Rhabdomyosarcoma of the Mandible

Raman Kamboj,¹ Honey Arora,² Keerthilatha M. Pai,³ and Suhas S⁴

¹Department of Conservative Dentistry and Endodontics, Darshan Dental College, Udaipur, India

²Department of Oral Medicine & Radiology, Subharti Dental College, Meerut, India

³Department of Oral Medicine & Radiology, Manipal College of Dental Sciences, Manipal, India

⁴Department of Oral Medicine and Radiology, Sri Siddhartha Dental College, Tumkur, India

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Abstract

Sarcomas usually occur in young individuals. We report a case of rhabdomyosarcoma occurring in a 28-year-old man who presented with a 5-month history of episodic pain in the right mandible. This case is significant because very few cases of this entity in the jaw have been reported in young individuals. Surgery along with radiation and chemotherapy proved successful in treating this case. Long-term follow-up is needed in such unusual cases to clarify treatment outcomes.

Introduction

Rhabdomyosarcoma (RMS), a malignant tumour of striated muscle, is relatively uncommon in the oral cavity (basically, the head and neck region). RMS is seen more often in the extremities in adults as compared to children, and is derived from primitive mesenchyme that retained capacity for skeletal muscle differentiation (1). We report a case of RMS arising in a healthy young individual in the posterior mandibular region. Oral RMS is rare, accounting for around 0.04% of all head and neck malignancies. In the head and neck region, the ethmoid sinuses are the most common site in adults, and, due to the closer proximity of the sinuses to parameningeal locations such tumours show a poor prognosis compared to those in the mandible. Conversely, due to the lack of bony barriers, oral cavity lesions involving the cheek or tongue display a poorer prognosis compared to jaw bone. Overall, the survival rate for RMS is poorer in adults than in children (2).

Case report

A 28-year-old man reported to the Department of Oral Medicine & Radiology at Manipal College of Dental Sciences (Manipal, India) with a 5-month history of episodic pain in the right mandible. Pain was spontaneous in onset, moderate

in intensity, and localised. He had experienced 2-3 episodes of pain, which were subsequently relieved using analgesics. The patient did not report any history of swelling, fever, or discharge of pus. His medical history was significant for weight loss. Family history was not significant. Personal history revealed absence of abusive oral habits. Extraoral examination did not reveal significant facial asymmetry, and mouth opening remained adequate. No signs of inflammation were evident in the skin overlying the right mandible. A very strong putrid odour emanated from the oral cavity. Examination of lymph nodes revealed a non-tender, stony, hard, 2×2-cm right submandibular lymph node fixed to the underlying structures. Intraoral examination (Fig. 1) revealed presence of an ulceroproliferative growth along the right mandibular alveolus, about 6×3 cm in size and extending from the right mandibular second premolar to the retromolar pad region. This growth was covered with yellowish-brown slough. Bucco-lingually, the growth extended along the buccal vestibular sulcus into the adjacent buccal mucosa and lingually into the linguoalveolar sulcus. The ulceration in the centre of the growth appeared shallow, with irregular, raised, and proliferating everted edges. Grade II mobility was noted with the right mandibular second premolar and first and second molars. The right mandibular first molar was displaced buccally and the second molar was displaced lingually from the arch. Palpation revealed that the growth was tender. The edges

Correspondence to :

E-mail : drarora27@gmail.com

Fig.1 Intraoral view shows ulceroproliferative growth along the right mandibular alveolus, extending about 6×3 cm from the right second premolar to the right retromolar pad region

Fig.2 Orthopantomography shows the irregular osteolytic lesion in the region of the right mandibular third molar and extending to the ramus

and base of the ulceroproliferative growth were markedly indurated and fixed to the underlying bone. Although the ulcer appeared shallow, its base extended deeper. No paraesthesia was evident in the lower lip region. The presentation of a non-healing ulcer causing displacement and mobility of teeth associated with weight loss suggested a malignant process. Presence of such a lesion in a young patient without oral habits may indicate a lesion with poor prognosis. The most common malignancy affecting the oral cavity is squamous cell carcinoma; however, due to the young age of the patient and the absence of abusive oral habits, this was not considered first in the differential diagnosis. In this case, non-Hodgkin lymphoma was considered high among the differential diagnoses, as lymphoma of bone may cause vague pain or discomfort misinterpreted as toothache. The possibility of human immunodeficiency virus (HIV) infection predisposing to extranodal non-Hodgkin lymphoma was raised. Osteosarcoma arising from the mandibular alveolus was also considered because mandibular tumours arise more frequently in the posterior body and horizontal ramus, and swelling and pain are the most common symptoms. Loosening of teeth and paraesthesia may occur. Squamous cell carcinoma of the gingiva was considered next, as this entity is less commonly associated with tobacco smoking. Gingival carcinomas often destroy the underlying bone structure, causing tooth mobility. Fungal infections like histoplasmosis or blastomycosis were also considered; however, due to the absence of pulmonary symptoms, which would be likely to occur with inhalation of

spores, they were quite low in the list of differential diagnoses. Another possibility was metastasis to soft tissue from an unknown primary, but this is more common among middle-aged men. With the most common site in the gingiva, such lesions typically present as a nodular mass representing hyperplastic or reactive growth, or occasionally as an ulcer. Adjacent teeth may become loose with increased destruction of underlying alveoli.

Orthopantomography (Fig. 2) revealed an irregular osteolytic lesion extending from the right mandibular second premolar to the right mandibular third molar and extending into the anterior border of the ascending ramus. The right mandibular third molar was mesioangularly impacted. Erosion of the superior border of the inferior alveolar canal was evident on the right side. Enzyme-linked immunosorbent assay for HIV yielded negative results. Incisional biopsy revealed poorly differentiated tumour. Under *GA*, peripheral mandibular osteotomy and right neck dissection in the supraomohyoid region were performed, followed by insertion of a reconstruction plate in the region of the right angle. The resected tissue was sent for histopathological examination. Histopathological study of the excised specimen revealed the presence of spindle to oval-shaped cells with moderate to abundant eosinophilic cytoplasm and oval to spindle-shaped cells with bizarre nuclei showing coarse chromatin and prominent nucleoli (Figs. 3, 4). Rhabdoid-like cells were seen, and areas with a herring bone-like pattern were present. Pleomorphic tumour giant cells were present. Focal areas of necrosis were seen at the edge of the biopsy

Fig.3 Staining with hematoxylin and eosin shows oval to spindle-shaped cells with bizarre nuclei, coarse chromatin, and prominent nucleoli. Magnification, $\times 400$.

Fig.5 Staining for desmin, showing positive results in cytoplasm. Magnification, $\times 400$.

Fig.4 Staining with hematoxylin and eosin shows pleomorphic tumour giant cells. Magnification, $\times 400$.

specimen. Inflammatory cells comprising neutrophils, lymphocytes, and eosinophils were seen scattered throughout the tumour. The histopathological diagnosis was pleomorphic-type RMS, subsequently confirmed by positive results for myogenin and desmin (Fig. 5). DNA karyotyping was performed to find any evidence of chromosomal aberration, but results were normal. Because of delays in getting marker studies done, the histopathological reports were only available after a month; thereafter the patient was recalled and a bone scan was performed. Bone scan revealed the presence of a primary tumour in the right mandible with osteoblastic metastasis to the right scapula. During the recall, it was noticed that the surgical site had not healed, but had instead developed into an extensive lesion. A diffuse

extraoral swelling measuring 5×6 cm was also evident, and the patient had developed trismus. Orthopantomography revealed bone erosion extending to involve the left mandibular lateral incisors. Radiation therapy (66 Gy in 33 fractions) was administered using a 6-MV linear accelerator along with cisplatin at 100 mg/kg as a sensitizer every third week until the completion of radiotherapy. The patient subsequently experienced improvements and remained well up to 3 years, then developed multiple bone metastases and died within a year.

Discussion

RMS is considered to be the most common malignant soft tissue tumour, accounting for 5–10% of all childhood malignancies(3). The five most common tumours overall in a study by Samaila(4) on malignant tumours in children in Zaria, Nigeria, were RMS, Burkitt lymphoma, retinoblastoma, non-Hodgkin lymphoma and neuroblastoma. RMS was also the most common soft tissue sarcoma in children under 15 years old in Ibadan, Nigeria. The most frequent site is the head and neck, which accounts for 40% of all cases.

The following four basic microscopic patterns are recognised: embryonal; alveolar; pleomorphic; and undifferentiated. RMS primarily occurs in the first decade of life, and is also seen in teenagers and young adults, but is rare among individuals over 45 years old, and approximately 60% of all cases occur in males. Embryonal RMS is most common in the first 10 years of life and accounts for about 60% of all cases affecting the oral and perioral regions(3). Alveolar RMS tends to affect a somewhat older age group and is

more common in the soft tissues of the extremities(3). Pleomorphic RMS represents <5% of all cases and shows peak prevalence in patients over 40 years old. Most head and neck lesions are embryonal or alveolar types; pleomorphic RMS occurs primarily on the extremities(5).

In the head and neck region, the orbit is the location most frequently affected, followed by the nasal cavity and nasopharynx(4). According to Bras et al. and O'Day et al, the palate is the most common intraoral site, whereas Yamamoto et al.(6) described the tongue as the most common site. The tumour is most often a painless, infiltrative mass (>1 cm diameter) that may grow rapidly with paraesthesia and/or pain, presumably because of involvement of the adjacent nerves(7). RMS of the mandible is relatively rare, with an incidence of 3.5% according to Dito and Batsakis(8). Head and neck RMS shows distinct prognostic and biological behaviour, and can be anatomically divided into the following two categories: parameningeal (including RMS of the nose, nasopharynx, paranasal sinuses, middle ear, mastoid, infratemporal fossa and pterygopalatine fossa); and non-parameningeal (including RMS of the scalp, orbit, parotid gland, oral cavity, oropharynx and larynx). Parameningeal RMS shows a poor prognosis, while non-parameningeal RMS has a better prognosis(8).

Although the exact histogenesis of RMS remains undetermined, the tumour is widely accepted to result from the malignant proliferation of embryonic mesenchymal tissue rather than degeneration of healthy striated muscles, which is why RMS can develop in areas in which mature striated muscle is not normally present(1). Genetic factors, previous radiation treatment, and viruses have been mentioned as possible trigger mechanisms(1). Non-familial, sporadic cases of RMS show a high frequency and diversity of p53 mutation. Wild-type p53 controls cell proliferation at the G1/S checkpoint in the cell cycle, and the mutated type presumably loses this regulatory function so that the affected tissue undergoes tumorous growth(9). A second line of genetic study concerns the loss of heterozygosity in the short arm of chromosome 11 (11p), which occurs in embryonal RMS. Loss of heterozygosity with inactivation of the paternal Rb gene, that is, by DNA methylation or other events, would lead to tumorous growth(10). A third line of study regards translocation between the long arms of chromosomes 2 and 13, designated t(2; 13)(q35; q14). This type of cytogenetic abnormality is mainly found in alveolar-type RMS. The translocation results in fusion of the PAX3

transcriptor regulator gene with a transcription factor gene, ALV, near the translocation site on chromosome 2. This fusion in turn presumably results in transcriptional deregulation and tumourigenesis(10).

Early diagnosis is essential, as the extent of disease at presentation has an important relationship with survival. Electron microscopy and immunohistochemistry can be very helpful in differentiating RMS from other spindle cell malignancies. Immunohistochemically, desmin, muscle-specific actin, and myoglobin represent valuable markers(11). Desmin is an intermediate, 8- to 10-nm, filamentous protein (molecular weight, 53,000) found within actin microfilaments in the cytoplasm of striated muscle cells. This protein is very specific for myogenic differentiation, but is less sensitive than muscle-specific actin(12).

Treatment involves surgery, chemotherapy, and radiotherapy. A study by Yamaguchi et al.(13) found surgery as the most reliable treatment for sarcomas of the oral and maxillofacial region. Adequate excision with safe surgical margins as the initial therapy is important for better survival. If the tumour cannot be resected completely, chemotherapy is administered, generally using vincristine, actinomycin D, and cyclophosphamide(9). A study by Feng et al.(14) suggested that combined therapy including radiotherapy after surgical treatment may increase the 5-year survival rate.

The most common site of metastasis for RMS is thought to be the lungs. The prognosis for survival is directly related to the stage of disease at diagnosis, anatomical localisation, histological type and degree of tumour cell anaplasia(1, 5).

Based on the prognosis of each histologic type, RMS is classified into the following four groups(15):

1. Favourable prognosis: botryoid or spindle cell type
2. Intermediate prognosis: embryonal
3. Poor prognosis: alveolar and undifferentiated
4. Subtypes for which prognosis is not presently known: RMS with rhabdoid features

The natural history of RMS has been found to be more aggressive in adults and survival is poorer than that for children. This poor prognosis in adults is thought to be due to the advanced stage of tumour on diagnosis, occurrence of unfavourable histopathological subtype (alveolar), reduced tolerance of treatment and other unknown biological factors(5). Patients with no evidence of metastatic disease show a favourable prognosis, with a 5-year survival rate of

71%, whereas patients with metastasis have a 5-year survival rate of only 27% (6).

The present case highlights the risk of mortality associated with advanced RMS, even with the advent of multi-modal treatment.

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