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Fungal Infections during Radiation Therapy of Oral Cancers

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Abstract

To study the prevalence of oral or oro-pharyngeal fungal infections during radiotherapy of oral cancer.120 patients receiving a 6-7 week course of radiation therapy alone (on Telecobalt machine) for treatments of oral cancer were enrolled in the study. Patients were clinically examined for signs of oral and oropharyngeal candidiasis at baseline and weekly thereafter during their radiation treatment. The scraping or swabs from the oral cavity were obtained and confirmed by use of a 10% KOH preparation.Overall oral candidiasis was recorded in 46.66% (56/120) of the patients, with Candida albicans – 54. Increasing trend in radiation reactions, like severe odynophagia, dysphagia, grade 2 & 3 mucositis and oral secondary infection with increasing fungal or bacterial growth were significantly associated symbiotically from 3rd to 6th week of radiation therapy. During radical radiotherapy corticosteroid like dexamethasone 4mg i.v, b.id for 1 – 2 weeks is usually used for control of acute reactions like mucositis (Grade 2 and 3), odynophagia and dysphagia (severe). The use of corticosteroid during radiotherapy possibly suppresses the cellularimmunity and phagocytosis adding to its contribution towards increasing secondary infection. In our study 46.6% subjects developed oral candidiasis and corticosteroid for mucositis was used in 55.4% (61/110) of the patients for RTOG Grade 2 and 3 acute radiation reactions. Predisposing factors should be treated or eliminated were feasible. Antifungal agents play an important role in the management of fungal infectionsFungal infections during radiation therapy or Head & Neck cancers are common. Under suitable circumstances the normal commensal turns pathogenic. These infections contribute to increased acute radiation reacting, which in turn necessitates treatment interruptions.

Key Words: Fungal Infections, Radiation Therapy, Oral Cancer.

INTRODUCTION

Candidiasis describes a group of yeast like fungal infections involving the skin and mucous membranes. Infection is caused by Candida species, typically, Candida albicans. In the general population, carriage rates have been reported to range from 20% to 75% without any symptoms. It is seen as early as in 45% of neonates and 45-65% of healthy children. By tradition, the most commonly used classification of oral candidiasis divides the infection into 4 types (1) acute pseudo membranous candidiasis (thrush), (2) acute atrophic (erythematous) candidiasis, (3) chronic hyperplastic candidiasis, and (4) chronic atrophic (erythematous) candidiasis.[1,2]

These are normal commensal of the mouth and generally cause no problems in healthy people. C albicans is a harmless commensal organism inhabiting the mouths of almost 50% of the population; however, under suitable circumstances, it can become an opportunistic pathogen. A suitable circumstance may be a disturbance in the oral flora or a decrease in the immune defenses.[1-3]

Overgrowth of Candida, however, leads to local discomfort, altered taste sensation, dysphagia from overgrowth resulting in poor nutrition, slow recovery, and prolonged hospital stay. In immunocompromised patients, infection can spread through the bloodstream or upper gastrointestinal tract leading to severe infection with significant morbidity and mortality. Systemic candidiasis carries a mortality rate of 71% to 79%. The common clinical presentation is with symptoms of soreness, burning, altered taste and signs of white pseudo membranous plaques, patches (thrush), erythematous lesions, and angular Cheilitis.[2]

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Fungal Infection in Radiotherapy

Common Clinical Situations where fungal infections are encountered are in Head & Neck Cancer, Oral Cancers, Esophageal Cancer, Lung Cancer, and Cancer Cervix. Risk factors for oral colonization by Candida during radical radiation therapy are Xerostomia, Oral prostheses, Alcohol use, Smoking [4]. The function of the saliva is to maintain oral hygiene. Saliva washes the pathogens and food particles in the oral cavity and oropharynx. It contains antimicrobial agents like thiocyanate ions, proteolytic enzymes (lysozyme), antibodies which are specific anti-Candida antibodies, lactoferrin, sialoperoxidase, and histidine-rich polypeptides.

Radiation (RT) induced Xerostomia

Salivary function is extremely sensitive to irradiation of salivary glands. The principle damage is to the acinar & duct system and this is proportional to increasing radiation dose and increasing volume of parotid gland included in the radiation portal. The related changes in salivary components are, overall increase in total salt content and pronounced decrease in water content.

It is observed that Dose of > 40Gy (Radiotherapy Dose - Gray) to the salivary gland results in significant decrease in the salivary flow rate. The reduction in salivary flow at the end of radiotherapy (RT) is approximately 83.3%; it is about 1.32 ml/min prior to radiotherapy and reduces to 0.22 ml/min by the end of radiotherapy. After radiotherapy during the follow-up period at 3rd month, it is reduced to about 93.4 % of the baseline. Over all reduction in buffering capacity of the saliva is about 44.3%.[5]

Aims and Objectives

To study the prevalence of oral or oro-pharyngeal fungal infections during radiotherapy of oral cancer.

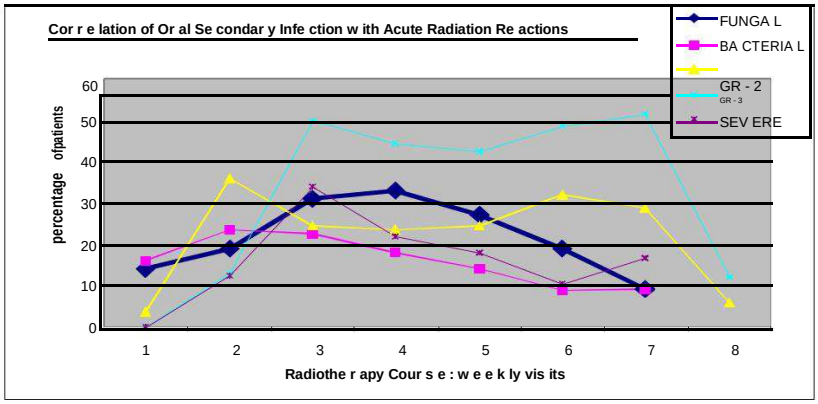

Figure :1Oral secondary infection with acute radiations reactions

MATERIAL AND METHODS

120 patients receiving a 6-7 week course of radiation therapy alone (on Telecobalt machine) for treatments of oral cancer were enrolled in the study. Patients were clinically examined for signs of oral and oropharyngeal candidiasis at baseline and weekly thereafter during their radiation treatment (Picture: 1). Infection was defined as positive clinical signs of white intraoral plaques and/or halitosis. The scraping or swabs from the oral cavity were obtained and confirmed by use of a 10% KOH preparation.

Patients with infection were treated with fluconazole (200 mg [loading dose] and 100 mg/day for 7 days to 14 days). If a clinical cure was not achieved in 14 days, the patients were treated with Itraconazole 100mg b.i.d to achieve a clinical cure. Fungal cultures employed an oral swab or scraping. Acute radiation reactions are recorded weekly as per RTOG grading criteria[6,7].

RESULTS

Overall oral candidiasis was recorded in 46.66% (56/120) of the patients, with Candida albicans – 54, Aspergillosis –2 and bacterial infections were seen in 41.66% (50/120). 1-patient had aspergillosis in the ear. Increasing trend in radiation reactions, like severe odynophagia, dysphagia, grade 2 & 3 mucositis and oral secondary infection with increasing fungal or bacterial growth were significantly associated symbiotically from 3rdto 6th week of radiation therapy (Figure: 1). 4 patients had relapse of fungal infection after a gap of 1 –3 weeks requiring second line itraconazole therapy.

DISCUSSION

Radiation therapy of oral cavity and head & neck region is associated with acute radiation reactions like mucositis, odynophagia, and dysphagia. During radical radiotherapy corticosteroid like dexamethasone 4mg i.v, b.id for 1 – 2 weeks is usually used for control of acute reactions like mucositis (Grade 2 and 3), odynophagia and dysphagia (severe). The use of corticosteroid during radiotherapy possibly suppresses the cellular immunity and phagocytosis adding to its contribution towards increasing secondary infection. In our study 46.6% subjects developed oral candidiasis and corticosteroid for mucositis was used in 55.4% (61/110) of the patients for RTOG Grade 2 and 3 acute radiation reactions. There is a simultaneous increase in the oral fungal infections and mucositis and corticosteroid use during 3rd & 4th week of radiotherapy (Figure 1).

In a similar study by Endod Ramirez a significant increase in positive Candida cultures was seen in 46 patients on radiotherapy. Here 62% of patients developed candidiasis by the end of radiotherapy The median external radiation dose at which, positive culture was seen was 22.5 Gy and overt candidiasis at 28.6 Gy[4] i.e., during 2nd and 3rd week of radiotherapy. Post Radiotherapy, Candida colonization is maximum at 6 months with considerable minimum salivary flow. By one year it was observed that slight recovery in salivary flow is seen, due to recovery of minor salivary glands and globlet cell leading to reduction in candidiasis nearing normal [8]. This demonstrates that even slight recovery of salivary flow can restore the oral ecological system and reduce candiasis.

MANAGEMENT

The symptoms of acute radiation reaction with oral or oropharyngeal candidiasis significantly reduces the oral intake of food and liquids and significantly reduce the quality of life. Maintenance of adequate nutrition and hydration is essential during radiation therapy.[9]

Predisposing factors should be treated or eliminated were feasible. Good hygiene is important. Antifungal agents play an important role in the management of fungal infections. I. Systemic drugs like: Fluconazole, Amphotericin B, Itraconazole, Voricon azole and II. Topical antifungal like a) Imidazole/triazoles: Clotrimazole, Econazole, Ketoconazole, Miconazole, Oxiconazole, Sulconazole, Terconazole (vaginal candidiasis only), b) Ciclopirox olamine, c) Polyene antibiotics: Nystatin, Topical amphotericin B lotion, e) Other topical agents: Drying agents, Powders, Gentian violet, Castellani's paint, Potassium permanganate compresses, Iodochlorhydroxyquin, f) Evolving agents: Naftifine, Terbinafine etc[7] are currently available for the treatment of candidiasis.

Oral & Oropharyngeal candidiasis: initial episodes can be treated with clotrimazole troches (one 10-mg troche 5 times daily) or nystatin (available as a suspension of 100,000 U/mL [4-6 mL q.i.d.] or as flavored 200,000 U pastilles [one or two 4or as flavored 200,000 U pastilles [one or two 4-5 times daily] for 7-14 days). Oral fluconazole (100 mg/d for 14-21 days orally) is as effective as and in some studies superior to topical therapy. Itraconazole (200 mg/d for 7-14 days orally) is as efficacious as

fluconazole. Suppressive therapy is effectivefor the prevention of recurrent infections, but to reduce the likelihood of development of antifungal resistance, it should be used only if the recurrences are frequent or disabling. Amphotericin B oral suspension (1 mL q.i.d. of the 100 mg/mL suspension) is sometimes effective in patients whodo not respond toitraconazole.

Pre radiation dental prophylaxis and thorough disinfection of the denture or its discontinued use of denture is recommended. Antifungal susceptibility testing is not generally needed but can be useful in patients with refractory infection[9]. Role of prophylactic oral fluconazole, use of bioadhesive Buccal Tablets and biological response modifiers during radiotherapy is being explored[10,11]. The polymorphonuclear cells play a very important role in the protection against intra-tracheal infection with Candida albicans hence there is a possible role of like granulocyte macrophage stimulating factor etc.

It is currently being recognized that head and neck cancer radiation is commonly associated with Candida glabrata colonization, which had never been described as the infecting organism. This pathogen requires 800 mg/day of fluconazole for clinical resolution. The antifungal susceptibilities 79 oral Candida glabrata isolates to fluconazole and voriconazole were compared. The mean inhibitory concentrations (MICs) at which 90% of the isolates are inhibited is 1 µg of voriconazole/ml v/s 32 µg of fluconazole/ml. C. glabrata is inherently more resistant to fluconazole.[12,13] C. albicans appears to develop resistance rapidly to fluconazole. Voriconazole is a new broad-spectrum triazole antifungal drug, like fluconazole, which disrupts the fungal membrane by inhibition of the cytochrome P-450-dependent 14- -lanosterol demethylase, preventing the conversion of lanosterol to ergosterol.[14]

Most effective intervention for Xerostomia is Prevention with meticulous radiotherapy Planning. Beam arrangement to spare salivary glands, Sparing > 50% of Salivary glands using 3D Conformal RT technique (3D CRT) or Intensity Modulated Radiation Therapy (IMRT).[15] Radio protectors like WR 2721 (Amifostine), Oral Pilocarpine Hydrochloride.

CONCLUSION

In our study the oral candidiasis was noted in 46.6% of the 120patients undergoing radiotherapy to oral cavity. Increasing trend in radiation reactions, like severe odynophagia, dysphagia, grade 2 & 3 mucositis and oral secondary infection with increasing fungal or bacterial growth were significantly associated symbiotically from 3rdto 6th week of radiation therapy.

Oral secondary infections during radiation therapy or Head & Neck cancers are common. Under suitable circumstances the normal commensal turns pathogenic. These infections contribute to increased acute radiation reacting, which in turn necessitates treatment interruptions. Treatment interruptions are unacceptable as they contribute to decrease cure rates. Hence there is a need to incorporate various salivary gland sparing radiation therapy techniques and protective measures. .

FUTURE PERSPECTIVE

Recent Technological innovation in radiation delivery like IMRT, Tomotherapy, nano particle amifostine etc, can considerably decrease damage to salivary glands. Topical treatments, oral bioadhesive extended release buccal tablets with optimized delivery of local antifungal, nano-particle delivery technology and DNA micro array study and newer drug susceptibility testing will throw more light into this vexing problem of management of fungal infections of immunocompromised patients. There is a need for a standardized antifungal susceptibility testing methods and reliable commercial test kits[16].

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