Radiation induced oral mucositis – A case report with review of literature

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Abstract
Oral mucositis is a frequently occurring and debilitating complication of radiation therapy for head and neck cancer. It is an early effect of radiation and results from mitotic death of the basal cells of the oral epithelium. It usually appears 2 weeks after initiation of radiotherapy. Many treatments have already been discussed regarding the management of this condition, but some reports show little evidence supporting the effectiveness of some of these interventions. The role of the general practitioner in the prevention and management of radiation induced mucositis is critical. The general practioner must collaborate with the oncologist, dental surgeon to ensure comprehensive treatment of this condition. Here we report a case of radiation induced oral mucosities in 62 year old male patient.

Keywords: Oral mucositis, Cancer, Radiation therapy, Treatment.

Introduction
Radiotherapy plays an important role in the management of head and neck cancer. The majority of new cases of invasive head and neck cancer will need radiotherapy as a primary treatment, as an adjunct to surgery, in combination with chemotherapy, or as palliation.[1]

The radiation dose needed for the treatment of cancer is based on location and type of malignancy, and whether or not radiotherapy will be used solely or in combination with other modalities. Most patients with head and neck carcinomas, treated with a curative intent, receive a dose between 50 and 70 Gy. Combining this with brachytherapy provides excellent control for early tumors. This dose is usually given over a five- to seven-week period, once a day, five days a week, 2 Gy per fraction.[2]

Damage to oral mucosa is strongly related to radiation dose, fraction size, volume of irradiated tissue, fractionation scheme, and type of ionizing irradiation.[3-6] Radiation-induced mucositis occurs as a function of cumulative tissue dose. Mucositis is a common complication of cancer therapy, which significantly affects the mucosa. Oral mucositis refers to the oral erythematous and ulcerative lesions commonly observed in patients undergoing cancer therapy.[7] Ulcerative mucositis mostly occurs at doses of 30 Gy. This corresponds to a period about 2 to 3 weeks after the onset of radiotherapy. They are painful and affect nutrition and quality of life of the patient, and contribute to local and systemic infections.[7]

Studies show severe oral mucositis occurred in 29-66% of all patients receiving radiation therapy for head and neck cancer. The incidence of oral mucositis was especially high in patients: (i) With primary tumors in the oral cavity, oropharynx, or nasopharynx; (ii) who also received concomitant chemotherapy; (iii) who received a total dose over 5,000 cGy; and (iv) who were treated with altered fractionation radiation schedules.[9,10] Here we report a case of radiation induced oral mucosities in 62 year old male patient.

Case Report
A 62 year old male patient name Mahadevappa residence of davangere came to department with chief complaint of pain and burning sensation in mouth since 2 months. Pain was continuous increases on taking both normal as well as spicy food, relived by having water. His past medical history revealed, patient is known case of carcinoma of perriform fossa since 8 months, since 4 months he was on radiation therapy along with medication. Family history was not significant. His personal history patient was chronic bidi smoker since 35 years one packet per day. On general physical examination all his vital signs within normal limit. Extra oral examination revealed black colour discoloration present on neck extending from right to left ear, lower border of mandible extending till clavicle and shoulder. Intraoral examination revealed fissuring and cracking of right and left corner of mouth. A whitish yellow scrapable pseudomembranous layer present over labial mucosa right and left buccal mucosa, floor of the mouth and both ventral as well as dorsal surface of the tongue and hard palate associated with pus discharge from gingival sulcus with severe halitosis. Erosions with erythematous areas present over posterior aspect of soft palate and both right and left buccal mucosa extending up to vestibule as well as retromolar area. On palpation the lesions were extreamly tender and scrapable leaving bleeding spots. Considering the history and clinical signs and symptoms we arrived at provisional diagnosis of radiation induced oral mucosities with differential diagnosis of pesudomembranous candidosis. Patient had treated symptomatically.

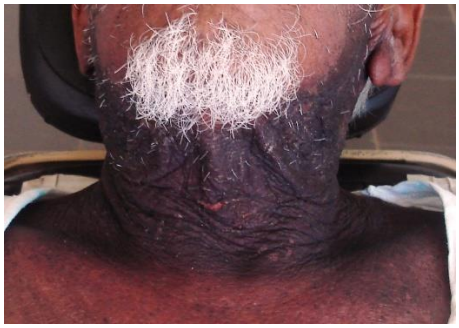

Fig. 1: Front view of patient showing radiation therapy given to neck area

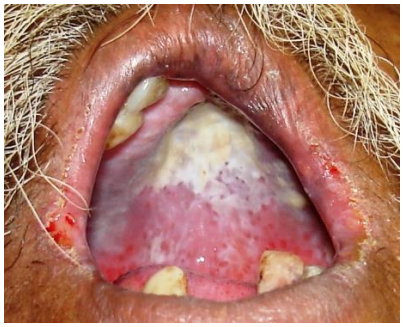

Fig. 2: Intra-oral view of radiation induced mucositis

Table 1: Mucositis prevention therapies[19]

S. No	Methods	Agents used
1	Oral Hygiene	
2	Infection Prevention	a. Antimicrobial Lozenges b. Chlorhexidine c. Clindamicin d. Acyclovir, Valacyclovir, Famcyclovir e. Fluconazole, Clotrimazole, Nystatin
3	Anti-Inflammatory Agents	a. Dinoprostone b. Misoprostol c. Prednisone d. Pentoxifylline e. Benzydamine
4	Reactive Oxygen Species Inhibitors	a. Amifostine b. N-acetylcysteine c. Manganese Superoxide Dismutase
5	Salivary Function Modifiers	a. Propantheline b. Pilocarpine
6	Azelastine	
7	Cryotherapy	
8	Glutamine	
9	Coating Agents	Sucralfate b. Hydroxypropylcellulose Gel c. Polyvinylpyrrolidone and Sodium Hyaluronate
10	Laser Therapy	
11	Growth Factors	a. Epidermal Growth Factor (EGF) b. Granulocyte Colony Stimulating Factor (GCSF) c. Granulocyte Macrophage Colony Stimulating Factor (GMCSF) d. Transforming Growth Factor Beta 3 (TGFb3) e. Interleukin 11 (IL-11) f. Fibroblast Growth Factors (FGFs) i. Keratinocyte Growth Factor 1 (KGF1, FGF7) ii. Fibroblast Growth Factor 10 (FGF10) iii. Fibroblast Growth Factor 20 (FGF20)

Table 2: Different treatment modalities by different authors for oral mucosities.[20]

Authors	Application doses	Results
1. Locally applied nonpharmacological methods		
a) Oral hygiene		
Shieh et al.[21]	Instructions on oral care	Significant reduction
Rugg et al.[22]	Smoking during RT	Higher mucositis incidence in smokers
b) Radiation shields		
Perch et al.[23]	Midline mucosa sparing blocks	Decreased mucositis without affecting tumor control
Keus et al.[24]	Customized beam shaping	Lower incidence of mucositis
2. Locally applied pharmacotherapeutics		
Mouth-coating agents		
Sucralfate		
Scherlacher et al.[25]	Sucralfate vs. standard oral hygiene	Significant reduction of incidence and severity of mucositis
Allison et al.[26]	Sucralfate+fluconazole vs. standard oral care	Significant reduced severity and symptomatic relief
Franzen et al.[27]	Sucralfate vs. placebo	Sig. lower incidence of severe mucositis
Kaolin-pectin		
Barker et al.[28]	Oral hygiene+sucralfate vs. diphenhydramine+kaolin-pec	No difference
f) Antiseptic and antibiotic agents		
Hydrogen peroxide		
Feber et al.[29]	Hydrogen peroxide vs. saline	Significantly more oral discomfort
Chlorhexidine		
Foote et al.[30]	Chlorhexidine vs. placebo	Slight aggravation
PVP-iodine		
Rahn et al.[31]	Nystatin, rutosides, immuno-globuines, panthenol±PVP-iodine	Significant reduction
g) Antifungal agents		
Amphotericin B		
Symonds et al.[32]	Amphotericin+tobramycin+ polymyxin vs. placebo	Significant reduction of the incidence of severe mucositis
h) Anti-inflammatory agents		
Chamomile		
Carl et al.[33]	Chamomile vs. historical group	Low incidence of mucositis
Betamethasone		
Abdelaal et al.[34]	High-dose betamethasone	Impressive prevention of mucositis incidence
Benzydamine		
Epstein et al.[35]	Benzydamine vs. placebo	Significant reduction of incidence and severity
i) Cytoprotectants		
Glutamine		
Huang et al.[36]	Glutamine suspension vs. placebo sig.	Reduction of severity and duration
Prostaglandin E2		

Matejka et al.[37]	PGE2 tablets four times a day	Reduction of mucositis severity
j) Multiagent mouthrinses		
Rothwell et al.[38]	Hydrocortisone, nystatin, tetracyclines, diphenhydramine vs. placebo	Significant reduction of incidence
k) Agents influencing mucosal proliferation Silver nitrate		
Maciejewski et al.[39]	Applied to one side of buccal mucosa	Significant reduction compared with contralateral side
3) Systemically applied pharmacotherapeutics		
n) Agents influencing mucosal proliferation Beta carotene		
Mills et al.[40]	Betacarotene or nothing	Decreased severity in the treatment group
o) Cytoprotectants Amifostine		
Koukourakis et al.[41]	Amifostine vs. saline	Significant reduction of mucositis
p) Immunmodulatory drugs Indomethacin		
Pillsbury et al.[42]	Indomethacin vs. placebo	Significant delay of mucositis onset
q) Hematopoetic growth factors GM-CSF		
Wagner et al.[43]	RT + GM-CSF vs. historical control	Significant lower severity of mucositis
G-CSF		
Schneider et al.[44]	RT±G-CSF	Sig. reduced incidence of severe mucositis

Discussion

Mucositis is an early effect of radiation and results from mitotic death of the basal cells of the oral epithelium. It usually appears 2 weeks after initiation of radiotherapy.[11] During this period, mucositis evolves from asymptomatic focal hyperemia and edema to symptomatic patchy, then confluent desquamation.[8] It is an integral part of radiotherapy in terms of morbidity, since during a course of curative radiation about 80% of the patients will develop pseudomembranous mucositis. The early radiation reaction causes local discomfort as well as difficulties in drinking, eating, swallowing, and speech. Therefore, it can give rise to nutritional problems, and in severe cases nasogastric feeding, which is very uncomfortable, may become necessary.[4]

Clinically, oral mucositis usually presents with erythema accompanied by dryness, pain, and burning symptoms. Severe ulceration and the inability to tolerate even liquid may occur. The damaged oral mucosa and the reduced immunity resulting from cancer therapy also may give rise to opportunistic infections. Complications of salivery gland dysfunction and trauma also can modify the evaluation of mucositis. [4,5,7]

Pathophysiology

The exact pathophysiology of mucositis is not fully elucidated, but it is thought to have two mechanisms: direct mucositis and indirect mucositis, caused by chemotherapy and/or radiation therapy.

Direct Mucositis: The epithelial cells of the oral mucosa undergo rapid turnover, usually every 7 to 14 days, which makes these cells susceptible to the effects of cytotoxic therapy. Both chemotherapy and radiation therapy can interfere with the maturity and cellular growth of epithelial cells, causing changes to normal turnover and cell death.[12]

Indirect Mucositis: Oral mucositis can also be caused by the indirect invasion of Gram-negative bacteria and fungal species. Patients are at increased risk for oral infections when they are neutropinic, and this usually happens when indirect stomatotoxicity appears.[12] Various methods to assess the grade of mucositis in cancer patients have been described; these are based on the presence of signs such as erythema and lesions in isolation or associated with symptoms such as pain and swallowing difficulties.[13]

Oral mucositis may be classified into five grades according to the World Health Organization grading system, as follows: grade 0 - indicated absence of mucositis; grade; I - presence of a painless ulcer, erythema or mild sensitivity; grade, II - presence of painful erythema or ulcers that do not interfere with the patient's ability to take food; grade III - confluent ulceration that interfere with the patient's ability to take solid food; and grade IV – severe symptoms requiring enteral or parenteral support.[13,14]

The new pathophysiology concepts of mucositis involves four phases as described below by different authors.

Phase I: Initial inflammatory/vascular phase: During this phase, exposed cells (epithelial, endothelial, and connective tissue cells) in the buccal mucosa release free radicals, modified proteins, and proinflammatory cytokines, including interleukin-1B, prostaglandins, and tumor necrosis factor (TNF). These inflammatory mediators cause further damage either directly or indirectly by increasing vascular permeability, thereby enhancing cytotoxic drug uptake into the oral mucosa.

Phase II: Epithelial phase: In this phase, radiotherapy retards cell division in the oral mucosal epithelium, leading to reduced epithelial turnover and renewal, resulting in epithelial breakdown. At this stage, microtrauma from day-to-day activities such as speech, swallowing, and mastication leads to ulceration.

Phase III: Ulcerative/bacteriological phase (pseudomembraneous) Epithelial breakdown ultimately results in the ulcerative phase, which occurs within 1 week of therapy. Loss of epithelia and furious exudation lead to the formation of pseudomembranes and ulcers. In this phase, microbial colonization of damaged mucosal surfaces by Gram-negative organisms and yeast occurs, and this may be exacerbated by concomitant neutropenia.

Phase IV: Healing phase: The duration of this phase usually lasts from 12 to 16 days, and mainly depends on factors such as epithelial proliferation rate, hematopoietic recovery, reestablishment of the local microbial flora, and absence of factors interfering with wound healing viz. infection and mechanical irritation.

Risk Factors for the Development of Mucosal Injury Some of the major risk factors include age, nutritional status, type of malignancy, oral care during treatment, and neutrophil count before treatment. In general, younger patients are more prone to mucositis because of rapid epithelial mitotic rate, or the presence of more epidermal growth factor receptors.[12,13,15-17]

Treatment

Until now no effective intervention has been developed to prevent oral mucositis in radiotherapy. Prevention of severe mucositis is important because mucositis affects the patient's feeding status, physical and mental well-being and it can influence the course of radiotherapy. Further oral pain because of mucositis has a serious impact on the quality of life of patients. To prevent iatrogenic mucosal damage, irritating factors such as sharp or rough fillings should be smoothened or polished prior to radiotherapy, and prosthetic appliances should be closely evaluated.[18] Plaque control and oral hygiene should be maintained.[4,18] Teeth with a questionable prognosis and having to be removed before the start of radiotherapy.[11] In keeping with the aim of eliminating irritating factors, the use of tobacco, alcohol, and spicy and acidic foods should also be discouraged.[4] Recent systematic reviews and clinical trials have identified potentially effective approaches for the prevention of mucositis, namely: the use of allopurinol, growth factors and povidine-based mouthwashes, hydrolytic enzymes, amiphostine, sucralfate and antibiotics, honey, low-intensity laser, oral hygiene, analgesics and anti-inflammatory drugs, and other options (Table 1 and 2).

Only the administration of antibiotic lozenges has been shown to be of some use in the reduction of the severity of radiation mucositis. Results with the administration of growth factors and radical scavengers are promising and need further study, focused not only on the prevention of mucositis but also on the potential effects of these therapies on tumor response.[18]

Conclusion

Radiation-induced oral mucositis affects the quality of life of the patients and the family concerned. The present day management of oral mucositis is mostly palliative and or supportive care. Management includes good oral hygiene, avoiding irritating or abrasive substances, use of bland rinses, topical anesthetic agents, and systemic analgesics. Though, the newer guidelines are suggesting Palifermin, which is the first active mucositis drug as well as Amifostine, for radiation protection and cryotherapy for symptoms related to high-dose melphalan; the role of safe radiotherapy remains the ultimate goal in reducing the symptoms of radiation-induced oral mucositis. Future research for the newer drugs in the field of radiation-induced oral mucositis is a must, and the current management should focus more on palliative measures, such as pain management, nutritional support, and maintenance, of good oral hygiene.

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