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Changing trend in management of Osteoradionecrosis of the mandible: A case report

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Abstract

Osteoradionecrosis (ORN) is a condition that results following radiotherapy for head and neck cancer in an appreciable number of patients. ORN is irreversible and extremely difficult to treat. Number of theories about the pathogenesis of Osteoradionecrosis (ORN) has been proposed in the past including the theory of radiation, trauma, infection and widely accepted theory of hypoxia, hypovascularity and hypocellularity and recently fibro-atrophic theory of ORN was proposed. Each theory has consequent implications on treatment. Fibro atrophic theory replaces the use of hyperbaric oxygen (HBO) with drugs like Pentoxifylline, a vasodilator that also inhibits fibrosis, and Tocopherol (vitamin E) to reduce damage caused by free radicals. In this case report we have achieved impressive results in terms of reversing the process of ORN using these agents suggesting that this theory and these agents could form the basis of effective treatment and prevention of ORN.

Keywords: Osteoradionecrosis, Fibro atrophic theory, Pentoxifylline

1. Introduction

Osteoradionecrosis (ORN) has been defined as “irradiated bone which becomes devitalized and exposed through the overlying skin or mucosa, persisting without healing for 3 months in the absence of tumour recurrence”^[1]. The first report on Osteoradionecrosis (ORN) of the jaws following radiotherapy was published by Regaud in 1922^[2]. The most widely accepted theory of Marx given in 1983 stated hypoxia, hypovascularity and hypocellularity to be responsible for development of ORN^[3]. This has now been replaced by the fibro atrophic theory in 2004 by Delanian and Lefaix. According to this theory, radiation induces a fibro atrophic mechanism which includes free radical formation, endothelial function, inflammation, microvascular thrombosis which in turn lead to bone and tissue necrosis^[4]. The change in the understanding of the pathophysiology has helped in improvising the treatment modalities. Earlier Hyperbaric oxygen (HBO), sequestrectomy and antibiotics were the main stay of treatment. This concept has been replaced by adopting Tocopherol (Vitamin E) and Pentoxifylline for the medical management of ORN. These drugs work on the principal of fibro atrophic theory and aid in improving the vascularity of the bone and simultaneously prevent oxidative damage by reactive oxygen species. Our case report highlights the application of this changing concept in the treatment of ORN showing effective results.

2. Case Report

A 60 year old male patient had reported to our department of Oral & Maxillofacial Surgery with the chief complaint of pain in the front region of the lower jaw since 2 months. Patient gave a history of oral squamous cell carcinoma of the anterior mandibular alveolus which was treated with radiotherapy (7000Gy in 35 fractions) and chemotherapy (6 fractions) 8 months ago. After 5 months the patient was diagnosed with recurrence of squamous cell carcinoma of the anterior mandibular alveolus. The patient was treated with marginal resection sparing inferior border resection. Following 15 days of the resection, the patient developed pain with bone exposure covered with slough in the operated site. Patient had received conservative management before reporting to us which included antibiotic coverage (Tablet Moxikind500 mg TID for 5 days), wound debridement, Betadine irrigation and Zinc oxide eugenol packs for

a period of 2 months. Patient was a chronic betel nut chewer for the past 20 years. He had quit the habit since 4 months. The medical and dental histories were not significant. When the patient reported to us, the face was bilaterally symmetrical (Fig 1) there was no loss of sensation. The overlying skin was normal (no draining sinus/fistula). Lymph nodes were not palpable.

On intraoral examination, the mandibular arch was partially edentulous. The alveolar bone on the right and left mandibular anterior region was exposed extending from alveolar sockets of 42 to 44 and 32 to 34 respectively with intact mucosal cover in midline. Slough was noted in the exposed alveolar bone in the mandible (Fig.2). The surrounding mucosa was tender and inflamed.

Radiographic examination by OPG revealed the presence of ill-defined radiolucency extending from the mandibular 1st premolar on one side to the other that resulted due to previous resection in that region. Distortion was seen in the pattern of the bone trabeculae in relation to the region with multiple radio opaque spots, indicative of formation of sequestrum. The inferior border of the mandible was intact (Fig.3).

Culture and sensitivity was done on the sample taken from the slough which revealed the presence of *Candida albicans*.

Based on the clinical and radiological features, the patient was diagnosed with bilateral ORN of the mandible of Stage II [5].

The patient was treated with conservative sequestrectomy followed by Vitamin E Capsule (C. Evion 400mg OD for 30 days), Tablet Pentoxifylline (T. Trental 400 mg BD for 30 days) and Tablet Diclofenac (T. Divon Plus BD for 5 days followed by SOS). Chlorhexidine mouthwash and Candid – gum paint was given BD for 30 days. Patient was kept on a regular follow up for 5 months at intervals of 2 weeks. Conservative sequestrectomy of few exposed and loosened bone pieces were done on 2 follow up visits. Vitamin E capsule and Pentoxifylline tablets were continued for a period of 3 months following sequestrectomy.

Treatment resulted in fresh mucosal growth over the exposed bone with reduction in pain in subsequent visits.

3. Discussion

ORN affects the mandible more often than the maxilla or any other bones of the head and neck [6]. Incidence of ORN in the mandible is between 2% and 22% and the body of the mandible is the most often affected part [2]. This can be attributed to the reduced blood supply and the bone being denser posteriorly which is responsible for the presence of a greater dose of absorbed radiation [7].

The incidence of ORN is less common after hyperfractionated radiotherapy at 72–80 Gy, or moderately accelerated fractionated radiotherapy administered together with a boost of 64–72 Gy. Recent reports have suggested an increase in incidence of ORN in cases of chemoradiotherapy [8], while the use of intensity-modulated radiotherapy may reduce it. ORN is more common when brachytherapy is used but patients receiving radiation dose of less than 60 Gy rarely present with ORN. This occurs only when the mandible is in the area of treatment [6].

Risk factors associated with ORN are tooth affected with periodontal disease, alcohol abuse, use of tobacco and trauma due to dentures post radiation [9].

Fibro atrophic Theory

The most recent theory for ORN given by Delanian S and Lefaix JL in 2004 explains the mechanism of ORN as 3

phases. They are:

1. Prefibrotic phase
2. Continuative organised phase
3. Fibro atrophic phase

The prefibrotic phase appears to be due to vascular dysfunction [10].

This includes changes in endothelial cells which predominate, together with the acute inflammatory response.

This is followed by abnormal fibroblastic activity which predominates, and there is disorganisation of the extracellular matrix in the Continuative organised phase.

Then in the late fibro atrophic phase, tissue remodelling occurs with the formation of fragile healed tissues which in turn carries a serious inherent risk of late reactivated inflammation in the event of local injury. Table 1

Staging

Based on the clinical condition, the progress or course of the disease can be determined.

The staging system (Table 2) helps to associate the clinical stage of ORN with the prognosis.

This system helps in easy communication among the clinicians and avoids any confusion.

Management of ORN deals with application of the advances in understanding the cellular and molecular biology of radiation fibrosis which have prompted the use of drugs in the management of ORN [10].

ORN can be managed either conservatively, surgically or both. Conservative line of management includes options such as use of medications, Hyperbaric oxygen therapy, maintenance of oral hygiene. Surgical management involves options like sequestrectomy, vascularised composite tissue transfer.

Pentoxifylline - Mechanism of Action

Pentoxifylline acts on the erythrocytes and the activity of collagenases. The mechanism is explained in the table 3.

Tocopherol (Vitamin E) serves a scavenger for there active oxygen species generated during oxidative stress by protecting cell membranes against lipids peroxidation, partial inhibition of TGF- β 1, and expression of procollagen genes, there by fibrosis [2].

Dosage: Oral – 1000 IU / day [11].

Clodronate is bisphosphonate which inhibits bone resorption by decreasing the number and activity of osteoclasts. It acts directly on osteoblasts to increase bone formation and reduces fibroblast proliferation [2]. It also reduce inflammatory cytokines IL-1b, IL-6, and TNF- α [11].

Combination of pentoxifylline and tocopherol act synergistically and have potent anti-fibrotic action. The combination has the ability to reverse the development of fibrosis, this is not possible when the drugs are given alone. The combination reduces fibro atrophic changes in tissues and enhances wound healing by stimulating defective osteoblasts [11].

In our case report, combination of medical and surgical management was adopted. The patient was given Pentoxifylline 400 mg and Tocopherol 400 mg once daily. The drugs were continued for a period of 4 months with conservative sequestrectomy at 3 occasions.

Studies favouring our management

Upto 60% of the cases of ORN resolve with conservative management involving judicious use of medication and local

wound care.

Delanian S, Balla-Mekias Shave shown striking regression of chronic radiotherapy damage in a clinical trial of 43 patients treated by oral pentoxifylline and vitamin E. The combination therapy had reversed chronic radiation damage, concluded that it should be considered as a method of managing ORN [12]
 Delanian S, Depondt J performed a study involving 18 patients with mandibular ORN, pentoxifylline and vitamin E boosted by clodronate were effective treatment for mandibular ORN, with mucosal and bone healing occurring over a median period of 6 months [12].



Fig 3: OPG with radiolucency over right mandibular premolar to anterior region



Fig1: Extraoral Examination



Fig 2: Intraoral examination Slough was noted in the exposed alveolar bone

Table 1: Progression of ORN [2]

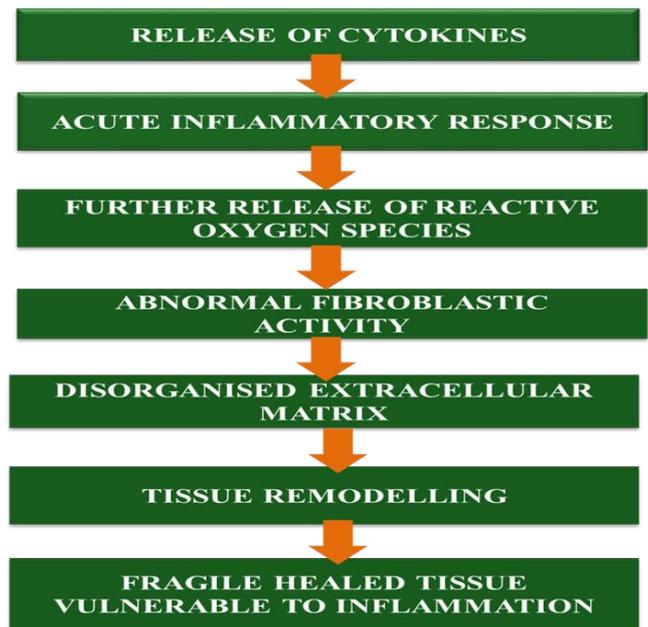


Table 2: Staging system for Osteoradionecrosis of the mandible [5]

Stage	Manifestation
STAGE 0	Exposure of mandibular bone for < 1 month No distinct changes on plain radiographs (Panoramic radiograph or Periapical film)
STAGE I I A I B	Exposure of mandibular bone for at least 1 month No distinct changes on plain radiographs (Panoramic radiograph or Periapical film) Asymptomatic otherwise, e.g. No pain or presence of cutaneous fistulas Symptomatic, e.g. pain or presence of cutaneous fistulas
STAGE II II A II B	Exposure of mandibular bone for at least 1 month Distinct changes on plain radiographs (Panoramic radiograph or Periapical film) But not involving the lower border of the mandible Asymptomatic otherwise, e.g. No pain or presence of cutaneous fistulas Symptomatic, e.g. pain or presence of cutaneous fistulas
STAGE III	Exposure of mandibular bone for at least 1 month Distinct changes on plain radiographs (Panoramic radiograph or Periapical film) Involving the lower border of the mandible, irrespective of any other signs and symptoms
NOTE	In case of doubt about the presence and/ or extent of radiographical bone involvement, the lower stage should be allotted

Table 3: Mechanism of action of Pentoxifylline ^[2]

Anti-TNF α effect
Increase erythrocyte flexibility
Dilates blood vessels
Inhibits inflammatory reactions in vivo
Inhibits proliferation of dermal fibroblasts
Production of extracellular matrix
Increase collagenase activity

4. Conclusion

The management of ORN in our case involves the use of drugs (conservative line of management). When administered in combination, the drugs produce synergistic actions thereby improving the efficacy of the drugs than when the drugs are used singly. Sequestrectomy can be conservative such as removal of loose bony fragments. The treatment of ORN has come a long way to the recent findings of Delanian and Lefaix. The current protocol of using drugs like Tocopherol and Pentoxifylline appear to be very effective in resolving ORN and inducing soft tissue growth over denuded bone. This case report highlights role of drugs and conservative sequestrectomy in the management of ORN.

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