Epithelioid rhabdomyosarcoma: Report of the first case in the jaw

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Objectives. Epithelioid rhabdomyosarcoma (EpiRMS) is a novel morphologically distinct variant of rhabdomyosarcoma, with an unusually challenging microscopic diagnosis. The occurrence of rhabdomyosarcomas in the jaws is extremely rare. This study presents the first case of EpiRMS in the jaw (mandible) and a literature review of the previous 35 cases of EpiRMS.

Study Design. Here, we report a case of EpiRMS affecting an 18-year-old male patient. Clinical, imaging, microscopic, and immunohistochemical features are discussed and previously reported cases of EpiRMS are reviewed.

Results. An 18-year-old male patient presented with an exophytic sessile growth on the buccal gingiva, and orthopantomography revealed irregular bone loss. Microscopic analysis showed a large number of cells with epithelioid appearance. Immunohistochemistry staining was positive for desmin, myogenin, MyoD1, smooth muscle actin, h-caldesmon, INI-1, and AE1-AE3. The patient's disease was staged as T4aN1M0 and was treated with surgical excision combined with chemotherapy.

Conclusions. The occurrence of RMS in the mandible is rare, and this is the first case of EpiRMS in the jaw. EpiRMS is an unusual histologic subtype that mimics other sarcomas and epithelial malignancies, making diagnosis a challenge. A specific immunohistochemistry panel aids in the diagnosis. EpiRMS has an aggressive course and an unfavorable prognosis. (Oral Surg Oral Med Oral Pathol Oral Radiol 2020;130:e308−e315)

Rhabdomyosarcoma (RMS) is a malignant mesenchymal neoplasm that exhibits varying degrees of skeletal muscle differentiation. It is the most common malignancy of soft tissues affecting patients up to 20 years of age.[1,2] Approximately 35% of all RMSs occur in the head and neck region.[3] Oral RMSs are classified as nonorbital and nonparameningeal and represent 28% of head and neck RMSs.[4] Oral manifestations of RMS may occur in about a fifth of cases, involving the oral and paraoral regions, as reported in the literature.[5]

RMS is currently classified into 3 main histologic subtypes: embryonal, alveolar, and pleomorphic. Other variants include spindle cell RMS and sclerosing RMS.[1] The biologic behavior of RMS is aggressive, although current treatment modalities have increased survival. The prognosis is worse in adults, a fact attributed, in part, to decreased tolerance of aggressive chemotherapeutic regimens.

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The epithelioid variant of RMS was first described by Seidal et al. in 1989.[6] This variant is characterized by epithelioid features reminiscent of a poorly differentiated carcinoma or melanoma and mostly affects older adults. Only 36 cases of epithelioid rhabdomyosarcoma (EpiRMS), including the current case, have been published in the English language literature (Table I). To our knowledge, this is the first report of EpiRMS affecting the jaw.

CASE REPORT

An 18-year-old male patient presented to the Dentistry Hospital Emergency Service complaining of a painful growth in the left posterior region of the mandible after a third molar extraction in this region 15 days ago. Extraoral examination showed a diffuse swelling, and the left submandibular lymph node was palpable, mobile, and nontender. Intraoral examination revealed an exophytic, lobulated, sessile growth on the buccal gingiva (Figure 1A), extending from the left mandibular first molar to the distal side of the third molar and obliterating the buccal vestibule. Orthopantomography revealed irregular bone loss (Figure 1B) extending from the region of tooth #38 to the mandibular branch. Cone beam computed tomography (CBCT) showed destruction of both the buccal and the lingual bone cortical plates (Figure 1C), along with erosion of the superior border of the mandibular canal.

Incisional biopsy was performed and the specimen submitted for histopathologic examination. Microscopic features included large polygonal tumor cells arranged in sheets and intermixed with spindle cells (Figure 2A). The cytologic appearance of the cells varied, with a predominance of cells exhibiting

Table I. Clinical and immunohistochemical features of the 36 reported cases of epithelioid rhabdomyosarcomas

Author, year	*Case*	*Age (y)/ Gender*	*Site*	*Side*	*Size (cm)*	*Treatment*	*Margin status*	*Recurrence (months)*	*Metastasis (months)*	*Follow-up (months)*	*Immunohistochemistry*
Seidal et al., 1989	1	60/F	Minor pelvis, broad ligament	NA	6	CT, RT	NA	Yes (32, 80)	Abdominal, pulmonary	Alive (84)	Desmin, actin (++) Vimentin (+) Cytokeratin CAM5.2, AE1/AE3, EMA, myoglobin (−)
Suárez-Vilela et al., 2004	2	70/M	Retroauricular and submandibular and supraclavicular LN	R	5.5	CT	NA	NA	LN	DOD (3)	Desmin, vimentin, MIB-1 (++), myogenin, CAM5.2, AE1/AE3, myoglobin, CD99, E-cadherin, EMA, p53 (+) SMA, HHF-35, CEA, PLAP, collagen IV, NSE, H-caldesmon, melan-A, CK7, CK20, CD3, CD20, CD68, CD23, CD34, CD45 (−)
Fujiwaki et al., 2008	3	51/F	Fallopian tube	L	6.5	SE, CT	NA	NA	Multiple LN	DOD (6)	myo-D1, desmin, myoglobin, HHF-35, vimentin (++) S-100, HMB45, CD45, keratin, AE1/AE3, CD10 (−)
Bowe et al., 2011	4	72/M	Parotid basin LN	R	3.6	SE, CT	NA	No	No	ANED (12)	desmin, myogenin, HHF-35, CD10, and vimentin (++) S-100, HMB-45, melan-A, pancytokeratin cocktail, p63, SMA, calponin, renal cell carcinoma, MOC-31 (−)
Jo et al., 2011	5	77/F	Left atrium	NA	3	SE	NA	NA	NA	NA	Desmin, myf-4 (++) all cases S-100 (−) all cases Cytokeratin (−) 12 cases EMA (+) 2 cases PLAP (+) 1 case
	6	71/M	Knee (IM)	NA	NA	SE, RT, CT	Wide	Yes (4 / 6)	Lung (1), inguinal LN (8)	DOD (10)	
	7	73/M	Back (IM)	NA	8	SE	Marginal	SN	Pleural fluid (3)	DUC (12)	
	8	70/M	Neck (IM)	NA	5.3	SE LN, CT	NA	NA	Neck LN (0)	DOD (5)	
	9	76/F	Neck LN*	NA	NA	RT	NA	NA	Mediastinal and neck LN (0)	DOD (2)	

(*continued on next page*)

Table I. Continued

Author, year	*Case*	*Age (y)/ Gender*	*Site*	*Side*	*Size (cm)*	*Treatment*	*Margin status*	*Recurrence (months)*	*Metastasis (months)*	*Follow-up (months)*	*Immunohistochemistry*
	10	71/NA	Mediastinal LN*	NA	NA	NA	NA	NA	Mediastinal LN (0)	NA	
	11	34/M	Arm (IM)	NA	8	SE, RT, CT	Marginal	NA	Lung (0, 11, 24), bone (43)	DOD (60)	
	12	67/M	Hypopharynx and neck LN	NA	3.7	SE	NA	NA	Right neck LN (0)	NA	
	13	65/F	Anterior abdominal wall (SC)	NA	4.5	NA	NA	NA	NA	NA	
	14	24/M	Thigh (IM)	NA	8.5	SE, CT	Wide	No	Lung (0), liver	DOD (6)	
	15	14/F	Elbow (IM)	NA	NA	SE, RT, CT	Wide	No	No	ANED (47)	
	16	39/M	Forearm (IM)	NA	8	SE, RT, CT	Positive	Yes with SN (8)	Axillary LN (8), lung (9)	DOD (10)	
	17	76/M	Shoulder (IM)	NA	8	SE	Wide	No	Lung (24)	DOD (24)	
	18	72/M	Chest wall (IM)	NA	5	SE, CT	Wide	No	No	ANED (36)	
	19	52/M	Neck (IM)	NA	NA	NA	NA	NA	NA	NA	
	20	78/F	Scalp (SC)	NA	6	SE	NA	No	No	DOAC (4)	
Marburger et al., 2012	21	60/M	Shoulder	NA	1.2	SE, CT, RT	NA	No	Axillary LN	AWD	Desmin, myogenin, MyoD1, cytokeratin (++)
Feasel et al., 2014	22	75/M	Base of neck	L	3.3	NA	NA	NA	NA	NA	Desmin, MyoD1 (++) CK903, myogenin (+) Melan-A, S-100, SOX10, p63, CK5/6 (−)
Zin et al., 2014	23	9/M	Head and neck, parameningeal	NA	NA	CT, SE	Free of disease	No	LN	ANED (96)	Desmin, INI-1, myogenin (++)
	24	6/M	Head and neck, parameningeal	NA	3.3	CT, SE	Free of disease	No	LN	ANED (120)	AP-2 b (−) all cases EMA, MNF116 (+) cases 25 and 26
	25	13/F	Arm	NA	4	CT, SE	Free of disease	No	No	ANED (72)	
	26	8/F	Arm	NA	8.3	CT, SE	Free of disease	No	No	ANED (24)	
	27	8/M	Orbit	NA	4	CT, SE	Free of disease	No	No	ANED (48)	
Yu et al., 2015	28	19/F	Thigh	L	15	NA	Positive	NA	NA	DOD (4)	Desmin, myogenin, MyoD1, SMA, MSA (++) all cases S100, HMB-45, CD99, LCA, CD20, PAX5,
	29	78/M	Waist and back	L	12	SE, RT	Positive	Yes (7/9)	No	ANED (13)	
	30	62/M	Chest wall	L	12.5	SE, SE LN	Positive	No	Axillary LN (0)	ANED (2)	
	31	55/M	Femur	L	2.5	SE, CT	Positive	No	Lung (6)	DOD (14)	

(*continued on next page*)

Table I. Continued

Author, year	*Case*	*Age (y)/ Gender*	*Site*	*Side*	*Size (cm)*	*Treatment*	*Margin status*	*Recurrence (months)*	*Metastasis (months)*	*Follow-up (months)*	*Immunohistochemistry*
	32	84/F	Upper eyelid	L	NA	SE	Positive	No	Left preauricular region (0)	DOD (7)	CD3, ALK-1, CD30 (−) all cases AE1/AE3, CAM5.2 (+) 5 cases EMA (+) 2 cases
	33	39/M	Thyroid gland	Not applicable	3.5	SE, RT, CT	Positive	No	No	ANED (6)	
	34	54/F	Gallbladder	Not applicable	NA	SE	Positive	NA	NA	NA	Synaptophysin, CGA, NSE, CD56 (+) cases 28, 32, and 33
Jokoji et al., 2015	35	65/F	Kidney and retroperitoneum	R	NA	CT	NA	NA	Left cervical LN	DOD (6)	Desmin, vimentin, INI-1, myogenin (+) Cytokeratin, LCA, S-100, Sox10, Melan A, SMA, h-Caldesmon, MDM2, CDK4, p16 and MyoD1 (−)
Aguiar et al., 2019	36	18/M	Mandible	L	6	SE, SE LN, CT	Positive	Yes (2)	Neck LN (0)	DOD (2)	Desmin, myogenin, MyoD1, INI-1, AE1/AE3, h-caldesmon and SMA (++) HMB-45, HHF-35, S-100 (−)

ANED, alive, no evidence of disease; *AWD,* alive with disease; *CT,* chemotherapy; *DOAC,* dead of another cause; *DOD,* dead of disease; *DUC,* dead of unknown cause; *IM,* intramuscular; *L,* left; *LN,* lymph node; *NA,* not available; *R,* right; *RT,* radiation therapy; *SC,* subcutaneous; *SE,* surgical excision; *SN,* satellite nodule.
*Metastatic lesion for evaluation.

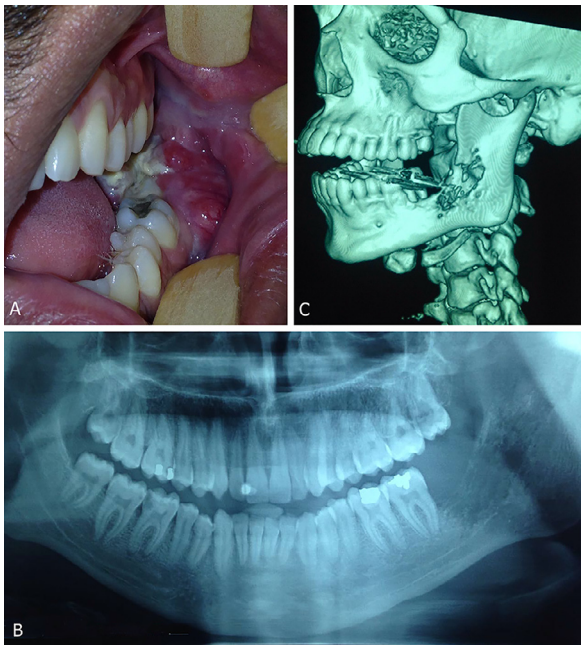

Fig. 1. Clinical and imaging features. **A,** Clinical presentation of expansive tumor growth with a lobulated and ulcerated surface, located in the left posterior region of the mandible. **B,** Orthopantomogram showing irregular bone destruction in the posterior left mandible. **C,** Cone beam computed tomography scan demonstrating cortical bone destruction.

abundant amphophilic to eosinophilic cytoplasm and large vesicular nuclei with irregular nuclear contours (Figures 2B and 2D). Nucleoli were large and prominent, similar to those seen in melanoma (see Figure 2D). Cells with an epithelioid appearance represented up to 85% of all tumor cells. Multinucleated and rhabdoid cells were also present. Fascicles exhibited packed spindle cells with varying degrees of pleomorphism, elongated and hyperchromatic nuclei, and a moderate amount of eosinophilic cytoplasm (Figure 2C). The stroma was scarce and vascularized, exhibiting small hyperemic vessels. The inflammatory infiltrate was also scarce, and the borders of the lesion were very ill-defined. Mitotic figures were easily identified, with greater than 13 per 10 high-power fields (× 400).

Immunohistochemistry was performed on 4-μm-thick formalin-fixed, paraffin-embedded tissue sections; the main features of the antibodies used are summarized in Table II. The tumor showed diffuse and strong immunoreactivity to desmin, myogenin, and MyoD1 (Figures 3A to 3C). H-caldesmon and smooth muscle actin (SMA) were also strongly positive. A strong nuclear staining of all cells was found for INI-1 (Figure 3D). Immunoreactivity to AE1-AE3 pancytokeratin was strong and diffuse (Figure 3F). The mean number of Ki-67−positive cells was 49.6 per 10 high-power fields (Figure 3E). Tumor cells were negative for HMB-45, HHF-35, and S-100.

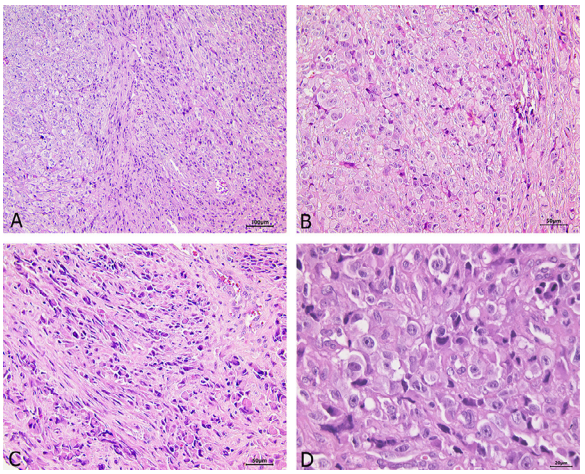

Fig. 2. Microscopic findings. **A,** Solid proliferation of large polygonal tumor cells arranged in sheets, intermixed with spindle cells. Stroma is scarce. **B,** A solid sheet of round and large cells, with abundant amphophilic to eosinophilic cytoplasm. **C,** Fascicles exhibiting packed spindle cells with varied degrees of pleomorphism. Rhabdoid cells are noted. **D,** Varied cytologic appearance, with cells exhibiting large vesicular nuclei with irregular nuclear contours, and large and prominent nucleoli.

The provisional diagnosis was malignant mesenchymal tumor. The patient was referred for medical treatment, which included hemimandibulectomy, followed by ipsilateral neck dissection. A surgical specimen was submitted for histopathologic examination.

The excised tumor measured 6 × 5.5 × 4 cm and exhibited a nodular, fleshy cut surface. Necrosis was grossly identified. The surgical specimen showed the same microscopic features as described for the incisional biopsy, with an extensive necrotic area. The final diagnosis was EpiRMS. The surgical margins were positive, and metastatic foci were identified in 1 of the 25 lymph nodes dissected. Metastasis screening followed a basic clinical protocol, including meticulous physical examination and computed tomography (CT), with scans of the head and neck and thoracic regions. Those examinations did not detect tumor foci elsewhere in the body, and the patient's disease was staged as T4aN1M0. The patient was nonresponsive to 2 chemotherapeutic protocols (first-line chemotherapy with doxorubicin + ifosfamide + mesna; second-line chemotherapy with vincristine + actinomycin + cyclophosphamide) and died 5 months after surgery.

DISCUSSION

EpiRMS was first recognized by Seidal et al. in 1989,[6] when reporting a series of cases of RMS in older patients. However, meticulous characterization of this unusual variant of RMS was only published in 2011.[7] In a literature review, we retrieved 36 cases of EpiRMS,

Table II. Specification of the antibodies used for immunohistochemistry

Antibody	*Manufacturer*	*Clone*	*Dilution*	*Pretreatment*
Desmin	Dako	D33	1:100	Citrate buffer
SMA	Dako	1 A4	1:100	Citrate buffer
H-caldesmon	Cell Marque	E89	1:150	Citrate buffer
S-100	Dako	Polyclonal rabbit	1:500	None
Vimentin	Spring Bioscience	SP20	1:100	Citrate buffer
AE1-AE3	Dako	M3515	1:100	Citrate buffer
HHF-35	Dako	HHF35	1:400	None
HMB45	Cell Marque	HMB-45	1:50	Citrate buffer
INI-1	BD Biosciences	25/BAF47	1:50	None
MyoD1	Novocastra	MYO18	1:50	Citrate buffer
Myogenin	Dako	F5 D	1:100	Citrate buffer
Ki-67	Dako	MIB-1	1:100	Citrate buffer

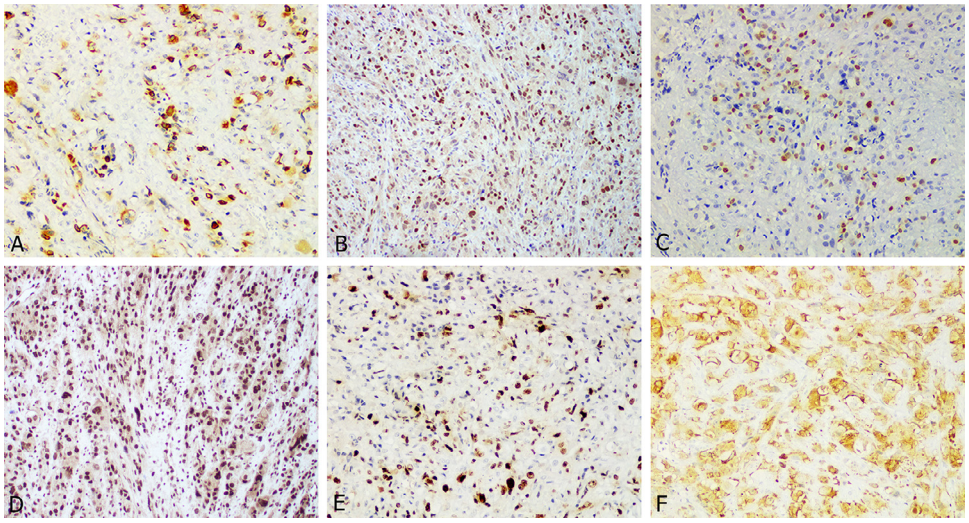

Fig. 3. Immunohistochemical findings. Tumor cells immunopositive for: **A,** Desmin. **B,** Myogenin. **C,** Myo-D1. **D,** INI-1. **E,** Ki-67. **F,** AE1-AE3.

including the current case, and their clinical and immunohistochemical data are summarized in Table I.

Of the reported cases (see Table I), 62.9% occurred in males and 37.1% in females (information missing for 1 case), with a male-to-female ratio of 1.7:1 (age range 6−84 years; mean age 51.8 years). In contrast to other histologic types of RMS, which show a marked preference for a particular age range, EpiRMS affects both children and adults.[7-9] Accordingly, the mean age of 5 cases reported by Zin et al.[8] was 8.8 years, representing the youngest sample in the literature.

The average size of the lesions was 6.1 cm (range 1.2−15 cm). Metastasis occurred in 70% of cases (data available for 30 cases). Five cases recurred, and 1 case showed a satellite nodule (data available for 22 cases). The most common treatment was chemotherapy combined with surgical excision of the lesion (27.8%), followed by surgical excision alone (19.4%) and a combination of surgical excision, chemotherapy, and radiation therapy (16.7%). Treatment data were not available for 5 cases.

The most common location of EpiRMS differs from that of RMS in general, with the former preferentially affecting the trunk (41.7%), head and neck region (33.3%), and extremities (25%) (see Table I). However, the definitive anatomic distribution of EpiRMS has not yet been determined because of the low number of cases reported. The head and neck region represents the most common site for RMS in children, and the oral cavity is involved in 10% to 12% of all head and neck RMS cases. The tongue, palate, and cheek are the most common sites of RMS in the oral cavity.[9] The occurrence of RMS in the posterior mandibular region, including the intraosseous areas, is very unusual. Two studies have reported RMS in the mandible and the maxilla diagnosed as embryonal and alveolar RMS.[4,6-11] The present report is the first one of EpiRMS affecting the jaw. However, it is important to

stress that ruling out an underlying soft tissue tumor or a metastatic origin is obligatory before determining the primary site of the tumor. This is also applicable to RMS in the jaw. In the present case, the diagnosis of a metastatic disease was ruled out after clinical and CT examinations. However, the definition of metastatic disease depends on the type of imaging used. More sensitive imaging techniques, such as positron emission tomography (PET) or magnetic resonance imaging (MRI), would be necessary to demonstrate other tumor foci. Unfortunately, in this case, the aggressive course of the tumor did not allow for a more meticulous investigation.

It is important to stress that in a review including 321 RMS cases, the authors described intrabony cases.[5] Although some of these intrabony cases could represent extension from soft tissue to bone or metastatic deposits from occult primary sites, theoretically, primary lesions in these areas should not be ruled out. RMS results from malignant change of primitive mesenchymal cells, rather than differentiated muscle cells. Thus, typical RMS has been described in other areas where striated muscle is absent, as in the present case.

Necrosis, local infiltration, and absence of circumscription are the macroscopic features of EpiRMS and were also observed in the current case.[7,8] Microscopically, the sheet-like growth of epithelioid cells predominates in EpiRMS, without any alveolar arrangement, although a fascicular pattern can be identified. Tumor cells contain abundant amphophilic-to-eosinophilic cytoplasm, with large vesicular nuclei and prominent nucleoli. This gives a melanocytic appearance to the tumor cells, especially considering that cross-striations are not observed, in contrast to conventional, embryonal, alveolar, or pleomorphic RMS.

Cells of rhabdoid appearance were focally identified in the present case and also in previously described EpiRMS cases.[7,12] Rhabdoid inclusions are relatively nonspecific and can be present in many entities, including mesothelioma, melanoma, proximal-type epithelioid sarcoma, and myoepithelial carcinoma of soft tissues.[7]

The morphologic appearance of EpiRMS resembles that of carcinomas or melanomas. In many cases, the lesion is initially evaluated as an epithelial or melanocytic malignancy and is only appreciated to be mesenchymal in the absence of immunohistochemical evidence of epithelial or melanocytic differentiation.[7] Indeed, a diagnosis of melanoma was the first impression for the current case. Thus, a detailed immunohistochemical analysis is essential for the final diagnosis. Rhabdoid markers should not be clearly demonstrated, and in cases such as the one presented here, epithelial markers, such as cytokeratins, have been distinctly observed.[7,12-15] The positivity for cytokeratins can represent a potential pitfall for a differential diagnosis of dedifferentiated carcinoma or sarcomatoid carcinoma. In this scenario, more specific markers, such as INI-1, and markers of skeletal muscle differentiation (MyoD1 and/or myogenin), would be necessary for a final diagnosis. The *INI-1* gene is a member of the SW1/SNF complex, which mobilizes nucleosomes and exposes DNA to transcription factors. Both INI-1 alleles are inactivated in malignant rhabdoid tumors and also in epithelioid sarcomas. Immunostaining for INI-1 is maintained in RMS and can be used to distinguish this tumor from malignant rhabdoid tumors.[16-18]

The current case was positive for INI-1, desmin, MyoD1, and myogenin, as in previous reports.[8] In this respect, as noted in the other reports, desmin seems to be the most stable marker for EpiRMS.[7,8,13-15,19]

Because of its rarity, it is possible that EpiRMS has been under-recognized because other sarcomas can share morphologic features with RMS. Considering only the current case, other sarcomas affecting the jaws, such as epithelioid angiosarcoma, dedifferentiated liposarcoma, malignant nerve sheath tumor, epithelial−myoepithelial carcinoma, extrarenal rhabdoid tumor, differentiated carcinoma, malignant melanoma, and epithelioid sarcoma, could be included in the differential diagnosis. For the present case, the absence of S-100 and HMB-45 immunoexpression led us to exclude melanoma. Epithelial leiomyosarcomas may also be positive for desmin and SMA but do not express myogenin or MyoD1. Proximal-type epithelial sarcomas and extrarenal rhabdoid tumors have loss of INI-1, which is retained in EpiRMS. Despite its epithelioid appearance, dedifferentiated carcinoma will be negative for skeletal muscle−specific markers. The expression of cytokeratins can occur in EpiRMS, but the co-expression of specific markers of skeletal muscle differentiation, such as myogenin and/or MyoD1, allows for the differentiation of epithelial tumors. However, myogenin is focal in most cases,[8,14] possibly because of the poor differentiation of tumor cells. Besides myogenin, EpiRMS also expresses MyoD1 and SMA, as was observed here.

Cytogenetic (karyotype) data were not analyzed in the present case study. However, the cases tested for the *FOXO1* gene were negative, excluding any relationship between EpiRMS and alveolar RMS.[7,8,14,19] Nevertheless, we could not exclude a relationship with embryonal RMS, which would help explain the occurrence of pediatric EpiRMS with a more favorable clinical course.[8]

The current RMS-specific protocols have increased the survival rates among pediatric patients, although the prognosis continues to be poor for adults.[2] The best prognostic indicator in children is the clinical stage,[10] and survival varies across histologic subtypes.[2,8,14] Some authors reported a favorable course for EpiRMS

in children, similar to cases of embryonal RMS.[8,14] However, those authors found an aggressive clinical course in adults and a poor prognosis independent of histology. In the cases reported by Jo et al.,[7] the prognosis remained poor regardless of treatment modalities. Moreover, other cases of patients who did not survive have been reported in the literature.[12,14,19,20] For EpiRMS, the clinical course, as determined thus far, is aggressive. In the present case, the patient attended a private service for third molar extraction. At that time, the dentist failed to notice the tumor on the orthopantomogram, which probably showed bone loss in the same region of the extracted tooth and could have aided in an early diagnosis. Unfortunately, the patient died 5 months after surgery. In the series reported by Jo et al.,[7] 7 patients died 5 years after surgery. Metastases occurred in 70% of cases, and 38% of patients died as a result of the disease (see Table I). Thus, early recognition of EpiRMS is not merely of academic interest. Knowledge of this new entity is important to guide specific protocols toward more efficient treatments.

CONCLUSIONS

The occurrence of RMS in the mandible is rare, and this is the first case of EpiRMS in the jaw. EpiRMS is an unusual histologic subtype that mimics other sarcomas, melanoma, and epithelial malignancies, making its diagnosis a challenge. A specific immunohistochemistry panel aids in the diagnosis. EpiRMS has an aggressive course and an unfavorable prognosis.

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