Sublingual Recurring Extra osseous Ewing Sarcoma: A Rare Case Report and Review of Literature

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Case Report

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Abstract

Background: Extera skeletal (Extraosseous) Ewing sarcoma is a rare primary tumor of the soft tissue, with an extremely high mortality rate and a bad prognosis which primarily affects young individuals. It occurs without particular clinical signs and can impact several different areas, which may delay diagnosis. Histopathological examination and immunohistochemistry are crucial for making a definite diagnosis. Besides this, early diagnosis is necessary for succeeding of the management.

Case report: The objective of the present case report was to document a rare case of EES which originated from the floor of the mouth. A 37-year-old male patient came to our clinic with sublingual rapidly growing swelling. He was suffering from difficulty in opening his mouth and a feeling of dysphagia. The patient revealed during a history-taking procedure that he had undergone one surgery to remove the mass that had previously developed in the same area, knowing that he had been diagnosed in the first as a non-specific inflammatory reaction. Clinical examinations revealed a dome shape soft tissue mass. The biopsy specimen underwent histopathological and immunohistochemical analysis, which demonstrated poorly differentiated small blue round cells with positive immuno-expression of CD-99, NKX2-2, FLI-1, and Vimentin. The final diagnosis was EES based on the clinical presentation, histopathological pattern, and findings of the immunohistochemistry investigations. Radiotherapy and chemotherapy were chosen as treatment modalities for the case. Unfortunately, the patient died after three months due to the occurrence of multiple distant metastasis areas.

Conclusion: Regardless of the relative rarity of Extraosseous Ewing sarcoma, it should be taken into account as a possible differential diagnosis for intraoral soft tissue masses, and accurate diagnosis with precise histopathological and immunohistochemical evaluations should be done as soon as possible. Moreover, improvement of management procedures of such cases generally provides the best chances for patient survival.

Introduction

The Ewing's sarcoma Family of Tumors (EFT) includes classic Ewing's Sarcoma (ES) of bone, Extraskeletal (Extraosseous) Ewing's Sarcoma (EES) and malignant peripheral primitive Neuroectodermal Tumor (PNET) of bone and soft tissue [1].

James Ewing was the first who mentioned ES of bone which was in 1921. ES most commonly arises in the skeleton of adolescents and young adults. Extraosseous Ewing's sarcoma (EES) is a rare entity with about 15% of cases which was first stated by Tefft et al. in 1969. Obviously, it has the same histopathological, immunohistochemical, and molecular findings of the bony ES but usually appears in soft tissues [2,3].

EES is considered as an uncommon tumor, especially in the oral and maxillofacial regions which mainly affects young people as mentioned previously. It usually follows an aggressive course, with a high recurrence and very high mortality rates, especially in metastatic forms. Due to unclear clinical signs in
patients, the probability of occurrence in different locations, outcomes of poor prognosis, and delay in diagnosis commonly occur [4].

EES can be described as a tumor of soft tissue origin with round cells of small size. Although the origin of it is not clear. It was reported that it may be originated from neuroectodermal cells. Moreover, other origin sites such as primitive mesenchymal cells of bone marrow and immature reticular cells can be involved. Besides, it was documented that the existence of genetic translocation between (11; 22) (q24; q12) or (21; 22) (q22; q12) may have a role in its origin [5].

The existence of EES in the head and neck is extremely rare. It has been reported in many areas such as the scalp, face, orbit, nasal cavity, paranasal sinus, nasopharynx, parapharyngeal space, larynx, hard palate, submandibular gland, parotid gland, thyroid gland, and soft tissues of the neck [6]. To the best of our knowledge, few cases were documented involving the sublingual region (floor of mouth) such as the current presented case.

Apparently, the diagnosis of this tumor depends on the histopathological and immunohistochemical examination to rule out any other tumors. An accurate diagnosis offers early intervention which leads to high chances of survival. The current report revealed a rare case of EES that originated from the floor of the mouth and highlighted the importance of histopathological and immunohistochemistry investigations in the differential diagnosis of this rare tumor when occurs at an unusual site.

**Case Report**

A 37-year-old male, presented to Royal Smile Maxillofacial Center, Cairo, Egypt complaining of a recurring painful swelling in the left sublingual region associated with difficulty in swallowing. Clinical intraoral examination revealed a right ulcerous-proliferative lesion in the floor of the mouth of 3*1 cm in size, a fleshy dome in shape with irregular margins, and occupying most of the sublingual left region (Fig. 1A). When performing the extra-oral examination, there was no swelling nor asymmetry. Furthermore, there were palpable asymptomatic bilateral submandibular lymph nodes. The medical history of the patient revealed a history of suffering from renal failure.

By taking a full history, the patient mentioned that he was subjected before to one surgery to remove the tumor mass that has been aroused in the same place once previously with an earlier diagnosis of it as a non-specific inflammatory reaction. Following investigations, the patient underwent another surgery, and the incisional biopsy was sent to Dr. Hatem Amer’s Oral and Maxillofacial Pathology Lab. Cairo, Egypt for achieving a diagnosis through a proper histopathological examination of the specimen (Fig. 1B).

**Gross Appearance And Histopathological Evaluation**

Grossly appearance of the lesion revealed a well-circumscribed, encapsulated mass with a fleshy appearance as shown in (Fig. 1C). The Hematoxylin-eosin staining sections showed a lobulated lesion
composed of sheets of round small malignant cells (Fig. 2A). Areas of comedo-necrosis were also noted (Fig. 2B). The shown malignant small round cells are characterized by hyperchromatic nuclei with finely stippled chromatin and scanty cytoplasm. Additionally, areas of the minor salivary gland were seen around the fibrous capsule (Fig. 2C&D). Our diagnosis was a malignant small round cell tumor. Consequently, differential diagnosis was considered including malignant lymphoma, malignant salivary gland tumor, small cell carcinoma, and EES.

**Immunohistochemical Analysis**

Bearing in mind that immunohistochemistry is the mainstay of diagnosis, and in order to exclude other malignancies, immunohistochemistry assessments were performed. The tumor cells showed positivity for CD-99, FLI1, NKX2-2, and Vimentin as shown in (Fig. 3A-D) and were negative in reaction for pancytokeratin, leukocyte common antigen (LCA), myogenin and CD-38 markers. These features were conclusive of ES (Fig. 4A-D).

Besides the previous investigations, a PET CT scan with contrast injection was performed which showed multiple suspicious lesions in the liver, spleen, and kidney with no pulmonary or bone metastases. A referral of the patient was done to start the treatment plan with chemotherapy and radiotherapy. However, three months later, the patient was transported to the hospital's emergency department, and he died after a few days despite the measures of reanimation.

**Discussion**

EES is considered as an extremely malignant tumor which usually composes of undifferentiated small round cells of unknown origin and shows neuroectodermal differentiation of variable degrees [7].

The occurrence of Ewing’s sarcoma in the oral and maxillofacial area is not usual which represents only 4% of soft tissue tumors and about 1.5-4% of childhood sarcomas [8]. However, very few cases originating from the sublingual region have been reported to date.

In a clinical aspect, approximately 75% of patients with EES present with a rapidly growing enlargement that is usually with less pain than its bony counterpart, and 30% of patients exhibit distant metastases at the time of diagnosis [9]. These tumors tend to spread locally, invade surrounding facial surfaces, and moreover invade muscles and bone. The rarity of EES makes it challenging to determine the optimal diagnosis and management of these tumors. However, recent progress in chemotherapy and radiotherapy, and the use of aggressive surgical procedures have improved the overall survival rate of these cases [5].

Herein, a 37-year-old patient suffered from a recurring painful swelling with difficulty in swallowing in the left sublingual region. Consistent with this case, the typical peak incidence of this tumor is between 5 and
25 years of age and occurs more frequently in males than in females. Some studies have reported a male prevalence of between 1.4.

1 and 2.4:1 in the head and neck areas which matches this case. However, a recent report establishes a relatively balanced gender distribution, with only a minor female predominance of 1.05: 1 [10,11]. After the biopsy was taken from the patient, histopathology revealed a strong blue color that demarcates Ewing’s sarcoma which goes to the blue round cell tumors group. Thus, immunohistochemistry was an elemental assessment to exclude the differential diagnosis. In the current case, the CD-99 marker was used which is known as a cell membrane glycoprotein that usually appears in all ES and PNET with a positive immunoreaction in 98% of the cases [11].

The CD-99 marker has also been identified in many other blue round cell tumors such as rhabdomyosarcoma, small cell carcinoma, lymphomas, and sarcoma such as poorly differentiated synovial sarcoma [6]. In this current report, the probability of another blue round cell tumor such as rhabdomyosarcoma, small, and lymphomas (plasmablastic lymphoma) can be ruled out due to the negativity reaction to leukocyte common antigen (LCA), myogenin, pancytokeratin and CD -38 markers (Table.1).

Table 1

| Extraskeletal Ewing sarcoma in comparison with other blue round cell tumors according to the WHO. |
Interestingly, the presence of this tumor in the sublingual region is a rare finding, so very little information in the literature was reported about the presentation of the extraosseous type in this location. Therefore, a definite clinical description of this entity in the sublingual region was not covered. The signs and the characteristic symptoms of this sarcoma are varied which usually depends on the site of origin. Throughout the years, numerous therapeutic modalities have been established, depending on the site and extension of the tumor. Many treatment modalities were reported for EES such as surgery, chemotherapy, and radiotherapy [12].

EES presents with a poor prognosis which usually increases in presence of some risk factors such as old age, pelvic involvement, high WBC, elevated LDH, and low Hb at the time of diagnosis. In addition, initial tumor size was also reported as a risk factor and was considered as a strong prognostic factor in the disease. Yet, it was reported that using neoadjuvant chemotherapy as a treatment modality revealed a great histopathological response for ESS previously diagnosed cases [13].

Management of the patient in the current case report was done using both chemo/radiotherapies. Unfortunately, despite appropriate treatment, the lesion proceeded from a localized form to a metastatic form. In our opinion, the major causative factor would be the late diagnosis of this tumor which resulted
in a delay in the handling of the case which finally led to the lack of response to the management and ended up with the development of multiorgan metastasis.

**Conclusion**

Ewing’s sarcoma is an aggressive malignant tumor that usually develops from the bone. The extra-osseous type is rare and infrequent when occurs in the soft tissues, especially the sublingual region. Confusion in diagnosis and delayed therapeutic intervention is due to the absence of specific clinical signs. So, accurate histopathological and immunohistochemical assessments are considered important aids to reach out the precise diagnosis, and consequently, improvement of management procedures of such cases generally provides the best chances for patient survival.

**Abbreviations**

ES: Ewing's Sarcoma; EES: Extraskeletal (Extraosseous) Ewing's Sarcoma; PET/CT scan: Positron Emission Tomography/Computed Tomography scan; PNET: Peripheral Primitive Neuroectodermal Tumor.

** Declarations**

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

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

**Availability of data and material**

The data used during the current study are available from the corresponding author on reasonable request.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors’ contributions**
Formal Drafted the manuscript, Data curation: LA. Surgical work: HA³. Laboratory work: HA¹. Critical revision of the manuscript: MA, LA, YA. Final approval: All authors.

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Figures
Figure 1

A. Intraoral photograph showing exophytic dome shape mass in left floor of the mouth. B. Surgical removal of the lesion with preservation of the vital structure. C. Gross specimen showing well-circumscribed and encapsulated mass with fleshy appearance.

Figure 2

Extra-skeletal Ewing sarcoma photomicrographs, Hematoxylin and eosin (H&E) staining. A. Lobulated hypercellular tumor composed of a sheet of small round cells covered by stratified squamous epithelium (x40). B. The small round tumor cells surround focal areas of comedo-necrosis (x40). C. Sheets of uniform and densely packed small blue cells invading the minor salivary gland (x100). D. Sheet of monotonous small round cells showing round nuclei with finely granular nuclear chromatin, a smaller population of cells appear as scattered pyknotic (dark) cells, corresponding to apoptotic debris. (x200).
Figure 3

Figure 4

Immunohistochemical expression showing: A. Strong positive for vimentin (X 200). B. Tumor cells with strong immunoreactivity for CD99(X 200). C. Tumor cells show strong nuclear immunoreactivity for FLI1 (X 200). D. NKX2-2 shows diffuse nuclear immunoreactivity in the tumor cells (X 200).