapular region (Fig. 1-A). The computed tomography (CT) scans showed a large expansile, osteolytic lesion of the right scapula (Fig. 1-B).

The patient subsequently was admitted to our clinic for consultation with regard to a painless buccal gingival swelling in the left lower molar region, which he noticed about 1 month earlier. The oral tumor was a sessile, 20×25 mm mass in the lower vestibule region with overlying oral mucosal necrosis (Fig. 2-A). The panoramic

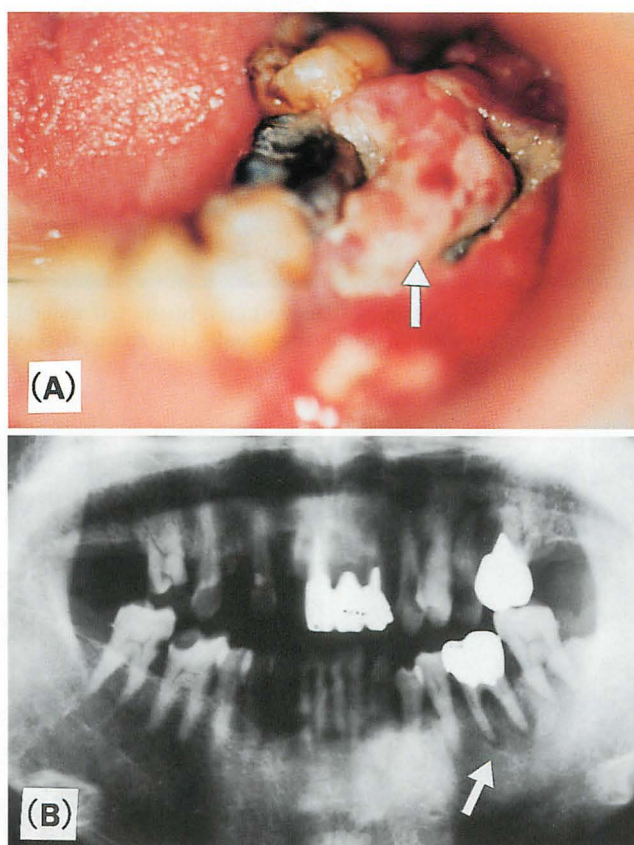


Fig. 2. Initial oral examination. (A) Gingival tumor mass with overlying mucosal necrosis (arrow). (B) Panoramic radiograph showing ill-defined radiolucency surrounding the mandibular first and second molars (arrow).

radiograph revealed an ill-defined lytic process in the left mandibular area, suspicious for an erosive-type aggressive process associated with the bone (Fig. 2-B). The some lymph nodes of the upper cervical region were located posterior to the left mandibular angle. The mass was elastic and hard on palpation, without mobility. CT scan of oral region showed a low-density mass with relatively clear borders on the cortical bone in the left mandible (Fig. 3-A) and multiple large coalescent chain

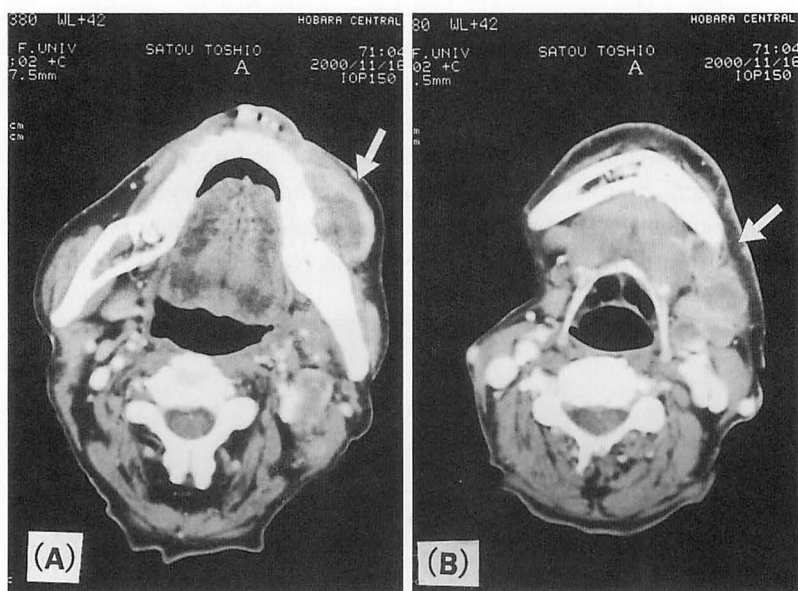


Fig. 3. (A) Axial CT scans showing soft tissue lesion of the left mandible (arrow). (B) Axial CT scans showing multiple large coalescent chain of cervical lymph nodes (arrow).

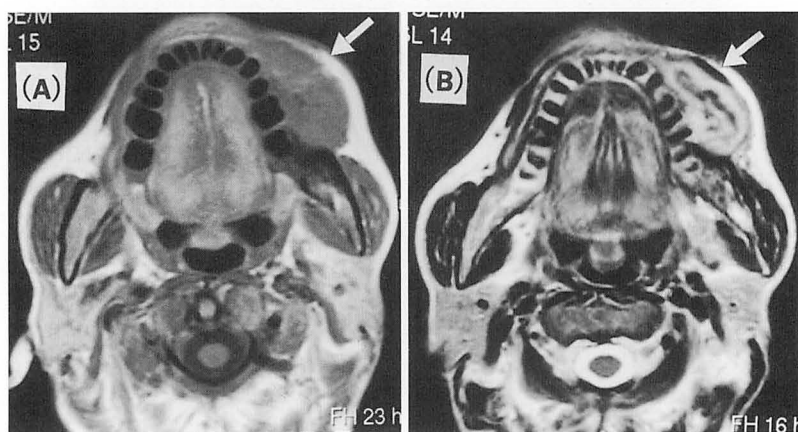


Fig. 4. (A) Axial MRI (T1-weighted image) showing lesion with homogenous low signal intensity (arrow). (B) MRI (T2-weighted image) showing lesion with a central hypodensity adherent to molar teeth sockets (arrow).

of cervical lymph nodes (Fig. 3-B). Magnetic resonance imaging (MRI) showed the oral soft mass adhesive to the lateral side of the mandible (Fig. 4-A, B). Our clinical diagnosis was suspicion of a highly malignant tumor.

On the same day, a biopsy of the oral lesion was performed. The initial pathological diagnosis was suspicion of un-differentiated carcinoma, which showed solid, sheet-like growth pattern of poorly differentiated polyhedral cells (Fig. 5-A). A second biopsy of the oral lesion was tried after 2 weeks. The lesion showed blood vessels lined with atypical endothelial cells in foci (Fig. 5-B). At the same time, a biopsy of the right scapular region was performed. Oral histologic features were consistent with the scapular lesion. In order to confirm the diagnosis, silver reticulin staining and immunohistochemical staining were performed. Silver reticulin staining exhibited the characteristic reticulin network (Fig. 6-A). Positive immunohistochemical staining of Factor VIII related antigen (FVIII-RAg) and CD34 were identified in most of the tumor cells (Fig. 6-B). Final pathologic diagnosis of the oral and scapular lesions was EA.

A few days later, he was hospitalized. Evaluation of other sites showed multiple metastatic tumors, lung, suprarenal gland, brain stem region, mediastinal lymph nodes, and duodenum. Because the diagnosis was stage IV, radiotherapy was selected as a palliative treatment for pain control. A total dose of 30 Gy was delivered to the right scapular tumor. His general condition continued to deteriorate due to widespread metastases and he died 35 days after his first visit to our

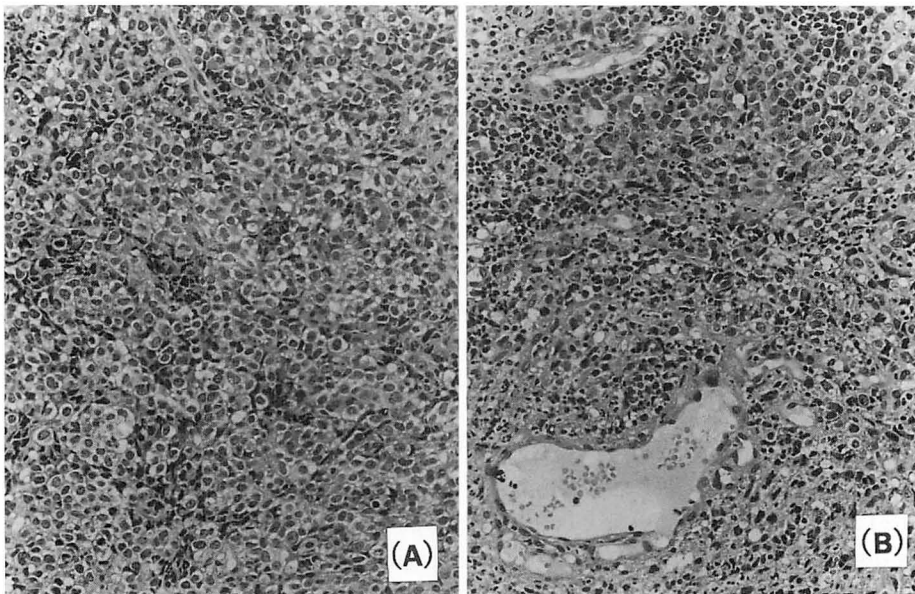


Fig. 5. Histological appearance of the oral tumor. (A) The initial biopsy showed solid, sheet-like growth pattern of poorly differentiated polyhedral cells (HE, $\times 200$). (B) The second biopsy showed blood vessels lined with atypical endothelial cells in foci (HE, $\times 200$).

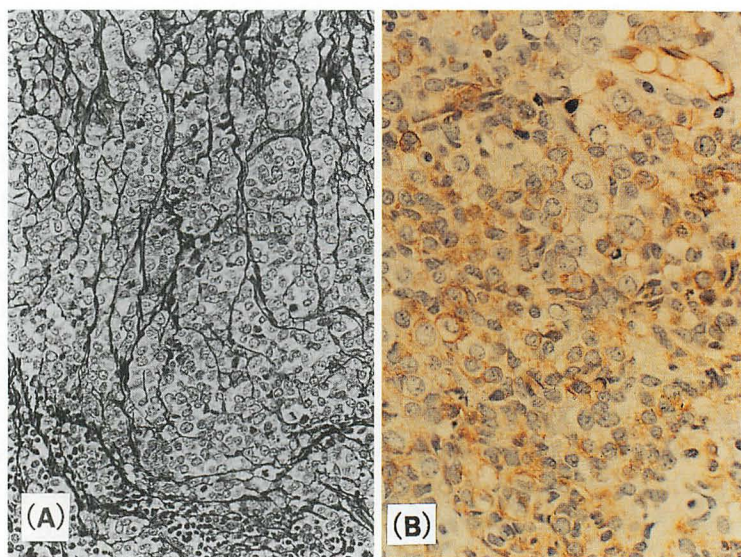


Fig. 6. (A) Silver impregnation demonstrates characteristic reticulin network (silver reticulin stain, $\times 200$). (B) Immunohistochemical staining is positive for CD34 in most of the tumor cells (CD34 stain, $\times 200$).

clinic. An autopsy was not performed.

DISCUSSION

EA has characteristic morphological features and is a specific entity within the angiosarcomas. Fletcher *et al.*⁵⁾ reported eight cases of EA arising in deep soft tissue, usually intramuscular soft tissue. Cardinal morphologic features were diffuse, sheet-like growth patterns with only focally apparent vascular differentiation, and epithelioid tumor cells with a degree of intracytoplasmic vacuolation/lumen formation. Clinically, deep-seated EAs are high-grade neoplasms that rapidly develop metastases. The presence of intracytoplasmic lumina/vacuoles (sometimes containing red blood cells) combined with the characteristic reticulin pattern and striking positivity for FVIII-RAg provide the clearest means of distinction from an epithelial metastasis⁵⁾. Watanabe *et al.*⁷⁾ reported two cases of EA in the intestinal tract. These tumors revealed the same histology as Fletcher *et al.*⁵⁾ observed, mimicking un-differentiated carcinoma. In our tumor, the initial oral biopsy was diagnosed as suspicion of un-differentiated carcinoma.

Oral angiosarcoma including epithelioid type is extremely rare and is thought to be a distinct and characteristic clinicopathological entity. There have been reported only six cases^{3,5,6,8,9,10)} with immunohistochemical staining for pathologic diagnosis in the recent literature. A summary of all seven cases (including our case) of oral angiosarcoma is given in Table 1. In the seven cases, 3 cases including our case were pathologically diagnosed as EA. These tumors tended to occur in the elderly.

Table 1. Recent literature of oral angiosarcoma using Immunohistochemical staining for pathologic diagnosis

Related Reference/Year (Patho. Diag.)	Age/ Gender	Oral Symptoms	Site of Tumour	Clinical course	Immunohistochemical staining
Fletcher <i>et al.</i> , 1991 (Epithelioid angios.)	63/M	Fungating gingival lesion	Maxilla/Aorta/ Buttock (primary)	Alive at 2.5 years after initial visit.	FVIII-RAG (+), CD34 (+), Keratin (+)
Freedman and Kerpel, 1992 (Epithelioid angios.)	32/M	Swelling	Posterior Maxilla (primary)	Alive at 18 months after resection	FVIII-RAG (+) Ulex europeus (+)
Munoz <i>et al.</i> , 1998 (Angios.)	68/M	Soft mass	Retromolar mandible	Died 2 months after initial diag. (Local recurr.)	FVIII-RAG (+), Vimentin (+), Keratin (–)
Loudon <i>et al.</i> , 2000 (Angios.)	68/M	Soft mass	Mandible (primary)	Died 8 months after initial diag.	FVIII-RAG (patchy and weak +), CD31 (intensely +), Cytokeratin (faint +), Vimentin (difusely +)
Medina <i>et al.</i> , 2001 (Angios.)	67/F	Gingival mass	Anterior mandible/ Uterus (primary)	Died 15 months after diag.	FVIII-RAG (+), Vimentin (+), Keratin (–), Cistin (–)
Pouloupoulos <i>et al.</i> , 2001 (Angios.)	61/F	Bleedy gingival mass	Mandible/Breast (primary)	Died 2 months after removal of gingival mass	FVIII-RAG (+)
Present case, (Epithelioid angios.)	71/M	Gingival mass	Mandible/ Scapula/Widespread metastases	Died 1 month after initial diag.	CD34 (+), FVIII-RAG (+), S-100 protein (–), HMB-45 (–)

* FVIII-RAG= Factor VIII related antigen

Males predominate over females by a ratio of 5 to 2. Clinically, the oral tumors mainly occurred in gingiva and revealed round or ovoid nodule. The surfaces were ulcerated, but the lesions were generally painless, firm on palpation and capable of spontaneous bleeding. Four of the seven cases listed in Table 1 had multiple metastatic tumors and the prognoses were poor, since five of seven cases died within 15 months after oral tumor resection or initial diagnosis.

Because of the characteristic epithelioid arrangement, EA must be differentiated from primary, metastatic carcinoma and many sarcomas with epithelioid features^{3,7)}. Immunohistochemical staining sometimes gives useful information on the cellular nature in malignant vascular tumors. Mediana *et al.*⁹⁾ observed that angiosarcoma was characterized by the formation of irregular vascular channels lined by one or more layers of atypical endothelial cells, often of immature appearance and accompanied by solid masses of poorly differentiated or anaplastic tissues, and that the immunohistochemical findings helped exclude other diagnostic possibilities by demonstrating for FVIII-RAg, vimentin, CD31, and CD34 and negative reactivity for smooth muscle actin, desmin, keratin, and estrogen/progesterone receptors. However, Fletcher *et al.*⁵⁾ reported that all eight cases immunohistochemically coexpressed keratin as well as endothelial markers and observed that EAs could be potentially immunoreactive for keratins. This could be misleading if a diagnosis of carcinoma or epithelioid sarcoma is being entertained. In this connection, two of the four cases listed in Table 1 were keratin positive. All cases of Table 1 were finally diagnosed using immunohistochemical findings combined with reticulin staining^{3,6,9,10)}. In our case, the initial oral histology showed sheet-like epithelioid arrangements, but the second oral biopsy had blood vessels with atypical epithelioid endothelial cells in foci. And also two antibodies, FVIII-RAg and CD34, and silver impregnation gave helpful information for final diagnosis. All seven cases in Table 1 were FVIII-RAg positive, but other putative endothelial markers expressed differently. FVIII-RAg is generally regarded as a very specific, albeit not remarkably sensitive marker of endothelial differentiation. Fletcher *et al.*⁵⁾ observed that this antigen was much more reliably expressed in epithelioid endothelial tumors than in conventional angiosarcomas. Consistent positivity for CD34 also strongly points to endothelial differentiation, because even though it is not an entirely specific antibody, it shows little or no tendency to be expressed by epithelial neoplasms⁹⁾. Flick *et al.*²⁾ also stressed that FVIII-RAg is of value in confirming the endothelial origin of the tumor, whereas the reticulin stain demonstrates that the malignant cells are located on the luminal side of the vessels.

Oral angiosarcoma has a great propensity to mimic benign inflammatory disease such as chronic periodontal disease or pyogenic granuloma^{8,11,12)}. As an attempt to analyze the metastatic sequence of the angiosarcoma, it has been suggested that the local gingival inflammation is a possible cause for the attraction of metastatic cells towards the attached gingiva. Malignant cells may be entrapped by the rich capillary network of chronically inflamed gingivitis¹⁰⁾. In our case with the initial

complaint in the scapula region, there might have been the possibility that the inflamed gingival lesion from the mandibular periodontitis was an indication of a metastatic deposit. Frick *et al.*²⁾ reported a case of angiosarcoma of the scapula and tongue and they thought the tongue tumor to be the first metastatic site. In our case, however, it was not possible to determine positively if the lesion began in the scapula or deep soft tissues and spread to the oral area or the reverse occurred.

In conclusion, this case showed that it was essential to use the vascular markers, such as FVIII-Rag and CD34, for a correct diagnosis of EA. The oral EA described here almost certainly represents a metastatic focus, rather than the primary site of tumor origin. This is because clinical history and EAs appear to arise in deep, rather than in more superficial tissues.

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