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Case Review

Oral Embryonal Rhabdomyosarcom in an Adult Addict Man: a case report and review of literature

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ABSTRACT

Background: Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children, but rare in adults, especially those in the middle age and older. Embryonal rhabdomyosarcoma in the head and neck region is relatively common, but rarely found intra-orally. A clear etiologic risk factor for the neoplastic growth of this malignancy has not been identified yet.

Method: Here, we report a case of an adult addict patient, with locally extensive embryonal rhabdomyosarcoma (ERMS) of tuberosity and palate, who received chemotherapy and radiotherapy, but died due to the progression of the disease 15 months after the diagnosis.

We also carried out an overview of previous articles reporting this sarcoma in the oral cavity through searching keywords on the following online databases, without any date limitations: Pubmed, Scopous, MEDLINE, Google Scholar, and MD-Consult.

Our search revealed only 8 articles reporting the occurrence of embryonal RMS in the maxilla among adults and none of them referred to any addict patient.

Conclusion: The occurrence of oral ERMS in adults is a rare phenomenon associated with poor prognosis. Furthermore, addiction can contribute to more rapid tumor growth, treatment resistance, and reduced survival through mutagenic induction, immunosuppression, and angiogenesis.

Keywords: Addiction, Oral Rhabdomyosarcoma, Opiate, Embryonal type

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Introduction

Rhabdomyosarcoma (RMS) is a malignant soft tissue neoplasm that is derived from primary mesenchyme cells (PMCs), and tends to develop neoplastic skeletal muscle (1).

RMS is the most common soft tissue sarcoma in children and adolescents. It accounts for about 60% of soft tissue sarcomas in children, but its prevalence among adolescents is much lower, reaching about 2-5% (2, 3). These tumors usually affect the extremities, but sometimes also involve the head and neck (4).

The clinical manifestation of this neoplasm varies according to its anatomical position, but it is usually a fast growing and painless mass. Destructive behavior and bone invasion are common outcomes (5, 6).

A clear etiologic risk factor for the neoplastic growth of this malignancy has not yet been identified. The malignancy has been seen with a higher incidence in some rare congenital syndromes, such as Beckwith-Wiedemann, Li-Fraumeni syndrome, Neurofibromatosis type 1 (NF1), Costello and Noonan syndromes. Also, some studies have suggested that exposure to X-rays during pregnancy, or parental use of drugs such as marijuana and cocaine, would increase the risk of RMS.

RMS was first described by Weber in 1854, and has always been recognized by pathologists and physicians in various clinical and histopathological forms (7). Based on morphologic, histologic and biologic differences, rhabdomyosarcomas are divided into embryonal, alveolar, botryoid, pleomorphic, spindle cell and anaplastic subtypes (1).

Embryonal RMS is histopathologically a mixture of undifferentiated, spindle-shaped, round-bottomed and muscle-like cells (rhabdomyoblast), along with bulky eosinophilic cytoplasm in dense or loose forms in a myxoid matrix (8).

Alveolar rhabdomyosarcoma (ARMS) tumors are very similar to alveoli tissue in the lungs. The cells in ARMS are small with little cytoplasm. They clump together several times and fibrovascular septae interrupt this aggregation (1). Botryoid rhabdomyosarcoma arises from ERMS. Microscopic features represent a hypercellular zone immediately beneath the epithelium, resembling growth rings in trees, with less cellular density in deeper layers. Pleomorphic rhabdomyosarcoma (PRMS) is rich in large atypical, polygonal, pleomorphic rhabdomyoblasts. These cells vary from spindle to racquet-shaped, or multinucleated with abundant eosinophilic cytoplasm. Spindle cell rhabdomyosarcoma is a more differentiated type with a higher proportion of cells expressing markers of mature muscles (myoglobin, troponin T and muscle specific actin), compared to other variants. Anaplastic rhabdomyosarcoma is rich in multipolar mitotic figures and anaplastic cells with lobate hyperchromatic, large nuclei (4).

RMS treatment has been significantly improved over the past decade, due to the application of multi-modal protocols, and accelerated treatment for these patients. Modern therapy is a combination of primary chemotherapy, surgery (if possible), and radiotherapy to control the local residuals (9).

RMS tumors are detected accurately by a combination of clinical findings, histopathology and immunohistochemical reactions (10, 11).

Disease prognosis depends directly on disease stage at the time of diagnosis, anatomical position, histological type and degrees of anaplasia (12).

This study reports a case of RMS that is uncommon in terms of location and age. The latest diagnostic methods have been used to verify the type of lesion, and to differentiate from other sarcomas. In addition, we have included an overview of articles previously reporting this sarcoma in the oral cavity.

Case report

The patient was a 24-year-old male with a 7-year history of opium and crystal addiction. He referred to the Oral and Maxillofacial Medicine Department, Dental Faculty, Tehran University of Medical Sciences with a complaint of rapid, progressive and painless unilaterally facial swelling, starting 20 days earlier, and the upper lip paresthesia and tearing from the previous week. Extra-oral examination revealed swelling on the left side of the face, disseminated from the inferior orbital fissure to the middle third of the face (approximately along the canthus-tragus line) (Fig 1). The skin covering the lesion was intact, without redness, warmth and beating in touch. Intra-oral examination represented an exophytic, red to purple mass from the distal surface of left maxillary lateral tooth to the posterior tuberosity. The mass disseminated on buccal side to the depth of the vestibule, and on palatal side to the midline. The crown of the lateral and canine teeth had been completely decayed. An ulcer covered by fibrino leukocytic

exudate was seen in the anterior portion of the lesion. We found a granular epithelial surface on the posterior part of the lesion at the buccal side (Fig 2). The consistency of the lesion was rubbery, and the left premolars had motility. Aspiration was negative.

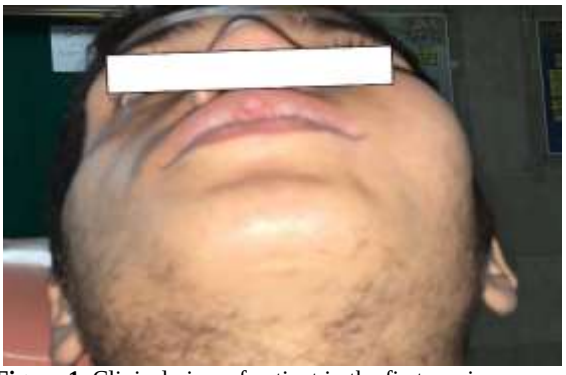

Figure 1. Clinical view of patient in the first session

Figure 2. Intra oral photograph of patient showing the swelling that extended almost to the palate, vestibule depth and the palatal side

Periapical radiography from the 4th to 7th left maxillary teeth was ordered. An inter-radicular radiolucency with unclear border displayed, the teeth were floating in air. No resorption was observed in the teeth. Periodontal ligaments and lamina dura of the teeth were not followed well (Fig 3). At the end of the first session, CBCT imaging was arranged. Four days later, the CBCT view revealed an ill-defined radiolucent lesion from the left maxillary central tooth to the tuberosity, and from the alveolar crest to the floor of the orbit. The mouth eaten view at the border of sinus [1], and orbital floor and destruction of the medial wall of the nasal cavity, involvement of ethmoid air cells and posterior displacement of the anterior wall of the sphenoid sinus were revealed (Fig 4). Accordingly, we considered differential diagnosis of one malignancy. An incisional biopsy was taken under local anesthesia. Histopathology assessment of the lesion reported a malignant neoplasm of mesenchymal origin including scattered pleomorphic and small round cells with eosinophilic-rich cytoplasm in a myxoid loose stroma but the type of sarcoma was not differentiated (Fig 5). Thus, immunohistochemistry (IHC) staining was ordered. IHC was positive for Vimentin, Desmin, Myogenin and $MyoD_1$ antibodies, and negative for CD_{20} and CD_3; proliferative activity for Ki67 was about 50-55% (Dako, Denmark) (Fig 6-8). Finally, ERMS was confirmed. Spiral neck CT scan (with contrast), and face CT scan (axial, coronal, sagittal, 3D reconstruction and without contrast), performed in the Oncology Department of Imam Khomeini Hospital, exhibited soft tissue mass in the left maxillary bone and sinus. The anterior wall of the maxillary sinus was destroyed, and the mass bulged to the nasopharynx medially. Few small left zone II and III lymph nodes were present. The spiral CT from the brain and chest (with contrast) showed no abnormality and there was no evidence of structural shift toward midline.

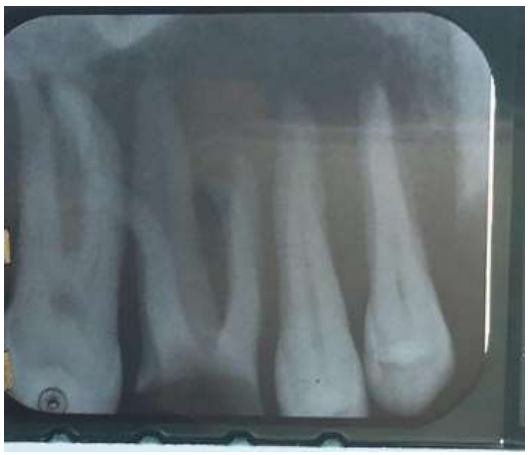

Figure 3. Intra oral periapical radiograph shows ill-defined radiolucency and hanging in air view

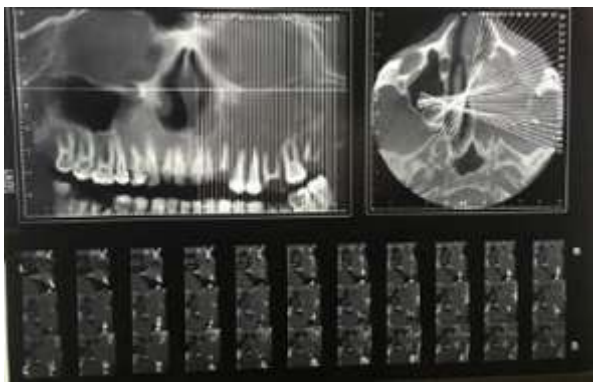

Figure 4. CBCT showing an unidentified radiolucent lesion from the left maxillary first molar to the tuberosity and from the crest apex to the orbit floor

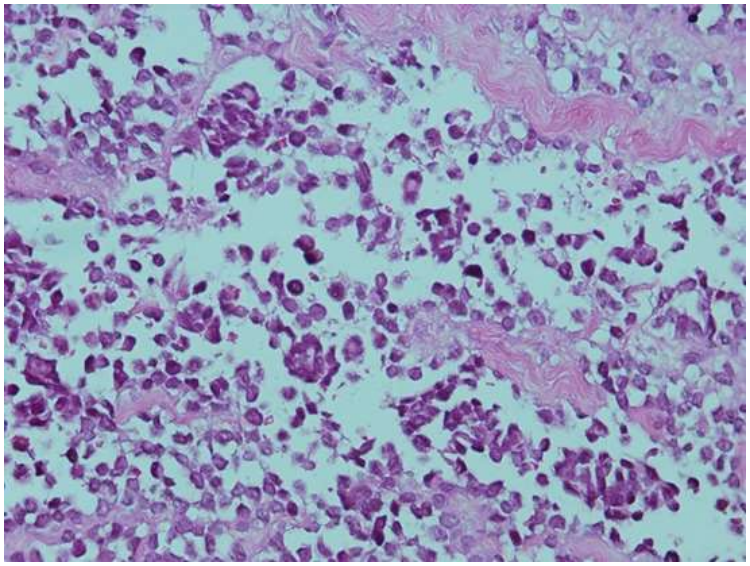

Figure 5. Photomicrograph of the incisional biopsy, (H&E, original magnification ×400)

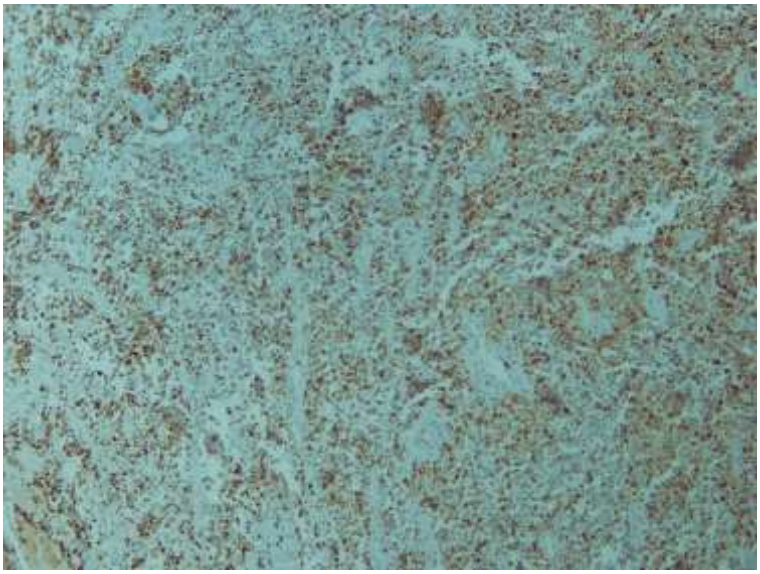

Figure 6. Immunohistochemistry of Ki67 in tissue (×100)

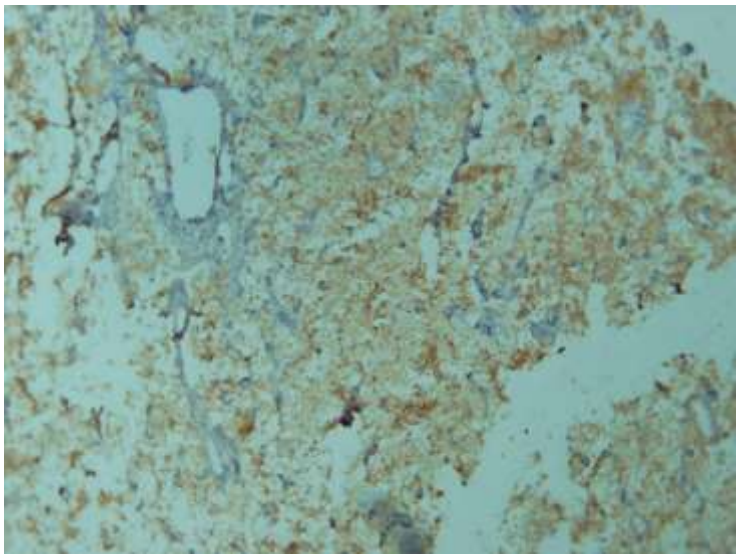

Figure 7. Immunohistochemistry of MyoD1 in tissue (×100)

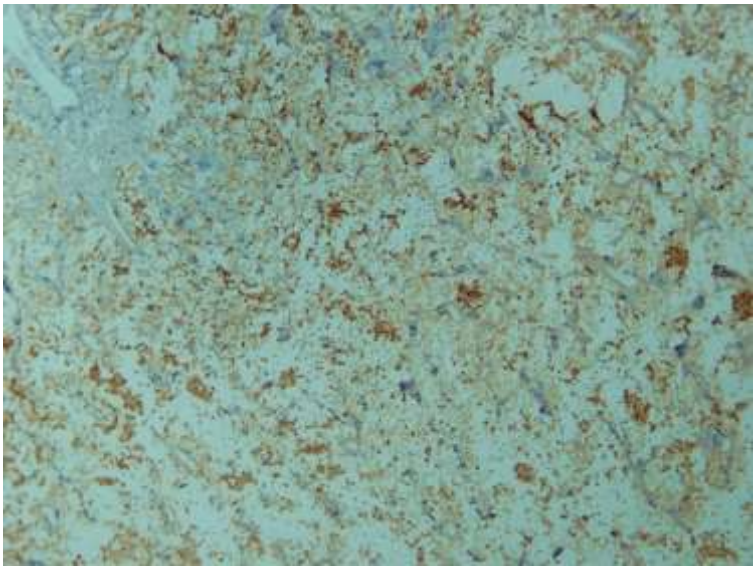

Figure 8. Immunohistochemistry of Myogenin in tissue (×100)

Figure 9. Exacerbation of lesion after changing the chemotherapy dosage

Chemotherapy was started with Vincristine, Actinomycin D, Endoxan and GCSF. During the first eight sessions of the treatment, a significant recovery was observed, but subsequently, the lesion enlarged dramatically, due to the lack of patient cooperation in his treatment plan, and a change in the dosage of the medications (Fig 9). So, chemotherapy was returned to the previous dose for the remaining sessions, and radiotherapy was considered after the completion of the chemotherapy. Pancytopenia resulted, following the fifteenth session of radiotherapy, causing flare up of the lesion. The patient was hospitalized and we monitored his condition through contact with his physician and family members. Several weeks later, the patient died.

Literature review

In literature review, we searched for papers on oral RMS, published in English, using the online search engines Pubmed, Scopous, MEDLINE, Google Scholar, and MD-consult. Keywords used included Oral Rhabdomyosarcoma, Maxillary and/or Mandibular Rhabdomyosarcoma, Embryonal and/or Alveolar Rhabdomyosarcoma, Adult and/or Children Rhabdomyosarcoma, alone or in combination. We imposed no time limit, so time range defaulted to 1970-2018. We accepted case reports or case series articles that reported any type of oral Rhabdomyosarcoma in any site of the oral cavity.

Out of a total of 1072 abstracts, 254 articles were on subject. After further sifting, 40 case reports and case-series, reporting RMS in the oral cavity, were extracted in PDF format. These 40 articles reported 109 oral RMS cases, broken

down as follows: Embryonal RMS (n=60), Alveolar RMS (n=38), concurrent ERMS and ARMS (n=3), undifferentiated form (n=2), spindle-shaped cells (n=3), botryoid RMS (n=1) and Pleomorphic RMS (n=2). Of these, 23 cases had occurred in the maxilla and hard palate, and 43 ones had reported cases of this sarcoma in adults, of which only 20 cases were ERMS. Thirty studies had used immunohistochemistry with different antibodies in the diagnostic process of the lesions. None of the studies had referred to any addict patient.

According to our review, only 9 articles had reported the occurrence of embryonal RMS in the maxilla among adults (Table 1).

Table 1. List of articles evaluated in this paper

Author/Year	Location	Sex	Age (year)	Subtype	Positive immunohistochemical staining	Management
Pap GS, 1980 (44)	Mandible	F	6	Undifferentiated sarcoma		C-R
Yamamoto H, 1984 (45)	Mandible	M	7	Embryonal		C-R-S
Sadeghi EM, 1988 (12)	Tuberosity, soft palate	M	26	Embryonal		
Peters E, 1989 (46)		5M 3F	7-46	4- Embryonal 4- Alveolar		
LazzaroB,1990 (47)	Parotid	M	24	Embryonal		C-R
Nakhleh RE, 1991 (24)	Tongue	8F 4M	18-36	4- Embryonal 8- Alveolar		
Doval DC, 1994 (48)		2M	3.5 32	Alveolar Embryonal		C-S C-R
Chen SY, 1995 (6)	palate	2M 2F	7-22	4- Embryonal		3-S-C SR
Pavithran K, 1997 (18)		5M 3F	3.5-45	5- Embryonal 3- Alveolar		
Moller P, 199 (49)	Nasal cavity	F	9	Embryonal		C-R
AL-Khateeb T, 2002 (50)		3F 6M	4-17	6- Embryonal 2- Alveolar		
Loducca SV [51], 2003	Mandible	F	6	Undiffrentiated Embryonal	Vimentin-desmin-MSA	C-R-S
Seth T [52],2004	Lip	F	2/5	Embryonal	Desmin S100	C-S
Duraes GV, 2005 (53)	Zygoma, ramous	M	4	Embryonal	Desmin-MSA	C
Franca CM, 2006 (26)	Buccal mucosal, maxillary ridge	1F 1M	18-19	1-Embryonal 1- Alveolar		
Chi AC, 2007 (54)	Maxillary gingiva	1 F	33	Embryonal	desmin, myogenin, MyoD1	C-R-S
Yasuda T, 2008 (17)		3F 1M	61-76	4- Alveolar		
Chen SC, 2010 (55)	Orbit	M	13	Alveolar	MSA-MYOD1	R-C
Miloglu O, 2011 (56)	Buccal mucosa	F	13	Alveolar	Vimentin-Desmin-Myoglobin-MSA	R-C
Sahni P, 2013 (57)	Mandible	M	36	Embryonal	Desmin-Myogenin	C-S-R
Nema SK, 2017 (58)	Buccal mucosal, nasal	M	3	Alveolar	Desmin	
Wu PX, 2014 (27)	Nasal	M	60	Embryonal	Myogenin-MSA-Desmin-Vimentin-CD56-CD99	
Shrutha SP, 2015 (59)	Maxillary ridge	M	1	Alveolar	Vimentin-desmin-myoglobin-MSA	C
Lav R, 2015 (60)	Maxilla	M	25	Embryonal	Desmin-Myogenin	
Ananthaeni A, 2016 (61)	Tuberosity, palate	F	50	Alveolar	Vimentin-MYOD1	
Datta S, 2016 (62)	Palate, superior retromolar pad	F	17	Embryonal	Desmin-MYOD1-Myogenin-MSA	

Table 1. List of articles evaluated in this paper

Sood N, 2016 (20)	Nasal	M	56	Alveolar	Myogenin-PAX8	
Mclnturff M, 2017 (63)	Buccal mucosal	F	19	Embryonal	Desmin-Myogenin-MYOD1	
Radzikowska J, 2016 (64)		24M 12F	1-22	14- Embryonal 3- Alveolar 3- Embryonal /Alveolar		
Mungan S, 2016 (65)	Larynx	M	64	Pleomorphic	Desmin-actin-Myogenin	S-R
Arul AS, 2014 (15)	Buccal mucosal	M	36	Embryonal		C-R
Johhana CA, 2017 (5)	Retromolar pad	F	13	Embryonal		C-S
Sepulveda I, 2017 (66)	Nasal	F	22	Alveolar	Actin-Myogenin	C-R
Vhriterhire R, 2017 (67)	Maxilla	M	23	Embryonal		
Smith MH, 2017 (68)		3M	22-39	Spindle		
Latrou I, 2017 (19)		5F 4M	4m-15y	4- Embryonal 5- Alveolar		
Silva Cunha JL, 2018 (69)	Buccal mucosa	F	13	Botryoid	Desmin, myogenin, Ki67	C-R
Motallebnejad M, 2018 (70)	Maxillary gingiva	F	32	Embryonal		
Kusafuka K, 2018 (71)	Floor of the mouth	F	19	spindle cell	vimentin, MyoD1, bcl-2, desmin, cytokeratin (CK)7, CK5/6, MDM2.	S-R
Amtha R, 2018 (72)	Tongue	M	42	Pleomorphic	Desmin, actin	
Joy T, 2018 (73)	Mandibular gingiva	M	52	Spindle cell		C-R
De Albuquerque RF, 2018 (74)	Maxilla	M	25	Embryonal		S-C-R

Discussion

The diagnosis of cancer in children and adults is a life-altering event for them and their families. Cancer is the second leading cause of death, after accidents, in children aged 5 to 14 years and after cardiovascular events in adults. Depending on the type of cancer and relevant treatment, patients who survive more than 5 years may be at an increased risk of recurrence or progression of primary cancer or other malignancy, chronic disease, and functional disabilities. Therefore, it is very necessary to consider long-term monitoring of these patients (13).

Sarcomas are a heterogeneous group of malignant tumors originating from bone or soft tissue. More than 100 different subtypes of sarcomas have been identified in adults and children; the most common types in adults are, undifferentiated pleomorphic sarcoma (malignant fibrous histocytoma), liposarcoma and leiomyosarcoma (14).

Age

RMS comprises only about 2-5% of all adult soft tissue sarcomas. ERMS is the most prevalent subtype in children under the age of 10 years (15).

Our target case showed the occurrence of ERMS in the age range of 20-30 years (24 years), which is very uncommon for this sarcoma. ARMS represents 16% of cases in adolescents and adults (16), and PRMS is the most common tumor in people over 40 years (15).

Since RMS is uncommon among people over the age of 20 years, published reports of cases in this age range are rare. Yasuda et al. (2009) reported five cases of alveolar RMS in patients between 61-67 years old (17). Another study in 2017 reported 3 cases of RMS in patients older than 22 years (18). Again in 2017, Latrou reported 9 cases of oral RMS, of which 5 ones were under 10 years of age, and 4 cases were between 10 and 20 years old. No case was reported between the ages of 20 and 30 years (19).

According to the data from the review articles in our study, RMS had been reported in the first 10 years of life in 44 cases, between 10 to 20 years in 25 cases, and over 20 years in 34 cases.

Gender

RMS is highly male-dominated in children, but in adults, there is no tendency towards males

(20). The case reported in this paper is a 24-year-old man.

Location

The three most common sites of RMS involvement in the head and neck include:

1- orbital

2- Para-meningeal (nasal cavity, paranasal sinuses, nasopharynx and infratemporal fossa)

3- Superficial areas including throat, scalp, buccal mucosa, parotid, outer ear, tonsils and face.

Most adults are afflicted in their extremities, but head and neck involvement is seen only in 15% of cases with often the paranasal sinuses involvement. Head and neck involvement occurs in children (21), but our case was an adult patient.

Also, ERMS in the head and neck region is relatively common, but intra-orally, it is rare. PRMS is the most common form in the oral cavity, especially in the tongue (15). In those rare intra-oral cases, the most common site varied. Some authors have reported that the most common sites are palate and the tongue. Case reports indicate that mandibular gingiva is more involved compared to maxillary gingiva (21, 22).

In a study conducted by O'Day *et al.* (1965), the palate was the most common site in the oral cavity and the cheek, labial mucosa, buccal fold and tongue were reported to be in the next ranks (23).

In our case, the appearance of intra-oral ERMS was in the maxillary and palatal gingivae, along with the involvement of the maxillary sinus, ethmoid, sphenoid, orbit floor and nasal areas that is uncommon. The appearance of rhabdomyosarcoma, either primary or spreading from other surrounding areas to the oral cavity, is uncommon and rare. In the presented case in this paper, regardless of the primary source of the sarcoma, the maxilla or the sinus, the appearance of mass in the oral cavity was important to us. Based on the articles reviewed in this study, the buccal mucosa is the most common intra-oral region involved, followed by the palate.

Our case is uncommon in terms of age, type of RMS, and intra-oral involvement. Very few cases match our combination of age, location and type. Arul *et al.* (2014) reported the occurrence of ERMS in a 36-year-old male with buccal mucosa involvement and the lateral posterior part of the hard palate, but there was no involvement of the sinus, orbit and nose (15).

Diagnosis

Age at the time of the onset of the tumor, and the anatomical location are two important factors contributing to the differential diagnosis of the tumor, in cases where the histology has non-specific results; for example, SCC, melanoma and lymphoma are often seen among those over the age of 40 years (24).

Because the histological profile of RMS varies and it is a member of a weakly differentiated tumors, it can imitate the appearance of other round cell malignancies. Where there is no evidence of muscle synthesis, the use of IHC, PCR-PT and chromosomal investigations is necessary to confirm the diagnosis (20).

The differentiation of this sarcoma from other sarcomas, as well as the differentiation of different types of RMS is very important. For example, the ERMS form typically has less invasive clinical behavior and better prognosis compared to the ARMS form (16). Immunohistochemical antibodies commonly used for confirmation of diagnosis include desmin, vimentin, muscle-specific actin (MSA), myoglobin, MyoD1, and myogenin. Desmin shows the muscle differentiation, and vimentin is an antibody sensitive to mesenchymal tissue, but not specific to RMS. These two antibodies together represent myogenic tumors. MSA is very sensitive to myogenic phenotypes, but it cannot distinguish smooth muscle from skeletal muscle; myoglobin shows the differentiation of adult skeletal muscle (25). Myogenin and MyoD1, Myogenic transcriptional regulators, are critical factors in the differentiation of mesenchymal progenitor cells to the mature myogenic cell. They express earlier than myosin, myoglobin, actin and desmin, in skeletal muscle. Hence, these proteins are absent in adult muscle and more sensitive than myoglobin, and more specific than desmin and actin (24).

Near the C-terminus of the MyoD1 protein is the target for anti-MyoD1 antibody. Nucleus staining is more prominent and specific than cytoplasmic staining (24). Some studies have reported more cytoplasmic staining for ARMS than for ERMS. MyoD1 immunostaining is positive in almost all RMS cases (23) (Fig 7).

It has been found that138–158 amino acids of the myogenin molecule are the targeted locations for anti-myogenin antibody. Similar myo-D1,

Nucleus staining is considered positive staining. Myogenin is a highly sensitive and specific marker for RMS, but rarely is seen in non-RMS and non-neoplastic, skeletal muscle. Alveolar subtype of Rhabdomyosarcomas is stained more widespread and strongly than ERMS. It is hypnotized that ERMS originates before the expression of myogenin in early myogenesis process, whereas ARMS cells results later in the myogenic process (22, 25) (Fig 8).

Ki67 is a nuclear protein associated with cellular proliferation, expressed from early G1-phase in cell cycle and IHC staining correlates with aggressive behavior of tumors. This protein is a high sensitive but low specific marker in different soft tissue sarcomas. Ki67 index is positively correlated with mitotic count, and histologic grade. The Ki67 high index sarcomas, similar to our case, showed less favorable prognosis than the low index tumors (18) (Fig 6).

In the case reported in this paper, IHC staining was positive for vimentin, desmin, myogenin, and MyoD1 antibodies, and CD3 and CD20 antibodies were used to eliminate the presence of other small round cell tumors, such as leukemia and Lymphoma.

Negative IHC antibodies in RMS cases include cytokeratin, S-100, CD45 and CD99. The reviewed articles in this study showed that the immunohistochemical staining method had been used to confirm the diagnosis of RMS in 30 out of 103 patients, of which 7 were approximately the same as our suggested antibodies. França *et al.* (2006), used desmin, vimentin, myogenin, and MSA antibodies to verify the type of ERMS in the maxillary ridge of a 19-year-old patient (26).

MYOD1 has more sensitivity and specificity than MSA. In a case introduced by Wu PX in 2014, myogenin, desmin, MSA, vimentin and CD56, CD99 antibodies were used (27).

Treatment

RMS treatment is multi-modal; that is, a combination of surgery, radiotherapy and chemotherapy is used for treatment (28, 29).

Sustained chemotherapy has increased the disease-free survival rate from subclinical micrometastasis, and combined chemotherapy can help eliminate metastatic disease. Commonly used drugs include the combination of Vincristine, Dactinomycin, Cyclophosphamide and Adriamycin (30).

The 103 RMS patients reviewed in this study had experienced chemotherapy and surgery (n=16), radiotherapy and surgery (n=3), surgery, chemotherapy and radiotherapy (n=14), radiotherapy and chemotherapy (n=27), chemotherapy alone (n=7), no treatment (n= 34) and only biopsy (n=2). In our case, due to the large size of the lesion and its spread to the critical anatomic areas, and insufficient surgical access, surgery was not considered as a primary treatment. The patient was treated with chemotherapy and radiotherapy. In a similar case reported by Sadeghi *et al.* (1987), after verifying the type of ERMS, a 26-year-old male patient underwent chemotherapy and radiotherapy (12).

Predisposing background for developing the disease

Of the various drugs that are used addictively, opiates are among the substances causing major health problems in the world. Among various opiates, opium is one of the most commonly used (31).

The acute effects of opium, including numbness and sleepiness, have been known for many years. Today, many studies have suggested the link between opium and various types of cancers, including lung, bladder, gastric, oral, esophagus and larynx cancer (32, 33).

In addition, opium has been introduced as a primer for the emergence of various types of cancer in the early stage. The relationship between the increase of the cancer incidence and the consumption of opium may be affected by other risk factors such as age, sex, concurrent consumption of tobacco and alcohol, underlying infections such as hepatitis and AIDS, and poor socio-economic status (34).

Opium smoke and residue contain compounds that have mutagenic activity, and induce changes in sister chromatids, which are mainly heterocyclic compounds derived from the morphine content of opium (35, 36).

Chronic use of opioids, especially those containing morphine, leads to immuno-suppression by reducing the production of antibodies, the activity of natural killer cells, the expression of cytokines, phagocytic and chemotactic activities, and lymphocytic proliferation (37, 38).

Since the immune system is vital in preventing the formation of tumors and metastases, the consequence of immuno-suppressive drugs can lead to the development and growth of cancer (39).

Morphine also induces angiogenesis through increasing the concentration of calcium and

nitric oxide in endothelial cells, vascular permeability, unregulated proliferation, endothelial cell disruption and migration, protease release and migration, and transactivation of fibroblast growth factor 1 receptors in non-endothelial cellular system. Angiogenesis plays a key role in the incidence and metastasis of cancers (40).

Even in patients undergoing methadone maintenance, a higher mortality rate has been observed (41).

Our patient was addicted to opium for more than 7 years. This may be one of the causes of the disease, rapid tumor growth, high resistance to the treatment, and reduced survival rate.

Prognosis

RMS in terms of prognosis is classified in three categories:

ERMS ⟶ intermediate

ARMS type and undifferentiated ⟶ poor

Botryoidal and spindle ⟶ favorable

Factors such as tumor stage at the time of diagnosis (lymphadenopathy, metastasis, large size), unhealthy post-operative margin, and inappropriate location (insufficient access) worsen the prognosis. About 20% of patients have metastases at the time of RMS diagnosis, and the lung, lymph nodes and bone marrow are the most commonly involved locations. Although age and type of histology seem to be major prognostic factors in children, the effect of these factors in adults is still controversial and challenged (42).

According to some studies, adults have lower outcome and survival rates than children under the age of 10, because of biological differences and the clinical nature of sarcoma; referral, follow-up, late diagnosis and subsequently more advanced manifestations (43).

Factors that have contributed to the worsening of prognosis in our case include the lesion growth as a painless swelling, misconceptions about dental infections that delayed the patient's visit to a doctor, large size of the lesion at diagnosis, age over 20 years, inaccessibility to surgery, and involvement of the sinuses, orbit, and nasal area as well as addiction (21).

In our case, according to the patient, the onset of the symptoms was almost 20 days prior to his first visit, and it took about 1 month from that first visit to the beginning of chemotherapy. The patient died 15 months after the start of chemotherapy. Overall, the survival rate of the patient was less than 2 years since the onset of symptoms, indicating poor prognosis.

Conclusion

The occurrence of oral ERMS in adults is a rare phenomenon associated with poor prognosis. Additionally, addiction can contribute to more rapid tumor growth, treatment resistance, and reduced survival through mutagenic induction, immuno-suppression, and angiogenesis. Promoting awareness in patients and specialists of alarming symptoms such as rapid growth and painless masses, together with the use of new diagnostic methods, such as immuno-histochemistry and the application of poly-therapy methods, can be effective factors in improving the disease prognosis and in prolonging survival of patients.

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Disclosures

Declarations of interest: none

Conflict of interest

The authors claim to have no financial interests, either directly or indirectly.

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Clinical Implications and Study Limitation

Lack of patient collaboration and difficulty in accessing the patient's information after the referral of the patient to the hospital. Moreover, searching, evaluation and data extraction of articles was time consuming.

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