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REVIEW ARTICLE

Oropharyngeal candidiasis in head and neck cancer patients treated with radiation: update 2011

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Abstract
Background Oropharyngeal candidiasis (OPC) is a major cause of morbidity in patients with malignancies. It is a common complication of head and neck radiation therapy and can result in pain, dysgeusia (taste changes), anorexia, malnutrition, and esophageal or systemic dissemination. Clinicians should be aware of current epidemiology, elements of diagnosis, and therapeutic trials guiding the recent recommendations for prophylaxis and management of OPC, a disease often incorrectly perceived as benign.
Methods This review discusses OPC with focus in head and neck cancer patients receiving radiotherapy.
Results Local treatments are recommended as first-line therapy in milder forms of OPC. In the setting of local therapy, products that provide prolonged contact time and are not sucrose sweetened may result in successful prevention and management with low risk of oral/dental complications.
Conclusion Diagnosis and management of OPC is required in head and neck cancer patients treated with radiation. Local therapy is suggested as first-line treatment for OPC, unless severe clinical infection or high risk immune suppression necessitate systemic therapy. The availability of effective locally delivered (topical) medications may provide potential for prophylaxis for carriers of *Candida* species in head and cancer patients during radiation therapy.

Keywords Oropharyngeal candidiasis · Radiotherapy · Head and neck cancer

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Introduction

Candida species are frequently present in the oral flora. Under certain physiological and pathological conditions, the yeast may change status from that of commensal to a pathogen, particularly in patients with malignancies. *Candida albicans* yeast is the main resident commensal flora of the digestive mucosa and the genital area, identified in approximately 10% to 20% of healthy adults, followed by *Candida glabrata* and *Candida tropicalis* [1, 48]. Conversely, *Candida krusei*, *Candida famata*, *Candida lusitaniae*, *Candida guilliermondii*, and *Candida dubliniensis* are rare and transient in the gut. *C. dubliniensis* has been identified in oropharyngeal candidiasis (OPC) in human immunodeficiency virus (HIV) infected patients [9]. *Candida parapsilosis* is classically a commensal of healthy skin, but

not mucous membranes. Among these species, *C. albicans* is responsible for the vast majority of clinical oropharyngeal infections (> 80%), due to specific physiological properties detailed below. *C. glabrata* and *C. tropicalis* may be emerging causes of oropharyngeal infection [37], but their pathogenic role in the absence of co-infection with *C. albicans* remains controversial [9, 23]. Non-albicans species have been identified in head and neck cancer patients [39].

In patients with local or systemic susceptibility, clinical OPC infection may present as painful infection that affects the quality of life and may extend to the esophagus or result in systemic infection. The main clinical forms described are pseudomembranous (thrush), erythematous, and angular cheilitis. Hyperplastic and invasive candidiasis may also occur. In addition to head and neck cancer patients, hematology–oncology patients are frequently the subject of this infection. Contemporary therapeutic guidance for clinicians in managing this infection, however, derives primarily from clinical trials in immune-suppressed patients with HIV infection [2, 15, 30].

Epidemiological issues

OPC is a common disorder of patients during and following radiation therapy. It is preceded by a stage of colonization of the oral mucosa, whose frequency has been estimated between 12% and 96% depending on the series (reviewed in [44]). Recent data on the frequency of OPC in patients with cancer is limited, and the prevalence of OPC is probably underestimated. The reported frequency varies greatly depending on the series, given the disparities in the populations studied and diagnostic criteria [13]. Overall, the prevalence reported is 5–60% in solid tumors, 20–80% in autologous bone marrow transplantation, and 20% in patients infected with HIV since the introduction of highly active antiretroviral therapy [13].

In a recent systematic review of 39 English literature publications between 1989 and 2007, Lalla et al. [25] found that both head and neck radiotherapy and chemotherapy were associated with a significantly increased risk for oral fungal infection. The review revealed that 50% of head and neck cancer patients were colonized with fungi in the oral cavity before the onset of radiation therapy. During radiation therapy, the proportion of patients with oral fungal colonization increased to 74.5%. Interestingly, this increased proportion of patients colonized was largely maintained in the immediate post-radiotherapy period (71.4%). Increased colonization during and after radiation therapy also translated into increased rates of clinical oral fungal infection. For patients receiving head and neck radiotherapy alone, the weighted prevalence of clinical oral fungal infection was 7.5% pre-treatment, 37.4% during treatment, and 32.6% after the end of radiation therapy [25].

Among patients with solid tumors, those with head and neck neoplasms treated with regional radiotherapy [17] have a much higher risk of OPC (see Table 1). In a recent study that included 21 patients with cancer of the upper airway, the proportion of patients colonized by *Candida* in saliva reached 45% in early care, 57% during treatment with surgery/radiotherapy, and 75% at the end of treatment [21]. In this series, 52% of patients developed clinical candidiasis. In another study published in 2008 on 212 patients treated with radiotherapy for head and neck malignancies, the authors reported a similar frequency of OPC (45%) [22]. Tobacco use increases colonization and risk of fungal infection during cancer therapy [43]. In patients with advanced cancer, the occurrence of OPC is associated with poor functional performance score [12, 13]. These findings suggest that vigilance for development of clinical infection is needed, and the prevalence suggests that prophylaxis of infection may be warranted.

The increase in non-*C. albicans* infection in head and neck cancer patients has been reported [41]. In radiation therapy, the widespread use of azole prophylaxis has been accompanied by an increase in oral colonization by non- *C. albicans* strains. Non-*C. albicans* strains account for 22–30% of *Candida* isolates in a series in the 1980s and 45% in the 1990s [20, 45]. In a recent systematic review of patients receiving chemotherapy and/or radiation therapy to the head/neck, 46.2% of patients were colonized in the oral cavity with *C. albicans*, 16.6% with *C. tropicalis*, 5.5% with *C. glabrata*, and 3% with *C. krusei* [25]. The emergence of non-*C. albicans* strains, including *C. glabrata* in oropharyngeal flora (carrier) or in OPC (clinical infection) has also been reported in patients with head and neck malignancies treated by radiotherapy [11, 37, 38]. Mann et

Table 1 Risk factors for oropharyngeal candidiasis (and their management), in head and neck cancer patients

Condition	Management
Oral tumor	Oncological treatment
Comorbidities	
Tobacco use	Cessation
Poor oral hygiene	Oral hygiene instruction
Oral prostheses	Clean prosthesis, no use at night
Medications	
Xerostomic	Modify medications when possible; manage dry mouth
Antibacterial	Fungal prophylaxis; treatment of infection
Immunosuppressive	Modify medications when possible
Myelosuppressive	Modify medications when possible
Hyposalivation	Hydration, sialogogues

al. [28] studied the ecological impact of the use of prophylactic azole antifungal agents (posaconazole, fluconazole, or itraconazole) in patients receiving allogeneic bone marrow transplantation or with acute myeloid leukemia. At the beginning of care, from 34–50% of patients were colonized by yeast. The proportion of *C. glabrata* was increased two- to fourfold when patients were prescribed posaconazole and itraconazole, respectively, and that of *C. krusei* doubled when on fluconazole. The strains of *C. glabrata* isolated from the first sampling multiplied their azole minimum inhibitory concentrations by a factor of 4 at the end of antifungal treatment. Other non-*C. albicans* strains that have been isolated in patients receiving head and neck radiation therapy include *C. tropicalis* and *C. krusei* [3]. Molecular typing of strains has shown a great similarity of isolates collected at the beginning and end of treatment, suggesting prolonged colonization and acquisition of resistance to treatment rather than the acquisition of new resistant strains.

Pathophysiological mechanisms

C. albicans is a commensal organism in the oral flora of a number of healthy subjects [1, 48]. The development of OPC is the result of an imbalance between fungal virulence factors and host defenses. Increased risk of clinical disease is seen in people who smoke tobacco products, in patients with dry mouth and in patients using local or systemic steroid medications and antibiotics. Factors contributing to the increased risk of OPC in head and neck cancer patients receiving radiation therapy (RT) include local mucosal injury second to cancer therapy as well as hyposalivation. Hyposalivation increases the risk of colonization and infection, as does the use of oral prostheses. A number of constituents of saliva provide mucosal defense (reviewed in [14]). Long-term dry mouth (sicca syndrome) can also contribute to persistent increased risk of OPC in this population.

Nonspecific defenses

The epithelial barrier provides a barrier to infection. The flow of saliva across mucosal surfaces may eliminate yeasts and bacteria during swallowing, which may be facilitated by the binding of *C. albicans* to salivary mucins and proteoglycans. The reduction in this flow (due to mucositis, radiation, chemotherapy, or hyposalivation) leads to an increase in salivary yeast colonization as has been shown in Sjogren's syndrome and in patients with head and neck cancer [18, 36] during and following radiation therapy. Salivary antimicrobial factors include lysozyme, lactoferrin, histatins, defensins, and antibodies (secretory immunoglobulin A), which inhibit fungal colonization, including epithelial adhesion. The pH of saliva is also a component of mucosal defense. Acid may induce overexpression of fungal virulence factors such as secreted aspartyl proteinase (SAP) and is therefore an important element of the potential virulence of *Candida*. The resident bacterial flora competes with the yeast for access to nutrients and limits the proliferation of pathogens. Any qualitative or quantitative change in saliva may impact resident bacterial flora and promote the proliferation of yeasts.

Innate immunity

Effector killer cells, macrophages, and Langerhans cells may provide host defense. Macrophages and Langerhans cells in particular ensure the phagocytosis of yeasts and presentation to T cells in the connective tissue. The major effectors of adaptive immunity are T lymphocytes. The oral mucosa and skin contain no B lymphocytes, but are rich in CD8+ and CD4+ T lymphocytes, with CD45RO+ memory phenotype, capable of inducing a protective immune response with cytotoxic TH1 cells.

Fungal virulence factors

Although OPC develops in patients with altered local and general host defense, fungal virulence factors are also necessary for the transition from colonization to infection. The first step is epithelial adhesion, involving protein and glycoprotein adhesins such as mp65 (65 kDa mannoprotein). The second step is fungal replication and tissue invasion, based on the capabilities of filamentation of *C. albicans*, and the secretion of phospholipases and proteases, including aspartyl proteases SAP 1, 2, and 3 expressed specifically in OPC, but not seen during colonization. In the case of limited host defenses, switching of the fungal phenotype may occur (the "switch" is described elsewhere) [42].

A number of factors contribute to the pathological state of transition from commensal yeast to pathogenic parasite in patients with malignancies. Cancer chemotherapy may lead to damage to the mucosal barrier that may result in epithelial atrophy and mucosal ulceration, which may be associated with increased adherence and invasion of *Candida*. Risk of systemic fungal infection is increased in patients with myelosuppression due to malignant disease or cancer therapy and particularly in people with loss of the mucosal barrier. Most myelosuppressed patients receive broad spectrum antibiotic prophylaxis, which may impact the resident bacterial flora and favor the proliferation of yeasts [44]. The quantitative and qualitative salivary changes induced by chemotherapy and regional radiotherapy cause changes in oral microflora and local fungal growth (reviewed in [42]). Oral colonization and OPC may represent risk for systemic candidiasis, and the importance of oropharyngeal

and rectal colonization has been shown to be directly correlated with the risk of invasive candidiasis [27].

Clinical challenges

Clinical forms

Three main clinical forms are described [42], pseudomembranous (thrush), erythematous (atrophic) and cheilitis, which can present affecting the tongue (glossitis), oral cavity (stomatitis), and the labial commissure (cheilitis). The pseudomembranous form (Fig. 1) is the presence of white lesions that can become confluent, resting on an erythematous base (Fig. 2). These lesions can develop in all regions of the oral cavity including the tongue, buccal mucosa, hard and soft palate, and pharyngeal tissue.

The erythematous form (Fig. 3) is characterized by a diffuse erythema of the affected oral mucosa. The mucous membranes may appear dry, red, and glazed. When involving the tongue, it is often present in the mid-dorsum with loss of lingual papillae and erythema and may have a palatal contact lesion ("kissing" lesion). Candidiasis may have variable symptoms: none or minimal complaints, burning sensitivity and pain sensation of dry mouth, odynophagia, dysgeusia (often described as a metallic taste in the mouth), and smell of yeast infection. Angular cheilitis (Fig. 4) may present associated with OPC or independently, although the source of infection at the corners of the mouth is oral colonization. Commissural involvement may present as erythematous, sometimes hyperkeratotic with fissuring, and sensitivity (with pain at the corners of the mouth). Severe cases may result in ulceration and cracking at the corners of the mouth.

The presentation of candidiasis may overlap mucositis making clinical diagnosis of candidiasis challenging. The

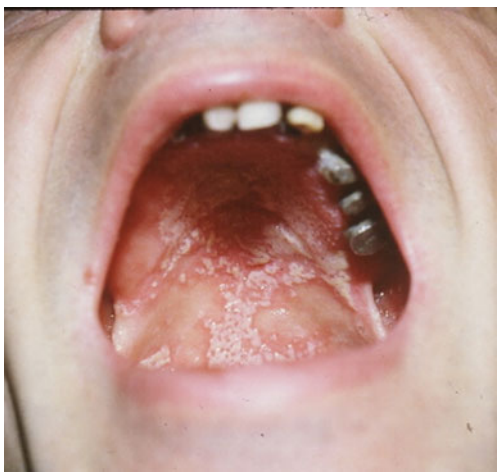

Fig. 1 Pseudomembranous form (thrush)

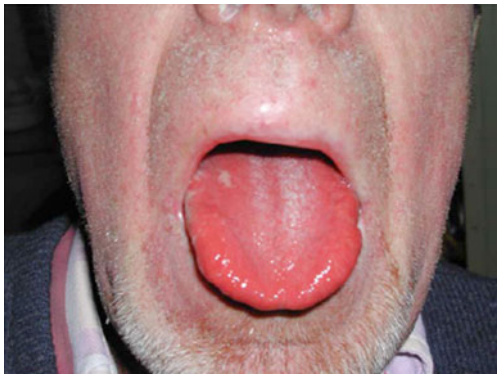

Fig. 2 Pseudomembranous form (humid)

World Health Organization clinical severity scale for oral mucositis is based on the degree of tissue changes, pain and inability to eat solid foods, ranging from 0 (none) to 4 (mucositis so severe that alimentation is impossible) [46]. Similarly, in severe OPC cases, infection can cause severe pain and anorexia that affects the quality of life of patients and may lead to weight loss, altering the overall condition, and complicating the management of these patients. In some cases, differentiation between candidiasis and mucositis can be determined by the presence of angular cheilitis, the presence of erythema outside of the high dose radiation volume and pseudomembranous presentation. Microbiological study including the presence of positive culture or smear is not diagnostic of infection, as they may be positive in colonization; however, mucositis in the absence of *Candida* species does rule out candidiasis.

The differential diagnosis of fungal glossitis includes geographic tongue, herpetic lesions, tobacco keratosis, oral hypersensitivity, denture reaction, and hairy leukoplakia. These lesions occur in very different patients unrelated to

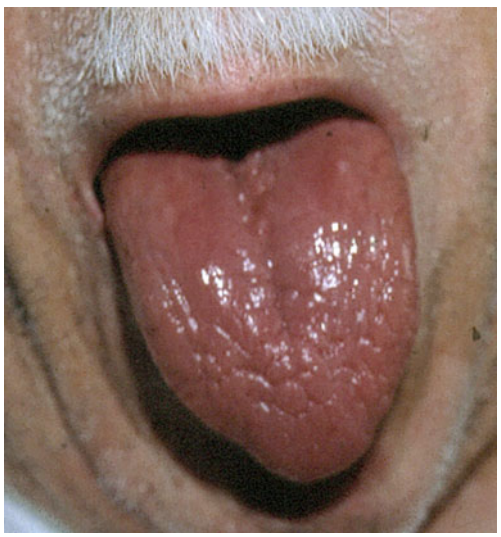

Fig. 3 Erythematous/atrophic form (dry)

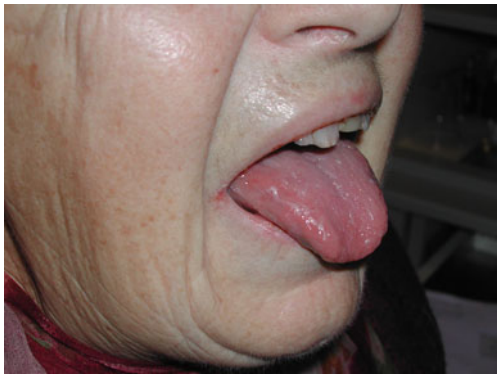

Fig. 4 Angular cheilitis associated with OPC

oncology. The differential diagnosis of angular cheilitis includes iron deficiency, folate deficiency, eczema, herpes, impetigo, lip-licking habit, and syphilis.

Diagnostic tools

The diagnosis of superficial candidiasis may be based upon classical presentation and response to antifungal therapy or may require microbiological sampling of a lesion on a simple swab, which shows budding yeast with pseudofilaments on direct examination. Treatment of the oral smear with potassium hydroxide improves the visibility of the fungal organisms by destroying the human cells. For speciation, culture on Sabouraud medium is positive in 48 h. In general, it is not necessary to determine fungal sensitivity to medications. Increasingly mixed oral *Candida* infections, with a shift to non-*C. albicans* species and resistance to azoles, may make fungal sensitivity determination valuable in the future. In cases of atypical presentation, culture may be required. It should be required also in cases that do not respond to antifungal medications, which may represent resistance to the antifungal treatment (particularly in patients with azole polytreatments), or incorrect diagnosis. In OPC in HIV, "breakpoints" for sensitivity/resistance of different strains of *Candida* to antifungal agents have been shown to be correlated with clinical outcome [40]. Currently, antigenic or serological tests play no role in diagnosis. The differential diagnosis may be difficult during therapy (where oral mucositis is present) and early following radiation therapy (as mucositis resolves), but it is during these times that infection may be associated with increased impact resulting from increased risk of extension of local infection or systemic infection.

Approach to management

Identification of the risk factors (Table 1) for infection should be made, and risk factors managed whenever possible. Management of risk factors is frequently not addressed, and poor response to treatment or rapid recurrence is common. If risk factors are managed, more effective and durable treatment outcomes will be achieved. This includes a review of current medications and modifications of medications that increase infection risk if possible, management of hyposalivation, instructions for denture use and denture hygiene, and ceasing tobacco use.

International guidelines support the following therapeutic principles [8, 31, 47]:

1. Focus as much as possible on local treatment for local pathology.
2. Use molecules with low risk of drug interactions, and low risk of fungal resistance.
3. Non-specific antiseptic solutions are generally ineffective in the treatment of clinical candidiasis.

Local treatments are recommended as first-line therapy in milder forms of candidiasis [4]. Topical agents require intraoral residence time sufficient to interact with organisms and the oral environment. Topical forms of azole or polyene antibiotics may be administered in the form of suspension or cream applied intra-orally. Recommendations for use include maintaining contact time on the mucosa as long as possible (2 min), rinsing, gargling, and swallowing. The agents are nystatin and amphotericin B (Europe) [19], applied five to six times daily. Some products, including oral rinse forms of nystatin, are highly sugar sweetened, leading to increased caries risk, particularly in the patients with hyposalivation [24, 34]. A number of topical azoles are available (Table 2). Topical fluconazole rinses have been examined in cancer patients with candidiasis, and effective outcomes were seen [18]. Topical clotrimazole is available as an oral lozenge and cream. Topical miconazole delivered to the oral cavity in chewing gum has shown effect [47]. Topical miconazole is available in cream form. A new delivery mechanism is the recently developed miconazole muco-adhesive tablet (Loramyc® EU; Oravig® USA), which may have several advantages over other topical agents including once daily application, broad spectrum activity against various strains of *Candida*, and lack of sugar sweetening. A non-inferiority pivotal trial, carried out in Europe and North Africa, assessed the efficacy of miconazole muco-adhesive buccal tablets in oral candidiasis in head and neck cancer patients who had previously received RT. Clinical success was obtained in 56% of cases at day 15 in the Loramyc® group, which received 50 mg miconazole in a single daily application as compared to 52.5% in the miconazole oral gel group, which received a total of 500 mg miconazole over four applications each day. Compliance with Loramyc® use was excellent in this trial, and side effects were minimal [4]. However, this agent is more expensive than other topical agents for OPC.

Table 2 Topical antifungal therapies (indicated for local/regional candidiasis; reduced risk of systemic effects and drug interactions)

Medication	Form	Advantages/disadvantages
Polyenes		
Nystatin	Cream	Low risk of fungal resistance, apply to denture surfaces, corners of the mouth
Nystatin	Suspension	Rinse application, short duration contact time, frequent dosing, highly sucrose sweetened, high caries risk (if dentate), may cause nausea with use
AmphotericinB(EU)	Suspension	Rinse application, short duration contact time, frequent dosing, highly sucrose sweetened, high caries risk (if dentate), may cause nausea with use
Azoles		
Miconazole	MBT	Low risk of fungal resistance, once daily application
Miconazole	Cream	Low risk of fungal resistance, apply to denture surfaces, corners of mouth
Clotrimazole	Lozenge	Low risk of fungal resistance, 5× daily application

MBT mucobuccal tablet

Systemic treatments are typically used in case of failure of local treatment or immediately with severe clinical OPC and in high risk (myelosuppressed, immunocompromised) patients. Systemic therapy is most commonly fluconazole (Triflucan®, Diflucan®), whose effectiveness is widely proven and superior to that of ketoconazole or topical treatments such as nystatin and clotrimazole (reviewed in [7]). The tolerance of fluconazole is excellent; digestive disorders are rare and modest, cytolysis usually mild and infrequent (1–10% depending on the terrain and series). Among the systemically used azoles, fluconazole is the molecule with the fewest drug interactions. The dose recommended in the latest recommendations of the Infectious Diseases Society of America for OPC treatment is 200 mg on day 1 (loading dose) then 100 mg/day for 7–14 days for acute infection [31]. Fluconazole is secreted in saliva following systemic delivery; therefore, an increased effect may be anticipated following systemic delivery in patients without dry mouth and may be enhanced by prescription of sialogogues where saliva secretion is increased following systemic dosing with fluconazole.

Fluconazole can be used for secondary prophylaxis in cases of "severe or frequent" recurrences at a dosage of 50–200 mg/day or 100–400 mg/week, with proven efficacy superior to that of oral polyenes, and increased convenience of use [10, 29, 31, 35]. Daily administration may be more effective than weekly schemes [20]. Recent data also suggest the effectiveness of fluconazole prophylaxis for severe mucositis in patients receiving local radiotherapy for head and neck neoplasms [29]. One concern with widespread fluconazole use is the emergence of fluconazole-resistant fungal species [28]. Other molecules are available due to documented resistance to fluconazole. These include itraconazole (Sporanox®), which has a broader antifungal spectrum but increased gastrointestinal and liver intolerance and a greater risk of drug interactions. The suspension dosage form, taken fasting, is preferred to the capsule form, which is less well-absorbed (capsules should be administered with a fatty meal). Voriconazole and posaconazole have demonstrated efficacy similar to that of fluconazole in esophageal candidiasis in immunocompromised patients and should not be used for treatment of initial or mild cases of OPC. Only in limited situations, such as candidiasis due to *C. krusei* or documented resistance to fluconazole, is use of second-line antifungals warranted. A Cochrane review of prophylaxis of candidiasis has been published [8].

Amphotericin B (Fungizone® EU) and echinocandins (caspofungin, anidulafungin, and micafungin) molecules are also effective, delivered intravenously, and are used in the case of high risk patients with failure of topical and oral agents.

The management of OPC is essential in chemo-radiotherapy patients, particularly those with mucositis, for which specific recommendations are regularly updated. Targeted management of mucositis is based upon pain control, nutritional support, good oral hygiene (soft toothbrush), and regular rinsing of the oral cavity with saline or sodium bicarbonate rinses, correction of oral dryness, bleeding control, cryotherapy, and low level laser therapy [5, 6, 23, 26, 33]. The use of chlorhexidine is not recommended for prevention or treatment of mucositis, but may have value as a broad spectrum antiseptic (including limited antifungal activity) and to assist in microbial control to reduce gingivitis and caries risk [16, 26, 32]. If used in patients with oral mucositis, formulations without alcohol may be preferable.

In conclusion, OPC is a common problem in patients receiving radiation therapy to the head and neck. It can lead to several complications including burning, dysgeusia, aggravation of mucositis, impairment of nutritional intake due to the preceding factors, and also to systemic fungal infection. Prompt diagnosis and management of OPC in these patients is important to prevent these complications and achieve optimal treatment outcomes.

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