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Intraoral angiosarcoma with unusual clinical presentation: A case report☆

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ABSTRACT

Introduction: Angiosarcoma is a rare and highly aggressive soft tissue malignancy originating from vascular and lymphatic endothelial cells. Epithelioid angiosarcoma is the rarest subtype of angiosarcoma, characterized by the proliferation of large polygonal cells with an epithelioid feature. The occurrence of these tumors in the oral cavity is highly uncommon, and immunohistochemistry staining is essential to differentiate epithelioid angiosarcoma from mimicking lesions.

Aim: To present a case of intraoral angiosarcoma with an unusual clinical presentation and behavior and to report, to the best of our knowledge, a first primary appendix epithelioid angiosarcoma with metastasis foci in the oral cavity.

Objectives: To discuss the clinical, histological, and immunochemical features of an unusual case of intraoral angiosarcoma.

Case report: A 53-year-old Saudi female with an uncommon clinical presentation of intraoral angiosarcoma. The patient reported the lesion being painless, slowly growing, and of a six-month duration. The microscopic examination and immunohistochemical evaluation showed epithelioid angiosarcoma. The tumor cells were positive to ERG, FLI 1, and CD31 (focal) and negative to CK HMW, CD45, S100, HMB 45, D2-4, and CD 34.

Discussion: Due to the extremely rare occurrence and non-characteristic presentation of angiosarcoma in the oral cavity, many lesions maybe included in the differential diagnosis. Thus, making the diagnosis of intraoral angiosarcoma difficult.

1. Introduction

Angiosarcomas are a highly aggressive and rare subtype of soft tissue sarcomas. The progenitor cells are thought to originate from endothelial cells of blood and lymphatic vessels [1]. Angiosarcomas account for approximately 1–2% of all soft tissue sarcomas [2].

Abbreviations: IHC, immunohistochemistry; EA, epithelioid angiosarcoma; OPG, orthopantomogram radiograph; ECOG PS, Eastern Cooperative Oncology Group Performance Status; M, Male; F, Female; NM:, Not mentioned.

☆ We confirmed that informed consent was obtained from the subject. We confirmed that the IRP approval was obtained.

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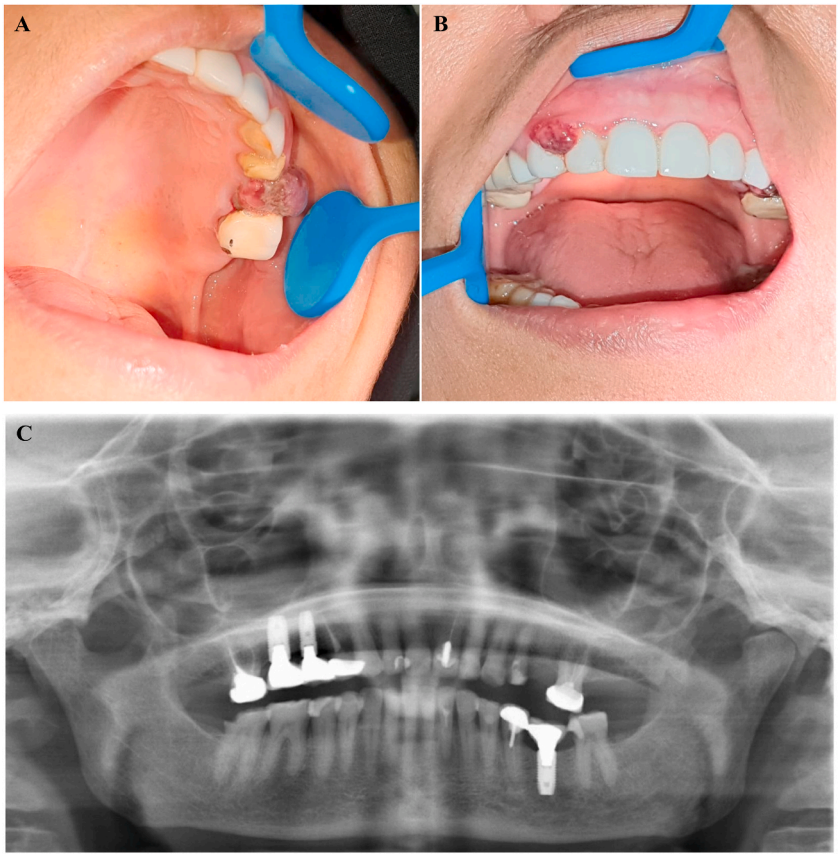

Fig. 1. Initial clinical presentation of the lesions: A) Exophytic pedunculated rubbery red to bluish nodular mass. B) Exophytic pink to reddish sessile mass on the dental papilla. C) OPG radiograph showing no destruction or invasion of the adjacent structures. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

The tumor usually occurs in elderly patients, with a slight male predilection with a peak incidence in the 7th decade. Even-though, the most common site of primary disease is cutaneous; it can develop in other anatomic locations like the breast and lower extremity and is less likely in the thyroid, cervical spine, adrenal gland, colon, and spleen [3].

The scalp is the most affected in the head and neck region. The occurrence of these tumors in the oral cavity is uncommon [4]. Intra-oral angiosarcoma usually presents as a red to purplish painful ill-defined mass with rapid growth and aggressive behavior that causes erosion of bone and destruction of adjacent structures [5,6]. The site most often enouncing for metastasis is the lung. Other sites like the liver, bone, soft tissue, and lymph node are frequently involved. The main route of metastasis is the bloodstream [7].

Angiosarcomas show a wide variety of histopathological cytology and architecture, including spindle, solid and epithelioid cells. They may range from well-differentiated lesions with a vasoformative growth pattern and well-developed anastomosing vessels lined by atypical endothelial cells to a poorly differentiated malignancy of epithelioid to spindle cells arranged in solid sheets without a prominent vasoformative pattern [8]. Reaching the definitive histopathologic diagnosis of angiosarcoma is difficult, making the use of immunohistochemistry (IHC) and a panel of endothelial markers necessary [9,10].

The principal treatment of a local lesion is radical surgery. Palliative chemotherapy and radiotherapy are used for metastatic lesions [3,5,11].

This case report aims to present a case of intraoral angiosarcoma with an unusual clinical presentation and behavior at the time of presentation, describing the clinical, histological, and immunochemical features. To the best of our knowledge, this may be the first reported case of primary appendix epithelioid angiosarcoma with metastasis to the oral cavity.

2. Case report

A 53-year-old married Saudi female was referred by her dentist to our Oral Medicine clinic with a chief complaint of swelling in the jaw starting six months ago. The swelling was located under a three-unit bridge constructed to replace the missing upper left second premolar. The treating dentist removed the bridge, but the lesion did not eventually disappear or reduce size. The patient reported the swelling to be painless and slow-growing.

The patient had hypertension, dilated cardiac myopathy, and a history of cardiac surgery many years ago. She was under medical

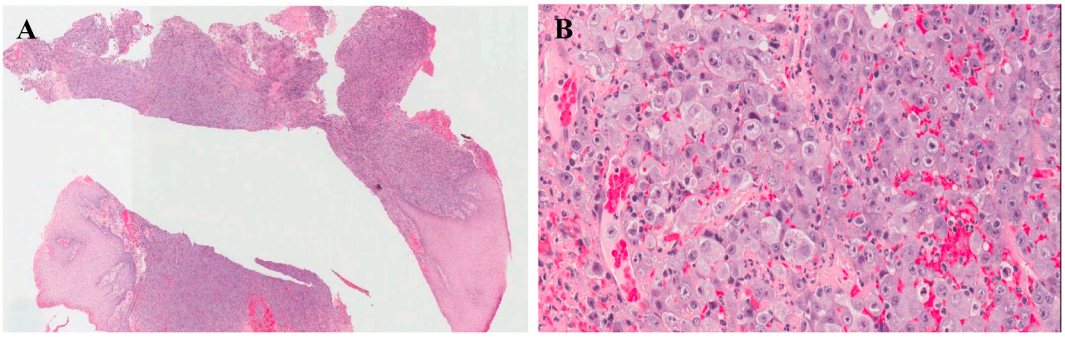

Fig. 2. Hematoxylin and eosin-stained microscopic photographs of the lesion in the area of missing upper left second premolar: A) Low power revealing the tissue diffusely infiltrated by the tumor cells. B) higher magnification showing irregular vascular space with multilayering of endothelial cells, the tumor cells have abundant cytoplasm with large nuclei, prominent nucleoli and some abnormal mitotic figures.

care for these conditions and was on the following medications; nitroglycerin sublingual, valsartan, atorvastatin, spironolactone, and furosemide. The extraoral examination was unremarkable.

Upon initial intraoral examination, two lesions were found. The first and larger lesion was an exophytic pedunculated red to bluish nodular mass with a smooth surface located in the area of missing upper left second premolar. It was rubbery in consistency, with a size of about 1.5 cm × 1 cm. The second lesion presented as a pink to reddish sessile mass on the dental papilla between the upper right lateral incisor and canine. It had a smooth texture, soft consistency and measured 0.4 cm × 0.7 cm in size. Both lesions were well-circumscribed and showed no bone erosion or destruction of adjacent structures on the orthopantomogram radiograph (OPG) [Fig. 1(A-C)]. The clinical differential diagnosis of the lesions included, but was not limited to, pyogenic granuloma, peripheral giant cell granuloma, peripheral ossifying fibroma, peripheral odontogenic lesion, and less possible Kaposi sarcoma and metastatic lesion to the oral cavity.

The lesion in the upper second premolar area was excised under local anesthesia (mepivacaine 2%, appx 1 ml) using a diode laser at 940 nm wavelength (Epic Biolase, Irvine, CA) with an initiated E4-4mm surgical tip. The tip was first applied in contact mode with a focused beam using the Circumferential Incision Technique to excise the tissue (3.5 W, continuous wave mode). Bleeding was then stopped using the hemostasis setting (0.5 W, continuous wave mode), and no suturing was needed. The specimen was sent for histopathological examination. Microscopic examination showed that the tissue was diffusely infiltrated by a sheet of atypical epithelioid cells with abundant eosinophilic cytoplasm, large vesicular nuclei with prominent nucleoli, and abnormal mitosis. The lesion was vasoformative with irregularly shaped anastomosing vascular channels. The endothelial lining cells showed multilayering and intraluminal tufting. The tumor cells were strongly and diffusely positive to ERG and FLI 1, also positive to CK 5.2, CK7 and CD31 (focal), and negative to CK HMW, CD45, S100, HMB 45, D2-4 and CD 34. Based on the histopathologic and immunohistochemical staining, the diagnosis was epithelioid angiosarcoma [Figs. 2(A and B) and 3 (A-I)].

Two weeks later, during the first post-biopsy visit, the site of the previous excision was found to have healed well without any reported post-operative pain. However, the second lesion had increased in size to reach about 0.6 cm × 1 cm, and three additional smaller asymptomatic lesions were noticed in the mandibular jaw. The largest of the three was located on the lingual interdental papilla between the lower right second premolar and first molar. The other two were located on the lower buccal interdental papilla of the left side, one between the two premolars and the second between the second premolar and first molar [Fig. 4(A-D)]. The extra-oral examination was also unremarkable, and the patient had no complaints. At this stage, the patient was diagnosed with suspicious metastatic epithelioid angiosarcoma (EA) with an unknown primary.

The patient was then referred to the Otolaryngology-Head and Neck Surgery Department in the same institute for further investigation and management. Where she underwent surgical removal of the oral lesions, which came as epithelioid angiosarcoma too with positive margin. An abdominal and pelvic CT scan with contrast showed a fluid-filled and dilated appendix up to 1.7 cm with a nodular enhancing wall along with surrounding stranding and peritoneal reflection thickening, concerning for appendiceal malignant neoplasm with local secondary inflammatory versus infiltrative procedure.

Noteworthy, one month later to her initial visit to our Oral Medicine clinic, the patient came to the Emergency Department at our institute complaining of severe abdominal pain and was diagnosed with appendicitis. As a result, she was admitted and underwent appendectomy under general anesthesia. The histopathologic report for the excised appendix and cecum tissue was also found to be epithelioid angiosarcoma [Fig. 5(A and B)], which was later considered the primary site for the lesion.

A whole-body FGD PET/CT showed two left frontal and occipital hyperdense cortical lesions with low FDG avid. In addition to left peritoneal metastatic deposit with increased metabolic activity and multiple metabolic osseous lytic lesions (spine, pelvis, left proximal head of humerus, and femoral) keeping with metastasis. A brain MRI with contrast showed multifocal hemorrhagic brain metastases and focal osseous metabolic deposit in the left parietal bone.

The patient left ventricular ejection fraction was 30% and was unfit for chemotherapy. So, she was started on palliative radiotherapy for oral cavity masses, which were complicated with mucositis and difficulty swallowing. She was improved on supportive treatment. Also, she received palliative whole-brain radiotherapy of a uniform dose of 20 Gy in 5 fractions over one week. She was also started on palliative Sunitinib, 37.5 mg once daily continuously, and was intolerant to it with severe fatigue, and Eastern Cooperative

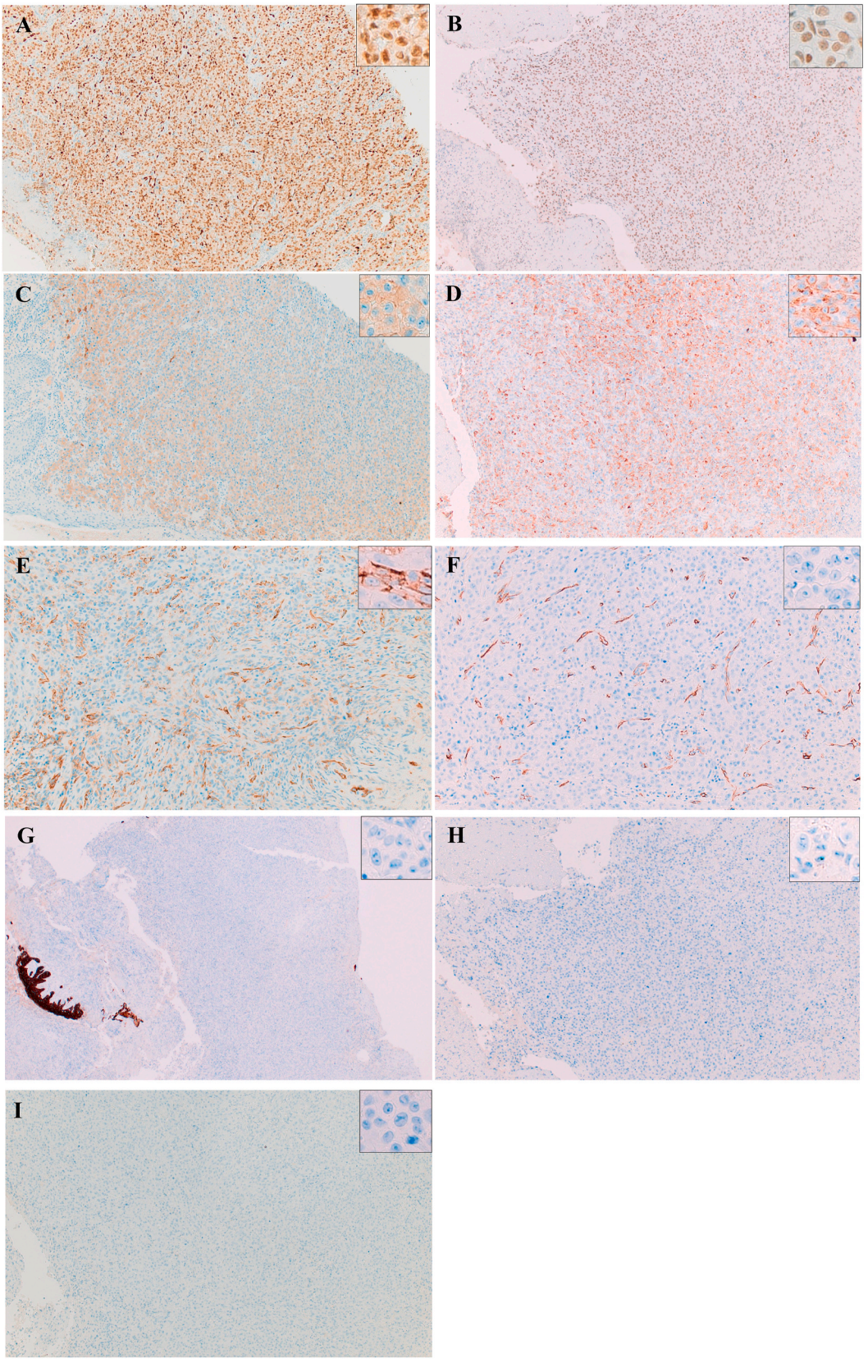

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Fig. 3. Immunohistochemical staining showing the tumor cells: positive to ERG (A), FLI-1 (B), CK 5,2 (C), CK 7 (D); focally positive to CD31(E); negative to CD34 (F), CK HMW (G), S100 (H), HMB 45 (I).

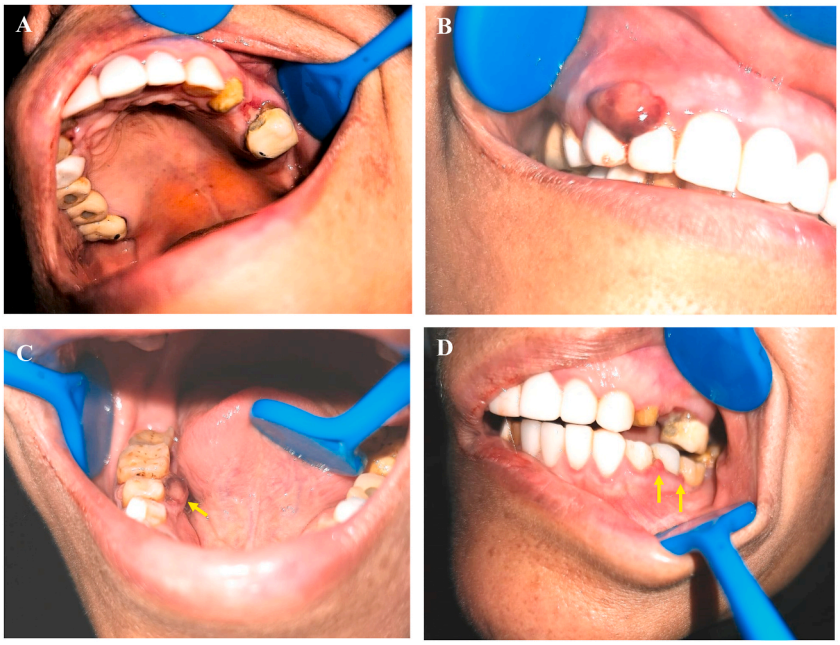

Fig. 4. Intraoral photographs two weeks post-laser excision showing: Healing of surgical site (A); Dental papilla lesion increasing in size (B); Appearance of three new lesions indicated by arrows (C and D).

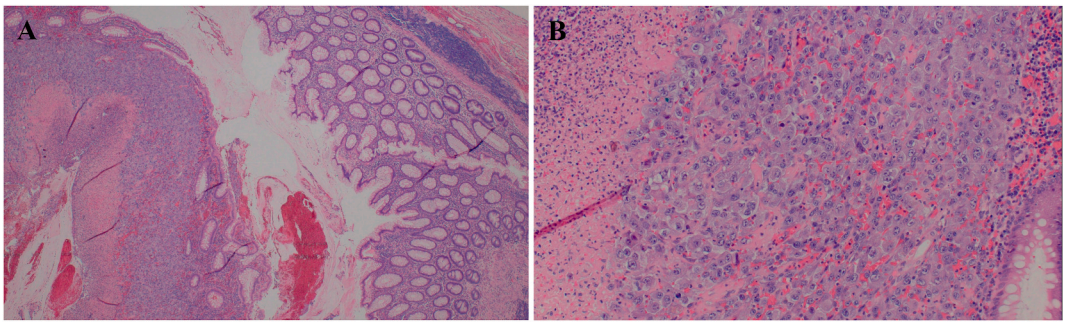

Fig. 5. Hemoxylin and eosin-stained sections revealing tumor cells infiltrating the appendix: Low power (A); Higher power (B).

Oncology Group Performance Status (ECOG PS) was G3. Alternatively, the patient started on Regrafinib 80mg once daily for three weeks, followed by one week off therapy every four weeks. However, she presented to the emergency department confused with poor oral intake, and ECOG PS was G4. So, the patient was referred to the palliative medicine department for take over for terminal and supportive care. The patient died of the disease shortly thereafter.

3. Discussion

Epithelioid angiosarcoma is a morphologic subtype of angiosarcoma that was described for the first time by Weiss et al. [12]. It is a scarce variant of soft tissue sarcoma with a highly aggressive behavior [2].

Before the diagnosis, intraoral angiosarcoma usually presents with various signs and symptoms. It has been reported as a painful, rapidly progressive, and highly aggressive ovoid to round nodule (s) that extends to adjacent structures and usually causes bone erosion and destruction [5,6].

The etiology of epithelioid angiosarcoma remains unknown. However, many risk factors for developing epithelioid angiosarcoma have been identified, including previous radiation to the affected site, chemical exposure to vinyl chloride, thorium dioxide, arsenic, and possible UV exposure, chronic lymphedema, familial syndromes like neurofibromatosis, Maffucci syndrome, and Klippel-Trenaunay syndrome [13,14]. Moreover, different genetic mutations associated with angiosarcomas have been reported in the

Table 1
Clinicopathological and immunohistochemical features of metastatic epithelioid angiosarcoma involving the oral cavity and gnathic bones previously published in the literature including our case.

Authors	Primary site	Age/ gender	clinical	IHC	treatment	prognosis
Our case	appendix	53/F	Well circumscribed multiple & painless reddish to blue exophytic mass in maxillary gingiva. OPG did not show any bone erosion or destruction of adjacent structures on orthopantomogram radiograph	positive to ERG and FLI 1, also positive to CK 5.2, CK7 and CD31 (focal), and negative to CK HMW, CD45, S100, HMB 45, D2-4 and CD 34	Surgical, palliative radio & chemotherapy	Died about 10 months after 1st visit
Peacock Z. S. 2013	Kidney	64/M	Dull, constant pain in the right preauricular area; full mandibular opening, mass associated with the right mandibular condyle and medial soft tissue., CT scan showed a poorly defined radiolucency involving the medial condyle and sigmoid notch of the mandible	Positive for: keratin, EMA, CD10, CD31, FLI-1) FVIII Negative for: RCC PAX-2, S-100, HMB45, CD34	surgical	Alive 2.5y after resection
Fukushima J. 2005	Scapular region	71/M	Painless, hard & non-mobile buccal gingival sessile swelling of Left lower molar region, necrotic overlying mucosa, OPG revealed ill-define lytic process	Positive for: factor VIII, CD 34, silver reticuline	Palliative radiotherapy	Died after 35 days of 1st visit
Fanburg-Smith JC 2003	Skin of forehead	65/M	Right upper gingiva	Not specify[a]	NM	Died within 2 years
Fanburg-Smith JC 2003	Skin	69/M	Maxillary gingiva	Not specify[a]	NM	Died after 1 y
Fletcher 1991	Buttock	63/M	Fungated gingival maxillary lesion,	positive Factor VIII, CD 34, Keratin	chemotherapy	Alive 2.5 y after 1st visit

M: male. F: female. NM: not mentioned. OPG: orthopantomogram.
[a] The authors mentioned a list of IHC stains without specifying each case (positive for Factor VIIIrag in 19/21, CD31 in 16/19, CD34 in 7/12 and all cases were negative for pankeratin, S100 protein, HMB45, desmin, actins, and leukocyte common antigen).

literature [15].

There are only six cases of metastatic epithelioid angiosarcoma involving the oral cavity and gnathic bone previously reported in the literature (including our case) [4,16–18]. These cases tended to occur mainly in the elderly with male predilection and the skin as the main primary site. The primary site of the lesion was known in all cases at the time of metastasis, with apparent effects on adjacent bone (when a radiograph was performed) except in our case. A summary of these cases is given in Table 1. In this reported case, the lesion was the only one affecting a female patient at a slightly younger age and initially presented as a painless, slow-growing mass that had a clinical resemblance to pyogenic granuloma, causing no destruction to adjacent structures. The patient had no known risk factor for developing epithelioid angiosarcoma; no history of nausea, vomiting, gastrointestinal bleeding, abdominal discomfort, bowel obstruction, or sudden weight loss, which may have suggested a malignant nature of the underlying lesion [2,19]. Thus, interestingly, presenting a variable behavior to which such lesions usually manifest [20].

The histopathologic diagnosis of epithelioid angiosarcoma depending only on morphological features is unreliable and challenging since it may be confused with other lesions presenting with epithelioid cells such as epithelioid sarcoma, metastatic carcinoma, and melanoma [21]. Consequently, the use of Immunohistochemistry (IHC) is strongly helpful in distinguishing epithelioid angiosarcoma from other lesions and making the definitive diagnosis [22]. In this presented case, the negativity to S-100 and HMB-45 expression excluded melanoma, while positivity to FLI-1 and CD 31 excluded carcinoma and epithelioid sarcoma.

Epithelioid angiosarcoma generally shows positivity to CD31 and 34, Fli 1, ERG and claudin-5, with the expression of immunohistochemical stains CD31 and CD34 being variable [9,10,23]. ERG, on the other hand, has the highest sensitivity (reaching 100%) and a high specificity [23–25]. This raises the importance of using such an endothelial marker in cases where the widely used stains are negative, weak or focally positive to detect vascular and endothelial differentiation. Additionally, tumors with epithelioid morphology may express keratins and epithelial membrane antigen (EMA) [9,10].

CD31, being the golden standard for diagnosing angiosarcoma, with high sensitivity and good specificity, was only focally positive in our case. Moreover, in this case, epithelioid angiosarcoma was entirely negative for CD34. This is not unusual, as it has been similarly reported by others previously [9,10,23–25].

Various factors may affect the survival of patients with angiosarcoma, including treatment strategy, gender, age more than 65 years, distance metastasis, lesion depth, histologic parameter, and site of presentation. Patients with non-cutaneous lesions, presenting with metastatic angiosarcoma, and having epithelioid morphology and necrosis are associated with a worse prognosis, while patients with resectable angiosarcoma with vasoformative architecture have a better prognosis [13,26].

Multi-disciplinary care has significantly improved the overall survival of patients with angiosarcoma. When angiosarcoma presents with metastasis, at the time of diagnosis, adjunctive radiotherapy or/and chemotherapy, in addition to surgical removal, are indicated. Compared to supportive care, both radiotherapy and chemotherapy improve survival [3,11,27].

There is no significant impact of systemic therapy type on the overall survival [22]. However, the objectives of neoadjuvant systemic treatment are to down-size the tumor, which facilitates surgical resection, early eradication of micrometastases, and treatment of metastasis [27,28].

Due to the limited number of intraoral angiosarcoma cases reported in the literature, there is no clear conclusion concerning the best approach for treatment. However, early diagnosis and complete surgical excision remain essential and are considered the most important predictors for a better outcome and survival [26].

4. Conclusion

This case report, up to our knowledge, is the first reported case of a primary appendix angiosarcoma with metastasis to the oral cavity. It highlights the fact that the initial clinical presentation and behavior of malignant oral lesions, such as epithelioid angiosarcoma, may mimic benign lesions. Thus, making a histopathologic examination, using the proper selection of an IHC staining panel, necessary to reach an accurate diagnosis.

Author contribution statement

All authors listed have significantly contributed to the investigation, development and writing of this article.

Data availability statement

The authors have nothing to acknowledge.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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