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Original Research Article

An Observational Assessment of Unusual Oral Candidiasis in a Patient with a Normal Immune System

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Abstract

Aim: Unusual Oral Candidiasis in a Patient with a Normal Immune System.

Materials and Methods: This study was conducted in the Department of Microbiology, Nalanda Medical College and Hospital, Patna, Bihar, India from December 2017 to November 2018. Data such as sex, age, general disease, a use of dentures, complaints of dry mouth, smoking or alcohol consumption, culture results in potato dextrose agar (PDA) and chromogenic agar (CA) medium, and duration of anti- fungal drug administration were collected. The diagnosis of oral candidiasis in this study was made according to the clinical features established in other studies based on clinical tests [1,3,8]. In this study, a total of 180 clinical specimens (2 for every 90 patients) were collected by rubbing the palatal mucosa and tongue of patients with a sterile cotton swab who visited the Oral medicine Department for culture of Candida strains. All specimens were plated on PDA medium and CA medium. CA medium was obtained by purchasing Candida Chromogenic Agar powder, made by the Department of microbiology, according to the manufacturer's instructions, and distributed 20 mL each in a 60 mm× 15 mm petri dish. After smear, the medium was cultured for 48 hours in incubator (IN-20A) at 37°C. On the PDA medium, all colonies were cream-colored, and the colonies' size and margin were varied.

Results: As a result of surveying the number of each disease group and the percentage of all patients, 4 patients with blood and blood forming organs diseases and certain disorders involving the immune mechanism (2.4%), 37 patients with endocrine, nutritional and metabolic diseases (22.0%), 11 patients with mental and behavioural disorders (6.5%), 8 patients with nervous system diseases (4.8%), 2 patients with eye and appendage diseases (1.2%), 9 patients with circulatory system diseases (20.8%), 6 patients respiratory system disease (3.6%), 14 patients with digestive system disease (8.3%), 4 patients with skin and subcutaneous tissue disease (2.4%), 16 patients with musculoskeletal and connective tissue diseases (9.5%), 10 patients with urogenital diseases (6.0%), and 1 patient with pregnancy, childbirth and delivery (0.6%), of which endocrine, nutrition and metabolic dis- eases accounted for the highest proportion.

Conclusion: Patients complaining of dry mouth could not be confirmed using test methods such as saliva secretion. In addition, this study had its own limitations in that it was not possible to perform large sample sizes, candida species identification, and antifungal susceptibility tests.

Keywords: Oral Candidiasis, Immune System,

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Introduction

Oral candidiasis, commonly known as oral thrush, is a fungal infection of the mouth predominantly caused by Candida species, particularly Candida albicans. It typically affects immunocompromised individuals, such as those with HIV/AIDS, cancer patients undergoing chemotherapy, or individuals on prolonged corticosteroid therapy. However, the occurrence of oral candidiasis in immunocompetent patients, while rare, poses significant clinical interest and diagnostic challenges. This introduction explores an unconventional case of oral candidiasis in an immunocompetent patient, emphasizing the need for heightened clinical awareness and a broader diagnostic approach. Oral candidiasis in immunocompetent patients often presents atypically, making diagnosis less straightforward [1-4]. In such individuals, contributing factors might include local oral conditions, such as poor oral

hygiene, use of dentures, or broad-spectrum antibiotic therapy, which disrupts normal oral flora. The manifestation of oral candidiasis in the absence of systemic immunosuppression necessitates a comprehensive evaluation to identify underlying local or systemic predisposing factors. The clinical presentation of oral candidiasis can range from asymptomatic colonization to severe mucosal involvement. Typical manifestations include white, creamy plaques on the oral mucosa, tongue, and oropharynx, which can be easily scraped off, revealing erythematous and sometimes bleeding mucosa underneath. However, in immunocompetent patients, these lesions might present atypically, mimicking other oral pathologies, such as leukoplakia or lichen planus, complicating the diagnostic process. A definitive diagnosis of oral candidiasis is established through clinical examination and microbiological testing, including direct microscopy of scrapings, culture on selective media, and histopathological examination. Molecular methods such as polymerase chain reaction (PCR) and matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry have also enhanced the accuracy of Candida species identification, facilitating targeted antifungal therapy [5-8]. While immunocompromised states are well-known risk factors for oral candidiasis, the pathophysiology in immunocompetent individuals is less understood. Recent studies suggest that localized immunological deficits, disruptions in oral microbiota, and genetic predispositions might contribute to susceptibility. For instance, the use of broad-spectrum antibiotics can significantly reduce commensal bacterial populations, allowing opportunistic fungal overgrowth. Additionally, certain genetic polymorphisms in immune-related genes have been implicated in increased susceptibility to fungal infections. Polymorphisms in the dectin-1 gene, which encodes a pattern recognition receptor involved in antifungal immunity, have been associated with recurrent mucocutaneous candidiasis in otherwise healthy individuals. Such genetic insights underscore the complexity of host-fungal interactions and the need for personalized approaches in managing oral candidiasis. The management of oral candidiasis in immunocompetent patients involves addressing both the infection and any underlying predisposing factors. Antifungal agents, including topical formulations such as nystatin or clotrimazole, and systemic agents like fluconazole or itraconazole, are commonly used. Treatment duration typically spans 7-14 days, depending on the severity and response to therapy [9-13]. In addition to pharmacological interventions, improving oral hygiene, managing local factors like denture use, and minimizing unnecessary antibiotic use are crucial in preventing recurrence. Regular dental check-ups and patient education on maintaining oral health can also play significant roles in mitigating risk factors.

Materials and Methods

This study was conducted in the Department of Microbiology, Nalanda Medical College and Hospital, Patna, Bihar, India from December 2017 to November 2018. Data such as sex, age, general disease, a use of dentures, complaints of dry mouth, smoking or alcohol consumption, culture results in potato dextrose agar (PDA) and chromogenic agar (CA) medium, and duration of anti- fungal drug administration were collected. The diagnosis of oral candidiasis in this study was made according to the clinical features established in other studies based on clinical tests [1,3,8]. In this study, a total of 180 clinical specimens (2 for every 90 patients) were collected by rubbing the palatal mucosa and tongue of patients with a sterile cotton swab who visited the Oral medicine Department for culture of Candida strains. All specimens were plated on PDA medium and CA medium. CA medium was obtained by purchasing Candida Chromogenic Agar powder, made by the Department of microbiology, according to the manufacturer's instructions, and distributed 20 mL each in a 60 mm× 15 mm petri dish. After smear, the medium was cultured for 48 hours in incubator (IN-20A) at 37°C. On the PDA medium, all colonies were cream-colored, and the colonies' size and margin were varied. Colonies in CA medium was confirmed to be cultured by pigmentation as described in the manufacturer's instructions and in Odds and Bernaerts. [9]. In addition, when the number of colonies was observed 5 or less in the PDA medium and CA medium, it was deter- mined as negative. In medical records, sex (male or female); age (<20 years, 20-40 years old, 40-60 years old, >60 years old); presence of systemic disease, presence or absence of dentures (yes or no); presence of dry mouth (yes or no); smoking and alcohol consumption (yes or no); culture results in PDA and CA medium (yes or no); and duration of antifungal treatment (less than 4 weeks, more than 4 weeks to 8 weeks or less, more than 8 weeks to 12 weeks or less, more than 12 weeks to 16 weeks or less) were investigated. When examining the type of systemic disease, all cases with multiple systemic diseases were also investigated. All statistical tests were performed by using Statistical Package for the Social Sciences (SPSS) software, version 22.0 (IBM Corp., Armonk, NY, USA), and the correlation of local factors with the duration of antifungal drug administration was analyzed by using the Mann–Whitney U test and Kruskal–Wallis test at the 5% significance level ($p<0.05$).

Results

As for the male and female ratio, 41 males (45.6%) and 49 females (54.4%) were surveyed, with a large percentage of patients over 60s. Systemic diseases

were not found in 11.9% of patients, and systemic diseases were investigated in the remaining patients based on the 10th revision of the International Classification of Diseases (ICD) (Table 2). As a result of surveying the number of each disease group and the percentage of all patients, 4 patients with blood and blood forming organs diseases and certain disorders involving the immune mechanism (2.4%), 37 patients with endocrine, nutritional and metabolic diseases (22.0%), 11 patients with mental and behavioural disorders (6.5%), 8 patients with nervous system diseases (4.8%), 2 patients with eye and appendage diseases (1.2%), 9 patients with circulatory system diseases (20.8%), 6 patients respiratory system disease (3.6%), 14 patients with digestive system disease (8.3%), 4 patients with skin and subcutaneous tissue disease (2.4%), 16 patients with musculoskeletal and connective tissue diseases (9.5%), 10 patients with urogenital diseases (6.0%), and 1 patient with pregnancy, childbirth and delivery (0.6%), of which endocrine, nutrition and metabolic dis- eases accounted for the highest proportion (Table 1). Also, 25.6% of patients used dentures, 44.4% of patients complained of dry mouth, and 8.9% patients were a smoker or an alcohol consumer (Table 2). As a result of smears by using sterile cotton swabs in the oral cavity of 90 patients with oral candidiasis, 83 had colonies formed on PDA medium (92.2%) and 53 had colonies formed on CA medium (58.9%) (Table 2). For oral candidiasis patients, Diflucan dry syrup 350 mg/35 mL [10 mg/mL] was applied topically in the oral cavity at 50 mg per day for treatment. The duration of drug administration was high between 5 and 8 weeks (Table 2). Statistical analysis was performed by using the Mann– Whitney U test and Kruskal–Wallis at the 5% significance level, which was for local factors of the duration of anti- fungal drug administration. As a result, there was statistical significance between the culture results of CA medium and the duration of antifungal treatment (p=0.012;).

Table 1 Systemic diseases

Code	Systemic diseases	
N/S	Non-specific symptoms and signs	20 (11.9)
I	Certain infectious and parasitic diseases	0
II	Neoplasms	0
III	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	4 (2.4)
IV	Endocrine, nutritional and metabolic diseases	37 (22.0)
V	Mental and behavioural disorders	11 (6.5)
VI	Diseases of the nervous system	8 (4.8)
VII	Diseases of the eye and adnexa	2 (1.2)
VIII	Diseases of the ear and mastoid process	0
IX	Diseases of the circulatory system	9 (20.8)
X	Diseases of the respiratory system	6 (3.6)
XI	Diseases of the digestive system	14 (8.3)
XII	Diseases of the skin and subcutaneous tissue	4 (2.4)
XIII	Diseases of the musculoskeletal system and connective tissue	16 (9.5)
XIV	Diseases of the genitourinary system	10 (6.0)
XV	Pregnancy, childbirth and the puerperium	1 (0.6)

Table 2 Results of investigation by each local factors and statistical analysis

Local factor	n (%)	95% Cl	p-value
Sex			0.140[a]
Female	49 (54.4)	3.45 (2.80-4.10)	
Male	41 (45.6)	4.51 (3.63-5.49)	
Age (y)			0.147[b]
<20	1 (1.1)	13	
20-40	5 (5.6)	2.60 (1.00-5.80)	
40-60	19 (21.1)	3.53 (2.68-4.37)	
>60	65 (72.2)	4.02 (3.34-4.75)	
Denture wearer			0.096[a]
No	67 (74.4)	3.69 (3.03-4.40)	
Yes	23 (25.6)	4.65 (3.61-5.70)	
Complaints of dry mouth			0.240[a]
No	50 (55.6)	4.20 (3.40-4.92)	

Yes	40 (44.4)	3.60 (2.80-4.60)	
Smoking and drinking			0.102[b]
No	56 (62.2)	4.07 (3.36-4.79)	
Only smoking	6 (6.7)	6.33 (5.00-9.00)	
Only drinking	20 (22.2)	3.40 (2.40-4.40)	
Both yes	8 (8.9)	2.50 (1.50-4.00)	
Culture on PDA medium			0.474[a]
No	7 (7.8)	3.29 (1.57-5.57)	
Yes	83 (92.2)	3.99 (3.41-4.66)	
Culture on CA medium			0.012[a]*
No	37 (41.1)	3.16 (2.30-4.14)	
Yes	53 (58.9)	4.47 (3.72-5.15)	
Duration of antifungal treatment (wk)			-
≤4	36 (40.0)	-	
5-8	44 (48.9)	-	
9-12	8 (8.9)	-	
13-16	2 (2.2)	-	

Discussion

Oral candidiasis is usually diagnosed through visual ex- amination of removable white plaque or erythema tissue in the oral cavity, and microscopic examination of a sample of the oral mucosa with characteristic findings. Also, diagnosis of oral candidiasis can be based on clinical and micro-biological test [8]. To reach an accurate diagnosis, it is an essential to make a balance between clinical findings and laboratory data; meanwhile, sometimes antifungal therapy would be initiated to aid the diagnosis process [1]. The prevalence of Candida strains which are part of the oral flora is diverse geographically, but has been reported in several studies to be average 35% [1]. The presence of a fungus simply does not indicate an infection [8]. Also, the incidence rate varies with age and certain predisposing fac- tors [10]. Oral candidiasis affects a large part of the population, especially children and the elderly, and is considered an opportunistic infection that occurs more often in people with weakened immunity [8]. Candida strains are more often isolated from the oral mucosa of women [1], and become more sensitive to external stimuli with aging [11]. In this study, women developed oral candidiasis more frequently than men, but there was no significant difference, and oral candidiasis was more common among women over 60 years of age. A study by Reinhardt et al. [8] also found that women are more often affected by oral candidiasis than men, and women are more likely to be treated for symptoms of oral candidiasis and the incidence rate increases with age. In addition, it is known that older people, especially those who have difficulty in oral hygiene and a use of dentures, have a higher incidence of the disease [2,8,10]. The oral mucosa is likely to be damaged by acquired systemic diseases, and candidiasis is often reported to be as- sociated with systemic diseases (e.g. diabetes mellitus, cardiovascular disease, depression, immune suppression) [12]. However, the relationship between the presence of systemic disease and oral candidiasis is unclear according to literature evidence [8]. Systemic factors such as diabetes mellitus immunosuppression, malignancies, malnutrition, and use of antibiotics, or diseases such as stomatitis, dry mouth, and pemphigus are known to be very susceptible to oral candidiasis [2,8]. In this study, more than 80% of patients diagnosed with oral candidiasis had at least one systemic disease. Among them, it is believed that the endocrine, nutritional and metabolic disease groups show a high proportion, and it is estimated that the presence of systemic conditions such as diabetes mellitus and malnutrition may have been more susceptible to candida infection. Oral candidiasis is said to be particularly common dis-ease in people who wear dentures [8], but the proportion of patients diagnosed with oral candidiasis in this study was 25.6%. According to an epidemiologic study by Gendreau and Loewy [13], the prevalence of denture stomatitis among denture wearers was 15% to 70%. In cases reported by Gendreau and Loewy [13], the incidence of denture stoma- titis is higher in elderly denture wearers and women, and there are etiological factors including poor dental hygiene, continuous use and nighttime use of removable dentures, plaque accumulation, bacteria and yeast contamination. Furthermore, if the denture doesn't fit, it can cause mucosal trauma. All of these factors appear to increase the ability of C. albicans to colonize both the denture and oral mucosa surfaces. Antifungal therapy can eradicate C. albicans contamination and relieve symptoms of stomatitis; however, stomatitis recurs when antifungal therapy is stopped unless the dentures

are kept clean [13]. Denture hygiene is vital for removing nutrients, including exfoliated epithelial cells, which can serve as an essential nitrogen source for yeast growth. In addition, denture cleaning interferes with the maturity of the microorganism environment established un- der the denture. Denture should be stored in an antibacterial solution at night as there may be microorganisms on the porous surface of the denture that cannot be removed by physical cleaning. A variety of solutions are used including alkaline peroxide, alkaline hypochlorite, acids, disinfectants and enzymes [1]. Saliva plays a central role in maintaining oral homeostasis, function and health. The prevalence and consequences of dry mouth are increasing due to the aging, growing population, the effects of some systemic diseases, medications and drugs that reduce saliva production [14]. According to Ohga et al. [15], dry mouth is mainly caused by decreased saliva secretion and is known to be a high-risk factor for oral candidiasis [15,16]. According to Torres et al. [17], the signs and symptoms of dry mouth are closely related to changes in the oral microbial community. A decrease in the stimulated total salivary flow rate (SWS) can alter the oral microflora, thus increasing the risk of oral candidiasis [17]. However, in this study, 44.4% of patients with oral candidiasis complained of dry mouth, but it was difficult to prove the association between dry mouth and oral candidiasis infection. Smoking is a factor that can induce erythematous oral candidiasis. In particular, there is a high risk of developing median rhomboid glossitis. If one quit smoking, Candida infection could disappear without antifungal therapy [1,10]. The components of tobacco smoke can cause chronic inflammation in the oral mucosa, impair innate immune mechanisms against pathogens, and inhibit cell growth through apoptosis mechanisms. The smoking reduces the production of salivary enzymes and immunoglobulins, and affects lymphocyte production, resulting in microscopic im- balance of the oral cavity [18]. According to the Weinstein et al.'s study [19], there is no difference between smokers and non-smoker samples in bacterial composition, but median rhomboid glossitis, chronic hyperplastic candidiasis, and other diseases were associated with smoking [19]. Drinking alcohol is a contributing factor to oral candidiasis, and frequent drinking is considered a risk factor for devel- oping oral candidiasis. C. albicans induces high levels of acetaldehyde production by oxidizing saliva ethanol, which acetaldehyde increases permeability of the oral mucosa. Furthermore, this acetaldehyde affects the oral mucosa, causing atrophic regions on the epithelial surface that lacks extracellular lipids due to alcohol consumption. In addition, a glucose concentration of 18 g/dL, which can be easily obtained from alcohol, promotes the occurrence of oral candidiasis by increasing biofilm formation and C. albicans adhesion [20]. In this study, 8.9% of those who did smoke and drink alcohol were lower, but in Gonçalves et al. [21] and Epstein et al. [22]'s studies, an important association was observed between oral candidiasis and smoking or alcohol consumption. PDA medium can be used for yeast and fungal culture and counting in food and dairy products. Among microorganisms, Aspergillus niger, C. albicans, and Saccharomyces cerevisiae can grow. We could not find any details on the sensitivity or specificity of the PDA medium. However, in an experiment by Madhavan et al. [23], when comparing the results of candida culture in CA medium with candida culture in PDA medium, all 7 species studied (C. albicans, Candida dubliniensis, C. tropicalis, C. glabrata, Candida rugosa, C. krusei and Candida parapsilosis) appeared as cream and found no difference in colony color. Other characteristics, such as colony size, margins, and height, vary by species. These colony characteristics were the same as observed using CA medium [23].

CA medium is a differential culture medium that allows selective isolation of yeast and at the same time identifies colonies of C. albicans, C. tropicalis and C. krusei. It is technically simple and fast, and cost of testing is low com- pared to the conventional methods [24]. More than 95% of clinical seperation of C. albicans, C. tropicalis and C. krusei were correctly identified based on colony morphology and pigmentation in CA medium [24], providing reliable and rapid identification of the most common C. albicans, and presumptive identification of C. tropicalis and C. krusei [25]. In addition, according to the experimental results of Madhavan et al. [23], the sensitivity of the CA medium to identify C. albicans, C. dubliniensis, C. tropicalis, C. glabra- ta, C. rugosa, C. krusei and C. parapsilosis ranged between 25 and 100% at 30ºC, 14% and 100% at 35ºC, 56% and 100% at 37ºC. The specificity of the CA medium was 100% at 30ºC, between 97% and 100% at 35ºC, 92% and 100% at 37ºC [23]. In this study, 92,2% were cultured in PDA medium and 58.9% in CA medium. It shows a statistically significant difference between the culture results of CA medium and the duration of antifungal treatment ($p=0.012$; Table 3). In other words, when colony formation is observed in the CA medium, which is a Candida selective medium, it means that the administration period of the antifungal agent is prolonged. Also, the culture result of the CA medium can be considered when prescribing an antifungal agent.

There are several drugs to treat oral candidiasis. Although Nystatin and Miconazole are the most commonly used topical antifungal agents and are very effective, they take a long time to eradicate the infection. Miconazole is well tolerated, but may interact with other drugs. Therefore, it should

be considered before using the drug. Besides, amphotericin B or clotrimazole is not available in many countries. Nystatin and fluconazole are very effective in treating oral candidiasis. Especially, oral fluconazole use is effective in treating oral candidiasis that does not respond to topical treatment [26]. As a result of the meta-analysis of Lyu et al. [27], nystatin pills were significantly superior to placebo in the treatment of denture stomatitis; however, nystatin sus- pension was not superior to fluconazole in the treatment of oral candidiasis in infants, children, or human immunodeficiency virus/acquired immune deficiency syndrome patients [27]. Fluconazole is an excellent triazole line for the treatment of candida infections including oropharyngeal and esophageal candidiasis, vulvovaginal candidiasis and disseminated candidiasis. It is an oral and parenteral fungicide that inhibits the synthesis of ergosterol in yeast. Extensive clinical studies by Cha and Sobel [28] demonstrate fluconazole's surprising efficacy, favorable pharmacokinetics and a reliable safety profile. In a study by Epstein et al. [29], 10 women and 9 men diagnosed with oral candidiasis used fluconazole (2 mg/mL) aqueous solution three times a day as a topical treatment by rinsing and spitting for 1 week. As a result of this treatment, complete symptoms and clinical relief in 94% of patients was noted, fungal treatment was demonstrated in patients except for only one patient, and no side effects were reported [29]. Fluconazole was also shown to be superior to nystatin suspension in the treatment of pseudomembranous candidiasis in healthy infants [30]. Also, oral rinsing with fluconazole suspensions may be useful in managing dry mouth patients or patients with difficulty swallowing due to oral candidiasis [29]. Hence, in this study, we selected a method of topically applying Diflucan dry syrup 350 mg/35 mL [10 mg/mL] to oral candidiasis patients by rinsing the oral cavity of 50 mg daily for a minimum of 2 weeks to a maximum of 16 weeks.

Conclusion

In this study, objective data to support the diagnosis such as inter-observer or intra-observer reliability were lacking in the diagnosis based on clinical features of oral candidiasis. Patients complaining of dry mouth could not be confirmed using test methods such as saliva secretion. In addition, this study had its own limitations in that it was not possible to perform large sample sizes, candida species identification, and antifungal susceptibility tests. However, CA medium proved to be a valuable method of identifying Candida species even in resource-poor environments, and it was found that the duration of antifungal treatment was also relevant

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