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Case Study

PHARMACOLOGICAL MANAGEMENT OF ORAL LESIONS IN ADENOID CYSTIC CARCINOMA PATIENTS UNDERGOING RADIOTHERAPY

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ABSTRACT

Objective: This case report aimed to describe the pharmacological management of oral lesions in adenoid cystic submental carcinoma patients undergoing radiotherapy.

Methods: A 48 y old female undergoing radiotherapy complained of difficulty eating, swallowing, and speaking due to severe pain in her oral cavity for three weeks. Intra-oral examination revealed painful yellowish-white plaques that could not be scrapped on the tongue, maxillary and mandibular anterior gingiva, left and right buccal mucosa, and palate, diagnosed with oral candidiasis. We also found multiple shallow ulcers on the left buccal mucosa and upper labial mucosa that can be seen as oral mucositis.

Results: The patient was given nystatin oral suspension for oral candidiasis, benzydamine hydrochloride for the complaint of pain when swallowing, and saline for promoting wound healing and keeping the oral mucosa moist. These lesions healed in a week and she could eat solid food without pain.

Conclusion: Appropriate pharmacological management of oral lesions in a patient undergoing radiotherapy provides significant healing to better quality of life.

Keywords: Radiotherapy, Oral mucositis, Oral candidiasis, Nystatin oral suspension, Benzydamine, Saline

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INTRODUCTION

Cancer in the head and neck region ranks seventh of the most common cancers worldwide in 2018, with 890,000 new cases and 450,000 deaths [1]. Cancer is strongly associated with environmental and lifestyle risk factors such as alcohol consumption and tobacco use [2]. There are three principal risk factors for head and neck cancer. They are alcohol abuse, tobacco use, and human papillomavirus (HPV) infection [3]. Adenoid cystic carcinoma is a secretory gland malignancy which is characterized by slow growth and perineural invasion. It occurred the most in the salivary glands [3]. Head and neck cancer management requires a multidisciplinary approach from surgery, radiation oncology, radiological pathology, and support services, including physical and occupational therapy, speech and swallowing therapy and nutrition [3, 4]. The management of head and neck cancer is determined by the location of the cancer [3]. Since it is located in close proximity to important structures, its management has many challenges. In general, surgical resection is considered as the initial therapy for head and neck cancer in the early stage of cancer. Radiotherapy is considered for unresectable advanced tumors when surgery would result in significant functional impairment [5].

Radiotherapy has an important part in optimal management of head and neck cancer [4]. Around 80% of head and neck cancer patients will acquire radiotherapy in any case once during the cancer therapy. The main goal of radiotherapy is to limit the tumor cells reproductive that will lead to cell death by apoptosis, necrosis, mitotic catastrophe, aging, and autophagy. When radiotherapy is performed, not only cancer cells will be exposed to radiation but also the surrounding normal tissue. This will cause injury and cause a reaction from the tissues. The manifestations of the injury depend on the tissue sensitivity of radiation and the cumulative dose [7]. Conditions that can occur in the oral cavity include mucositis, xerostomia, caries, soft tissue necrosis, osteoradionecrosis, bacterial or fungal infections, periodontal disease, paralysis of the tongue muscles, hypogeusia, dysgeusia, and trismus [4, 8, 9]. This case report aimed to describe the pharmacological management of oral lesions in adenoid cystic submental carcinoma patients undergoing radiotherapy. Many incidences of oral lesions especially oral mucositis as side effect of radiotherapy, cause radiotherapy as a cancer treatment to be delayed, therefore, proper management of radiotherapy-associated oral lesions is crucial.

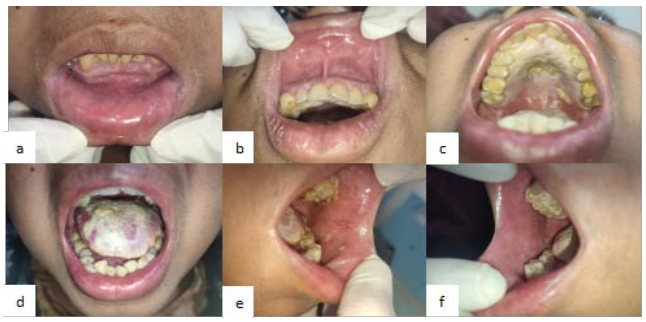

Fig. 1: Clinical features of the oral mucosa at the first visit. Yellowish white plaque that cannot be cleaned on the anterior gingiva of the mandible (a), maxilla (b), palate (c), dorsal of the tongue (d), left (e) and right (f) buccal mucosa and multiple ulcers on the left buccal mucosa (e)

CASE REPORT

A 49 y old female patient with a history of stage IV adenoid cystic carcinoma was referred to the Department of Oral Medicine from the Department of Radiation Oncology, dr. Hasan Sadikin Hospital with complaints of pain in her oral cavity for 2 w after undergoing radiotherapy, causing difficulty eating. Radiotherapy has been done for 20 times in the last 1 mo. She complained of severe pain and it interfere with opening her mouth, speaking, eating, and swallowing. She could only eat porridge with liquid consistency and drink milk.

She had been given a gel containing hyaluronic acid which was applied to the surface of her oral cavity but had not relieved the pain. The dose of radiotherapy given was 200 cGy per day and when she came to the Oral Medicine Department, the patient had received a cumulative dose of 40 Gy after 20 times of radiotherapy.

Extra-oral examination showed swelling in the submental area, pale conjunctiva, and non-icteric sclera. The submental lymph nodes are palpable and painful, measuring 7 cm, elastic, and mobile. Intra-oral examination revealed painful multiple yellowish-white plaques on the maxillary and mandibular gingiva, right and left buccal mucosa, palate, and tongue (fig. 1).

From the anamnesis and clinical examination, it can be concluded that the patient suffers from grade 3 oral mucositis and oral candidiasis. The management given related to oral lesions are non-pharmacological and pharmacological therapy. Non-pharmacological therapy is also an important therapy to support successful therapy. It consisted of instructions for maintaining oral hygiene by cleaning the teeth and tongue with gauze moistened with normal saline at least twice daily and frequently sipping water. The pharmacological therapy given was 100,000 IU nystatin oral suspension, 2 ml four times daily for 2 w, which was used by placing 2 ml of suspension on the tongue, swished and kept for at least 5 min before swallowing. Benzydamine HCl mouthwash was gargled 3 times a day before meal, and saline solution was used as a mouthwash 3 times a day.

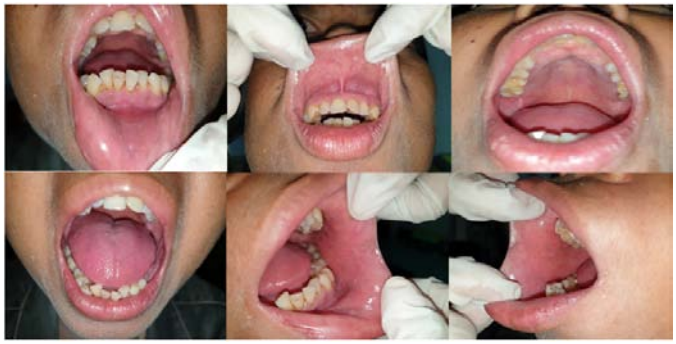

Fig. 2: Clinical features of the oral mucosa on the second visit. The mandibular and upper gingiva, palate, dorsum of the tongue, left and right buccal mucosa improved after 7 d of treatment

One week later, on the second visit, the patient was able to eat solid food because the pain in her mouth had decreased considerably. Intra-oral examination, white plaque and ulcers in the oral cavity were no longer visible (fig. 2).

DISCUSSION

Adenoid cystic carcinoma is a secretory glands malignancy, which is marked by slow growth and invasion to perineural. It occurs the most in salivary glands. Of the rare cancers, adenoid cystic carcinoma occurs 1% in the head and neck malignant tumors and 10% of salivary gland and more common in the minor salivary glands than in the major salivary glands [6]. Adenoid cystic carcinoma is found more frequently in women with a ratio of 60%:40% and occurs between the age of 30 and 90 y, with a highest incidence in patients between the ages of 40 and 70 y [10, 11].

Radiotherapy has an important part in the optimal management of head and neck cancer [4]. Approximately 80% of patients will undergo radiotherapy at least once during the therapy. The main goal of radiotherapy is to limit the reproductive potential of tumor cells that will induce cell death by apoptosis, necrosis, mitotic catastrophe, aging, and autophagy. When radiotherapy is performed, not only cancer cells will be exposed to radiation but also the surrounding normal tissues. This will cause injury and cause a reaction from the exposed tissues. The clinical manifestations of the resulting damage depend on the sensitivity of the irradiated tissue and the dose of radiation accumulated in the tissue [7]. The cumulative dose of 20 Gy is the threshold for mucosal tolerance, it releases proinflammatory cytokines from the vascular epithelium and connective tissue in the affected area, and causes hyperemia of the oral, tongue, and pharyngeal mucosa. When the cumulative dose achieves 30 Gy, mucosa lose the protective barrier due to basement membrane breakdown resulting in desquamation and mucosal ulceration [8]. Conditions that can occur in the oral cavity include mucositis, xerostomia, caries, soft tissue necrosis, osteoradionecrosis, bacterial or fungal infections, periodontal disease, paralysis of the tongue muscles, hypogeusia, dysgeusia, and trismus [4, 8, 9].

The conditions of patient in who they have difficulty eating can only consume liquid food and milk and have many ulcerative oral lesions are classified as grade 3 oral mucositis according to World Health Organization (WHO) criteria. The most common and earliest effect of radiotherapy, chemotherapy and radiochemotherapy in cancer patients or patients receiving hemopoietic stem cell transplantation is oral mucositis. Oral mucositis is defined as an inflammation of the oral mucosa caused by chemotherapy or ionizing radiation in radiotherapy accompanied by burning or tingling sensations [1, 12]. The incidence in head and neck cancer patients undergoing radiotherapy is around 80% [13]. The presence of pathogenic microorganisms in the oral cavity increases the severity of oral mucositis [14]. When the patient has oral mucositis, the patient will experience pain accompanied by discomfort and burning. This sensation can cause the patient to have difficulty in eating, drinking, speaking and swallowing [4]. This can lead to dehydration, limited intake of food and eventually malnutrition and/or cachexia [15]. Clinically, at first, oral mucositis appears as reddish lesions on the oral mucosa, then the epithelium and basement membrane are damaged and develop into ulcers. Ulcers in oral mucositis are quite typical, it is covered by a white pseudomembrane [1, 4]. The serious complication of oral mucositis is sepsis which can occur due to loss of protective function and the barrier epithelium and basement membrane [13].

WHO divides oral mucositis into 4 grades, namely: grade 0 is no oral mucositis; grade 1 is mucosal erythema and pain; grade 2 is erythema, ulceration, but still able to eat solid food; grade 3 is if there are many ulcers and the patient can only consuming liquid food; and grade 4 if there are so many ulcers that the patient cannot really eat [16]. The pathobiology of oral mucositis is complex and occurs in five stages. The first stage is the tissue injury initiation, where the radiation will induce cell damage that causes death in the basal layer of the epithelium. Reactive oxygen species (free radicals)

produced by radiation and play a role in initiating mucosal breakdown. This small and highly reactive molecule is a product of oxygen metabolism and can cause an extraordinary cellular breakdown. The second stage is the upregulation of inflammation through the generation of messenger signals. Free radicals are not also causing direct cell death, but also play a role in activating second messengers that send signals from receptors on the surface cell into the inside of the cell. This guides to upregulation of pro-inflammatory cytokines, tissue damage and cell death. The next step is signaling and amplification, wherein there is an upregulation of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), which is delivered particularly by macrophages, causing damage to mucosal cells, activating molecular route that strengthen the damage. The fourth stage is ulceration and inflammation. At this stage there are considerable infiltrate of inflammatory cell correlated with mucosal ulceration. The pro-inflammatory cytokines production is also further regulated in consequence of this secondary infection. The fifth stage is the healing stage. This stage is marked by epithelial proliferation and differentiation of cells and tissues, thereby restoring epithelial integrity [16]. The severity and extent of oral mucositis depends on certain factors such as sex, age, coexisting systemic disease, and race. The severity of oral mucositis is also influenced by specific factors such as epithelial type, environment, local microbial function, and genetic factors [15].

The appearance of a white, non-scrapable, painful plaque found on the maxillary and mandibular gingiva, the dorsum of the tongue, and the right and left buccal mucosa, as well as the palate in this patient, showed the appearance of oral candidiasis. Radiotherapy in head and neck cancer causes disruption of the mucosal barrier. This disruption of the mucosal is clinically seen after two to three weeks of radiotherapy. Combination of disruption barrier and dysbiosis sustain the colonization and invasion by commensal bacteria and fungi. Dysbiosis markedly disrupts microbial homeostasis in the mucosa, bring out to hyperactivation of pattern recognition receptors (PRRs), thereby predisposing to oral mucositis. Therefore, when the barrier disrupted, there is an overgrowth of commensal microorganisms through the activation of PRRs that will support ecosystem changes and hyperactivation of the inflammatory response in the oral cavity. Tissue inflammation associated radiation and cell apoptosis result from continuous radiotherapy schedule for several weeks. The association of mucosal barrier damage, hyposalivation, inflammation, and dysbiosis sustain fungal colonization and invasion. Fungal infections usually originate from Candida species which normally persist in the oral mucosa and gastrointestinal lumen as commensal microorganisms. This is supported by previous research, which states that after undergoing approximately 2 w of radiation therapy, the number of Candida is greatly increased [17].

The pathophysiology of fungal infections associated to microenvironment pH changes that support fungal virulence factors overexpression, changes in salivary composition, and immune dysregulation. Under physiological situation, mucin and proteoglycans in saliva attached to microorganisms and eliminate them by ingestion. Saliva also contains antimicrobial substances, such as lysozyme, secretory IgA, and lactoferrin which prevent the attachment of fungi and mucosa. In addition, saliva itself has candida-killing activity because it has various antifungal proteins, including histatin 5, LL-37, calprotein, lactoferrin and in different ways can kill C. albicans [18]. The management of oral candidiasis in this patient is Nystatin oral suspension given 4 times a day with a dose of 2 ml for 14 d. Nystatin oral suspension is used by placing it in the mouth, sucking it in for 5 min and then swallowing it [19, 20]. Nystatin belongs to the polyene group. This polyene group exhibits broad-spectrum antifungal activity in treating superficial and deep fungal infections [20]. Mechanism of action from polyene is by inhibiting the production of ergosterol which is very important for the integrity of the yeast cell membrane. Polyenes can also affect the attachment of fungi and epithelial cells [12]. Polyene is not absorbed by the gastrointestinal tract. Nystatin is derived from *Streptomyces noursei*. It binds to ergosterol of fungal, establish a pore, so the membrane to be more permeable, leading to leakage of K+, Na+, and H+so that it is fungicidal [21, 22]. Nystatin can also cause secondary cellular damage via autoxidation. This topical preparation of nystatin is also effective because it can be absorbed into the oral epithelium so that it can kill yeast hyphae in the tissue [23]. Nystatin also exhibits a good post-antifungal effect, whereby regrowth of the fungus can be inhibited after brief exposure to antifungal agents [23]. The selection of nystatin oral suspension for the management of oral candidiasis was in accordance with the recommendations of Infectious Diseases Society of America (IDSA) of nystatin oral suspension (100,000 U/ ml, 4-6 ml four times a day) for 7-14 d for the treatment of candidiasis in clinical practice guidelines updated in 2016 [21]. That is why topical nystatin is widely used and is still the first choice for oral candidiasis, especially in developing countries, because of its high efficacy, affordable price, and minimal adverse effects [20, 23].

During and after radiotherapy, there was a decrease in the amount of saliva, changes in saliva composition, and the concentration of antimicrobials in saliva. These changes in saliva will support the proliferation of yeast so that candida will thrive. A condition that is also often found in people undergoing radiotherapy is xerostomia. Xerostomia is defined as a subjective feeling of dry mouth characterized by decreased salivary volume and/or thickened saliva. In head and neck radiotherapy it can be caused by aberration of the salivary glands so that the volume of salivary secretion decreases or changes in composition and is usually accompanied by complaints of swallowing, speech, and health problems in the oral cavity [7, 19]. Complaints of painful swallowing in patients were overcome by giving benzydamine hydrochloride, which was used by gargling 3 times a day to overcome complaints of painful swallowing. Benzydamine is a non-steroidal anti-inflammatory drug that is widely recognized in clinical practice as well as in international guidelines as a topical drug for radiotherapy-associated mucositis. Apart from being a local anti-inflammatory, benzydamine also has analgesic, anesthetic, and antimicrobial properties [3]. In contrast to the activity of NSAIDs, benzydamine acts on local inflammatory factors and does not affect systemic physiological mechanisms. Benzydamine has been shown to have a good effect in suppressing the production of proinflammatory cytokines because it can inhibit the production of TNF-, IL-1β, and prostaglandins. Benzydamine also plays a role in preventing leukocyte-endothelial interactions, degranulation of neutrophil, vasodilation, and vascular permeability. Previous studies have also shown that benzydamine is effective in preventing and reducing the severity of oral mucositis [24]. Literature review states that benzydamine has been shown to significantly reduce the severity of oral mucositis, slow the severity of mucositis, reduce pain, and reduce dysphagia [24, 25]. The consideration of giving benzydamine is also because it is safe and well tolerated by patients [25, 26].

The mouthwash given in this case was normal saline which was gargled 3 times a day. Normal saline is the same isotonic solution as body fluids and patients with oral mucositis can tolerate the use of this solution. Normal saline facilitates hemostasis, thereby providing an optimal environment by maintaining a moist wound surface. Another function of normal saline is that it can diminish or absorb exudate, minimize pain and increase comfort [27]. The choice of normal saline as a mouthwash is because it is easy to use and easy to obtain with affordable price.

CONCLUSION

Management of oral lesions in patients receiving radiotherapy can improve the patient's quality of life and help properly the radiotherapy process so that optimal healing is achieved. Nystatin oral suspension was effective for the management of oral candidiasis in the patient undergoing radiotherapy. Benzydamine hydrochloride mouthwash and normal saline had successful effect in the management of oral mucositis.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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