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Spectrum of fungal infection in head and neck cancer patients on chemoradiotherapy

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ABSTRACT

Background: Radiotherapy for head and neck cancers (HNC) causes alteration of oral mucosal barrier predisposing it to colonization and infection. Such infections often result in pain and burning sensation thus contributing to major morbidity.
Objective:

1. To identify the fungi isolated from the patients undergoing radiotherapy for HNC.
2. To determine their antifungal susceptibility and week of colonization.
3. To find out association between oral fungal infection and severity of oral mucositis.

Materials and methods: Study was done on 50 patients of HNC treated with concurrent chemoradiotherapy. Three samples (throat, urine, blood) were collected for fungal culture and sensitivity. These samples were collected before the start of radiotherapy, during radiotherapy (2nd and 6th week) and post radiotherapy (10th week).
Results: Only 49 patients were available for analysis. Fungal infection was found in 27/49 patients (55.10%) out of which Non-*albicans Candida* was isolated in 18/49 (36.73%) and *Candida albicans* in 9/49 (18.36%) cases. About 66.66% (18/27) isolates were sensitive to fluconazole. Maximum isolation of yeast was during 6th week of radiotherapy. All grade 4 and 71.42% of grade 3 oral mucositis were found in patients who were positive for fungal infection.
Conclusion: The spectrum of fungal species in throat swab was: Non-*albicans Candida* and *Candida albicans* observed in 36.73% and 18.36% of patients respectively. Higher rate of fungal colonization and infection was found in patients with grade 3/4 oral mucositis. Prophylactic fluconazole in HNC patients on concurrent chemoradiotherapy has the potential to reduce emerging invasive fungal infection and its associated morbidity.

Introduction

Radiotherapy administered to patients with head and neck malignancies makes them particularly susceptible to oropharyngeal candidiasis. [1] *Candida* species are very often present as commensal in oral microbiota in about 50% of worldwide population. However, under immunosuppressive treatment (chemoradiotherapy), the yeast may transform from commensal to a pathogen, in patients with malignancies.

This candidal carriage state is not considered a disease, but when *Candida* species become pathogenic and invade host tissues, oral candidiasis occurs. This change usually constitutes an opportunistic infection by normally harmless micro-organisms because of local (i.e., mucosal), or systemic factors altering host immunity, in this case chemoradiotherapy.

Oral mucosal colonization and infection are common in patients receiving radiation therapy for head and neck malignancies. One of the prime causes for this is thought to be the resultant xerostomia due to destruction of glandular tissue by radiation. [2] *Candida albicans* is the most preponderant organism in these patients. However of late, Non-*albicans Candida* species has been seen to be an emerging cause of oropharyngeal candidiasis. [3] Oral candidiasis patients suffer from oral pain and burning which has a major effect on the quality of life.

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One of the acute side effects of head and neck radiotherapy is oral mucositis, one of the closest differential diagnosis of oral candidiasis, which is marked by erythema and oral ulcerations. The high prevalence of candidiasis during head and neck radiotherapy, combined with difficulties in differentiating infection and mucositis and the potential role of candidiasis in increasing the severity of mucositis has led to consider the need for timely diagnosis and management. [4–6]

It has been reported that *Candida* species especially *Candida albicans* was the most common organism causing fungal infections in patients with head and neck malignancies receiving radiotherapy, but since last decade there is emergence of Non-*albicans Candida*. Non-*albicans Candida* is more resistant to azoles antifungal drugs, hence rapid diagnosis followed by appropriate management may reduce the severity and morbidity of fungal infections in these patients.

Materials and methods

Newly diagnosed patients with loco-regionally advanced (AJCC stage III and IVA) squamous cell carcinoma of head and neck (oral cavity, oropharynx, hypopharynx, and larynx) who were advised concurrent chemoradiation (CCRT) were evaluated by a multidisciplinary approach, after taking proper consent.

They were subjected to pre-treatment evaluation consisting of complete medical and dental history, loco-regional and systemic examination along with routine blood counts, chest X-ray, and computed tomography/magnetic resonance imaging (CT/MRI) as indicated investigations to define the extent of disease. The patients with other risk factors for fungal infection such as diabetes, corticosteroids, recent use of antibiotics, intraoral prostheses and those having received antifungal therapy were excluded from the study. All patients in the study were instructed regarding maintenance of oro-dental hygiene.

A total of 50 patients were enrolled in the study. One patient expired after completion of the treatment, so data from 49 patients were evaluated.

Patients were treated with cobalt 60 teletherapy by conventional fractionated schedule concurrent with 3 weekly cisplatin (100 mg/m2) IV 2 h infusions which was repeated for 3 cycles according to the standard treatment protocols. Samples from throat, urine and blood were taken before treatment (zero week), during 2nd, 6th week of CCRT and 4 weeks after the completion of CCRT. Definitive diagnosis of oral candidiasis was done using following criteria [7,8]

i) Clinical presumptive diagnosis of candidiasis (criteria – I)
ii) Positive Direct microscopic observation of budding yeast cells in the direct smear and *Candida* species in culture from throat. (criteria – II)

Invasive candidiasis was diagnosed when *Candida* species was isolated in blood. *Candida* isolation in throat and urine depicted colonization. Isolation of yeasts of the genus *Candida* in urine may be due to microbiota from areas surrounding the urinary tract. Therefore culture was considered significant only if yeast was seen in direct microscopy and it correlated with clinical findings.

At each visit, throat, urine and blood samples were taken from each patient. Throat samples were collected by plain cotton swabs from the exudates in the throat. Urine samples were collected using midstream clean catch method. These samples were inoculated on to the duplicate set of Saboraud's Dextrose Agar (SDA) by a standardized technique and were incubated at 37 and 30 degree Celsius respectively for 21 days. Blood samples were inoculated in Biphasic Heart Infusion, incubated at 37 degree Celsius and were processed as per standard methods for culture and identification of fungi. *Candida* species and other yeasts were identified using Germ Tube Test, Hichrome Agar, Corn Meal Agar and Carbon and Nitrogen Assimilation tests. Antifungal susceptibility of *Candida* isolates was done by E-test in the department of Microbiology against these drugs – Amphotericin B, fluconazole and voriconazole. The results were evaluated according to CLSI guidelines, 2012.

In all cases, patient were evaluated weekly for response of tumour and toxicities [The Response Evaluation Criteria in Solid Tumours (RECIST) Criteria and Common Terminology Criteria for Adverse Effects (CTCAE) version 4.0]. After completion of treatment, evaluation was done immediately after 1 month (during last sampling) and after 6 weeks of completion of radiotherapy (for response assessment). Clinical examination, ENT examination with CT/MRI of head and neck were done 6 weeks after the completion of treatment.

Results

In the present study, out of 50 patients, data of 49 patients was assessed. Most of them presented with stage IVa (locoregionally advanced) disease. The median age of the patients in our study was 51 years (range 23–65 years).

Spectrum of fungal species

Out of the 49 throat swabs, urine and blood processed for fungal culture, 27 throat swabs and 5 urine culture revealed 10^5 (significant) colonization with *Candida* species. None of the patients had blood culture positive for fungus. In throat swab culture for fungus, the spectrum of fungal species observed was: Non-*albicans Candida* in 18/49 (36.73%) and *Candida albicans* in 9/49 (18.36%) of patients. The Non-*albicans Candida* included *Candida parapsilosis* in 8/49, *Candida tropicalis* in 5/49, *Candida krusei* in 2/49, *Candida guilliermondii* in 2/49 and *Candida glabrata* 1/49 of patients. [Table 1]

Antifungal susceptibility

The fungal isolates of most of the patients (66.66%) were sensitive to fluconazole, while resistance was observed in 33.33% cases (P = 0.271). All isolates of *Candida albicans* were sensitive to amphotericin B and voriconazole, whereas three isolates were resistant to fluconazole finally. All isolates of *Candida parapsilosis* showed sensitivity to amphotericin B, voriconazole and fluconazole. All isolates of *Candida tropicalis* were found sensitive to amphotericin B, voriconazole while one isolate was resistant to fluconazole finally. All isolates of *Candida krusei, Candida glabrata,* and *Candida guilliermondii* showed sensitivity to amphotericin B and voriconazole but were resistant to fluconazole. [Table 1]

Statistically significant association was observed between fungal species and fluconazole sensitivity (P = 0.006).

Week of colonization

In our study, 6 patients had positive fungal culture in the pre-radiotherapy period. A quantitative rise in oral and urine fungi (yeasts) was found during the course of radiotherapy with peak being in 6th week which persisted during post treatment follow-up of 1 month. [Table 2]

Incidence of oral mucositis

Severity of oral mucositis was observed and correlated with fungal colonization. Grade I oral mucositis was seen in 12.24% cases. Grade II mucositis was seen with highest incidence of

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