Clinical Case Report

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Intraosseous epithelioid haemangioendothelioma of the mandible

A case report and literature review

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Abstract

Introduction: Epithelioid haemangioendothelioma (EHE) is a rare vascular neoplasm that primarily occurs in the soft tissues of the extremities, with "intermediate" or "borderline" malignant biological characteristics and a propensity for recurrence and metastasis. Oral cavity involvement is extremely rare, with only 5 reported cases of intraosseous EHE of the mandible. Herein, we report an additional case and review the related literature.

Patient concerns: A 44-year-old man was referred to our institution with a 2-month history of left lower lip numbness and a 2-week history of painful swelling of the left mandible. He had received antibiotic treatment, which failed to ameliorate his symptoms. His medical and family histories were not significant.

Diagnosis: Enhanced computed tomography revealed a poorly defined, 4.5 × 3.5 × 1.0 cm osteolytic lesion in the angle and ramus of the mandible, as well as an eroded lingual cortex. Histopathological examination confirmed a diagnosis of EHE.

Interventions: Surgical resection was performed via segmental mandibulectomy and the defect was reconstructed using a vascularized fibular flap.

Outcomes: The patient did not exhibit signs of locoregional recurrence after 3 years of follow-up.

Conclusions: Intraosseous EHE of the mandible is an unpredictable lesion with a relatively benign course; however, the few reported cases of this disease do not highlight any factors that can predict the risk of locoregional recurrence or metastasis. There is also no consensus regarding the optimal treatment for intraosseous EHE; however, we recommend extensive local excision with close clinical follow-up.

Abbreviations: EHE = epithelioid haemangioendothelioma, SMA = smooth muscle actin.

Keywords: epithelioid haemangioendothelioma, mandible, vascular neoplasm

1. Introduction

Epithelioid haemangioendothelioma (EHE) is a rare neoplasm characterized by the presence of abnormally proliferating epithelioid or histiocytoid endothelial cells. The biological behavior of EHE is thought to be intermediate between that of angiosarcoma and hemangioma.[1] Accordingly, EHEs have a propensity for local recurrence and metastasis; however, tumor-specific mortality rates may depend on their anatomic site of origin. The first report of this tumor type by Weiss et al in 1982 indicated that the predominant sites of involvement were soft tissues such as those in the extremities, lungs, and liver.[2,3] Additionally, there are only approximately 30 reported cases of this tumor type in the oral cavity, with most cases involving the gingiva of the mandible or maxilla.[4] Intraosseous EHE of the mandible is extremely rare, with only 5 cases reported in the literature. Thus, based on its low incidence and histological similarity to other solid tumors, it is difficult to precisely diagnose EHE. Herein, we report an additional case of intraosseous EHE of the mandible, as well as the clinical and histological characteristics that were needed to reach the correct diagnosis. We also discuss current treatment regimens.

2. Case report

A 44-year-old man was referred to our institution with a 2-month history of left lower lip numbness and a 2-week history of rapid

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Informed Consent: Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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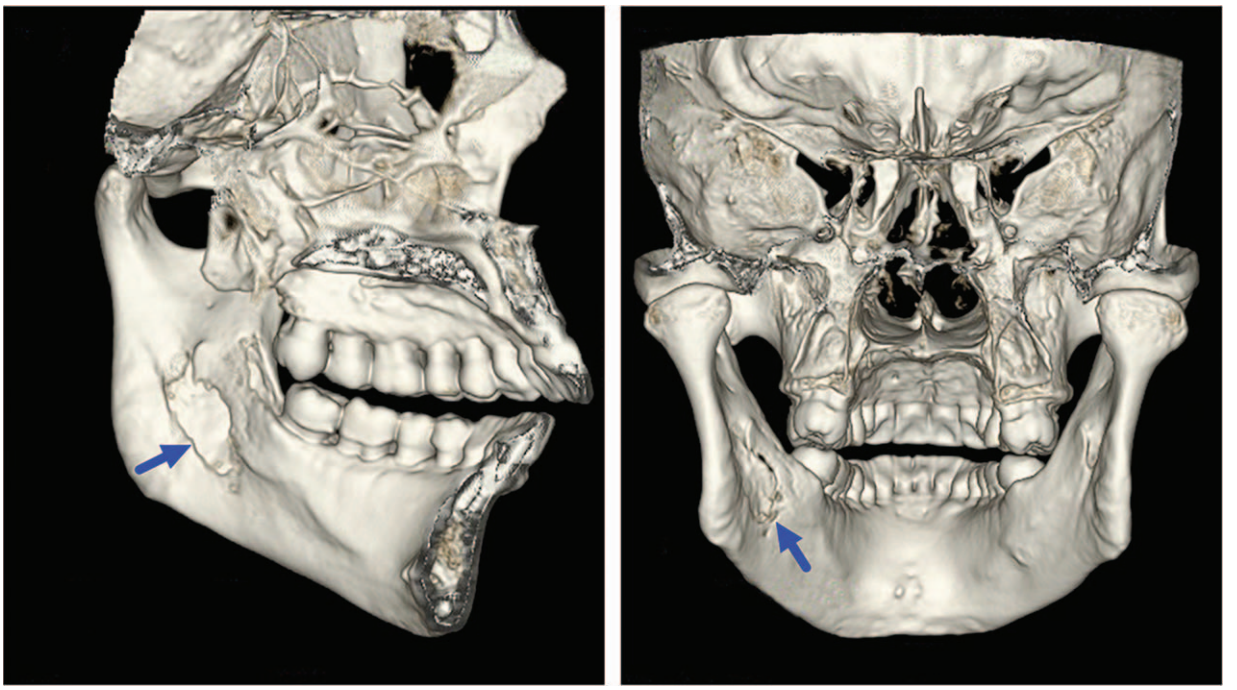

Figure 1. Radiography indicated a poorly defined, multilocular radiolucency located in the area of the left mandibular angle and ramus (arrow).

painful swelling of his left mandible. He had received antibiotic treatment, which failed to ameliorate his symptoms. His medical and family histories were not significant. An intraoral examination revealed a slight lingual expansion of the left ascending ramus of the mandible, which was accompanied by an intact and apparently normal mucosa. There were no similar lesions on the right side of his oral cavity and no palpable lymph nodes in the neck. Enhanced computed tomography revealed a poorly differentiated $4.5 \times 3.5 \times 1.0$ cm osteolytic lesion in the angle and ramus of the mandible, with lingual cortical destruction but no periosteal reaction (Fig. 1). Based on these clinical and radiological findings, we suspected a malignant mandibular tumor and performed segmental mandibular resection with neck dissection. The defect was reconstructed using a vascularized fibular flap, and the surgical wound healed within 1 week after the operation.

The surgical specimen was fixed using 10% formalin and embedded in paraffin. Hematoxylin and eosin staining revealed the presence of proliferating endothelial cells and the formation of small vascular channels (Fig. 2A). Furthermore, the endothelial

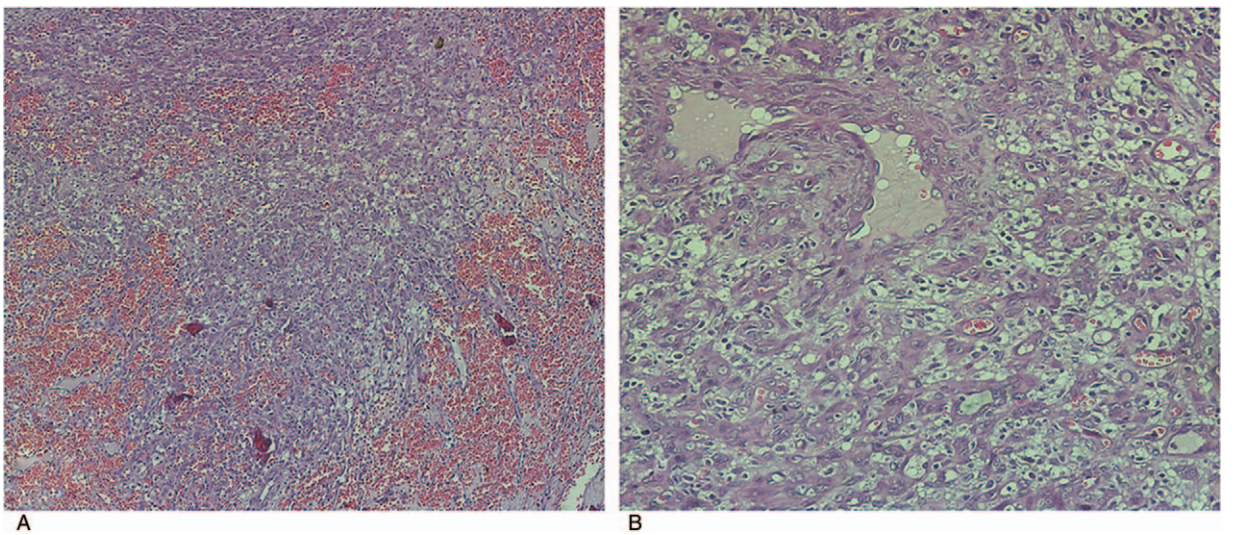

Figure 2. The tumor is composed of solid nests of polygonal endothelial cells with eosinophilic cytoplasm. (Hematoxylin and eosin stain. Original magnification: [A] ×100 and [B] ×200.).

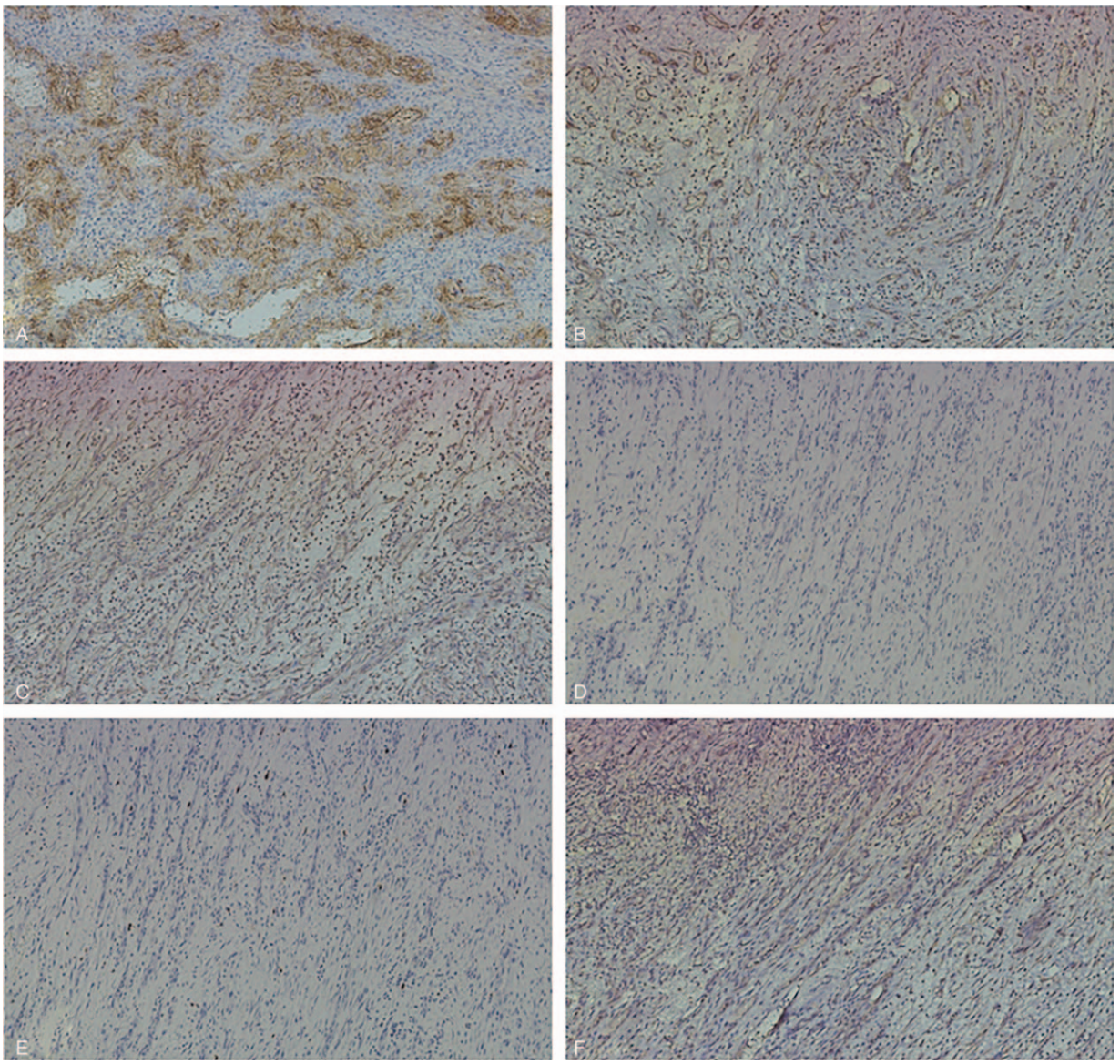

Figure 3. Immunohistochemical analysis revealed the tumor cells were positive for (A) factor VIII-related antigen, (B) CD31, and (C) vimentin, and negative for (D) pan-cytokeratin, (E) S-100, and (F) smooth muscle actin. (Immunohistochemical staining, original magnification: ×200.).

cells were large and polygonal, with abundant granular cytoplasm and occasional intracytoplasmic vacuoles (Fig. 2B). The tumor also contained a scant, loosely arranged fibrous stroma and a scattered infiltrate of mixed inflammatory cells. Mitotic activity and necrosis were not observed. Immunohistochemistry revealed that the tumor cells were positive for factor VIII-related antigen, CD31, and vimentin, but negative for pan-cytokeratin, S-100, and alpha smooth muscle actin (SMA) (Fig. 3). These features confirmed a diagnosis of EHE. Importantly, the patient did not exhibit any signs of local recurrence or metastasis after 3 years of follow-up.

3. Discussion

EHE neoplasms are angiocentric and characterized by the presence of epithelioid endothelial cells with inherent metastatic potential. Given the low prevalence of this neoplasm, as well as its varied biological behavior, many names have been assigned to this disease, including sclerosing angiogenic tumor, sclerosing epithelioid angiosarcoma, sclerosing endothelial tumor, malignant haemangioendothelioma, and sclerosing stromal angiosarcoma.

EHE was first described by Weiss et al in 1982,[2] and was reported to account for only 1% of all vascular neoplasms.[5] Although this lesion can occur in patients of almost any age, EHE remains rare among children and usually presents as a solitary mass in either deep or superficial soft tissues.[6] The most common site of EHE development is the tissues of the extremities, but it can also occur in bone, lung, liver, brain, nerves, and lymph nodes. In contrast, there are only 30 reported cases of EHE in the oral cavity.[7] The most commonly reported intraoral site for EHE development is the gingiva or alveolar mucosa,[4] with tumor diameters ranging from 1.5 to 4.5 cm, and affecting men and women at a ratio of 1:2.5.[8] Patients were usually referred

Table 1

Features of the present case and those of previously reported cases of epithelioid haemangioendothelioma of the mandible.

Author (s)	Year reported	Age, sex	Location	Clinical history and examination findings	Radiographic findings	Treatment	Follow-up	Comments
Yang et al Present study	2018	44 y, M	Left mandible	Numbness of the left lower lip and painful swell of the left mandible	A $4.5 \times 3.5 \times 1$ cm poorly defined osteolytic lesion in the angle and ramus of the mandible, the lingual cortex was eroded	Surgical resection was performed via segmenta lmandibulectomy and the defect was reconstructed using a vascularized fibular flap.	NED after 3 y	
Ventorre et al[13]	2008	63 y, M	Right mandibular ramus	Pain associated with paraesthesia of perimandibular soft tissues	A 1.0×1.0 cm osteolytic area, involving the right mandibular ramus	Probing excision, A reconstruction of the local oral mucosa was also performed with skin graft	NED after 12 mo	
Chi et al[8]	2005	23 y, F	Left posterior mandible	A symptomatic, located in extraction site of left mandibular third molar, intraoperatively appeared yellowish-tan in color	2.0×1.5 cm well-defined radiolucency	Enucleation followed by wider excision	NA	
Machalka et al[10]	2003	65 y, M	Anterior mandible, recurrence extended to the right mandibular body and angle	Gradual chin enlargement, pain, tooth mobility	Poorly defined unilocular radiolucency with scattered radiopacities	Initially treated by radical resection and bone autograft; first recurrence treated by partial resection;second recurrence treated by hemimandibulectomy followed by 50-Gy radiotherapy	Recurrence 4 y and 8 y after initial treatment, NED 5 y after last surgery	Microscopic examination of the second recurrence showed marked cellular atypia, increased mitotic activity, and focal necrosis (unlike the previous biopsies)
Eckardt et al[12]	2000	5 mo, M	Right mandible	A rapidly growing mass of the right mandible, right horizontal mandible extending from the canine tot the ascending ramus. No mucosal ulceration	An extensive tumor measuring 4.0×3.0 cm with bone destruction of the right mandible	A segmental mandibular resection with an autologous rib graft reconstruction	NED after 8 mo	
Hamakawa et al[11]	1999	76 y, F	Anterior mandible	4.5×4.0 cm rubbery hard submucosal mass of the anterior mandibular vestibule, mild tenderness	Ill-defined radiolucency with labial cortical expansion and resorption	NA	NED after 6 y	

F = female, Gy = gray, M = male, m = month, NA = no data available, NED = no evidence of disease, y = year.

based on the presence of a solitary, red-purplish, asymptomatic mass on the alveolar gingiva, buccal mucosa, tongue, palate, lip, maxilla, or mandible.[9] Patients occasionally reported experiencing tenderness, pain, or tingling, and other clinical findings have included mucous ulceration and tooth mobility.[8] Only 6 cases (including our case) of EHE of the mandible have been reported, and the characteristics of the patient in the present case are summarized in Table 1. Two cases involved the anterior mandible[10,11] and 4 cases involved the ramus.[8,12,13] However, our knowledge of this disease remains limited, given its low prevalence.

The radiographic appearance of EHEs ranges from well- to poorly defined radiolucencies, with or without radiopaque foci and periosteal reaction.[14] Although computed tomography and magnetic resonance imaging can detect bone destruction, they do not provide sufficient information for a pre-biopsy diagnosis based on the magnitude of involvement and compression of the inferior alveolar nerve. Previous reports have indicated that intraosseous EHEs may be multicentric,[3] although none of the reported jaw lesions exhibited a multicentric nature. In this context, an intraosseous lesion of the mandible can mimic a benign odontogenic tumor or cyst without absorption of root apices.

EHE is characterized by the presence of epithelioid endothelial cells with rich eosinophilic cytoplasm, nuclear and cellular pleomorphism, and dense nuclear chromatin. Tumor cells are commonly arranged in cords, nests, or short strands within the myxoid stroma, and frequently contain prominent intracytoplasmic signet ring-like vacuoles.[15] Unfortunately, there are no reliable clinical or histological criteria for predicting the biological behavior of this vascular tumor, including necrosis or an increased number of mitotic figures. Nevertheless, it has been suggested that more aggressive behavior is associated with mitotic activity, an increased proportion of spindle-shaped tumor cells, focal necrosis, significant cellular atypia, and metaplastic bone formation within the tumor.[2]

A diagnosis of EHE is generally based on immunohistochemistry results and molecular characteristics. For example, these tumors are typically positive for factor VIII-related antigen, CD31, CD34, FLI-1, vimentin, and UEA-1, but are typically negative for SMA, S100, CD68, EMA, MNF116, and CK7.[16] It may also be useful to perform fluorescence in situ hybridization or reverse-transcription polymerase chain reaction analysis to detect the presence of the WWTR1-CAMTA1 fusion gene.[5] Testing for CD34 expression alone is insufficient, as this marker is expressed by >90% of vascular tumors; therefore, staining for both CD31 and FLI-1 has been recommended for diagnosing EHE.[6] Moreover, EHE can be mistaken for carcinoma because it can exhibit epithelioid morphology and focal cytokeratin positivity in some cases.[17]

It is important to determine whether an EHE involves the mandible and has penetrated the cortex and infiltrated the gingival mucosa, or whether it originated in the gingiva with destruction of the alveolar ridge. This distinction can be made based on whether the bone destruction from the gingiva is limited to erosion. In our patient, marked bone resorption was noted in the mandible, and the cortical bone had expanded on the labial side, suggesting the presence of a primary intraosseous tumor of the mandible. Based on the patient's presentation, it was important to differentiate EHE from other lesions, such as an odontogenic tumor, pyogenic granuloma, giant cell tumor of bone, glomangiopericytoma, epithelioid angiosarcoma, sarcoma,

malignant melanoma, or carcinoma.[8,17] Most of these tumors can be distinguished based on microscopic examination and immunohistochemistry findings, with an epithelioid phenotype and positive cytokeratin staining suggestive of a carcinoma.

Owing to the low incidence of EHE, there is a paucity of effective evidenced-based treatment regimens. However, because EHE exhibits a propensity for local recurrence and metastasis, wide local excision with close clinical follow-up has been recommended.[6] Furthermore, the vascular nature of this tumor highlights the critical issue of intraoperative blood loss during surgical excision,[18] which could be managed based on preoperative angiographic evaluation and selective embolization of the main blood supply. In our case, the lesion was primarily confined to a small area of the mandible; thus, we avoided significant bleeding by ligating the inferior alveolar artery before the segmental mandibulectomy. Moreover, some reports have indicated that radiotherapy, chemotherapy, and targeted therapy are acceptable options for treating EHE of the bone.[19] However, as radiotherapy and chemotherapy have only each been used for one case of intraosseous EHE of the mandible, the effectiveness of these treatments in this setting requires further evaluation.

The literature indicates that 29.6% (8/27 cases) of intra-oral EHEs locally recur without developing distant metastases.[4] Thus, cases with abundant mitoses and histological atypia should be treated carefully, as it is impossible to predict the true recurrent and metastatic potential of intraoral EHE.[17] Furthermore, treatment of this disease is complicated by the lack of clear terminology and standard diagnostic criteria, as well as its anatomic site- and patient age-dependent biological behavior. Moreover, 2 patients with intraosseous EHE of the mandible experienced local recurrence after inappropriate treatment, highlighting the challenges of reaching a correct diagnosis before surgery. It may be necessary to perform a preoperative biopsy and obtain wide margins during local excision to successfully treat this tumor.

4. Conclusion

The clinical characteristics of intraosseous EHE of the mandible can strongly mimic those of an odontogenic tumor or pyogenic granuloma. Based on their potential for recurrence and metastasis, as well as the fact that radiotherapy and chemotherapy have not provided consistent positive results, extensive local excision combined with close clinical follow-up appears to be a good treatment choice for these tumors.

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