Ewing's Sarcoma Family Tumors in the Jaws: Case Report, Immunohistochemical Analysis and Literature Review

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Abstract. *Due to the low incidence of the Ewing's Sarcoma (ES) family tumors, the available epidemiology is likely to be unreliable, and at present, there are no standard diagnostic or clinical guidelines outlining their management. This report describes a case of peripheral primitive neuroectodermal tumor (ES/pPNET) which initially mimicked cystic lesions, and describes a comparison between ES and ES/pPNET in the jaws by the World Health Organization classification. This review addressed 63 cases published in the English literature between 1950 and 2016. The majority of cases were ES. Both ES and ES/pPNET mimicked other benign entities such as traumatic, cystic and inflammatory lesions. The patients who died of their disease had a history of metastatic tumors, and primary tumor located in the mandible and maxilla for ES and ES/pPNET, respectively. The differentiation of the ES family tumors from other small blue-cell tumors may be difficult and requires familiarity with histological and immunohistochemical features.*

The Ewing's Sarcoma (ES) family tumors constitute a group of undifferentiated small round blue-cell tumors presumed to be of neuroectodermal origin that are locally aggressive (1). ES family tumors comprise of osseous and extraosseous ES, atypical ES (large-cell variant), adamantinoma-like variant, primitive neuroectodermal tumors (PNET or ES/PNET), and Askin tumor (small, blue, round cell tumor of the thoracopulmonary region) (2, 3). PNET outside the central nervous system is called peripheral PNET (pPNET or ES/pPNET) developing from migrating embryonal cells of the neural crest (4). These tumor types possess genetic (Ewing sarcoma breakpoint region 1-related fusions) and histological features (3).

ES family tumors, considering ES and ES/PNET, account for 4-6% of primary malignant bone tumors and arise mainly in the long bones, but can also present in the pelvis, spinal cord and ribs (5). Head and neck affection occurs in only 1-4% of all cases. It seems to primarily affect children and young adults, with a slight male predominance (6). Approximately 20-25% of cases have clinically-apparent metastatic disease at the time of diagnosis. Isolated lung disease, usually bilateral, occurs in 25-45% of cases; the majority of patients (50-60%) have extrapulmonary disease (usually bone and bone marrow) (7). Due to the rarity of ES family tumors, mainly ES/pPNET, they are often not considered in differential diagnosis for radiolucent jaw lesions.

The aim of ES family tumor treatment is to achieve two major goals, local control and eradication of the systemic disease. Thus, most protocols consider three phases: initial chemotherapy to facilitate local control; local control, using surgery, irradiation, or both; and continuous chemotherapy (8). The most favorable group of patients has small-localized tumors that are amenable to surgical resection or local radiation therapy. The volume or size of the tumor has been noted as a prognostic factor for event-free survival but its effect on local control rates is less clear (9-12). Postoperative, and more recently, preoperative irradiation, has been applied to patients with marginally resected or poorly responding tumors (13). Rapid growth and propensity for metastasis are among the dominant features of ES family tumors; thus jaw involvement may be due to metastasis from another skeletal site (14, 15).

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Due to the low incidence of these tumors, the available epidemiology is likely to be unreliable, and at present there are no standard diagnostic or clinical guidelines outlining their management. In this article, we describe a rare case of ES/pPNET of the mandible, demonstrating the clinical, radiographic, histological and immunohistochemical details for diagnosis; and review the pertinent literature with regard to clinical, radiographic, follow-up and phenotypic information on ES and ES/pPNET tumors in the jaws.

Case Report

A 16-year-old White girl was referred to our Department of Stomatology with extrusion of the left mandibular first molar tooth associated with accentuated mobility and slight symptomatology. Radiolucent poorly defined round areas involving the radicular region of the first molar were observed in a panoramic radiograph. Moreover, the cone beam computed tomography (CBCT) examination revealed a hypodense area involving the roots of the first and second molar (Figure 1A). The bone destruction also extended to the interradicular alveolar crest of the first molar roots, and between the first and second molar, with scalloped appearance. The coronal reconstructions showed lingual cortical bone destruction (Figure 1C). An empty cavity, without epithelial lining, was surgically detected with a gingival incision to gain access to the lingual side. No specimens were obtained during the surgical exploration. The presumptive diagnosis was simple bone cyst. The cavity was filled with a blood clot. Twenty days afterwards, the patient returned without mobility of the tooth, highlighting the hypothetical diagnosis. The first molar was submitted to endodontic treatment, but the pulp was vital. After a further 30 days, the patient presented intraoral swelling on the buccal side, soft and floating on palpation, with signs and symptoms of infection, and considerable mobility of the first and second molars of the left mandible, in addition to regional inflammatory lymphadenopathy. The CBCT examination showed enlargement of the hypodense area with extension to the vestibular cortical (Figure 1B). Therefore, the patient was submitted to surgical drainage and antibiotic therapy. The content of the tumefaction was a serous fluid mixed with blood. Twenty days after this complication, the patient was asymptomatic again, so the cavity was surgically curetted with moderate bleeding. The specimens were membranous fragments and were sent for microscopic examination with a presumptive diagnosis of aneurysmal bone cyst. The teeth involved were removed.

The microscopic analysis showed a fibrous connective tissue capsule infiltrated by highly cellular tumor. The tumor was composed of islands and strands of small round blue cells with well-defined hyperchromatic nuclei and scant cytoplasm, characterizing primitive undifferentiated tumor cells (Figure 2). There were no histological features to suggest neural, osseous, cartilagenous, or muscle differentiation. Areas of coagulative necrosis and areas suggestive of tumor perivascular and intraosseous invasion were observed. Neither mitotic figures nor rosette-like structures were seen. Intracytoplasmic glycogen was demonstrated by periodic acid-Schiff (PAS) stain after diastase pretreatment (Figure 3A). An immunohistochemical study revealed diffuse and strong positivity for CD99, vimentin, S-100 protein and neuron-specific enolase (NSE) (Figure 3B-E), unlike that for chromogranin and desmin, which were expressed more focally and to a slighter degree (data not shown). No reaction was observed for pancytokeratin, cytokeratin 8 (CK8), synaptophysin, leukocyte common antigen (LCA), muscle-specific actin, calponin, myogenin and CD117 markers (data not shown). The histopathological and immunohistochemical features were consistent with ES/pPNET.

The patient was immediately referred to the Amaral Carvalho Cancer Hospital, where a CT and positron-emission tomography scan did not detect other foci of tumoral invasion beyond jaw. The team of physicians decided to perform conservative surgery and the area was free of neoplasia. Despite this result, they submitted the patient to radiotherapy and chemotherapy. After 6 years of follow-up, there is no sign of recurrent tumor or metastasis.

Literature Review

All cases of ES family tumors classified as ES or ES/pPNET in the jaws published in the English language literature between 1950 and 2016 were reviewed, including the new case analyzed immunohistochemically in this study. The literature review was conducted using the Medline and Lilacs databases using the term *oral Ewing's sarcoma, oral peripheral primitive neuroectodermal tumor, mandible and maxilla*. Data analysis included World Health Organization (WHO) classification, patient age, gender, location, clinical and radiographic features, provisional diagnosis, follow-up, status at the last examination, and immunohistochemical staining of tumors recorded. The articles derived from this search were independently screened by two authors based on the inclusion criteria. These were articles focused on case reports that included at least clinical information, immunohistochemical features and WHO classification into ES and ES/pPNET.

The review of the English language literature from 1950 to 2016 revealed 101 cases of ES family tumor in the jaws, in addition to our new case, thus totaling 102 cases. Interestingly, the majority of these cases were reported within the past decade, possibly indicating an increased awareness of the diagnosis. Of 102 cases, 63 were selected since they included information about the cases as established above (Table I).
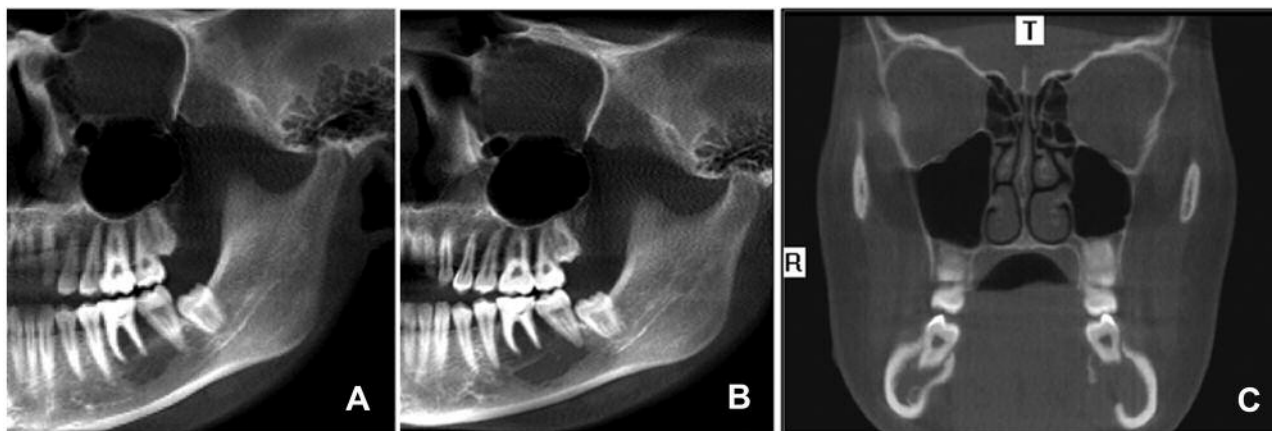
Figure 1. *Cone beam computed tomography of Ewing's sarcoma/peripheral primitive neuroectodermal tumor showing enlargement of hypodense osteolytic area (A and B) and coronal section showing lingual cortical bone resorption close to the first molar (C).*

With regard to WHO classification as ES and ES/pPNET, the majority of cases were ES (47 cases, 74.6%), and only 16 cases, including our case, were ES/pPNET (25.4%). The ES tumor was associated with a male-to-female ratio of almost 1:1, while for ES/pPNET, this ratio was 1:2. The mandible was involved in 70.2% of the ES cases and the maxilla in 29.8%, with a mandible-to-maxilla ratio of 2.3:1. For ES/pPNET, the mandible and maxilla were involved in 56.3% and 43.75% of the cases, respectively, with a mandible-to-maxilla ratio of 1.3:1. Age at diagnosis of ES ranged from 2 to 43 years, with an average age of 13.1 years. For ES/pPNET, the age ranged from 5 to 67 years, with a mean age at diagnosis of 26.3 years.

Of the 47 ES and 16 ES/pPNET cases, swelling was observed in the majority of cases, 66% and 75%, respectively. However, painful symptoms were in fact reported by a minority of patients (12 ES and four ES/pPNET cases); likewise, few patients reported conditions of fever and paresthesia. Radiographically, more than half of all cases showed osteolytic lesion with cortical destruction (53.2% of the ES and 62.5% of the ES/pPNET cases). Given the initial clinical features such as location and history of trauma added to loss of sensitivity and loosening of teeth, nonmalignant initial diagnoses were suggested. Eleven of the ES (23.4%) and six of the ES/pPNET cases (37.5%) had presumptive diagnosis of inflammatory perio-endo lesions. Provisional diagnosis of malignant lesions was established in only eight ES (17%) and three ES/pPNET (18.7%) cases. Therefore, the waiting time for the final diagnosis of ES ranged from 7 days to 19 months, with a mean of 3.9 months. For final diagnosis of ES/pPNET, this mean waiting time was longer, 4.8 months, ranging from 6 days to 12 months.

With regard to follow-up, including recurrence, metastasis and survival information, data for 35 cases of ES and 11 cases of ES/pPNET were available. Only three out of the 35 follow-up cases of ES (8.6%) had history of a recurrent tumor, with all occurring in males and in a mandibular site; and seven cases (20%) had metastasis. None of the patients with ES/pPNET had history of recurrent tumor, but two cases (12.5%) had metastatic lesion. The patients who died of ES (seven out of 35 ES, 20%) had primary tumor located in the mandible and history of metastatic tumors. On the other hand, for deaths resulting from ES/pPNET (three out of 11 ES/pPNET, 27.3%), the patients had a primary tumor located in the maxilla.

PAS without diastase was performed for 24 cases of ES, with all showing positivity. Immunohistochemical study showed that CD99 and vimentin markers were positive in all cases of ES in which these molecules were studied (34 cases for CD99 and 17 cases for vimentin), whereas the expression of neural differentiation markers NSE, S-100, neurofilaments, synaptophysin and chromogranin ranged from a slighter degree to negative reactivity. Actin, desmin, myoglobin, LCA, CK and epithelial membrane antigen (EMA) expressions were negative. Similarly to ES, all ES/pPNET tumors also showed negative immunoreactivity for these markers and strong positivity for CD99; vimentin was expressed from stronger to slighter degree. However, all cases of ES/pPNET presented strong positivity for at least one neural marker. Two out of three ES/pPNETs presented positive staining with PAS.

Discussion

ES family tumors are rare sarcomas with almost undifferentiated histological features, which affect the skeletal system (16). They are rare in the head and neck, mainly comprising of ES/pPNET (17), with the mandible
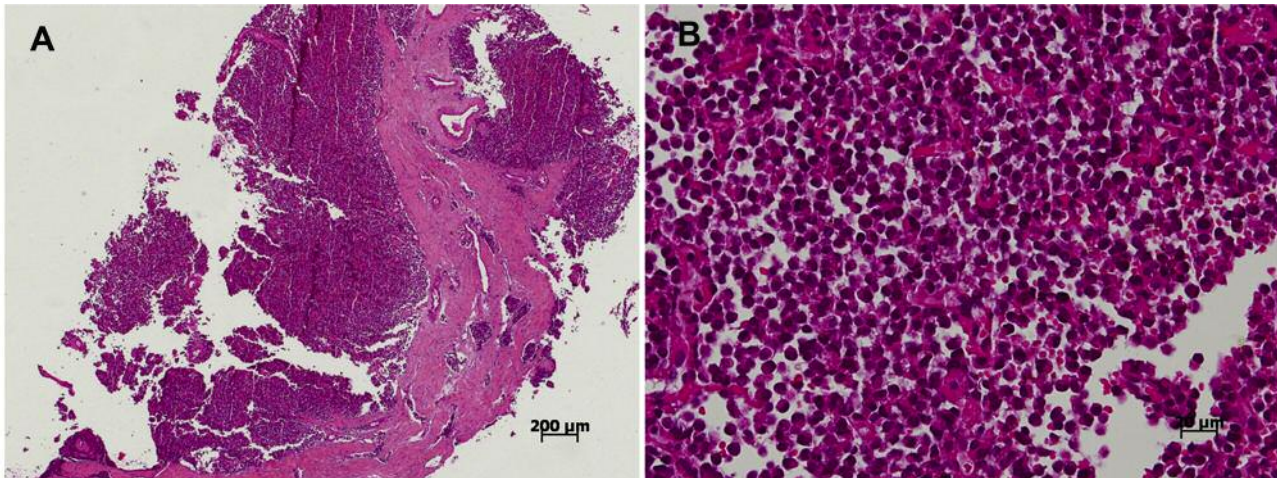
Figure 2. *Histopathological features of Ewing's sarcoma/peripheral primitive neuroectodermal tumor (ES/pPNET). A: ES/pPNET exhibiting fibrous connective tissue capsule infiltrated by highly cellular tumor (hematoxylin and eosin, ×4). B: Tumor island and strand of small round blue cells with well-defined hyperchromatic nuclei and scant cytoplasm (hematoxylin and eosin, ×40).*

and base of the skull being the two most common primary sites (5), followed by the orbit, and nasal cavity with or without the paranasal sinuses (18).

In the present case, the mandibular body was the primary site affected. Initially, a surgically-detected empty cavity, in addition to mobility of the left mandibular first molar, led us to think of a cyst as diagnostic hypothesis, *i.e.* simple bone cyst. After 30 days, an intraoral swelling with signs and symptoms of infection, and enlargement of the osteolytic area with lingual cortical bone destruction were observed. This crisis was treated and the cavity was later curetted, with moderate bleeding, which led us to the presumptive diagnosis of aneurismal bone cyst. The final diagnosis of ES/pPNET was only confirmed after microscopy associated with immunohistochemical analysis. Other authors have also misdiagnosed cases with clinical features similar to those of our case as being cysts (3, 19-21). Moreover, trauma (22-24) and acute inflammatory lesions (1, 3, 24-29, 30, 31) were also mentioned several times as provisional diagnosis. With regard to phenotypic aspects, we observed highly positive expression of CD99, vimentin, S-100 protein and NSE, representing ES family tumor with neuroectodermal differentiation or ES/pPNET (32-35).

Primary ES family tumors are among the rarest tumors of the jaws. The medical literature contains only single case reports or small case series including six patients (3, 24, 25, 36). To determine the exact number of children/young adults with primary ES or ES/pPNET of the jaws in the medical literature is very difficult, and in fact, the data reported are confusing. Firstly, in older reports, imaging methods must be regarded as insufficient to exclude metastases from primary central PNETs or medulloblastomas (37). Secondly, and most importantly, ES/pPNETs were often not separated from ES of the jaw and were reported together in case series and literature reviews (37, 38). Thirdly, immunohistochemical and molecular genetic data that enable separation of central PNETs from peripheral PNETs were not reported in most cases, particularly those published before 2000 (37, 39). Pooling of patient data would, however, enable such a comparison to be made, thereby identifying possible differences between ES and ES/pPNETs.

A Medline search for cases of ES family tumors in the jaws identified 63 cases in 50 articles with analysis of WHO classification, clinical and radiographic information, and immunohistochemical features of tumors, including the new case addressed in the present study. These cases reported in the English language literature consist mainly of single cases or small series of case reports. Nevertheless, no previous study has correlated the demographic data and histopathological features of ES family tumor on the basis of the WHO classification, *i.e.* as ES and ES/pPNET.

Considering the WHO classification, the results of our study revealed that the majority of the cases were ES without neuroectodermal differentiation. In the present review, both ES and ES/pPNET were more common in the mandible. In contrast, ES differed from ES/pPNET with regard to gender and average age at diagnosis. ES/pPNET appears to occur more frequently in young-adult female patients, unlike ES which was reported more often in adolescents and children. Overall, both ES and ES/pPNET led to lower survival for children compared with adolescents, but these findings differed from those of Stiller *et al.* (40). All recurrent and
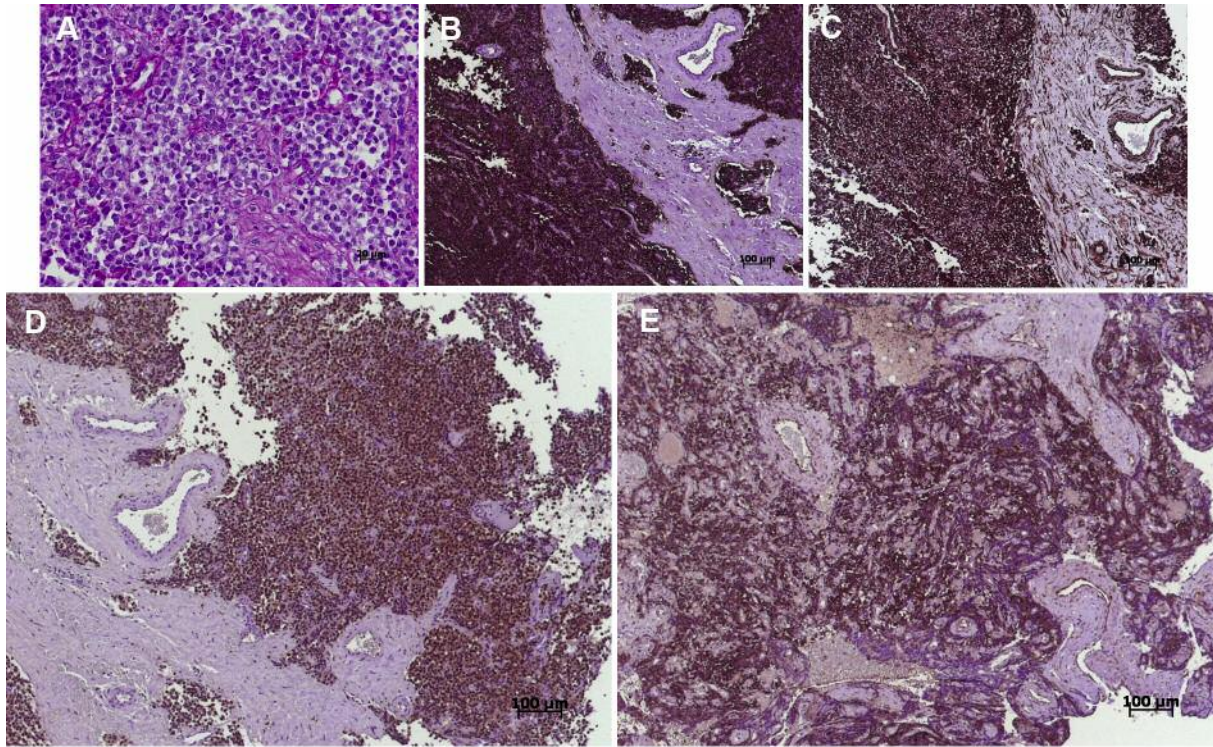
Figure 3. *Periodic acid-Schiff (PAS) and immunostaining in Ewing's sarcoma/peripheral primitive neuroectodermal tumor (ES/pPNET). A: PAS stain with diastase pretreatment (×40). Diffuse and strong positivity for CD99 (B), vimentin (C), S-100 protein (D) and neuron-specific enolase (E) (×10).*

metastatic cases had a previous history of tumor classified as ES which occurred in males and the mandible. On the other hand, of the deaths resulting from ES/pPNET, patients had primary tumor located in the maxilla. Thus, ES appears to correlate with metastasis and mortality, suggesting that it is more aggressive than ES/pPNET. The follow-up time of ES ranged between 1 month (29) and 22 years (3), while that for ES/pPNET ranged between 2 months (41) and 6 years. We also highlight that the incidence of metastasis was low, although ES family tumors are known to be associated with metastasis.

ES family tumors of the head and neck region represents a true diagnostic challenge and imposes surgical difficulties. Clinical and radiological features differ in several aspects from the typical appearance of the tumor in other anatomic regions. According to Ross *et al*., localized pain is the most common early symptom of ESFTs and some cases also present with systemic symptoms, such as fever (42). However, these differed from our findings from review as the majority of cases reported were shown to be painless. Furthermore, since many patients with ES are young and are often physically active, the pain is frequently mistaken for bone growth or injury, resulting in a delayed or misdiagnosis (42). ES family tumors often progress rapidly and result in

palpable swelling as observed in the majority of case studied (24, 25, 43-45). In the oral cavity, the affected area is seen with tooth mobility (29), corroborating our findings. Radiographically, ES family tumors present with poorly defined osteolytic lesions, cortical erosion, sunray spicules of periosteal bone, and displacement of teeth. Nevertheless, none of these radiographic signs are pathognomonic of ES family tumors (21). The atypical clinical features, absence of pathognomonic radiological signs and rarity might cause a delay in the final diagnosis and beginning of appropriate treatment.

ES and ES/pPNET, in addition to lymphoma, neuroblastoma and rhabdomyosarcoma, were often shown to present an identical histological appearance (43). Roessner *et al*. described these tumors as being composed of monomorphic, undifferentiated, small, blast-like round, blue cells typically containing intracytoplasmic glycogen (46). On the other hand, at present ES and ES/pPNET are defined as two separate diseases occurring at different sites with different origins. Therefore, ES and ES/pPNET represent two ends of the spectrum of the same tumoral entity, with diverse degrees of histological differentiation (4, 47). Thus, diagnosis of ES ans ES/pPNET is based on clinical parameters and histopathological and immunohistochemical examination (1, 47).

Table I. *Clinical information of 63 cases of Ewing's sarcoma family of tumors in the jaws classified as Ewing's sarcoma or peripheral primitive neuroectodermal tumor according to established criteria.*

WHO class	Case no.	Authors, year	Location	Gender	Age (years)	Clinical features	Radiograph features	Provisional diagnosis
Ewing's Sarcoma (n=47)	1	Bacchini *et al*., 1986 (36)	Mnd (P)	M	2	-	Osteolytic lesion, cortical destruction	Sarcoma
	2	*ibid*.	Mnd (R)	M	7	-	Osteolytic lesion, cortical destruction	Sarcoma
	3	*ibid*.	Mx (A)	F	7	-	Osteolytic lesion, cortical destruction	Sarcoma
	4	Van Den Bergh *et al*., 1988 (44)	Mnd (P)	M	12	Painful swelling, fever	Diffuse radiolucente around the impacted third molar, absence of the radiopaque lamina dura and destruction of the inferior mandibular cortex	-
	5	Wang *et al*., 1991 (22)	Mnd (R)	F	12	Paresthesia, pain	Ill-defined radiolucent lesion and destruction of the medial cortical plate	Traumatic ulceration
	6	Fonseca *et al*., 1992 (23)	Mnd (R)	M	4	Mandible nodule	-	Trauma
	7	Bessède *et al*., 1993 (49)	Mnd (A)	M	8	Painless mass	Bone resorption from the distal edge of the central incisor to the second premolar	-
	8	Yalcin *et al*., 1993 (45)	Mnd (R)	M	13	Facial swelling and moderately mobile third molar	Ill-defined osteolytic lesion extende into angle and mandibular ramus; destruction of cortical	-
	9	Berk *et al*., 1995 (43)	Mnd (P)	F	5	Swelling over the right unerupted first molar region	Radiolucent lesion displacing the developmental sac that contained the crown of the second molar	-
	10	Fiorillo *et al*., 1996 (24)	Mx (S)	F	22	Painless swelling	Extensive lytic lesion involving maxillary and zygomatic bones	Paranasal maxillary sinus inflammation
	11	*ibid*	Mx (A)	M	7	Painless swelling of the lower orbital region	Destructive lesion involving the right maxillary bone	Trauma
	12	Vaccani *et al*., 1999 (25)	Mnd (P)	M	11	Painful swelling	Mass with bony and softy tissue components	Mumps
	13	*ibid*	Mnd (P)	M	9	Painful swelling	-	-
	14	*ibid*	Mnd (P)	F	9	Painful swelling and cranial nerve involvement	-	-
	15	Fonseca *et al*., 2000 (39)	Mnd (P)	F	35	Painful swelling and paresthesia	Capsulated expansive lesion with opacity	Sarcoma
	16	Gorospe *et al*., 2001 (26)	Mnd (R)	F	12	Swelling and fever	Ill-defined lesion with cortical destruction	Acute suppurative inflammation
	17	Talesh *et al*., 2003 (15)	Mnd (R)	F	17	Ainful swelling	Radiolucent lesion with destruction of medullary and cortical bone of the mandibular condyle	-
	18	Wexler *et al*., 2003 (54)	Mx (A)	F	9	Expanding nasal mass	Nondestructive lesion	Nasal polyp
	19	Schultze-Mosgau *et al*., 2005 (48)	Mnd (P)	M	7	Slight painful swelling	Diffuse osteolytic lesion	-

Table I. *Continued*

WHO class	Case no.	Authors, year	Location	Gender	Age (years)	Clinical features	Radiograph features	Provisional diagnosis
	20	Infante-Cossio *et al*., 2005 (55)	Mx (P)	M	17	Nonpainful swelling	Lytic lesion involving maxillary sinus and zygomatic bone	-
	21	Lopes *et al*., 2007 (14)	Mnd (R)	M	14	Nonpainful Swelling and fever	Osteolytic lesion with cortical destruction and sun rays form	-
	22	Gosau *et al*., 2008 (27)	Mnd (P)	M	24	Swelling	Diffuse and ill-defined radiolucensy	Dental abscess
	23	Bornstein *et al*., 2008 (28)	Mx (S)	F	19	Swelling and acute tooth pain	No obvious pathosis	Acure perio-endo lesion
	24	Gupta *et al*., 2009 (50)	Mx (P)	M	30	Palatal swelling	Destruction of the bony nasal septum and the hard palate	-
	25	Makary *et al*., 2009 (56)	Mnd (P)	F	17	Loose molar teeth and swelling	Osteolytic lesion with buccal-lingual expansion and focal lingual cortex perforation	Sarcoma
	26	Brazão-Silva *et al*., 2010 (29)	Mnd (P)	F	4	Painful swelling and fever	Ill-defined mixed radiolucent and radiopaque lesion with vestibular plate destruction	Dental Abscess
	27	Davido *et al*., 2011 (21)	Mx (A)	M	25	Discrete painful swelling in the apical region	Ill-defined unilocular radiolucency	Periapical cyst
	28	Rao *et al*., 2011 (16)	Mnd (P)	F	11	Swelling	Ill-defined cystic lesion and erosion of bucal cortex	-
	29	Karimi *et al*., 2011 (30)	Mx (A)	F	43	Painful firm exophytic lesion	Round radiolucency with ragged borders at the site of nasopalatine canal	Infected nasopalatine canal cyst
	30	*ibid*	Mnd (R)	F	9	Intraoral soft tissue mass in the molar area	-	-
	31	*ibid*	Mnd (P)	M	9	Swelling	-	Odontogenic abscess
	32	Manor *et al*., 2012 (57)	Mnd (P)	M	4	Nonpainful gingival mass	Osteolytic region	-
	33	Yeshvanth *et al*., 2012 (58)	Mx (S)	F	29	Pedunculated mass nasal	Heterogeneously lesion with destruction of medial wall	-
	34	Mukherjee *et al*., 2012 (59)	Mnd (A)	F	8	Painless swelling	Ill-defined lytic destruction of cortical plates	-
	35	Keshani *et al*., 2013 (31)	Mnd (P)	F	16	Painful swelling and numbness of lower lip	Osteolytic region	Odontogenic abscess
	36	Yamaoka *et al*., 2013 (60)	Mx (S)	F	4	Excessive tearing, nasal obstruction and exophthalmos	-	-
	37	Krishna *et al*., 2013 (61)	Mnd (P)	F	3	Non-tender bony hard swelling and posterior teeth mobility	Ill-defined lytic lesion with cortical erosion and root resorption	-
	38	Ko *et al*., 2013 (51)	Mnd (A)	F	17	Numbness, painful swelling and anterior teeth mobility	Well-delineated multilocular lesion and absence of facial and lingual cortex	Central giant cell granuloma
	39	Nagpal *et al*., 2014 (62)	Mx (P)	M	15	Well-circumscribed, pinkish red swelling and posterior teeth mobility	Lytic lesion with focal areas of opacification, lateral nasal wall erosion and loss of lamina dura	Malignant lesion

Table I. *Continued*

Table I. *Continued*

WHO class	Case no.	Authors, year	Location	Gender	Age (years)	Clinical features	Radiograph features	Provisional diagnosis
	40	Sinha *et al.*, 2014 (63)	Mnd (P)	M	18	Painful swelling	-	Osteogenic sarcoma
	41	Tajima *et al.*, 2015 (64)	Mx (S)	M	15	Non-tender swelling of the cheek, but elastic hard on palpation	Destruction of the surrounding bones	Malignant lesion
	42	Owosho *et al.*, 2016 (3)	Mnd (P)	F	4	Gum and jaw swelling	-	Odontogenic cyst
	43	*ibid*	Mnd (R)	F	12	Loose tooth	Osteolytic lesion with permeation of inner cortex	-
	44	*ibid*	Mnd (R)	F	8	Jaw pain accompanied by high fevers	Osteolytic lesion with cortical breakthrough	Dental abscess
	45	*ibid*	Mnd (P)	F	8	Facial asymmetry	Osteolytic lesion associated with cortical disruption	-
	46	*ibid*	Mnd (A)	M	5	Loose teeth followed by jaw swelling	Osteolytic lesion	-
	47	*ibid*	Mx (P)	F	20	Loose teeth and soft tissue mass protruding from the palate	Osteolytic lesion	-
Peripheral Primitive Neuro-ectodermal Tumors (n=16)	48	Shah *et al.*, 1995 (19)	Mx (P)	M	42	Large swelling	Well-defined radiopaque lesion	Periapical cyst
	49	Özer *et al.*, 2002 (38)	Mnd (P)	F	6	Painless swelling	Destruction of the outer cortex	-
	50	Alrawi *et al.*, 2005 (1)	Mnd (R)	F	18	Central mass with erythema and prominence of chin	Ill-defined lytic lesion with obliteration of the mental foramen and alveolar canal	Gingivitis
	51	Votta *et al.*, 2005 (52)	Mnd (A)	F	18	Painless swelling of the chin	Low-density area with calcification and destruction of the facial cortex	-
	52	Solomon *et al.*, 2007 (20)	Mnd (R)	F	15	Painfull swelling	Condylar process lesion with spiculated periosteal formation	Perio-endo lesion
	53	Sun *et al.*, 2007 (32)	Mx (S)	F	49	Painless swelling in the palate	Bone destruction, invasion in the molar and medial wall destruction	Sarcoma
	54	Mohindra *et al.*, 2008 (41)	Mx (S)	M	5	Painless swelling	Lesion invading orbit and pterygopalatine fossa	-
	55	Hormozi *et al.*, 2010 (53)	Mx (P)	F	28	Swelling	Large tumor in the optic chiasma and parasellar region	-
	56	Yeh *et al.*, 2011 (65)	Mnd (R)	F	18	Painless swelling, numbness and problem with dental caries	Bony cortex erosion and involvement of mandibular canal	Facial cellulitis
	57	Yazc *et al.*, 2013 (66)	Mnd (P)	F	14	Painless swelling	Cortical invasion	-
	58	Krishnamurthy *et al.*, 2013 (33)	Mnd (R)	F	22	Painless swelling with numbness	Bony destruction with extension into the skull base	Malignant lesion
	59	Shah *et al.*, 2014 (34)	Mx (S)	M	67	Pain in the left maxillary second molar tooth	-	Chronic periodontitis

<div align="right">Table I. *Continued*</div>

Table I. *Continued*

WHO class	Case no.	Authors, year	Location	Gender	Age (years)	Clinical features	Radiograph features	Provisional diagnosis
	60	Wang *et al*., 2014 (35)	Mx (S)	M	16	Painful swelling	Cortical destruction	Malignant lesion
	61	*ibid*	Mnd	M	16	Painless swelling, numbness and dental caries	-	Facial cellulitis
	62	Kulkarni *et al*., 2016 (4)	Mx (S)	F	70	Epistaxis and headache	Destruction of all the walls of the maxillary sinus and erosion of the floor of the left orbit	Neoplastic lesion
	63	New case (2017)*	Mnd (P)	F	16	Extrusion, mobility of 36 tooth and empty cavity	Radiolucent areas in the apical region of 36 tooth and destruction of lingual plate	Simple bone cyst/ aneurysmal bone cyst

WHO, World Health Organization; M: male; F: female; Mx, maxilla; Mnd, mandible; P, posterior (distal to canine); A, anterior (incisor-canine); R, involvement of ramus; S, involvement of maxillary sinus. *This study.

With regard to the phenotypic aspects found in this review, all cases of ES and ES/pPNET which were analyzed for CD99, vimentin and PAS staining were positive. According to Schultze-Mosgau *et al*., although CD99 expression is not unique to Ewing's tumors, CD99 immunohistochemistry is mandatory in the diagnostic work-up of this tumor, because over 95% of ES family tumors are CD99-positive (48). Moreover, our review showed that ES/pPNETs were generally positive for neuronal markers such as NSE, neurofilaments, FLI-1 protein, S-100 protein, synaptophysin and chromogranin, as previously highlighted (1, 47, 48). Therefore, ES/pPNET displayed many properties of neurogenic tumors, but ES did not display such differentiated properties (47, 48). ES is considered the least differentiated, and ES/pPNET most differentiated member of the ES family tumors (47). However, further studies involving larger sample sizes and survival analyses are necessary to better understand the role of these molecules as markers of the biological behavior of the tumor.

Due to the high lethality of ES family tumors, a large proportion of the literature advocates an aggressive multidisciplinary treatment. This treatment in ES typically refers to a combination of surgery and radiochemotherapy (15, 25, 36, 49-51), with the same treatment being reported for ES/pPNET (20, 38, 52, 53). Most contemporary therapies call for multidrug chemotherapy, followed by local therapies (radiation/surgery) (42). The most important prognostic factor for ES is the presence or absence of metastasis at the time of diagnosis; additional prognostic factors have been suggested, including age, tumor size, and location (51). In our case, despite of the small tumor size and absence of metastasis, the team of

physicians opted for a conservative surgery, radiotherapy and chemotherapy approach. Positively, there are no signs of recurrent tumor at 6 years postoperatively; the maximum follow-up time reported in the literature was 2.5 years (20). Continued and long-term follow-up is mandatory to detect late recurrence.

Finally, although reported cases of ES family tumors are scarce, this review shows that the majority of these cases were ES, and only 16 cases, including our case, were ES/pPNET. This entity can mimic other benign entities such as traumatic, cystic and inflammatory lesions. Curiously, none of the patients with ES/pPNET had a history of recurrent tumor, but two cases had metastatic lesions. The differentiation of ES family tumors from other small, round, blue-cell tumors may be difficult. Consequently, the accurate diagnosis of ES and ES/pPNET requires familiarity with histological and immunohistochemical features. It is important to bear in mind that although the correlations may only be interpreted as a trend due to the rarity of this neoplasm and the low number of cases published in Medline and Lilacs databases, our findings may be useful to the pathologist, and may alert clinicians to the diagnosis, prognosis and recurrence of such tumors.

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