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Case Report

Recurrent High Grade Metachronous Fibrosarcoma of Oral Cavity: An Aggressive Orofacial Rarity Treated with Reradiation

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Abstract

Fibrosarcoma (FS) is a neoplasm affecting the long bones constituting about 1% of all malignancies and 0.05% of head and neck cases while oral cavity affection is rarer. FS are known for high local recurrence while metachronous lesions at two different sites within the oral cavity are rarely heard of. A 38-year-old male presented three years back with a non-healing ulcer right buccal mucosa. Biopsy was suggestive of FS for which he underwent surgical resection and adjuvant Radiotherapy (RT). After two years had recurrence of disease at the primary site, was managed with surgical resection. He again developed a second primary metachronous tumor after a year on hard palate which was confirmed by post inferior maxillectomy specimen Immunohistochemistry staining positive for vimentin, MIB-1 and CD 68 as high grade FS. Received re-radiation to the affected site to which he showed significant clinical and radiological response. Metachronous FSs are extremely rare in oral cavity which emphasize the need for active surveillance and close follow up in these cases. A thorough review of literature reveals that our case may be the earliest case of recurrent metachronous FS occurring at two different locations within the oral cavity requiring re-radiation.

Keywords: Fibrosarcoma; Metachronous; Oral cavity; Field-cancerization; Re-radiation

Abbreviations

FS: Fibrosarcomas; RT: Radiotherapy; MRI: Magnetic Resonance Imaging; HPR: Histopathology Report; Gy: Gray; IHC: Immunohistochemistry; PET: Positron-Emission-Tomography; FDG: Fluoro-Deoxy-Glucose; pan-CK: Pan-Cytokeratin; SMA: Smooth Muscle Actin; 3DCRT: 3-Dimensional Conformal Radio-Therapy; PR: Partial Response; EBV: Epstein-Barr virus; HPV: Human-Papilloma Virus; EGFR: Epidermal Growth Factor Receptor; mRNA: Messenger Ribonucleic Acid

Introduction

Fibrosarcomas (FS) are extremely uncommon malignant lesions originating from fibroblastic proliferation in long bones of extremity and soft tissues [1]. FS accounts for 1% of all malignancies, 5% of all intra-osseous tumors [1], 0.05% of head and neck tumors 2 and a mere 23% of all oral cavity lesions [2]. These are aggressive tumors with an increased propensity for local recurrence [2], though two recurrences in oral cavity at two different sites within a span of three years have been seldom reported and treated with re-radiation. We present this case to highlight an extremely rare and aggressive case of recurrent metachronous FS of buccal mucosa and hard palate which posed a diagnostic and therapeutic challenge due to its rarity, vast array of differential diagnosis, highly fulminant behaviour and scarcity of relevant literature. Radiotherapy (RT) remains the cornerstone of adjuvant therapy due to high probability of local recurrence [1] after upfront surgery while chemotherapy has shown inconsequential results.

Case Presentation

A 38-year-old male, known tobacco chewer with no comorbidity presented with a progressive non-healing ulcer right buccal mucosa of seven months duration in 2013. Clinically a 6x4 cm ulcero-proliferative lesion was seen which was confirmed on Magnetic Resonance Imaging (MRI) (Figure 1). Biopsy revealed spindle cells with oval hyper chromatic nuclei. Post-Commando-resection Histopathology Report (HPR) was suggestive of high grade fibrosarcoma with muscle infiltration. In view of high grade and muscle infiltration he was treated with adjuvant RT to a dose of 60 Gray (Gy) in 30 fractions. Patient was disease free till 2015 when he developed recurrence at the primary site for which he underwent wide local excision and flap reconstruction. Post-operative HPR showed spindle shaped cells with eosinphilic cytoplasm and hyper chromatic nuclei scattered in a fascicular pattern (Figure 2) with Immunohistochemistry (IHC) positive for vimentin (Figure 3) suggestive of recurrent FS. He was kept under active surveillance and regular follow-up.

In 2016, he developed a growth over hard palate. MRI showed a 3.2x2.8 cm soft tissue mass lesion postero-lateral aspect of hard palate (Figure 4). Biopsy revealed fascicules of spindle shaped dysplastic cells with nuclear pleomorphism. Positron-Emission-Tomography (PET) scan showed a localized Fluoro-Deoxy-Glucose (FDG) uptake of 8.86 right side hard palate. He underwent partial inferior-maxillectomy and tongue flap reconstruction (Figure 5). HPR showed uniform

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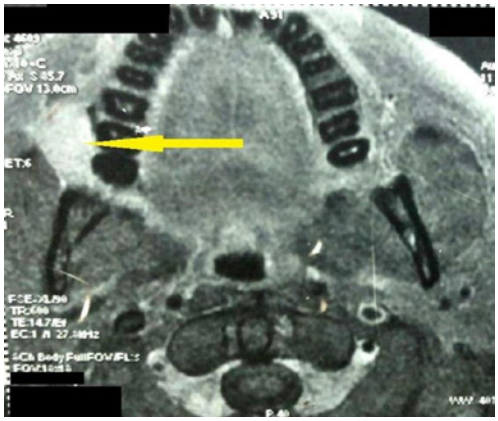

Figure 1: MRI face and neck (2013) showing a right buccal mucosa mass lesion with loss of interface with fat, alveolar margins and masseter (yellow pointer).

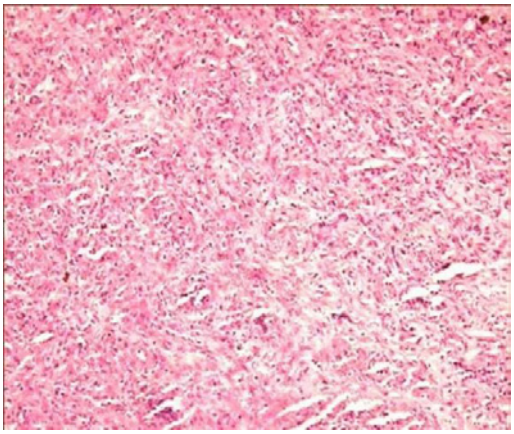

Figure 2: Post-operative HPR of recurrent buccal mucosa lesion (2015) showing spindle shaped cells with eosinphilic cytoplasm and hyperchromatic nuclei scattered in a fascicular pattern (H & E 10 X).

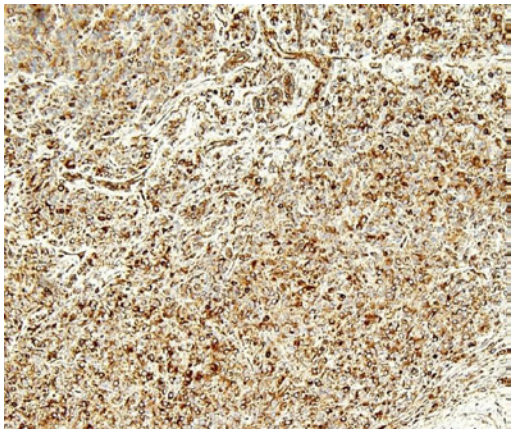

Figure 3: IHC picture showing positivity for vimentin (20 X).

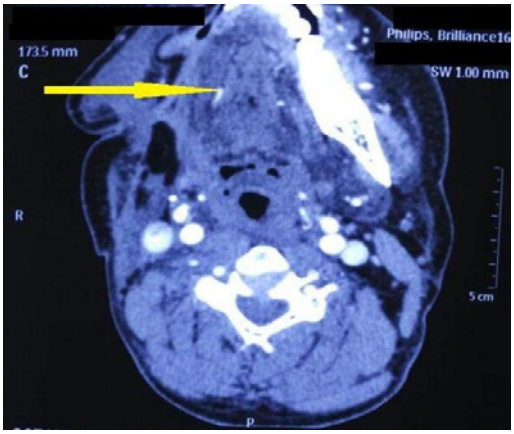

Figure 4: MRI face and neck (2016) showing a 3.2 x 2.8 cm soft tissue mass lesion postero-lateral aspect of hard palate (yellow pointer).

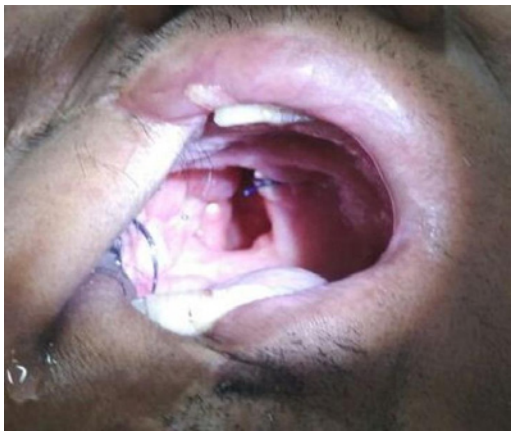

Figure 5: Post partial inferior-maxillectomy and tongue-flap reconstruction status of patient showing the hard palate defect.

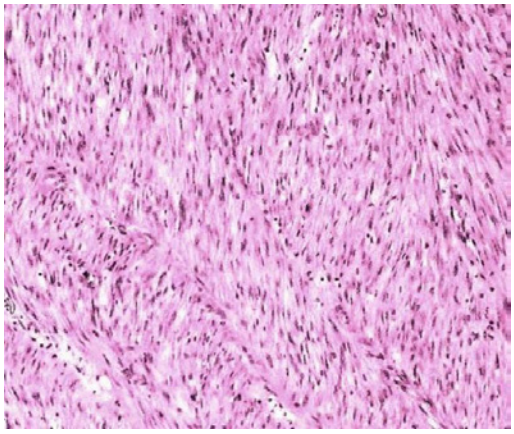

Figure 6: Post-operative HPR of hard palate lesion (2016) showing uniform spindle shaped cells with elongated, round or oval hyperchromatic nuclei arranged in a characteristic herringbone pattern with areas of cartilaginous changes (H & E 10X).

spindle shaped cells with elongated, round or oval hyperchromatic nuclei arranged in a characteristic herringbone pattern with areas of cartilaginous changes (Figure 6). IHC was positive for vimentin, MIB-1 (Figure 7) and CD-68 (Figure 8) while negative for pan-cytokeratin (pan-CK), P-40, S-100, melan-A, desmin, Smooth Muscle Actin (SMA), CD 99, CD-56, CD 20 and CD 45, confirming the diagnosis of high grade FS. In view of recurrence and high grade,

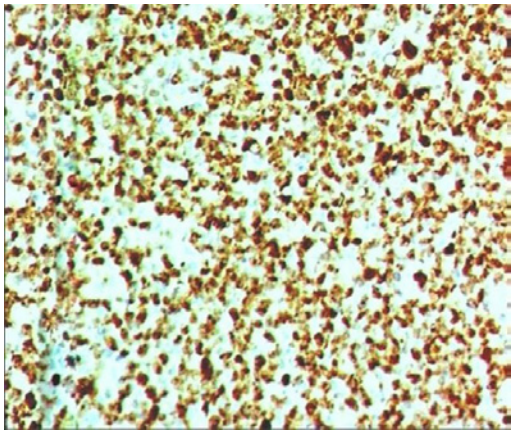

Figure 7: IHC picture showing positivity for MIB-1 (20X).

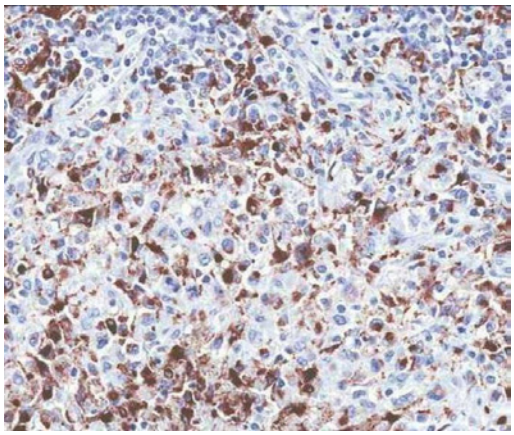

Figure 8: IHC picture showing positivity for CD-68 (20X).

patient was exhibited re-radiation to a dose of 60 Gy in 30 fractions by 3-dimensional conformal radio-therapy (3DCRT) technique which he tolerated well. Response assessment after three months with PET scan showed a Partial Response (PR) with a FDG uptake of 2.23. He is on close follow-up for over six months without any evidence of local recurrence or distant metastasis.

Discussion

FSs arises mainly in extremity long bones, knee [3], soft tissues of thigh, retroperitoneum [3], head and neck region with sporadic cases involving solitary sites of maxillary sinuses, maxilla [4], ethmoid sinuses, nasal cavity, thyroid gland, gingiva [3], tongue [5], buccal mucosa and hard palate with mandible having the largest number of reported cases. The exact aetiology of FS is still unknown though few factors like Paget's disease of bone, osteomyelitis, cystic bone disease, fibrous dysplasia, mucosal insult or scarring and even prior radiotherapy [2] to local site have been postulated. No association has been found with Epstein-Barr virus (EBV) or Human-Papilloma virus (HPV). Head and neck FSs shows a male predilection [2] and is common between third to fifth decades of life [2]. Oral cavity FS generally arise as a painless ulcer, lobulated sessile mucosal swelling or loosening of teeth. Cervical lymphadenopathy is extremely uncommon. Both high and low grade FS carry a local recurrence rate of 50-60% [1], distant metastasis rate of 20-25% [1,6] and overall survival rate of 21.8-83% [1].

Recurrence is mostly due to alterations in a preconditioned epithelium located near a surgical scar or post-RT site which become more susceptible to carcinogens [7] like tobacco and alcohol. As our case not only recurred at the initial site but also developed a second primary at a different site within oral cavity, the concept of field-cancerization comes into picture. Field-cancerization implies that malignancy arises as an anaplastic tendency involving multiple cells simultaneously into a multifocal development of neoplasm within the entire common field in response to a carcinogen. Clonal stem cells have been implicated in the development of recurrence and cancerization [8] which can be a potential target for cancer prevention and therapy. Increased expression of Epidermal Growth Factor Receptor (EGFR) [9], Messenger Ribonucleic Acid (mRNA), and Ki-67 have been found in tumor-associated mucosa, which is also evidenced by the positive IHC staining of MIB-1.

Oral cavity FS can often be misdiagnosed with squamous cell carcinoma, melanomas, lymphomas, soft tissue sarcoma, ulcerated granuloma, or an ossifying fibroma. The diagnosis is primarily by microscopic features and IHC. FS is known to demonstrate a characteristic intercalating fascicular pattern of spindle shaped cells with nuclear pleomorphism [1,4]. IHC stains positive for vimentin, MIB-1, a monoclonal antibody that identifies Ki 67 and focal positive for CD-68, a fibrocytic marker [1,4] which was seen in our case also. Markers like pan-CK, P-40, S-100, melan-A, desmin, SMA, CD 99, CD-56,CD 20 and CD 45 were negative, thus ruling out other pathologies or metastasis.

Surgical resection has been regarded as the upfront treatment of oral FS [1,2]. Prophylactic neck dissection is still not considered a standard of care [3]. Adjuvant RT plays a major role to improve high local failure rates in high grade tumors with positive surgical margins for local control of subclinical disease. Since no specific RT dosage schedule has been mentioned for oral cavity FS, we used an adjuvant dose of 60 Gy in 30 fractions in view of high grade and muscle invasion while 66-68Gy may be used for margin positive cases. For recurrence in a previously operated and irradiated volume, re-radiation is a potentially curative option [10]. Dose less than 50 Gy is considered inadequate while 60 Gy or higher has been described to be beneficial [10]. Re-resection is attempted in a small proportion of patients while no established evidence exists in literature regarding the role of chemotherapy. Tyrosine kinase inhibitors like imatinib and masitinib have been found useful in canine oral FS [11] but not in humans.

Conclusion

FS should always be considered in patients presenting with an oral ulcer or soft tissue mass with a supporting IHC differentiating it from other pathologies. Presently there are no definite treatment algorithms for this disease as most information and evidence is based on solitary case reports without any large prospective or retrospective clinical trials. It is crucial to understand and interpret the unique biology of FS in order to develop therapeutic strategies. Improved cytogenetic analysis, novel chemotherapeutic and targeted therapies, optimal RT dosages should be devised which can improve the disease

free survival, overall survival and quality of life of these patients. We emphasize the importance of active surveillance and therapeutic targeting of the genetically altered progeny of cells responsible for development of metachronous lesions to prevent field-cancerization.

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