

Clinical, histological, and immunohistochemical features of a mandibular metastasis from a primary cardiac angiosarcoma

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Primary cardiac angiosarcoma is an extremely rare malignant tumor. Distant metastases are common at the time of diagnosis but have never been reported in the jaw. A 45-year-old female patient with primary cardiac angiosarcoma was referred for dental care due to pain in the mandibular alveolar ridge. Oral examination revealed a red-violet lesion that was soft on palpation and had been present for 3 months. Histological analysis confirmed the diagnosis of metastatic cardiac angiosarcoma. The patient died of multiple metastases. (Oral Surg Oral Med Oral Pathol Oral Radiol 2013;116:e121-e127)

Angiosarcomas are aggressive malignant neoplasms composed of endothelial cells of vascular or lymphatic origin.¹ They represent approximately 3.6% of sarcomas and have a poor prognosis due to high rates of local recurrence and distant dissemination.² Most of these tumors arise spontaneously, although malignant transformation of preexisting benign or intermediate vascular lesions has been reported.^{2,3} Well-established predisposing conditions include radiation exposure; chronic lymphedema; exposure to toxic substances, such as vinyl chloride; and immunosuppression.⁴⁻⁷

Angiosarcomas usually present as sporadic cutaneous lesions, typically in the head and neck region of elderly patients, although they can arise in any anatomical site, including deep soft tissue, breast, visceral organs, and bone.⁸

Despite being composed of endothelial cells, primary angiosarcomas of the heart are very rare, and in approximately 66%-89% of cases, metastases of

cardiac lesions are usually detected at the time of diagnosis. The tumor disseminates primarily by the hematogenous route, and the most affected anatomical sites are the lungs, mediastinal lymph nodes, vertebra, and liver.^{9,10} Other metastatic sites that have been reported include brain, bladder, spleen, adrenal glands, pleura, diaphragm, kidneys, thyroid, and skin. To the best of our knowledge, metastasis of cardiac angiosarcomas to the oral cavity has never been reported, and only the abstract of the present case is currently available.¹¹

In this case report, the clinical, histological, and immunohistochemical features of a metastasis of a cardiac angiosarcoma to the mandible of a 45-year-old patient are discussed.

CASE REPORT

A 45-year-old female patient was referred to the Stomatology Clinic of the Federal University of Ceará (UFC) because of complaints of pain in the left mandibular alveolar ridge. The past medical history revealed a primary angiosarcoma of the heart diagnosed one month prior to referral (Figure 1), with metastases to the lung and mediastinal lymph nodes. Because the cardiac lesion could not be resected, the patient was treated with palliative radiotherapy, comprising a total tumor dose of 4000 cGys in 16 fractions and adjuvant chemotherapy.

During review of medical history, the patient reported that her left mandibular first premolar had been extracted 3 months prior, due to mobility, and that this corresponded to the site of the pain.

An oral examination revealed a mass in the left mandibular alveolar ridge, extending from the canine to the premolars, which resembled granulation tissue, and was non-tender and slightly compressible. This mass was first observed 3 months prior (Figure 2). Periapical radiography exhibited a bone destruction pattern characterized by ill-defined lytic changes in the crestal bone region and in the periapical region of the

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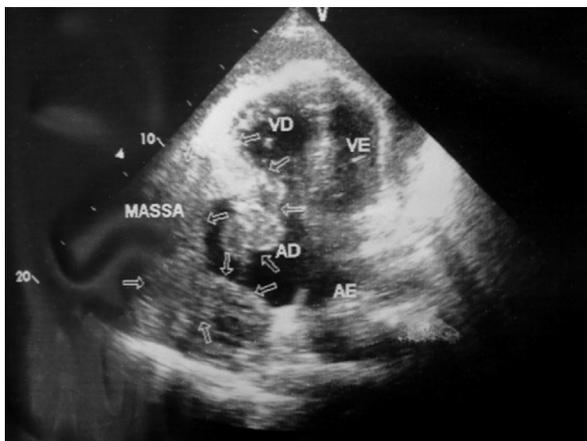


Fig. 1. Echocardiography showing an extensive cardiac lesion involving the right chambers.



Fig. 2. An oral lesion similar to granulation tissue presenting areas of spontaneous bleeding.

mandibular left lateral incisor, which did not present mobility (Figure 3).

At the second appointment, the incisor closest to the lesion was extracted due to extensive mobility, and an incisional biopsy was performed. Histological analysis showed a lesion composed predominantly of granulation tissue with vascular neoformation and extensive necrosis (Figure 4). However, in an isolated fragment, it was possible to visualize a few wide and poorly defined vascular slits lined by pleomorphic and hyperchromatic spindle cells (Figure 5). Additionally, occasional mitotic figures were observed (Figure 6). The histological analysis of the incisional biopsy of the cardiac primary lesion showed similar features (Figures 7 and 8).

Considering her clinical history of cardiac angiosarcoma, an immunohistochemical panel similar to the panel of the cardiac lesion was performed (Table I). In the oral lesion, tumor cells were strongly positive for CD31 (Figure 9) and CD34 (Figure 10), demonstrating the existence of various vascular lumens throughout the lesion. Muscle-specific actin

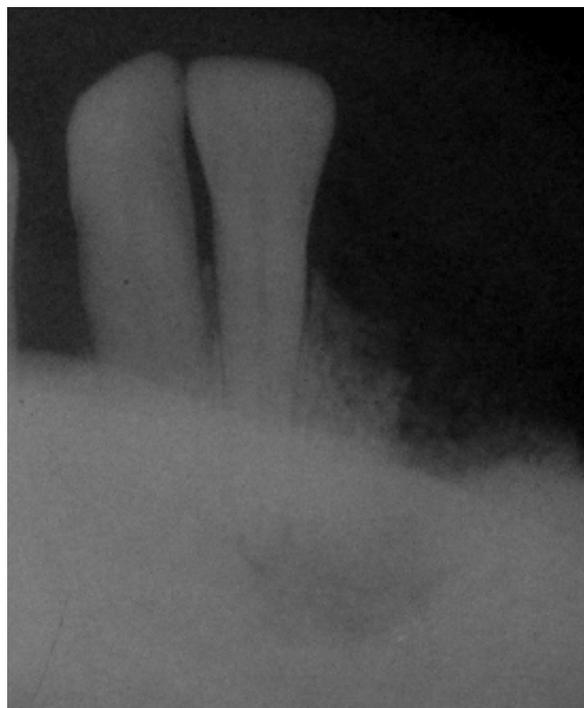


Fig. 3. Periapical radiography of the mandibular left incisors showing a bone destruction pattern characterized by ill-defined lytic changes in the periapical and crestal bone regions.

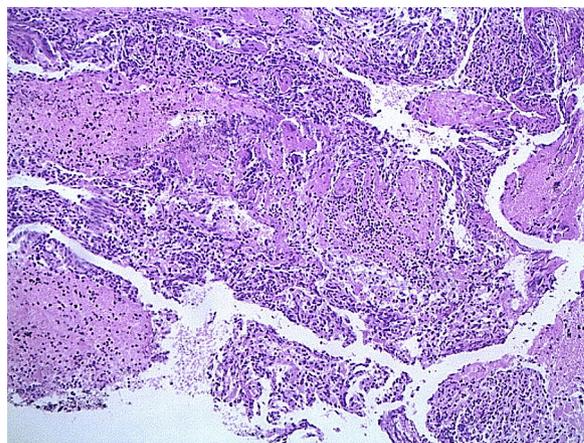


Fig. 4. Photomicrograph of the oral lesion demonstrating granulation tissue with vascular neoformation and areas of spindle cell proliferation with atypia (HE, original magnification $\times 100$).

expression was also observed in the vessels, particularly in the vascular walls. Additionally, focal expression of α -smooth muscle actin was observed, primarily in the perivascular region (Figure 11). Immunostaining for desmin, S-100 protein, HHV8, and AE1/AE3 was negative. Approximately 10% of cells expressed Ki-67 (Figure 12), and the diagnosis was compatible with secondary (metastatic) oral angiosarcoma.

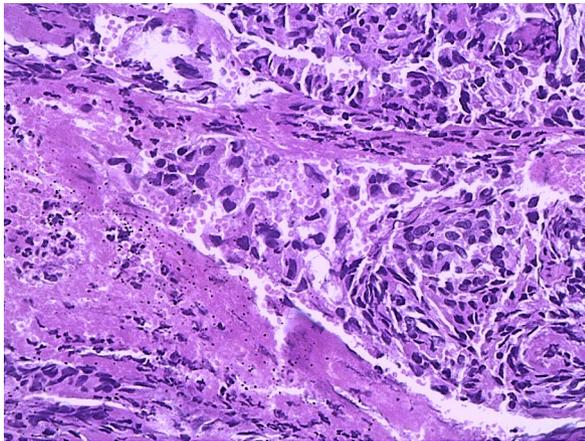


Fig. 5. Photomicrograph of the oral lesion showing wide and poorly defined vascular slits lined by pleomorphic and hyperchromatic spindle cells (HE, original magnification ×400).

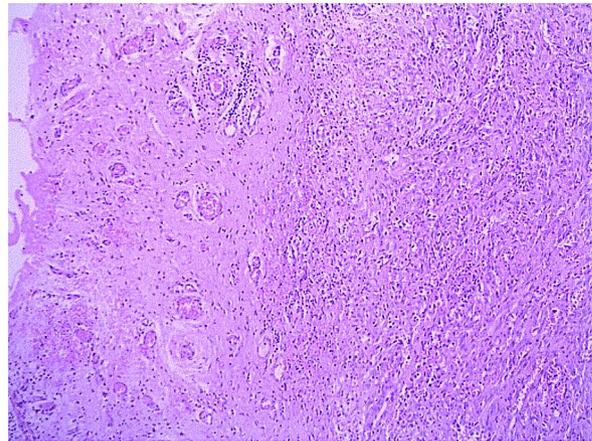


Fig. 7. Photomicrograph of the cardiac angiosarcoma exhibiting a richly cellular lesion with closely-packed vessels lined by plump endothelial cells (HE, original magnification ×100).

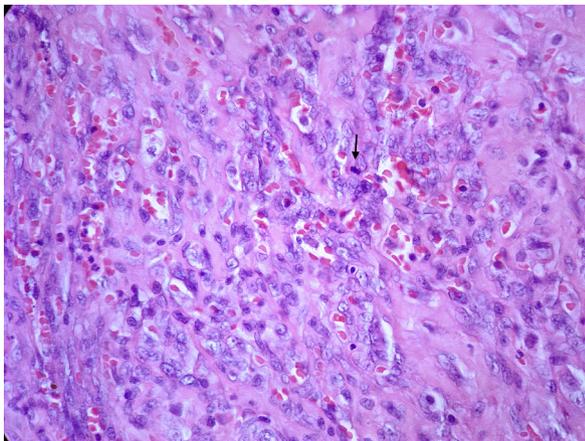


Fig. 6. Photomicrograph of the oral lesion showing fibrous connective tissue with dilated vessels, extravasated red blood cells and spindle cells with occasional mitotic figures (arrow) (HE, original magnification ×400).

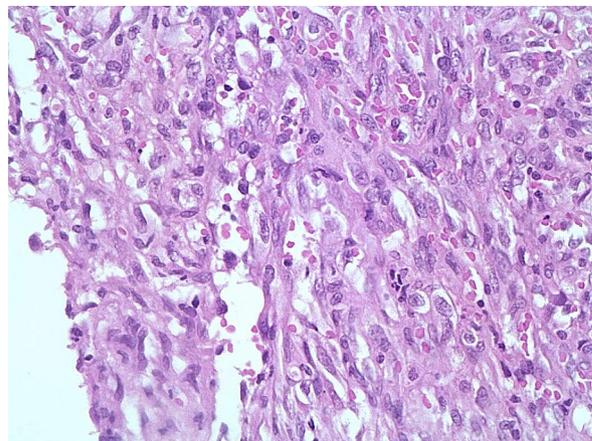


Fig. 8. Photomicrograph of the cardiac angiosarcoma exhibiting large pleomorphic spindle cells that appear to be vasoformative (HE, original magnification ×400).

Because the tumor was very aggressive, treatment of the oral lesion was palliative, and the patient died of multiple metastases 2 months after the diagnosis of cardiac angiosarcoma.

DISCUSSION

Whereas secondary or metastatic heart tumors are relatively common, primary cardiac tumors are extremely rare.¹² In a review of 731,309 cardiac autopsies, heart tumors, both benign and malignant, were found in 157 (0.021%) autopsy cases, corresponding to approximately 200 cases in 1 million.¹³ In the case of malignant neoplasms, Molina et al.¹⁴ identified only 21 cases (17%) in a series of 124 cardiac tumors. Histologically, malignant cardiac lesions can be classified as angiosarcomas, rhabdomyosarcomas,

malignant mesotheliomas, fibrosarcomas, or synovial sarcomas.¹⁵ Although cardiac angiosarcoma is a frequent histological-type, it is considered extremely rare amongst cardiac tumors.¹⁶

Cardiac angiosarcomas occur more frequently in the right atrium, are more common in men, and have a tendency to occur between the 3rd and 5th decades of life.^{9,10} The mean survival rate is approximately 6-11 months, and tumors follow an aggressive clinical course and respond poorly to chemotherapy.¹⁰

The metastatic sites of cardiac angiosarcomas include the lungs, mediastinal lymph nodes, vertebrae, liver, bone, adrenal glands, brain, bladder, spleen, diaphragm, kidneys, thyroid, and skin.^{9,10,17}

In case reports and case series published in English between 1966 and 2008, only 15 metastatic oral

Table I. Immunohistochemical evaluation of the oral and cardiac lesions

Antibody	Dilution	Clone	Source	Antigen retrieval	Oral lesion	Cardiac lesion
Muscle-specific actin	1:500	HHF35	Dako	pH 8.0, 30 min	+(V)	+/F
Desmin	1:100	DER-11	Dako	pH 8.0, 30 min	–	+(V)
CD31	1:100	JC70	Dako	pH 8.0, 30 min	+	+
CD34	1:100	QBend/10	Dako	pH 8.0, 30 min	+	+
PS100	1:2000	4C4.9	Dako	pH 8.0, 30 min	–	–
Alpha-smooth muscle actin	1:1500	1A4	Dako	pH 8.0, 8 min	+(V)/F	+(V)
AE1/AE3	1:100	AE1/AE3	Dako	pH 8.0, 30 min	–	–
Ki67	1:100	30/9	Dako	pH 8.0, 60 min	10%	NP
HHV8	1:50	ORF73	DBS	pH 8.0, 30 min	–	NP

DBS, diagnostic biosystems; +, positive reaction; –, negative reaction; F, focal reactivity; V, vessels; NP, not performed.

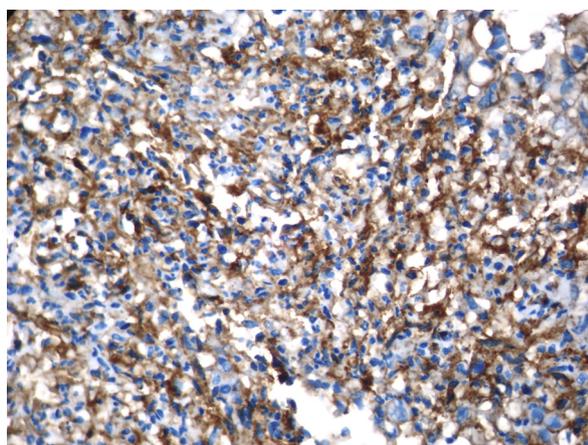


Fig. 9. Spindle cells and the vascular wall show intense immunostaining for CD31 (LSAB, original magnification $\times 400$).

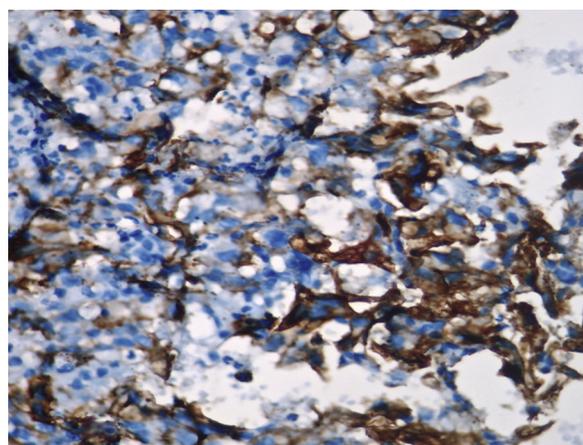


Fig. 10. Intense immunostaining for CD34 in spindle cells and the vascular wall (LSAB, original magnification $\times 400$).

angiosarcomas were reported (Table II).^{18–29} The age range varied from 38 to 75 years old, with a mean age of 62.3 years and a higher frequency in the 7th decade of life. Nine cases involved male patients, and the gingiva was the most frequent intra-oral site affected (11 cases). Oral metastases occurred mainly from primary angiosarcomas of the skin and breast, and metastases of cardiac angiosarcomas to the oral cavity have never been reported.

In addition to bleeding and pain, as observed in the present case, oral metastatic angiosarcomas can cause superinfection, dysphagia, and difficulty chewing.²⁶ Metastatic angiosarcomas also have a worse prognosis when compared to primary angiosarcomas arising in the same location.²⁷

The clinical presentation of oral angiosarcomas varies according to the degree of histological differentiation.² Clinically, oral angiosarcomas have been described as non-ulcerated, sessile, soft on palpation or slightly compressible lesions with ill-defined margins, which may be painless or slightly painful, and have a tendency to bleed.^{30–32} Radiographically, oral angiosarcomas frequently appear as osteolytic lesions that cause

widening of the periodontal ligament space and alveolar bone destruction, which may sometimes result in the appearance of floating teeth.^{33,34}

Oral angiosarcomas may cause tooth mobility, as described in the present case, which can lead to the erroneous diagnosis of inflammatory lesions or periodontal disease.^{20,34} Due to their non-characteristic clinical appearance, angiosarcomas have been misdiagnosed as pyogenic granulomas,³² hemangiomas,³¹ and odontogenic lesions.³⁵ Differential diagnosis includes pyogenic granuloma, intravascular endothelial hyperplasia, hemangioma, epithelioid hemangioendothelioma, Kaposi's sarcoma, hemangiopericytoma, fibrous histiocytoma, malignant melanoma, spindle cell carcinoma, sarcomas of muscular origin, and liposarcoma.^{2,27,36}

Histologically, oral angiosarcomas may present as well-differentiated neoplasms composed of anastomosing vascular channels, lined by spindle cells with atypia and scarce mitotic activity. Some angiosarcomas have been associated with extensive hemorrhage and necrosis, as observed in the present case. This makes malignant foci difficult to visualize, leading to the erroneous diagnosis of benign lesions. Poorly

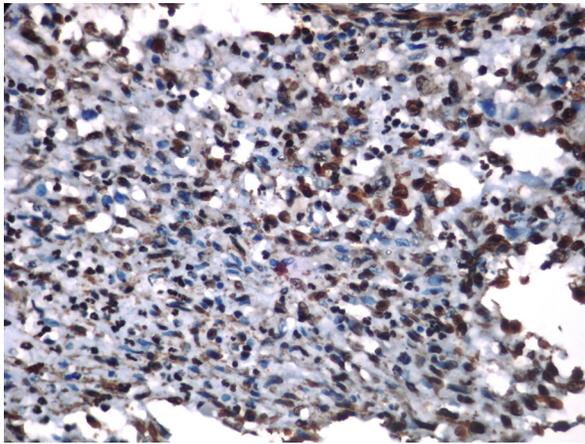


Fig. 11. Staining for α -smooth muscle actin was focally positive in spindle cells, which most likely corresponded to pericytes (LSAB, original magnification $\times 400$).

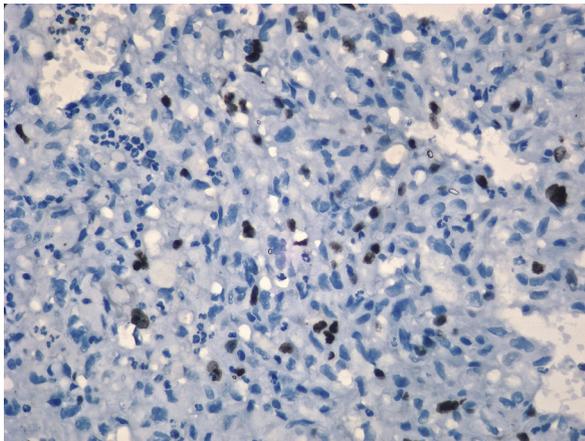


Fig. 12. Scattered spindle cells exhibiting strong nuclear staining for Ki-67 (10%) (LSAB, original magnification $\times 400$).

differentiated tumors composed of solid sheets of spindle cells without prominent vasoformative activity may also occur.^{2,27,36,37}

The association between clinical, histological, and immunohistochemical characteristics is mandatory to confirm the diagnosis of angiosarcoma.³² Immunohistochemically, angiosarcomas are usually positive for vimentin, CD31, CD34, and factor VIII-related antigen. Epithelioid angiosarcomas, which account for approximately 1/3 of angiosarcomas and may cause diagnostic confusion, are cytokeratin positive.^{2,36}

In the present case, the immunohistochemical panel was consistent with the panel of the primary tumor of cardiac origin, thus reinforcing the diagnosis of metastatic oral lesion. Immunostaining for desmin, S-100 protein, HHV8, and AE1/AE3 was negative, excluding lesions of muscular origin, malignant melanoma,

Table II. Reports of secondary (metastatic) oral angiosarcomas

Author, year	Age	Sex	Primary site	Oral site
Tanabe et al., 2008	75	M	Scalp	Gingiva
Kawasaki et al., 2005	71	M	Scapula	Oral NS
Fanburg-Smith, 2003	65	F	Skin (arm)	Gingiva
Fanburg-Smith, 2003	65	M	Skin (forehead)	Gingiva
Fanburg-Smith, 2003	69	M	Skin	Gingiva
Fanburg-Smith, 2003	69	M	Paranasal sinus	Gingiva
Poulopoulos, 2001	61	F	Breast	Gingiva
Medina et al., 2001	67	F	Uterus	Gingiva
Win et al., 1992	59	F	Breast	Gingiva
Nardi e Ficarra, 1988	49	M	Metatarsus	Mandible
Epstein et al., 1987	38	F	Breast	Gingiva
Carr e Green, 1985	66	M	Disseminated	Gingiva
Toth et al., 1981	64	M	Tibia	Gingiva
Brook et al., 1980	61	M	Omentum	Mandible and maxilla
Crymes et al., 1966	56	F	NS	Tongue

NS, not specified.

Kaposi's sarcoma, and undifferentiated squamous cell carcinoma. Tumor cells that were strongly positive for CD31 and CD34 confirmed the endothelial phenotype of the lesion.

α -smooth muscle actin staining was positive in vessels in both lesions and focally positive in the oral lesion, particularly in the perivascular region. α -smooth muscle actin can be expressed by pericytes. Although previous immunohistochemical studies of angiosarcomas have presented negative results for this marker,^{25,36} an immunohistochemical and ultrastructural study of angiosarcomas performed by Meis-Kindblom and Kindblom³⁷ showed that 24% of the evaluated tumors were positive for α -smooth muscle actin. In their study, electronic microscopy confirmed that the stained cells corresponded to pericytes, corroborating our results.

More than 10% of the tumor cells were stained with Ki-67, which demonstrates a high proliferation rate.³⁷ According to Meis-Kindblom and Kindblom,³⁷ a Ki-67 index above 10% has been associated with worse prognosis and death in patients with angiosarcomas. Correspondingly, Ge et al.¹⁷ reported that in benign or borderline vascular lesions, the Ki-67 index varied from 0% to 5%.

The treatment of cardiac angiosarcomas typically involves local resection, radiotherapy, and chemotherapy. In the present case, however, because the lesion was unresectable, the patient was treated with only radiotherapy and adjuvant chemotherapy and showed a rapid and fatal clinical course.

Cardiac angiosarcomas do not typically present significant clinical manifestations, and this may account for the late diagnosis. In the present case, we believe that the oral metastasis was present before the diagnosis

of the cardiac lesion because the patient had a history of tooth extraction due to mobility, which is one of the clinical manifestations of oral angiosarcomas. Furthermore, the extraction site corresponded to the site of the lesion.^{20,38}

In conclusion, we describe this rare case of an oral metastasis of a cardiac angiosarcoma.

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