Case Report

Parameningeal rhabdomyosarcoma of oro-facial region: A case report and update

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ABSTRACT

Rhabdomyosarcoma (RMS) is a fast growing, highly aggressive malignant tumor, consisting of cells derived from the progenitor cells of myoblasts called satellite cells that exhibit a profound tendency for myogenesis. Accounts for about 5-6% of childhood cancers, occurring in the first 10 years of life. Annual incidence of RMS ranges from 5 to 8/million in Asian and Caucasian children. About 35% of RMS arises in the head and neck region, and are classified as parameningeal (PM), orbital, nonorbital and non-PM forms. PM tumors carry the worst prognosis, and are associated with a high rate of recurrence, and generalized metastases through the hematogenic and/or lymphatic routes. We present a case of 20-year-old male with an exuberant, rapidly increasing swelling of the floor of the mouth. Computed tomography scan, blood investigation, histopathological examination and desmin immuno histo chemistry staining marker, were aids that led to a definitive diagnosis.

Key words: Desmin, rhabdomyosarcoma, soft tissue sarcomas

INTRODUCTION

Rhabdomyosarcoma (RMS) is the most aggressive malignant tumor of the striated skeletal muscle. The name is derived from Greek words *rhabdo* means rod *myo* means muscle, suggesting a muscular lesion. It was first described by Weber in 1854, and accounts for 6% of all malignancies in children under 10 years of age. It was Weber who distinguished histologically alveolar RMS from other types of solid tumors in children. Oral RMS is rare, and when it occurs, it is more frequent in the soft palate.[1,2]

We report a case of RMS of oro-facial region with emphasis on molecular etiopathogenesis that may be the cause of RMS in young adults.

CASE REPORT

A 20-year-old male presented with a complaint of swelling on the right side of face and difficulty in mouth opening since 4 weeks and associated with pain from only past 1 week. It was rapidly increasing in size and progressed from approximately 1 cm × 1 cm in the beginning to approximately 10 cm × 8 cm in size. Past medical and dental histories were noncontributory.

On extra-oral examination, a diffuse swelling was present, extending from the right medial canthus of the eye, to below the inferior border of mandible and crossing the midline extending up to ala-tragus line of the left side of the face. Ear lobe was elevated on the right side with obliteration of the nasolabial fold of both right and left side. Overlying skin was stretched, shiny. On palpation, there was a rise in local temperature; swelling was tender, hard in consistency with a smooth surface. No altered sensation in the region was noted. Bilateral multiple lymph nodes of submandibular and submental regions were involved, which were firm to hard in consistency and tender.

Intraoral examination was limited due to the extent of the lesion and decreased mouth opening. An exuberant growth was present on the right side of the mouth obliterating the right vestibule and the floor of the mouth causing in-competency of the lips. Surface was irregular, lobulated pushing the tongue to the left side. Swelling was firm to hard in consistency and tender on palpation. No discharge or parasthesia were noticed. In view of these clinical findings,

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a provisional diagnosis of malignant tumor was considered. A tumor staging of stage IV ($cT_4N_{2c}M_x$) was assigned.

Lymphoma, osteosarcoma, and fibrosarcoma were considered under differential diagnosis.

Radiographic survey through an orthopantomogram, revealed a massive infiltrative lesion extending from right condyle to left angle of the mandible with ill-defined borders. There was complete bone loss in relation to 46 giving a floating tooth appearance. Computed tomography (CT) of the face revealed an infiltrative lesion involving both rami and alveolar processes of the mandible, extending into infratemporal and pterygopalatine fossae of the right side with a large soft tissue component and bony speculation. This was suggestive of a rapidly growing malignant neoplasm. Three-dimensional-CT revealed a massive tumor involving posterior right mandible and extending to the left side without destruction of the mandibular margins [Figure 1].

Biochemical parameters such as serum alkaline phosphatase and lactate dehydrogenase levels were raised. Incisional biopsy done and specimen sent to Department of Oral Pathology of A.J. Institute of Dental Sciences Mangalore, Karnataka, India, which revealed features of a mixed type of RMS, that is, tumor cells arranged in clumps with large amount of eosinophilic cytoplasm containing rhabdomyoblasts ([Figures 2 and 3] combination of alveolar and embryonal type). A confirmatory immuno histo chemistry staining (IHC) for desmin was positive [Figures 4 and 5].

Hence, a final diagnosis of RMS was arrived at, with implied grave prognosis. Management protocol in terms of surgical debulking followed by external beam radiation therapy was planned. Even before the intervention was carried out, patient succumbed, due to late stage at which the disease was reported.

DISCUSSION

Rhabdomyosarcoma is an aggressive malignant skeletal muscle neoplasm arising from cells of embryonal mesenchyme of pluripotential trait. It is more prevalent in children under 10 years of age with male predominance. According to Simon *et al*. mean age of occurrence of RMS is 6.2 years,[3] with male predominance, in comparison, the age of our patient was 20 years.

Molecular pathogenesis in the form of chromosomal translocations between t (2;13) or t (1;13), is a genotypic feature seen in RMS. The genes specifically affected were paired box (PAX) gene proteins called PAX3, PAX7, which are tumor suppressor genes. These are seen, phenotypically as specific genetic markers on skeletal muscle satellite cells,

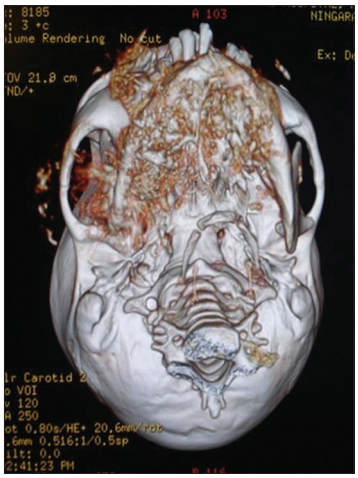

Figure 1: Three-dimensional computed tomography shows the extent of lesion

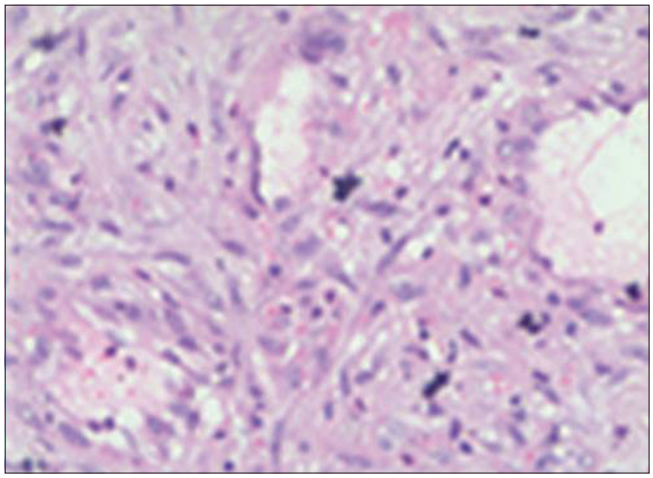

Figure 2: Histological section

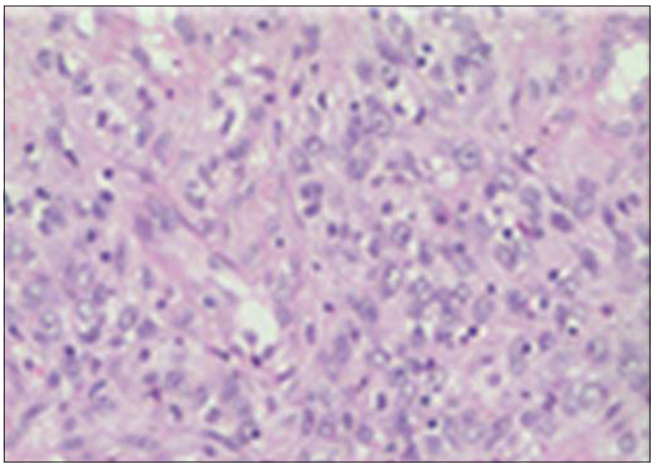

Figure 3: Microscopic section

which are small mononuclear pluripotential progenitor reservoir cells of skeletal muscle. In normalcy, these box proteins are the ones that regulate myogenesis providing muscle homeostasis. But in RMS there is a fusion of the 5′ end of the PAX3 gene located at 2q35, to the 3′ end of the

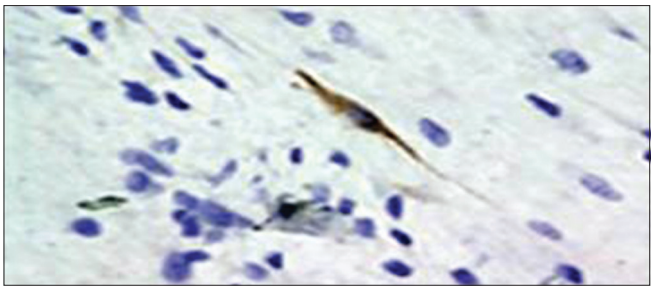

Figure 4: Desmin positive

forkhead domain FKHR gene located at 13q14 (2q35;13q14), causing a PAX3/PAX7 mRNA genotypic over-expression, with consequent un-coordinated phenotypic proliferation of myoblastic cells leading to oncogenesis of RMS.[4]

Another factor that can induce unregulated myogenic proliferation is the expression of insulin-like growth factor II (IGF-II). This is most abundant during fetal development and rapidly declines after birth. Over-expression of IGF-II has been identified in RMS, and this molecular abnormality might be implicated in oncogenesis of RMS.[4,5]

Hence, the above events leading to over-expression of PAX3, PAX7, PAX3-FKHR or IGF-II plus PAX3 could induce benign muscle tumors, but the development of an aggressive malignant phenotype required the over-expression of both IGF-II and PAX3-FKHR genes.[4,5]

Based on the anatomical site of involvement it has been broadly classified into parameningeal (PM) 50%, orbital and non-PM about 24.5%, and rest nonorbital forms.[3]

Parameningealtumors account for approximately 50% of all head and neck RMS and arise at sites with a particularly close anatomic relationship to the meninges. These include the nasopharynx and nasal cavity, middle ear and mastoid, paranasal sinuses, and the pterygopalatine and infratemporal fossae. PM tumors can be further subdivided, into those that are at high or standard risk for involvement of the meninges. Patients considered at high risk are characterized by the presence of one or more of the following features: Cranial nerve palsy, skull base bone erosion, and intracranial tumor extension.[6]

The above classification is important, as it carries a pointer towards the prognosis of the lesion.

Clinically RMS is a rapidly growing soft tissue mass, which can occur in any region of the head and neck where striated muscle or its mesenchymal progenitor cells exist. Depending upon the size of the lesion, there may be various features like facial asymmetry, abnormal phonation, dysphagia, cough, aural discharge and deviation of the jaw. Consequently, it

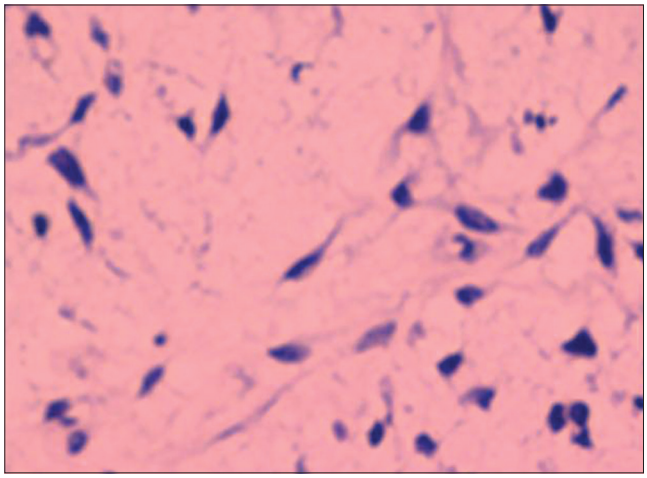

Figure 5: Rhabdomyosarcoma cells

may invade the underlying bone causing, pain, parasthesia, loosening of teeth along with trismus.

Intra-orally the most common site of occurrence is soft palate, followed by alveolus, posterior mandibular region, cheek, lip and possibly tongue. Gingiva and floor of the mouth are uncommon sites.[7] In our patient, sites such as buccal mucosa, maxillary and mandibular alveolar ridges, floor of the mouth were diffusely involved. Hence, the exact primary site could not be determined.

Rhabdomyosarcoma should be differentiated from other lesions such as lymphoma, soft tissue Ewing's sarcoma, osteosarcoma.

Histologically four basic forms of RMS are recognized: Embryonal, botryoid, alveolar and pleomorphic. Embryonal is most common out of the four and represents 70% of all cases.[2] In our case we found the features of both alveolar and embryonal, implying a mixed variety.

Embryonal RMS is most common and usually occurs before 8 years of age and frequently arises in the head and neck region. Botryoid is another variety and its gross appearance resembles a "cluster of grapes" and usually arises under mucosal surfaces. Botryoid type account for 5% of all RMS and have best prognosis and mostly found in below 5 year of age. Alveolar RMS is comprised of relatively small, poorly differentiated round and oval cells aggregated into irregular clusters or nests separated by fibrous septa. Pleomorphic type shows randomly arranged eosinophilic cells with considerable variation in cell size and shape.[1,3]

Light microscopy allows a histological classification of RMS cells in three groups: Round cell type, spindle cell type and rhabdomyoblastic type indicative of moderately differentiated tumor. Less differentiated, highly proliferating tumours with a grave prognosis consisted of

a mixed type of round and spindle cells. In our case, we found round to ovoid and spindle shaped cells arranged in an alveolar pattern with discoid backround.

Desmin is an intermediate filament protein of both smooth and striated muscles. Antibody to desmin reacts with striated (cardiac and skeletal) as well as smooth muscle cells. Anti-desmin antibody is useful in identification of tumors of myogeneic origin. In our case, IHC for desmin was positive, thereby ruling out the possibility of other malignancies.

Depending upon the extent of the lesion, the radiographic features vary, between, having ill-defined borders that are best described as ragged, to poorly demarcated and noncorticated margins. The radiographic borders may not be truly depictive of the estimate and extent of the tumor, because of its infiltrative nature, as in our case. If soft tissue lesion occurs adjacent to the bone, they may cause saucer-like erosion, or invasion as in squamous cell carcinoma.

Computed tomography is necessary to evaluate the proper extension of the tumor.

The hall mark of management in RMS is early diagnosis. Subsequent treatment of RMS includes a multidisciplinary approach such as radical surgical excision, followed by multi-agent chemotherapy (vincristine, dactinomycin, and cyclophosphamide). When there is extensive lesion, postoperative radiotherapy is advised. Since RMS tends to metastasize to bone marrow, bone marrow aspiration should be a part of the staging procedure.[4] The AMORE protocol is a local treatment regimen for head and neck RMS, consisting of Ablative surgery, Moulage technique brachytherapy and surgical reconstruction.[8,9] Morbidity, mortality and survival rates have been improved, due to the advancement in the treatment therapies.

CONCLUSION

Despite the advances in the understanding of the underlying pathogenesis and treatment of RMS, a delay in the diagnosis, might have a profound unfavorable impact on prognosis, as was in our case.

Hence, a very important means of a successful management are early detection and treatment.

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