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Case Report

Successful treatment of grade III osteoradionecrosis with mandibular fracture with pentoxifylline, tocopherol and clodronate

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ABSTRACT

Osteoradionecrosis (ORN) is one of the most severe complications after head and neck radiotherapy. Once established, ORN is difficult to manage and is traditionally considered to be irreversible. Since the recent understanding of the pathophysiology of ORN is based on the concept of radiation-induced fibrosis, a new therapeutic medical regimen has been proposed comprising the combination of pentoxifylline, tocopherol and clodronate (PENTOCLO). A 55-year-old woman presented with grade III ORN with large intraoral bone exposure, a fracture of the left posterior horizontal branch and an orocutaneous fistula. Because she refused surgery, medical treatment with PENTOCLO was proposed. After 55 months of treatment, there was complete mucosal coverage and complete consolidation of the fracture site around the orocutaneous fistula. PENTOCLO treatment can help some patients with grade III disease, as in this case. Further prospective randomized controlled trials are needed to confirm this result.

1. Introduction

Osteoradionecrosis (ORN) is one of the most dreaded and severe complications after radiotherapy (RT) for head and neck cancer. ORN occurs in 2 to 30% of irradiated patients and can cause significant morbidity and important loss of quality of life [1,2]. The total dose threshold for ORN is accepted to be 60 Gy, but it can occur when the total dose of radiation exceeds 50 Gy [3–5]. Once established, ORN is difficult to manage and is traditionally considered to be irreversible [6,7]. The incidence of ORN has dropped to 10% or less following improvements in radiation techniques and enhanced preventive dental care. Treatment of ORN is challenging, multimodal and complex. ORN can stabilize or worsen spontaneously, although it does not regress spontaneously [5].

Since recent understanding of the pathophysiology of ORN is based on the concept of radiation induced fibrosis (RIF), a new therapeutic medical regimen has been proposed comprising the combination of pentoxifylline, α-tocopherol and clodronate (PenToClo). This combination of drugs has the capacity to reverse RIF and can be an alternative to surgical treatment in patients who refuse or are deemed unfit for surgery [5,7–9].

We present a case of a 55-year-old woman with grade III (according to the Notani classification) mandibular ORN with a fracture of the left posterior horizontal branch successfully treated with the medical combination of PENTOCLO.

2. Case report

A 55-year-old woman presented in November 2010 with swelling on the left mandible associated with an active orocutaneous fistula. She did not report any pain, and the only complaint was the productive fistula that necessitated daily care. Her past medical history revealed two concomitant tumors. The first one was a lung adenocarcinoma for which she underwent a right superior lobectomy in January 2007 (pT2pN0). The second tumor was cT3N0M0 left oropharyngeal squamous cell carcinoma treated until April 2007. Treatment included radiotherapy and chemotherapy with a total dose of 70 Gy (IMRT, 35 fractions, 2 Gy/fraction) to the tumor site and 50 Gy to the bilateral II–IV neck nodes. She received carboplatin and 5-fluorouracil concomitantly on days 1, 22, and 43. No recurrence of the oropharyngeal and pulmonary tumors was found at follow-up. She was a heavy smoker (60 pack year) and a moderate drinker. She stopped smoking and drinking when she was undergoing chemoradiotherapy. She presented with poor nutritional status but did not need a gastrostomy or feeding tube during

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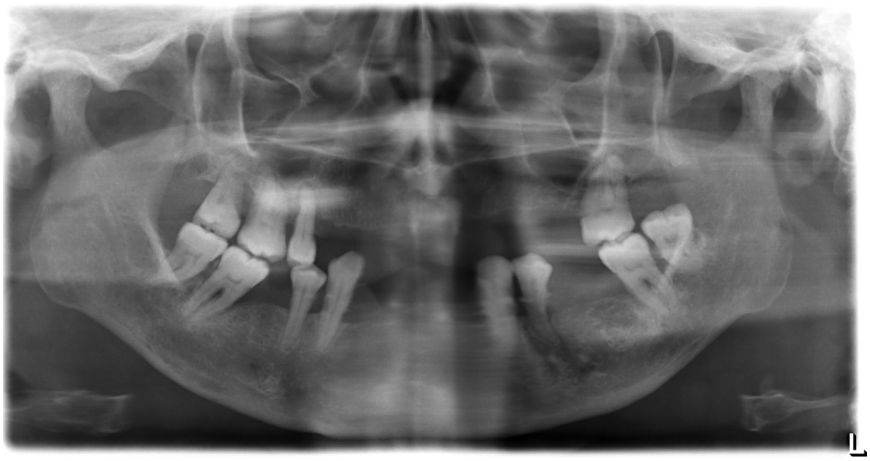


Fig. 1. Panoramic X-ray before chemoradiotherapy showing poor dental status with missing teeth and periodontal lesions around the residual teeth.

or after chemoradiotherapy. She underwent a complete dental evaluation before head and neck treatment. She was partially dentate, with a poor dental status, but she refused any tooth extraction before starting chemoradiotherapy (Fig. 1).

At clinical examination, 42 months after the completion of treatment, she presented with an area (2×1 cm) of exposed necrotic bone on the left mandibular alveolar crest around decayed teeth (canine, first premolar, 2d and 3d molars). There was also an extraoral fistulous track with a 2-mm diameter extending from the lingual wall of the mandible in the premolar region to the submandibular skin with purulent discharge. Her dental hygiene was poor, with a large amount of decay of the persistent teeth and an inadequate maxillary prosthesis. She presented with light trismus. The panoramic X-ray (November 2010) showed rarefaction of the bone and areas of osteolysis on the left horizontal branch of the mandible (Fig. 2). CT scan revealed a large area of ORN (Figs. 3 and 4) below the level of the alveolar canal. The ORN was classified a Grade III according to the Notani classification, and surgical treatment was proposed. The patient refused any kind of surgery because her father had died after surgical treatment for a head and neck tumor. Medical treatment was then suggested with pentoxifylline 400 mg twice a day and tocopherol 500 IU twice a day (PenTo). Treatment started in January 2011. She also received amoxicillin 875 mg and clavulanic acid 125 mg twice a day for 1 month as well as chlorhexidine mouthwash until there was an absence of clinical infection. She exhibited good adherence to the treatment. She required one sequestrectomy of a 10-mm bone fragment 3 months after initiating the PenTo treatment under local anesthesia. After 5 months of PenTo treatment, unfortunately, CT scan showed a left mandibular fracture with moderate displacement (Figs. 5 and 6). There were no additional clinical complaints, and, curiously, no. V3 anesthesia. There was no mobility at the fracture site. Progressive improvement in mucosal coverage at the previously exposed bone site was noted. The extraoral fistula showed a decrease in diameter, despite the mandibular fracture.

Given the patient's persistent refusal of surgical treatment, PenTo was continued at the same doses. Complete mucosal healing was achieved after 20 months of treatment (August 2012). The results of treatment were evaluated every 4 months. Clodronate was added to PenTo in April 2014 at a dose of 1600 mg in the morning 5/7 days. CT scan in March 2015 showed a complete homogenous bone bridge around the orocutaneous fistula (Figs. 7 and 8). The patient finally accepted a "short" surgery, and the closure of the fistula was attained in June 2015 using a facial artery musculomucosal (FAMM) flap. Extraction of all the residual teeth was completed at the same time. Evolution was favorable at the site of the fistula and at the different extraction sites. PenToClo was stopped in August 2015 after 55 months of treatment (39 months of PenTo and 16 months of PenToClo). Short- and long-term tolerance to PenToClo was excellent. There was no rebound effect.

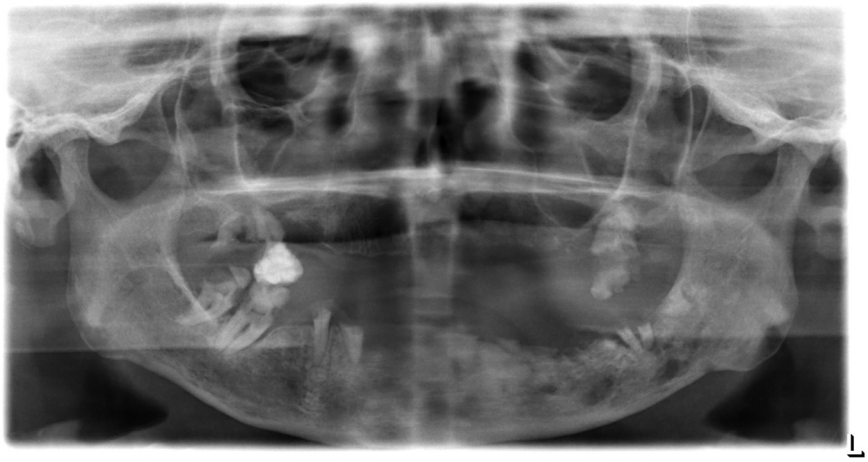


Fig. 2. Panoramic X-ray 42 months after chemoradiotherapy showing degradation of dental status, rarefaction of the bone and areas of osteolysis on the left horizontal branch of the mandible.

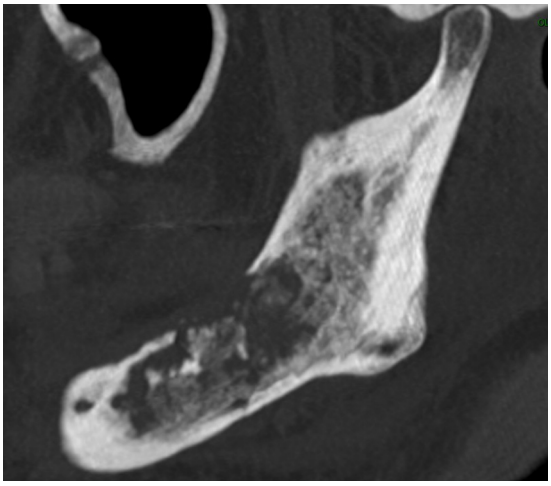


Fig. 3. CT scan 42 months after chemoradiotherapy showing the large ORN area from the mandibular angle to the parasymphyseal region with osteolysis of the superior mandibular cortical bone.

Mucosal coverage was complete and there was no recurrence of the fistula 6 months after the end of treatment. Unfortunately, the patient was diagnosed with esophageal squamous cell carcinoma in March 2016 (cT3NxMx) and died in April 2016.

3. Discussion

This case report illustrates the therapeutic potential of a medical treatment for grade III ORN, according to the Notani classification. The case, which involved the mandible below the level of the inferior alveolar canal with skin fistula and pathological fracture, was classically treated with segmental resection and free flap reconstruction. In this case, the PENTOCLO protocol achieved clinical and radiological improvement for 4 years, avoiding major surgery with reconstruction, despite the mandibular fracture.

The risk factors of ORN to which this patient was exposed included a total irradiation dose of 70 Gy, concomitant chemotherapy and poor nutritional and dental status. Elimination of toxic habits (tobacco and alcohol consumption) as well as improvement in local hygiene are the first control measures for ORN. The patient stopped tobacco and alcohol consumption, but her oral hygiene remained poor. Usually, local dental factors should be controlled before RT, but this was refused by the patient. The management of ORN comprises various conservative and surgical measures. A conservative approach is usually used for grades I and II, with a favorable response. Such an approach includes medical treatment with mouthwash, local wound irrigation, multiple courses and long-term use of antibiotics, analgesics, conservative surgical treatment with minimal surgical debridement, sequestrectomy, and hyperbaric oxygen therapy [1,4,10].

Radical surgical management is reserved for advanced or refractory ORN and comprises necrotic bone resection and reconstruction with free tissue transfer, usually the fibula free flap or maxiplate and pediculate muscle whenever possible [2]. Surgery was relatively contraindicated in our patient due to her poor general status.

The new therapeutic approach includes the use of pentoxifylline (PTX), α-tocopherol (TOCO) and clodronate (CLO) (PENTOCLO). This treatment is based on new understanding of the pathophysiology of ORN, specifically, that bone and soft tissue damage are primarily the result of RIF [6–9]. RIF constitutes late, local, unavoidable and irreversible damage to normal tissue after a high dose of radiation therapy. The endpoint of the RIF theory is the dysregulation of wound healing with the activation and dysregulation of fibroblastic activity, excessive free radical production, and induction of cell death by apoptosis or necrosis. The combination of osteoblast death, failed osteoblast repopulation and excessive proliferation of myofibroblasts leads to hypocellular bone with a reduction in the hard tissue matrix in favor of fibrous extracellular matrix production [5,8].

Delanian et al. described three successive phases in the RIF process [7,9] :

- the initial prefibrotic phase is characterized by changes in endothelial cells and acute inflammatory response, increased vascular permeability and local edema, destruction of endothelial cells and vascular thrombosis. The loss of the endothelial barrier allows for the seepage of cytokines that cause fibroblasts to become myofibroblasts. This phase occurs in the first few months after RT and is often asymptomatic ;

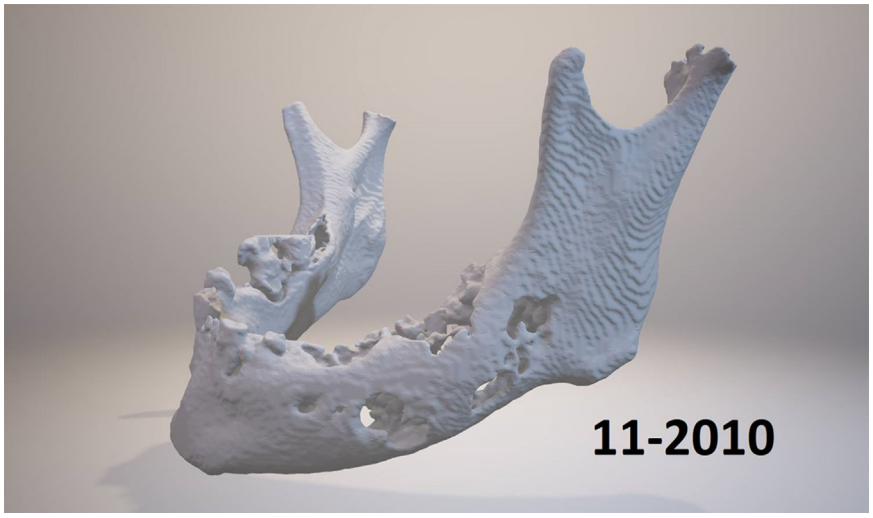
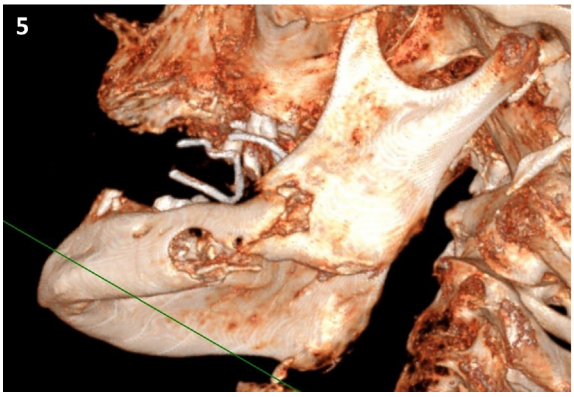
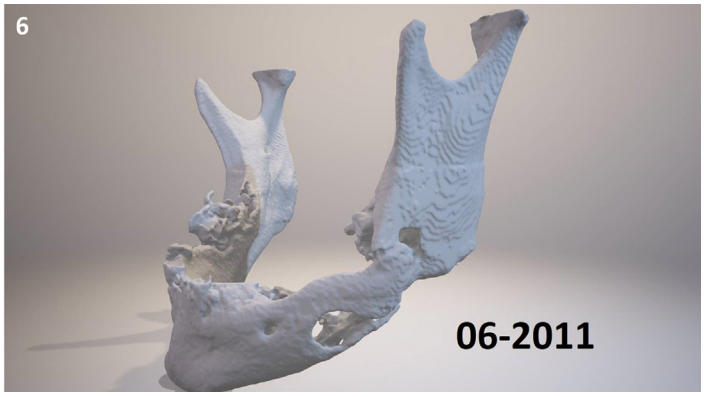


Fig. 4. 3D CT at the same time.





Figs. 5 and 6. 3D CT scan after 5 months of PENTO showing mandibular fracture with moderate displacement and modification of the bone around the fracture site.

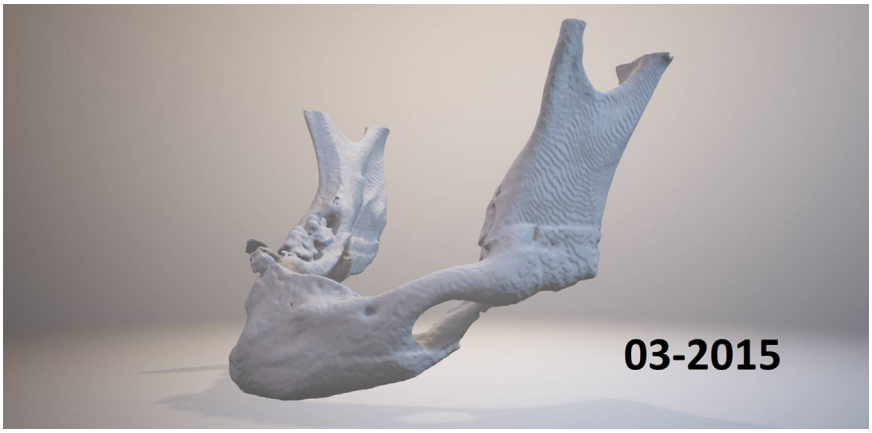


Fig. 7. 3D CT scan after 50 months of PENTOCLO treatment showing reconstruction of the crestal part of the mandible and consolidation of the fracture site.

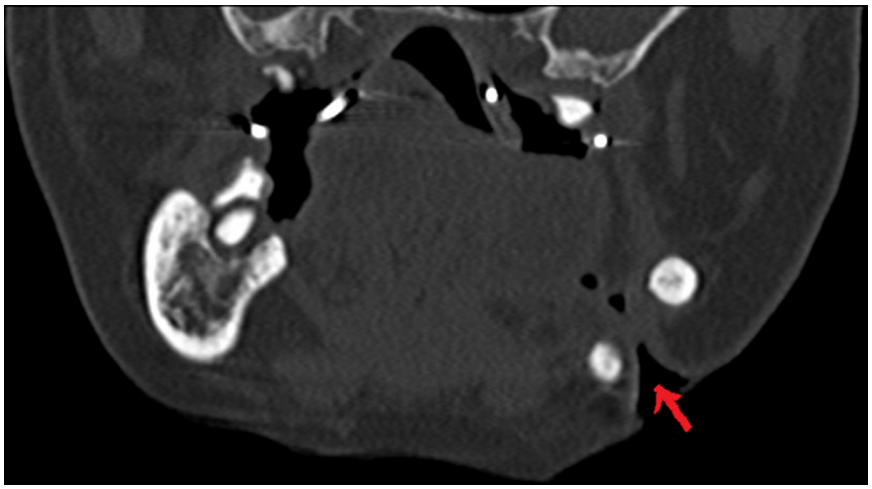


Fig. 8. Coronal CT scan after 50 months of PENTOCLO showing bone reconstruction around the orocutaneous fistula (red arrow).

- the constitutive organized phase is characterized by abnormal fibroblastic activity and disorganization of the extracellular matrix. This phase occurs during the first few years after RT ;
- the late fibroatrophic phase is characterized by the formation of fragile healed tissue from remodeled tissue, with late reactivation of the acute inflammatory response after injury. This phase can occur 5 to 30 years after the end of RT.

The combination of reduced cellularity, reduced vascularity, and fibrosis leads to fragile tissue that is susceptible to breakdown from simple trauma. The PENTOCLO combination is initiated to diminish the already established fibrotic process, reduce bone destruction and stimulate healing in combination and is based on the concept of antioxidant and antifibrotic treatment of fibroatrophy [3,6]. Although PENTOCLO was reported to be successful in

early-grade ORN, it was found to be insufficient for independent use in late grades [9].

Pentoxifylline (PTX) is usually indicated for the management of vascular disorders (i.e., intermittent claudication). It is a methylxanthine derivative that exerts an anti-tumor necrosis factor α effect, decreases platelet aggregation and thrombus formation, increases erythrocyte flexibility, decreases blood viscosity, and enhances microvascular blood flow [5,9]. PTX also inhibits inflammatory reactions in vivo, inhibits dermal fibroblast proliferation and extracellular matrix production, increases collagenase activity in vitro, and, ultimately, decreases fibrosis. PTX increases the level of oxygenation in the tissues. It is thought to reduce the cytokine cascade leading to ORN. Adverse events are rare (< 1%) and are typically gastrointestinal in nature (nausea, vomiting); other adverse events include tachycardia, vertigo, and headache. These events are resolved by transient reduction of dosage or discontinuation [8].

α-tocopherol (TOCO) is a liposoluble metabolite with antioxidant properties. TOCO scavenges reactive oxygen species generated during oxidative stress and protects cell membranes against lipid peroxidation. It partially inhibits TGF-β1 and procollagen gene expression and may reduce the oxidative damage induced by radiotherapy [5]. There are some controversies relating to the belief that it can potentially interfere with chemotherapy or radiotherapy, so patients with active cancer were not included in the study by Delanian et al. [11].

The combination of PTX and TOCO has a synergistic effect on the progression of inflammation and can reverse superficial RIF. They are well tolerated and inexpensive and offer a benefit to the patient. PTX or TOCO alone seems to be unable to reverse RIF [6,11]. This association has lower efficacy in late-grade ORN or refractory disease. Clodronate was added to potentiate treatment under these conditions.

Clodronate (CLO) is a first-generation oral nonaminobisphosphonate and was approved essentially for the treatment of malignant hypercalcemia. It can stimulate osteoblast function and reduce fibroblast proliferation without antiangiogenic effects. The inhibitory effect on osteoclasts is 100 to 20,000 times lower than second- and third-generation bisphosphonates. It has also antimacrophagic properties. CLO specifically targets osteoclasts and macrophages, can reduce bone destruction and fibroblast proliferation and increases bone formation [8,9]. Even if bisphosphonates are implicated in the development of MRONJ, CLO has little effect in osteonecrosis due to it poor efficacy in osteoclast death. CLO may be warranted in late-onset ORN or patients who are not responsive to PenTo [3].

The PENTOCLO treatment protocol comprises a daily dosage of 800 mg of pentoxifylline, 1000 UI of α- tocopherol, and 1600 mg of clodronate 5 days a week [6]. Although the time required to achieve a response after PenToClo treatment has not yet been determined, it can take 2 to 3 years. This treatment could be administered for as long as complete healing was observed. Prolonged treatment was safe and well tolerated. In the study by Robard [6] the mean duration of treatment was 82 days (32–266), which was shorter than that in the studies by McLeod [12] (14.8 months [4.0–46]) and Patel [3] (237 days [62–1080]). Healing time seems to increase with increasing severity of ORN [2], as was the case in our patient. In the series reported by Robard [6], healing time was longer after chemoradiation (169 days), and clinical healing was achieved earlier than radiological healing, as was found in this case report.

Spontaneous sequestrectomy occurred in two-thirds of patients during the first 6 months of taking PENTOCLO in the study by Delanian and seemed to accelerate the healing process [8]. Sometimes, additional management with limited surgical debridement can be helpful [3]. A rebound effect of RIF can occur when the treatment duration is shorter than 12 months [7].

Usually, pathological fracture necessitates radical resection of the necrotic bone with bleeding margins and reconstruction. Conservative measures are limited to early-grade ORN [10]. PENTOCLO can be used in later grades with the intention of stabilizing the ORN and controlling the symptoms, but not with the intention to cure. This case report does not prove that PENTOCLO is the treatment of choice for grade III ORN. However, in this particular case in which a patient refused any kind of surgery, given her poor dental and nutritional status, the result is of great interest.

The choice between mandibulectomy with free flap reconstruction and medical treatment with PENTOCLO is still not clear, but PENTOCLO treatment can help some patients with grade III disease with mandibular fracture, as in this case. Further prospective randomized controlled trials are needed to confirm this result.

Disclosure of interest

The author declares that she has no competing interest.

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