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EVALUATION OF CANDIDIASIS AND ITS SUSCEPTIBILITY PATTERN IN PATIENTS UNDERGOING RADIOTHERAPY AND CHEMOTHERAPY

Microbiology

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ABSTRACT

Background: Radiotherapy & chemotherapy, which lead to immunosuppression, act as favourable conditions for *Candida* to develop as pathogen.
Materials & Methods: We included 120 cases treated either with radiotherapy or chemotherapy after taking consent. Samples from tongue were collected with a sterile cotton swab and processed according to standard protocol. *Candida* species identification was done by germ tube test, Chrome agar media (HI media) and Corn meal agar. Antifungal susceptibility was done by disc diffusion method for Amphotericin B, Nystatin, Voriconazole, Fluconazole and Itraconazole.
Result: Out of 120 cases, 100 cases yielded positive for candidiasis. Out of 100 positive cases, 46% were presented with oral carcinoma, 11% presented with gastrointestinal carcinoma, 8% with breast carcinoma, 20% with other carcinoma and 15% with non-malignant cases. 86% patients were treated with radiotherapy and 14% with chemotherapy. Total 84 isolates were identified by both Chrome agar and Corn meal agar. Fungal isolates were *Candida albicans* (28%), *Candida tropicalis* (25%), *Candida parapsilosis* (11%), *Candida glabrata* (15%), *Candida krusei* (5%) and 16% unidentified *Candida* species. Nystatin and Amphotericin B were the most effective antifungal drugs. However, all *Candida krusei* were resistant against both of these drugs. Fluconazole was not much effective except *Candida tropicalis* which showed 60% sensitive. All *Candida albicans* & *Candida tropicalis* were resistant to voriconazole while all *Candida parapsilosis*, *Candida glabrata* & *Candida krusei* were resistant to itraconazole.
Conclusion: Non-albicans Candida are getting increased over *Candida albicans*. Only Chrome agar or Corn meal agar is not sufficient for species identification. Some other methods like sugar assimilation tests or molecular tests should be used. Not only fluconazole or itraconazole, even Amphotericin B, Nystatin and Voriconazole are showing marked resistance, so antifungal susceptibility test is necessary for target therapy to achieve better outcome.

KEYWORDS

radiotherapy, chemotherapy, Chrome agar, antifungal susceptibility test

INTRODUCTION

Candida species are commensals in human body which may be isolated up to one third mouth of normal individuals [1]. In normal individuals, immune systems are effective enough to control virulence and pathogenicity of *Candida*. But there are certain predisposing factors which favour growth of *Candida* to make insult of human health. These factors are like-salivary gland dysfunction, use of antibiotics and corticosteroids, denture, excessive tobacco use, changes in hormonal status, malignancy and immune suppression due to different causes [2].

In recent years, newer developed therapy methods for malignancy like radiotherapy and chemotherapy improved survival rates. But, at the same time, these methods also create favourable environment which support growth of *Candida* resulting in symptomatic candidiasis. Radiation induces hyposalivation due to destruction of salivary gland cells leading to xerostomia and mucosal ulceration [3]. Cytotoxic chemotherapy acts on basal cells of buccal epithelium, inhibit cell replication and cause cell lysis. This causes thinning and atrophy of buccal epithelium mucosal ulceration which favours growth of bacteria and fungi. Chemotherapy also acts as bone marrow suppressant leading to neutropenia, another favourable condition for candidiasis [4, 5]. The oral candida colonisation increases up to 93% and 75% in patients of oral cancer undergoing radiotherapy and chemotherapy respectively [4].

Oral candidiasis presents through a number of symptoms like pseudomembranous candidiasis (thrush), erythematous candidiasis, angular cheilitis, chronic hyperplastic candidiasis. The first two symptoms are the most common forms of intraoral candidiasis reported in oncology patients [3]. Recently, Chromogenic media are developed for rapid identification on the basis of different colours produced on these media [6]. Various *Candida species* are isolated as causative agents like *Candida albicans*, *Candida glabrata, Candida tropicalis, Candida krusei, Candida parapsilosis, Candida guillermondii, Candida kefyr and Candida dubliniensis* [1]. *Candida albicans* is the most predominant isolate (80%) due to more pathogenicity like secretion of phospholipases and proteases, including aspartyl proteases or phenotypic switching [7]. In recent two decades, non albicans Candida isolates are increasing in tendency due to different factors like immune-suppressants, prolonged use of broad-spectrum antibiotics and antifungal drugs [8].

Fluconazole is used as a predominant drug for oropharyngeal candidiasis. But in recent years, fluconazole resistant strains are increasing in *Candida albicans* [9]. Besides this, due to widespread use of fluconazole, fluconazole resistant species like *Candida tropicalis*, *Candida krusei*, and *Candida glabrata* are rising in numbers. These species are four to 32 times less susceptible to fluconazole than *C. albicans* [10]. So, early speciation and anti-fungal susceptibility should be done for effective treatment.

This study is aiming to compare between Chrome agar & Corn meal agar for isolation, fungal profile of patients treated with radiotherapy/chemotherapy and susceptible pattern to different drugs.

MATERIALS & METHOD

The study was conducted in Department of Microbiology, G S V Medical College & J K Cancer Institute, Kanpur from July 2011 to September 2011. A total 120 patients, treated either with radiotherapy or chemotherapy and with oral thrush, were enrolled in the study after taking consent. Samples from tongue were collected with a sterile cotton swab and processed according to standard protocol. Sabouraud's dextrose agar (SDA) with & without chloramphenicol

(Himedia), Cornmeal agar (CMA) with Tween 80 (Himedia) and Chrome agar media (Himedia) were used for culture samples. SDA with and without chloramphenicol, corn Meal agar with Tween 80 were prepared in laboratory according to manufacturer's instructions but preformed Chrome agar was used. Oral swabs collected from all the patients first were cultured on SDA with or without chloramphenicol and incubated at 37°C for 24-48 hours. Organism were identified using conventional methods that included colony morphology in SDA with and without chloramphenicol, Gram stain, Germ tube test [11], Cornmeal agar with Tween-80 inoculation [12], CHROM agar inoculation.

Chrome agar method of identification

Pre prepared Chrome agar (Himedia) was used for isolation and direct identification on the basis of colony colour. Samples were inoculated on plate and incubated at 35°C for 24-48 hours. Result was interpreted as per manufacturer's instructions (Table 1).

Table 1: Typical appearance of microorganisms on Chrome agar plates

Organisms	Colour production on Chrome agar
Candida albicans	Light green
Candida tropicalis	Metallic blue
Candida krusei	Violet, fuzzy
Candida glabrata	Creamy white pink
Candida parapsilosis	White

Antifungal susceptibility testing

Mueller-Hinton agar supplemented with 2% glucose and 0.5 µg of Methylene blue per ml at a depth of 4.0 mm with pH value of 5.6 was made in laboratory according to manufacturer's instruction (Himedia). Antifungal discs of Nystatin (50µg), Amphotericin B (100 U), Voriconazole (1µg), Fluconazole (25 µg) and Itraconazole (30µg) were also obtained from Himedia and used for susceptibility testing. A 0.5 McFarland standard of inoculum was prepared by picking 3-5 similar colonies from SDA and inoculating into 5 ml of sterile normal saline. A sterile cotton swab was dipped into the inoculum prepared. Swab was squeezed firmly against the side wall of the tube and streaked smoothly over the entire surface the plate. Antifungal discs were applied and plates were incubated at 37°C for 24-48 hours. *C. albicans* (ATCC90028), and *C. krusei* (ATCC6258), strains were used as Quality controls.

Statistical analysis: Data were expressed in ratio and percentage.

RESULT

Out of 120 cases, 100 cases yielded positive for candidiasis. Out of 100 positive cases, there were 62 males and 38 females (M:F=1.6:1). The maximum affected age group was 41-50 years, it was 33%. 87% patients were from Out-patient door and 13% were from In-patient door. Out of 100 positive cases, 46% were presented with oral carcinoma, 11% presented with gastrointestinal (git) carcinoma, 8% with breast carcinoma, 20% with other carcinoma and 15% with non-malignant cases (Table 2). 86% patients were treated with radiotherapy and 14% with chemotherapy. Patients treated with chemotherapy were- 10 of oral carcinoma, 2 of git carcinoma, 1 of other (right neck) carcinoma and 1 of non-malignant case.

Total 84 isolates were identified by both Chrome agar and Corn meal agar, 83 by Chrome agar and 75 by Corn meal agar (one additional *Candida krusei* identified only by Corn meal agar in patient treated by radiotherapy) (Table 3). *Candida albicans* (28%) followed by Candida tropicalis (25%) were the maximum isolates. Other isolates were *Candida glabrata* (15%), *Candida parapsilosis* (11%), *Candida krusei* (5%) and 16% unidentified *Candida* species (Figure 1).

Candida albicans and *Candida tropicalis* were identified in equal number by both media (28 & 25 respectively). Chrome agar identified 16 *Candida parapsilosis* & 10 *Candida glabrata* while Corn meal agar identified 5 *Candida parapsilosis* & 15 *Candida glabrata*. In fact, five *Candida parapsilosis* of Chrome agar were identified as *Candida glabrata* by Corn meal agar. We assumed the Corn meal agar finding as conclusive result. Four *Candida krusei* were identified by Chrome agar. Two *Candida krusei* were identified by Corn meal agar out of which one was identified only by Corn meal agar. Nystatin and Amphotericin B were the most effective antifungal drugs against all *Candida* species except *C krusei* which was resistant against both drugs. Fluconazole was effective in 60% Candida tropicalis. Other Candida species were not much sensitive to fluconazole. *Candida albicans* & *Candida tropicalis* were resistant to voriconazole and *Candida parapsilosis*, *Candida glabrata* & *Candida krusei* were resistant to itraconazole (Table 4).

Table 2: Showing different variables in patients

Age group(years)	Number
1-10	1
11-20	4
21-30	8
31-40	14
41-50	33
51-60	21
61-70	15
71-80	4
Sex	
Male	62
Female	38
Out-patient/In-patient	
OPD	87
IPD	13
Treatment given	
Radiotherapy	86
Chemotherapy	14
Cases	
Oral carcinoma (buccal mucosa, buccal cavity, tongue, alveolus, vallecula, epiglottis, Salivary gland tumor)	46
GIT carcinoma (oesophageal carcinoma, stomach, duodenum, anal canal, gall bladder, pancreas)	11
Breast Carcinoma	8
Other carcinoma	20
Nonmalignant	15
Symptoms	
Dry mouth	62
Pain in the oral cavity	54
Altered taste sensation	28
Halitosis	26
Dysphagia	18
Redness in the mucosa of oral cavity	68
Identifying media	
Chrome agar	83
Corn meal agar	75

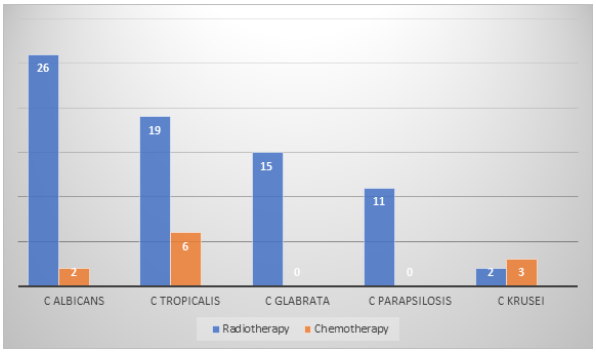
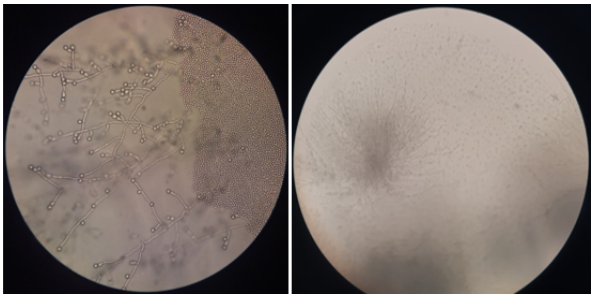


Figure1: Showing fungal isolates in patients



2(a) 2(b)

Figure 2: Showing Corn meal agar findings showing (a) *Candida albicans* (b) *Candida parapsilosis*

Figure 3: Showing growth of different *Candida* species on Chrome agar

Table 3: Comparison of Chrome agar and corn meal agar findings

Isolates	Chrome agar isolates			Corn meal agar isolates		
	RT	CT	Total	RT	CT	Total
C albicans	26	2	28	26	2	28
C tropicalis	19	6	25	19	6	25
C parapsilosis	16	0	16	5	0	5
C glabrata	10	0	10	15	0	15
C krusei	1	3	4	1	1	2
Unknown	14	3	17	20	5	25
Total	**86**	**14**	**100**	**86**	**14**	**100**

Table 4: Antifungal susceptibility profile of *Candida* species

Isolates	Nystatin	Amphotericin B	Voriconazole	Fluconazole	Itraconazole
C albicans	16/28 (57.1%)	24/28 (85.7%)	0	2/28 (7.1%)	3/28 (10.7%)
C tropicalis	22/25 (88%)	6/25 (24%)	0	15/25 (60%)	8/25 (32%)
C parapsilosis	9/11 (81.8%)	9/11 (81.8%)	3/11 (27.2%)	2/11 (18.2%)	0
C glabrata	12/15 (80%)	13/15 (86.7%)	3/15 (20%)	2/15 (13.3%)	0
C krusei	0	0	1/5 (20%)	0	0
Unknown	14/16 (87.5%)	10/16 (62.5%)	7/16 (43.8%)	5/16 (31.3%)	0
Total	73/100	62/100	14/100	26/100	11/100

DISCUSSION

Malignancy and its treatment modalities like radiotherapy & chemotherapy downregulate immunity which favour normal colonisation of Candida to develop as pathogens. Several studies have reported oral yeast colonization and infection ranging from 43% to 90% and 13% to 52%, respectively amongst cancer patients [13]. Some studies reported incidence of oral candidiasis in the range of 7% to 52% in cancer patients on chemotherapy and/or radiotherapy [14].

We included different types of malignant cases treated with either radiotherapy or chemotherapy. We found patients associated with oral carcinoma (46%) maximally followed by git malignancy (11%). This finding is in congruence with Jayachandran AL et al & Afraseyabi et al who also found oral & git carcinoma as more common cases [14, 15]. Most of the patients presented with dryness of mouth followed by pain in the oral cavity (62% & 54% respectively) which was also like Jayachandran AL et al [14]. Radiotherapy and chemotherapy cause dryness of mouth due to hyposalivation or cell lysis. Dryness of mouth results in disruption of mucosal barrier which facilitates infection by *Candida*.

Chromogenic agar is developed for rapid isolation and speciation of Candida species within 48 hours. This medium is easy to make and cost effective as compared to conventional media. Chromogenic agar contains specific enzymatic substrates which are cleaved by enzymes and produce colour. These enzymes are species specific which give presumptive clue for identification [16, 17]. Daef E et al used seminested polymerase chain reaction as a reference test and found very good sensitivity and specificity for *C albicans* (100%, 98.9%), *C tropicalis* (100%, 100%), *C glabrata* (100%, 99%) and *C krusei* (100%, 100%) [17].

In our study, we found very good sensitivity & specificity for *C albicans*, *C tropicalis* & *C parapsilosis*. We also found good specificity for *Candida glabrata* and *Candida krusei* (Table 5). These findings are in congruence with other studies [6, 18]. Five *C parapsilosis* identified by Chrome agar were reported as *C glabrata* by Corn meal agar. There may be possibility of misidentification of *C glabrata* as *C parapsilosis* due to mimicking colour [18]. We found germ tube positive in 27 *C albicans*. This was in agreement with other studies which exemplify that more than 5% of *Candida albicans* isolates may be germ tube test falsely negative and some non-Candida albicans like *C tropicalis* & *C parapsilosis* isolates may be germ tube falsely positive results [16].

Table 5: Showing sensitivity & specificity of Chrome agar against Corn meal agar in comparison with other similar studies

Species	Our study	Bharathi R [6]	Shettar SK et al [18]
C albicans	100%, 100%	100%, 96.4%	97.1%, 98.1%
C tropicalis	100%, 100%	100%, 96.8%	83.3%, 91.9%
C parapsilosis	100%, 88.4%	70.6%, 100%	-
C glabrata	66.7%, 85%	100%, 84.2%	100%, 92%
C krusei	50%, 96.9%	100%, 100%	87.5%, 92.3%

Various studies isolated *Candida albicans* in 70-80% and non-albicans Candida like *Candida glabrata* & *Candida tropicalis* in 5-8% of all patients. But, according to recent literatures, non-albicans Candida are getting increased in number at the cost of *Candida albicans* [19]. Jayachandran AL et al & Yogitha PVV et al isolated non-albicans Candida 54% & 39.5% respectively [14, 20]. Our study was also in agreement with these studies as we isolated 72% non-albicans Candida. Although some studies still reported *Candida albicans* more than 70% which was in contrast to ours study [2, 13, 21]. *Candida tropicalis* or *Candida glabrata* was the most common non-albicans Candida isolate in many studies [2, 14, 20, 22, 23]. We found *Candida tropicalis* as the most common non-albicans Candida. Non-albicans Candida species have clinical implication with tendency to invade systemic circulation. These are also fluconazole resistant or susceptible dose dependent to itraconazole with complex clinical course [3, 24]. In patients treated with radiotherapy or chemotherapy, most of the studies mentioned five isolates as we found [3, 20, 23].

Fluconazole has been used as prophylaxis for long time due to good bioavailability and lesser side effect [21]. So, this practice leaded not only for emergence of non-albicans Candida as pathogen, but also development of fluconazole resistance *Candida albicans*. In our study, we found only 7.1% *Candida albicans* sensitive to fluconazole similar to other study [25]. Other Candida species in our study also didn't show any satisfactory result except *Candida tropicalis* which showed 60% sensitive for fluconazole. There are three pathways to develop infection with drug resistance organism: (i) susceptible organism by the time get mutated and become resistant, (ii) the patient may be colonized or infected with more than one strain or species and an inherently resistant strain or species is selected or, (c) the patient may be colonized or infected with an inherently resistant species. Infectious disease society of America (IDSA) guidelines recommend administration of itraconazole or posaconazole for fluconazole resistance cases with voriconazole and amphotericin B reserved for refractory cases [21]. However, we didn't find any satisfactory result even with itraconazole and voriconazole. Some studies like Silke et al found very good result with fluconazole (87.7%), itraconazole (77.4%) and voriconazole (98.8%) [13]. Yogitha PVV et al found all their Candida species isolate sensitive for itraconazole but resistant to fluconazole [20].

In general, Nystatin & Amphotericin B were the maximal effective drugs in our study, 73% & 62% respectively. But, some studies found all their *Candida species* isolates to be 100% sensitive for these drugs which was in contrast to our study [13, 14, 20]. Although, some studies have decreasing trend of sensitivity to Nystatin [9, 25].

CONCLUSION

Patients treated with either radiotherapy or chemotherapy should frequently be examined for symptoms and signs related to oral candidiasis. For species identification, only Chrome agar or Corn meal agar is not a sufficient medium. Some other identification methods like sugar assimilation tests or molecular tests are necessary as species identification can guide the treatment approach. In our study, non-albicans Candida took the charge over Candida albicans as predominant isolates. Not only fluconazole or itraconazole, even Amphotericin B, Nystatin and Voriconazole are showing marked

resistance, so antifungal susceptibility test should always be done prior to therapy.

Limitations

We didn't take doses of radiotherapy/chemotherapy into account, so we can't correlate the infection with therapy given. We also didn't take samples prior to initiation of therapy, so we can't say that either colonising flora or new Candida species is involved in infection.

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