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Oral lesions induced by radiation exposure: An update and literature review

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Abstract
Introduction: Among the oral diseases we have those caused by electromagnetic radiation: in our article we considered solar radiation, artificial ultraviolet radiation and X-ray.
Materials and Methods: This review takes in exam the articles published on PubMed in which the link between different type of radiation and oral pathologies is analyzed. The pathologies appraised are: mucositis, osteoradionecrosis and actinic cheilitis.
Results: Oral mucositis involves patients receiving radiation therapy for head and neck cancer. Osteoradionecrosis is a complication of the bone related to radiation therapy. Actinic cheilitis is the main pathological manifestation of the oral cavity related to ultraviolet radiation.
Conclusion: Mucositis is debilitating injury and if severe, it can endanger the patient's life. Treatment is essential to improve the quality of life. On the other hand, dental visits before the start of therapy are protective factors. Actinic cheilitis is associated with a certain degree of carcinomatous transformation. Furthermore, primary prevention is fundamental.

Keywords: actinic cheilitis, oral radiation lesions, oral radiation mucositis, osteoradionecrosis

1. Introduction
One of the most frequently induced lesions caused by radiation therapy for head and neck tumours is mucositis [1, 2]. In addition to the oral mucosa, it can involve the tongue and the pharynx [3]. The lesion is characterized in the initial phases by a hyperaemia and erythema due to the release of inflammatory cytokines, followed by epithelial desquamation (with pseudome mbranes) and formation of an ulcerative lesion, on which bacterial super infection can occur that worsens the inflammatory and necrotic state; the final stages consist in healing and repair by deposition of fibrous tissue [4, 5]. The incidence in patients in radiation therapy for head and neck cancer amounts to 80% [6]. Osteoradionecrosis of the jaw is one of the main complications of radiotherapy [7]. It determines at the level of the jaws morphological and functional alterations, which can have an important impact on the quality of life of the patient. The prevalence rate of osteoradionecrosis after radiotherapy in scientific literature is variable: ranging from 1% to 30%, in particular between 10% and 15% [8]. A revision of 2018 reports is up to 56% prevalence [9]. In addition to gamma and x-rays, even solar or artificial ultraviolet radiation can cause oral lesions. The most frequent is the actinic cheilitis, pathology of the lips typically caused by these rays [10]. Miranda *et al*. [11] observed in a study on workers exposed to the sun that 9.4% of workers showed actinic cheilitis, and the risk was greater in workers exposed for more than 10 years. It is essential to know these lesions as they tend to develop malignant neoplasms if not treated early.

2. Materials and Methods
In this review the relationship between types of radiation and oral diseases is analyzed. The pathologies appraised are: mucositis, osteoradionecrosis, and actinic cheilitis. We used the keywords:

- Oral Radiation lesions, finding 2181 results.
- Oral Radiation mucositis, finding 1327 results.

- Osteoradionecrosis, finding 2325 results.
- Actinic Cheilitis, finding 295 results (Fig. 1)

Of these we have selected those with abstracts in English and with full text available. Preclinical work, not entirely relevant, has been discarded. Only works from the last 32 years were included except for the article of Cooke (1977) published on the British Dental Journal regarding the general causes of delay in diagnosis of oral cancer. If possible, we preferred to include reviews and systematic reviews reducing the number of results to 31 articles.

3. Results and Discussion

3.1 Mucositis

Mucositis, as mentioned above, are the main side effects of radiation therapy. Their complications can be represented by bacterial infection and by the obstruction of the digestive tract sometimes even dangerous for patient's life [12]. These are painful lesions for which many patients use opioids; dysphagia, weight loss and many alterations are present too [13, 14]. The differential diagnosis of oral mucositis considers: aphthous stomatitis, herpetic mucositis, oral thrush, oral trauma, gangrenous stomatitis and acute necrotizing stomatitis [15, 16]. Eilers *et al*. [17] identified factors correlated positively with the risk of development of oral mucositis induced by radiotherapy: lower age due to increased cell turnover, female gender, poor oral hygiene and salivary function, genetic factors, malnutrition, impairment of kidney function, smoking due to delayed healing, previous history of radiotherapy mucositis. Prevention of oral radiotherapy mucositis is based on: maintaining good oral hygiene, which has been seen to be the main factor in reducing the risk of development and progression of lesions; keratinocyte growth factor which has given promising results; amifostine; intraoral shield devices for radiation; low-energy helium-neon laser applied before radiotherapy [14]. Prevention of complications and symptoms is obtained through nutritional support, prophylaxis and treatment of super infections and of course analgesic therapy [18]. A recent prospective randomized study found that the risk and outcome of severe oral mucositis could be improved by oral cryotherapy [19]. Various studies have attempted to understand changes in the oral microbiota during radiation therapy for cancer [20], some of these have observed microbiota changes over time during treatment [21, 22]. Although the bacterial count decreases with increasing radiant dose, a core of microorganisms common to irradiated patients has been found (including Prevotella, Streptococcus, Bacteroidetes, Actinomyces, Veillonella, Capnocytophaga, Neisseria). The symptomatic treatment is based on the use (also systemic) of steroidal anti-inflammatory drugs, non-steroidal anti- inflammatories and steroid ointments for oral application. Injuries that do not respond to these drugs can be treated with multicomponent formulations Kampo (traditional Japanese herbal). Sometimes such formulations can be used in association with the former. Further studies are needed on the Kampo formulations [23]. Excellent results have been obtained by studying the efficacy of the human recombinant keratinocyte growth factor (palifermin), which has proved to be a promising treatment [24]. In particular, for the prevention and treatment of infections it is essential to instruct the patient to oral hygiene in order to reduce the potentially pathogenic bacterial flora. It will therefore be necessary to re-evaluate the patient over time [24]. It has also been shown that periodontal disease is an environmental factor related, if present, to an increase in the severity of mucositis [25].

3.2 Osteoradionecrosis

Osteoradionecrosis (ORN) is a portion of exposed bone, previously irradiated, which does not heal for at least 3-6 months. However, cases of radiologically evident bone necrosis with intact mucosa are reported [26]. There are numerous classifications for ORN, based on clinical features, radiology or on the response to treatment, but none is universally accepted because each has some defects [27]. A work by Kumar *et al*. [28] of 2018 examines 25 patients with cancer in the head-neck area presenting osteoradionecrosis (ORN) of the jaws. All these patients receive radiotherapy > 60 Gy. The most frequent symptom is the secretion of pus (46%). The average time span between completing radiotherapy and the ORN is 48 months. The mandibular alveolus was the main site for the development of ORN, although other sites in the head and neck area are also described in the literature [29]. Another work published in 2018 affirms that the main site for the ORN is the mandible. In addition, this study highlights the variables that influence the ORN prevalence: oral mucositis condition (PR = 3.03; 95% CI: 1.30-7.03), history of smoking (PR = 0.23; 95% CI: 0.07-0.74), number of teeth removed before radiotherapy (PR = 1.06; 95% CI: 1.01-1.11) and visit to the dentist before radiation (PR = 0.08; 95% CI: 1.02-1.11) [30]. A review of Madrid *et al*. of 2010 points out that probably the greatest risk factor for the development of ORN is dental extraction after radiation therapy, feature also confirmed by another very recent study [31]. Prevention must therefore provide for the extraction of teeth compromised by caries or periodontitis before the start of radiotherapy [32]. Treatment is very variable, and it depends on the extent of the injury. It can be a conservative management, which includes oral rinses and local debridement. A very recent meta-analysis evaluated the effect of the combined application of pentoxifylline and vitamin E (PENTO) for the ORN's treatment, finding that it shows a higher efficiency than other treatment methods [33]. However, in some cases aggressive treatment is required, with radical resection with free tissue transfer and reconstruction [34].

3.3 Actinic cheilitis

Actinic cheilitis is an inflammatory disease that affects the mucosa of the lips [10]. It's caused by chronic exposure to artificial or solar ultraviolet rays. Localization on the lower lip is the most common with 95% of cases [35]. The lips unlike the skin are much more sensitive to sunlight due to a thinner non-keratinized epithelium, with less sebaceous glands and melanin [36]. It's considered a potentially malignant lesion which can turn into squamous cell carcinoma. Actinic cheilitis clinically presents atrophy, erythema, dryness, vermillion border [37] and sometimes also leukoplakic lesions [38]. It's fundamental an early diagnosis of this pathology to prevent the development of neoplastic lesions. The delay in the diagnosis is often due to the poor knowledge of the lesion, the absence of symptoms in the patients and the initial harmless clinical appearance [39]. The malignant potential of the lesion cannot be evaluated clinically, therefore in the presence of border changes, colour, thickness or consistency, a biopsy and a histological examination must be performed [40]. The main possibilities for actinic cheilitis treatment are: vermilionectomy, topical 5-fluorouracil, chemical peels with trichloroacetic acid, carbone dioxide laser, electrocauterization [41]. Vermilionectomy consists in the partial or total excision of the vermillion. It's an invasive technique but allows the execution of histological

examinations of the removed piece. Topical 5-fluorouracil and chemical peels with trichloroacetic acid are less invasive but painful for the patient and they develop in 50-70% recurrence [42]. Carbone dioxide laser and electro cauterization are good and practical alternatives that allow a better control of intraoperative bleeding [43]. There are also new effective therapies like imiquimod, photodynamic therapy and YAG-laser [35]. Particularly, a recent review of the literature found that laser therapy appears to be the best option among non-surgical approaches for actinic cheilitis, and photodynamic therapy showed greater efficacy when combined sequentially with 5% imiquimod [44].

Figures

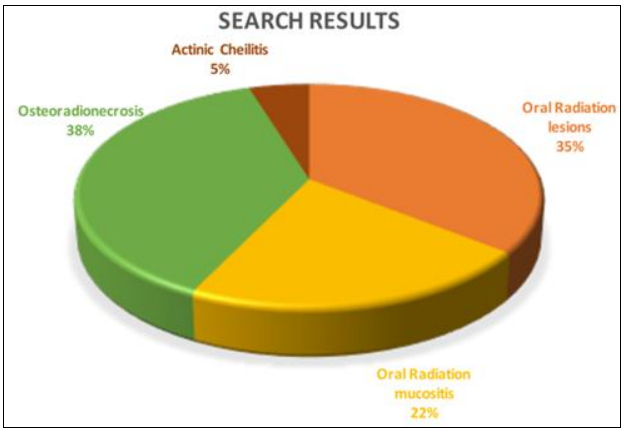

Fig 1: Distribution expressed as a percentage of the results obtained.

4. Conclusions

Oral mucositis are lesions that can seriously compromise the quality of life of patients. Careful diagnosis can lead early towards the best type of treatment, so as to alleviate pain and prevent infectious complications. Given their high incidence rate, the dentist must know these lesions and look for them in patients who are or have undergone radiotherapy. As far as the ORN is concerned, from the studies analyzed it is evident that risk factors such as smoking and oral mucositis increase the risk of developing this complication of radiotherapy. A general dental evaluation is certainly very important before starting radiotherapy, in particular to evaluate any preventive dental extractions. The lesions developed by ultraviolet rays in the oral cavity should not be underestimated. If ignored, they can lead to the development of malignant neoplasms sometimes lethal for the patient. Early diagnosis and treatment are essential. It is also important to perform histological examinations to evaluate the presence of cancer cells. In the literature there are no preventive plans described precisely for actinic cheilitis. General prevention for actinic keratoses of the skin using medical devices with photoprotection and photo repair action (DNA repair enzymes) [45] could be used also for these lesions.

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