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Management of osteonecrosis of the jaws induced by radiotherapy in oncological patients: preliminary results

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Abstract. – OBJECTIVE: Osteoradionecrosis (ORN) is a bone aseptic necrosis which develops on post-irradiated bone tissue of patients who underwent radiotherapy for head-neck tumors. The mandible presents a higher risk to develop ORN, if compared to the maxillary bone, due to its lower vascularization.

The aim of the present study is to clinically assess the regenerative ability by the epithelial and connective tissues, in response to ORN onset.

PATIENTS AND METHODS: Authors have verified the importance of the surgical-pharmacological treatment, as an effective protocol for eliminating the exposed bone sequestration, as well as the teeth eventually damaged by the radiotherapy, assessing that the epithelium can regenerate only on healthy and vital tissues.

RESULTS: The reported patient underwent resection of a portion of the left mandible with an incomplete healing after the surgery. A second curettage was scheduled in order to remove the bands of necrotic tissue and to obtain a clinical remission of symptoms.

CONCLUSIONS: In patients undergoing radiotherapy, the dental surgeon should be able to give an early diagnosis of the dental and maxillofacial related pathologies; he should also detect all the possible infective sources and administer any possible treatment in a short time, before the beginning or the prosecution of radiotherapy.

Key Words:
Osteoradionecrosis, Radiotherapy, Tissues healing.

Introduction

Bone tissue can be suffering from several diseases that could lead to a tissue necrosis, and some pathogenesis are paradoxically related to the treatments of other pathologies: this is the case of the BRONJ (Biphosphonates-Related OsteoNecrosis of the Jaws) and, undoubtedly, of the osteoradionecrosis (ORN). Osteoradionecrosis is an aseptic necrosis which occurs in patients who had undergone radiotherapy for tumors in the head-neck area, without persistence of neoplasia[1]. The physiopathology of ORN is determined by the concurrent presence of hypovascularization, hypocellularity and tissue hypoxia, which compromise the vitality of the bone tissue. The risk to incur an ORN is not predictable, but it has been verified that this risk is related to the dose of radiations which is generally more than 65 Gy and to the thickness of the irradiated bone[2,3]. According to the studies reported in literature, ORN onset is between 3 and 27 months after the end of radiotherapy, even if in rare cases it can develop even after 5 or more years from the radiations. The risk to develop ORN covers an indefinite period after irradiation[4,5].

After radiant therapy, the common lesion which early affects the maxillofacial area is the mucositis: it appears as a diffused erythema with disepithelized areas and ulcerations: the use of new irradiation techniques, such as advanced linear accelerators and radiosurgery treatment systems, has determined a reduction in the incidence and the severity of mucositis, however, the healing of mucositis could be complicated in smokers and patients with poor oral hygiene[6].

In the international literature there are only few cases of osteoradionecrosis of the mandible sufficiently severe to require a total mandibular resection[7]; however, this incidence would decrease by avoiding some traumatic dental treatments immediately after radiotherapy.

The risk of a second episode of ORN after a proper surgical-pharmacological treatment of the first appearance is low[8]. All literature shows a progressive reduction of cases of ORN with the incoming of the modern techniques of radiotherapy[9].

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Etiopathogenesis of ORN

ORN of the jaws was initially considered as the inevitable consequence of the triad: a) radiations therapy, b) trauma, c) bacterial infection.

Radiations cause damage to the bone tissue and they also reduce the ability of tissue vascularization: the consequent condition of hypovascularization and hypoxygenation damages the activity of the involved cells, as well as the synthesis of collagen and the entire process of tissue reparation[10].

Any type of trauma represents a front door inside the maxillary bones for those bacteria residing in the oral cavity. One of the traumas mostly related with the onset of ORN is tooth extraction[11].

A spontaneous onset of ORN (approximately 35% of cases) seems to be correlated with high doses of radiations (>65 Gy); this form of ORN normally appears within two years after radiotherapy[12]. With the passing of the months, the irradiated bone tissue becomes more fibrotic and hypovascularized[13].

The clinical diagnosis of ORN is based on the observation of the exposed bone. Radiological investigations typically show a reduced bone density, the destruction of the cortex, the loss of trabeculation of cancellous bone and, occasionally, pathologic fractures. The computerized tomography (CT) usually shows anomalies in the bone pattern, such as focal lytic areas, cortex irregularity and loss of spongiosa trabeculation on the symptomatic side: the normal anatomy of the soft tissues surrounding such lesions is deeply altered[13].

ORN is a pathology that tends to move forward very slowly, and it does not show the tendency to any spontaneous recovery. The aim of the present study is to clinically assess the regenerative ability by the epithelial and connective tissues, in response to ORN onset.

Patients and Methods

Authors have verified the importance of the surgical-pharmacological treatment, as an effective protocol for eliminating the exposed bone sequestration, as well as the teeth eventually damaged by the radiotherapy, assessing that the epithelium can regenerate only on healthy and vital tissues.

Exclusion criteria have established not to include such patients who underwent bisphosphonate therapy, as well as smokers, hard drinkers, patients with autoimmune pathologies or with hematologic disorders, patients at infective risk and all the patients wearing removable prostheses. According to the above criteria, 7 men and 1 woman, aged between 55 and 70 years, with a clinical history of carcinomas in the cervico-facial area (Table I), and recently treated with radiotherapy (cobalt therapy of 45-65 Gy or interstitial Curie-therapy), were recruited.

Following the cycles of radiotherapy, the patients underwent oral examination, revealing a generally compromised periodontal and dental condition.

We found 4 patients with radio-mucositis, 2 cases of aggressive caries associated with hyposalivation and reporting a sensations of xerostomia and dysgeusia, and 2 cases of osteonecrosis developed after radiation therapies. More specifically, all the patients who developed ORN underwent tooth extraction immediately after the end of the radiotherapy treatment, just in the area where ORN has been diagnosed.

We report the case history of one of these patients: a male of 57 years old with an history of multiple myeloma with the onset of the ORN on the mandible, after the radiotherapy.

The diagnosis was based on clinical examinations, which showed a chronic mucosal ulcer lo-

Table I. A synoptic table describing the samples reported in this research.

Patients	Sex	Age	Seat of the primary lesion	Arising complications
1	M	57	Mandible	Osteonecrosis
2	M	59	Maxilla	Aggressive tooth decay
3	M	56	Minor salivary glands	Radio-mucositis
4	F	55	Mandible	Osteonecrosis
5	M	56	Tongue	Aggressive tooth decay
6	M	67	Salivary glands (parotid)	Radio-mucositis
7	M	70	Lips	Radio-mucositis
8	M	68	Salivary glands (parotid)	Radio-mucositis

Figure 1. Clinical appearance of the bone sequestrum, following the osteonecrosis process, developed on the left side of mandibular bone, in the molar area: it's easily observable the necrotic bone with bacterial superinfection.

cated in the lower left area of the mandible, with an exposure of necrotic bone tissue, affected from a clinically evident bacterial infection (Figure 1).

Preparation To Treatment

To treating the osteonecrosis, the authors started with the cure of the decayed teeth together with a slight and supragingival ablation of the bacterial plaque and tartar by means of ultrasonic instruments, in order to reduce the bacterial contamination. Hematochemical and hemocoagulative examinations were performed, moreover, a cardiological examination was planned before to proceed with the surgical removing of the necrotic bone sequestrum. Blood pressure, glycemia and dental panoramic were also planned, and finally the patient was psychologically prepared for a proper approach to the operating room (preoperation counselling).

The Surgery

The surgery was performed under general anesthesia. After disinfection of the surgical area and administration of the proper anesthesia, the upper part of the left hemi-mandible was removed by means of tungsten burs and scalpels: anyway, the left mandibular region was preserved and all the necrotic tissue was removed, together with a large section of seemingly healthy bone tissue. The resection of a seemingly healthy portion of that tissue surrounding the lesion is an essential surgical passage to avoid a relapse of ORN in the same place. The surgery continued with the excision of the sub-mandibular and sub-digastric lymph nodes, in order to histologically verify the absence of a lymph node involvement and to determine the staging of the case.

Histological Examination

Bone and mucosa samples were collected during the surgery and properly sent to the labs to perform the histological examination.

Medical Therapy

At the end of surgical treatment, the patient received a broad-spectrum antibiotic therapy together with anti-inflammatory administered by intravenous administration. Daily rinses with saline solution and hydrogen peroxide were performed together with 0.12% chlorhexidine rinses; topical antimycotic therapy was also administered.

Results

After the surgery, patient showed an incomplete healing due to a severe post-surgical infection and to inconceivable violation of the prohibition of eating solid food in the first days after surgery. Therefore, a second curettage was scheduled in order to remove the residual necrotic tissue and to finally achieve a clinical healing (Figure 2).

Histological Examination

The report of the Laboratory of Anatomy and Pathologic Histology revealed the presence of fragmentation of the bony trabeculae, a fibrotic substitution of the fatty marrow and a chronic infiltrate of the adjacent tissues.

In the following weeks, the authors observed a progressive increase of the symptomatology, and despite the close observation by clinicians and dentists, it developed a bacterial infection on the sutures. The debridement of the inflamed tissue around the suture was thus performed, followed by the placement of a periodontal pack.

3 weeks later, the pain was greatly reduced and there was a slow and progressive regeneration of the mucosa.

Healing process was very slow, also due to the complications occurred during the therapeutic procedures: unfortunately, in this type of pa-

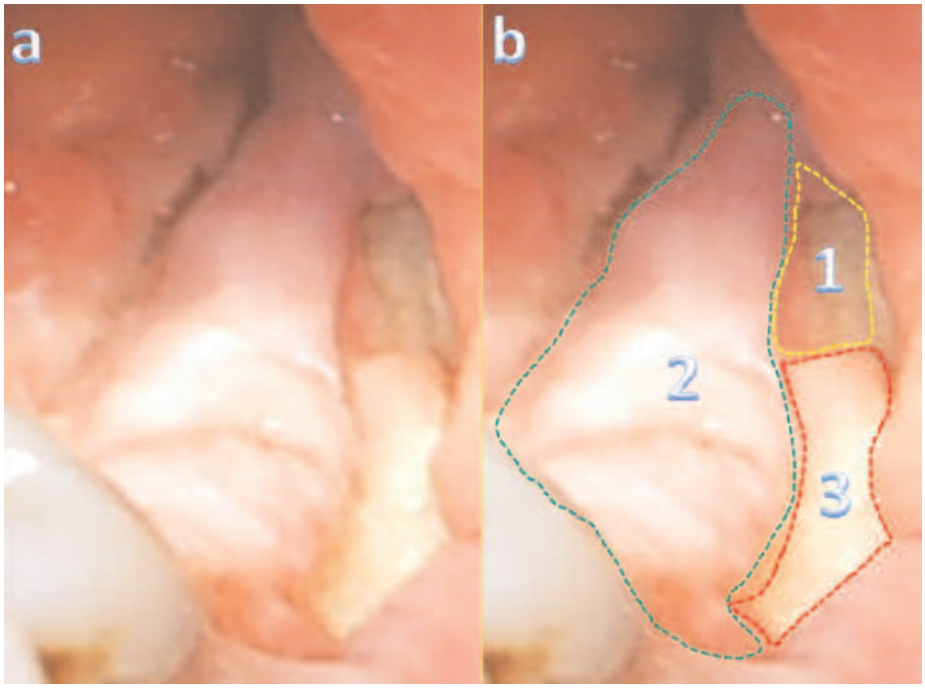

Figure 2. A slow and progressive regeneration of the mucous tissue is described in this picture. The figure ***A*** and the figure ***B*** are the same. In ***B***, 3 main areas have been highlighted. Area 1: is the zone where the early onset of bone necrosis appeared: now that area has been covered by new mucosa, after surgical-pharmacological treatment. Area 2: is the pre-existing mucosa showing signs of slight ischemia in marginal areas and a hypertrophy likely reactive to inflammation. Area 3: is the new bone dehiscence which came out in the second phase of observation of the patient.

tients, riepithelization is a very slow process and weekly treatments of hyperbaric oxygen therapy could have helped the replacement of the missing tissues; therefore, in this case, the authors were unable to provide oxygen therapy, due to the presence of oncologic patient.

Discussion

Radiotherapy is an important aid for the treatment of oncological patients. It is commonly used for a wide number of oncological pathologies, and its ability to treat cancer has been improved through the last ten years.

Modern irradiation techniques ensure both accurate dose distribution and precise beam delivery, without inducing the tissue toxicities arising from the use of chemotherapic drugs. However, early and late effects of irradiation still constitute a significant issue for clinicians: particularly complicated is the management of the ischemic avascular bone necrosis frequently observed on the maxillary bones of H&N oncological patients[1-14].

Prevention and Aggravating Factors

Regarding the prevention of ORN, the first approach should always improve the patients oral condition, taking into account that high-risk procedures, such as *major* oral surgery (cystectomy, drainage of the oral cavity, etc.) and *minor* oral surgery (simple or complex exodontia), should not be performed in the immediate post-irradiation period; radio-induced dental decay, frequently observed in patients undergoing radiotherapy, is often a result of the changes induced by radiations on the glandular salivary tissue: this condition leads to hyposalivation and xerostomia able to develop severe dental caries[14].

Prevention of ORN of the jaws is effective if before the radiotherapy the dentist can eliminate all the intraoral co-morbidity factors.

In many patients who underwent high-dose radiotherapy, it was found a severe bacterial infection, particularly from Gram-negative pathogens: it has been supposed that the selective elimination of these bacteria by administration of poly-antibiotic therapy (recent studies have associated Polimixine E + Tobramicine + Amphotericin B with encouraging results) has a prophylactic ef-

fect on the development of mucositis and on the superinfection of exposed necrotic bone in ORN. Thus, the eradication of these bacteria has been associated to a reduction of the mucositis[15].

In literature, contrasting data have been reported about the correlation between the fractionation of the dose of radiotherapy and the risk to develop ORN. For instance, a lower incidence of ORN was observed in the CHART therapy (Continuos Hyperfractionated Accelerated Radiotherapy), consisting in the administration of 54 Gy in 36 fractions, during 12 consecutive days (3 fractions a day of 1.5 Gy)[16].

Age does not seem to play an important role regarding the risk to develop ORN; instead, higher risks related to an onset of ORN were observed in the edentulous patients. Other patient-related co-factors include, for example, the presence of periodontitis, a poor oral hygiene and the smoking habit.

Therapy of ORN

The hyperbaric oxygen therapy (HBOT), associated with the topical surgery and with a proper antibiotic therapy, could aid the healing process of necrotic bone tissues, mainly thanks to the increased oxygenation of the treated tissues[17].

It will be useful to administer corticosteroids in long-term fractionated therapy. Unconventional therapeutic measures could be taken into consideration, such as: ultrasounds, electrotherapy or magneto-therapy; however, up to now, the surgical therapy is undoubtedly the most effective treatment. Surgery is strongly recommended in cases of recurring pain, pathological fractures and large areas of exposed necrotic bone. The immediate bone replacement, by using fibular grafts, scapular osteo-cutaneous flap or iliac crest grafts, determines an outstanding functional-esthetic result. Promising results have been observed with omental transfers[18].

Advantages from the Hyperbaric Oxygen Therapy (HBOT)

There is some evidences that the HBO is more effective than the conventional antibiotic prophylaxis (5% and 30% incidence of ORN, respectively).

HBO stimulates a neo-angiogenesis, improves the tissue perfusion and stimulates the formation of collagen[19]; therefore, HBO aids the healing process of the damaged tissues. Correctly, HBO should be used before and after radiotherapy, however, it should always considered that its use is strictly not recommended to oncological patients.

Osteonecrosis is a consequence of several factors, apart from radiations: literature reports many cases of osteonecrosis of the jaws related to the use of bisphosphonates, drugs commonly used in the treatment of osteoporosis and bone cancer metastasis. The American Association of Oral and Maxillofacial Surgeons (AAOMS) defined the bisphosphonate-related osteonecrosis of the jaws (BRONJ) as the presence of exposed necrotic bone in the maxillofacial region that does not heal within 8 weeks after clinical identification, in a patient currently or previously treated with BPs, who has never undergone radiotherapy to the jaws. Actually, it's well established that patients under oral bisphosphonate use show a lower risk for bone necrosis of jaw, and this bone necrosis seems to be generally more limited and more responsive to treatment if comparing to ONJ in patients taking intravenous formulations[20].

There are two fundamental aims in the treatment of ORN: the elimination of the necrotic bone and the improvement of vascularization in the remaining vital tissues, damaged by radiations. The first step in the treatment of osteoradionecrosis is the resective surgery of the avascular bone: the removal of the necrotic bone tissue eliminates any reservoir of infection and inflammation, but it does not influence the improvement of vascularization of the diseased but still vital adjoining tissue.

As osteoradionecrosis is the result of a hypovascularization and not necessarily the result of an infection, the antibiotic therapy is considered additional. The most important part of the treatment is the surgical one, and in fact HBO is an adjuvant too.

In this light, the approach to osteonecrosis can be surely complicated due to the frequency of infections of exposed bone: this additional side-effect is induced from the hypofunction of the salivary glands, following the radiotherapy; this effect can be reduced by a preventive stimulation of the residual secretory capacity of the salivary glands, by means of salivary substitutes; the surgical transposition of the submandibular gland was described as a successful methodology for the prevention of hyposalivation, but its indications are limited[6].

In our study we found that bone lesions are important side effects of the oncological radiotherapy, especially in tumors of the head and neck area[4].

In literature, ORN is histologically characterized by the destruction of osteocytes, the absence of osteoblasts and the lack of newly formed osteoid tissue; the thickened vessels, located in the irradiation area, are the result of fibrosis, endarteritis and periarteritis[10-13]. At the level of the bone marrow, there is an infiltrate of lymphocytes, macrophages and plasma cells[12,13]. Due to the complexity of the pathogenic process, it is impossible to define a clear separation between pathologic and healthy marrow. In fact, the bone section subject to radiations develops vascular degenerations leading to an high susceptibility to develop the osteoradionecrosis. Osteocytes and blood vessels are often irreversibly compromised but, in spite of this, non-vital bone fragments and lesions can however regenerate themselves.

In our study we have assessed how a correct and standardized protocol can be an useful aid in the right management of the osteonecrosis, reducing the risk of a relapse and a second surgery in the same site.

Conclusions

In patients undergoing radiotherapy, the dental surgeon should be able to give an early diagnosis of the dental pathologies, detect possible infective foci and administer any possible treatment in a short time, before the beginning of radiotherapy. Once the radiant therapy has started, traumas on mucosal tissues are to be absolutely avoided, as well as more invasive treatments on bone tissues.

Finally, patients should be thoroughly motivated to oral hygiene, and it is advisable to schedule oral hygiene sessions to prevent possible inflammations, parodontopathies and the consequent mobility of teeth. The regular oral prophylaxis and the daily fluoride applications are very important too. However, the treatment to follow cannot be standardized, as confirmed by literature data.

Among the different orientations of basic therapy, magnetotherapy could be also suggested; in case of tissues inflammation, adjuvant therapies should be used to stimulate the individual reactivity to bacterial infections, particularly *Staphylococcus* and *Actinomyces* (the most frequently detected pathogens); whereas in cases of sequestration, the clinician can have recourse to ultrasound therapy in association with conventional therapies. It is also advisable to provide a special diet to these patients, so to reduce some micotic infections particularly related to a diet rich in carbohydrates. Following the indications reported in this research article, together with a careful prophylaxis before radiotherapy and with the elimination of co-morbidity factors, we can reduce the incidence of complications resulting from radiations.

Furthermore, recent studies on pathogenic mechanisms, and recent gains in the use the antioxidants in terms of therapy, have helped to find a new practicable pathway in the desert of the management of osteoradionecrosis.

Consent statement

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Conflict of Interest

All Authors disclose any financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work.

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