



Invasive Fungal Infection of the Tongue in an Immunocompetent Patient Mimicking Squamous Cell Carcinoma

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Abstract

Invasive fungal infection is usually associated with immunocompromised patients, and its occurrence in immunocompetent patients is rare. In this case report, we present a patient who is immunocompetent and without apparent predisposing factors and was diagnosed with an invasive fungal infection from a tongue ulcer. He presented with a chronic ulcer on the tongue following an unintentional bite during a meal. Examination showed an ulcer on the left lateral border of the tongue with a rolled-out margin and indurated border, mimicking a squamous cell carcinoma. Histopathology examination from the biopsy of the tongue ulcer revealed the presence of fungal yeasts, with differential diagnosis of *Candida spp.*, *Histoplasma spp.*, and *Cryptococcus spp.* There were non-necrotizing granulomas that extended deep into the muscle layer. He was treated with oral fluconazole for three months and was advised to stop smoking. He subsequently had a complete resolution of the lesion without any complications.

Keywords: Invasive Fungal Infection; Tongue Ulcer; Immunocompetent; Antifungal Treatment

Introduction

The prevalence of fungal-related diseases is increasing globally with a high annual mortality rate of more than 1.5 million cases, which is comparable to that of tuberculosis and more than three times that of malaria [1]. According to the Invasive Fungal Infections Cooperative Group (IFICG) of the European Organization for Research and Treatment for Cancer (EORTC) and the Mycoses Study Group (MSG) of the National Institute of Allergy and Infectious Diseases (NIAID), a proven invasive fungal infection is defined as the presence of fungal elements in a tissue biopsy that is confirmed by histological examination and/or when the agent is isolated by culture from blood, tissue or cerebrospinal fluid [2]. The risk factors for acquiring invasive fungal infections include

primary or acquired immunodeficiency, cancer, bone marrow or organ transplant, diabetes mellitus, and those on immunosuppressive medications [3]. The occurrence of invasive fungal infection in immunocompetent patients is uncommon and rarely reported. We present a case of invasive fungal infection of the tongue in an immunocompetent patient that mimics a squamous cell carcinoma.

Case Presentation

A 56-year-old man, who is a chronic smoker for 40 years, presented with a non-healing tongue ulcer for four months. The ulcer appeared following an accidental bite on the tongue when eating. The ulcer was painful and gradually increasing in size. He is a police

officer and did not have significant past medical history. However, he had been taking kratom, locally known as ‘air ketum’, every day for the past one year with the false belief that it could prevent diabetes mellitus.

On examination, there was an ulcer at the left lateral border of the tongue measuring 2 x 2 cm (Figure 1).



Figure 1: Ulcer on the left lateral border of tongue with rolled out margin and indurated border.

The ulcer had a distinct rolled-out margin and indurated border. The base of the ulcer appeared erythematous. Oral hygiene was fair with no significant sharp tooth noticed.

Given the appearance of the tongue ulcer, a tongue malignancy was highly suspected. A biopsy of the tongue ulcer was performed under local anaesthesia. The histopathology examination revealed non-necrotizing granulomas formed by collections of epithelioid cells with occasional Langhan giant cells, surrounded by dense mixed inflammatory infiltrates of predominantly lymphocyte and plasma cells (Figure 2). The granulomatous inflammation extended deeply into the muscle layer (Figure 3). Immunohistochemical staining of CD68 expression revealed the epithelioid histiocytes that formed the granulomas (Figure 4). Periodic acid–Schiff staining (PAS) and Grocott–Gömöri methenamine silver stain (GMS) sections revealed numerous spherical to oval-shaped fungal yeasts with occasional single to multiple chain buds, scatteredly seen within the epithelium, ulcerated area, lamina propria, and muscle layer (Figures 5 and 6). Ziehl Neelsen and Warthin Starry staining were negative. These histopathology features were suggestive of non-necrotizing granulomatous inflammation as a result of inva-

sive fungal infections. The differential diagnosis included invasive candidiasis, histoplasmosis, and cryptococcosis. The patient was contacted and advised to undergo a repeat biopsy as the tissue sample taken in the previous biopsy was inadequate for a fungal culture and sensitivity test, but he refused.

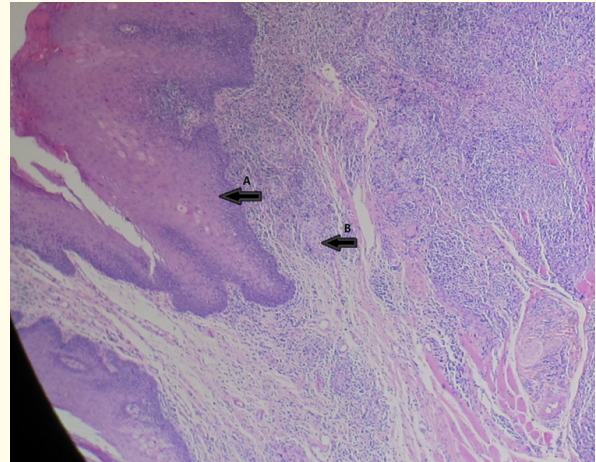


Figure 2: Haematoxylin and eosin (H&E) staining shows mucosal tissue surfaced by parakeratinized stratified squamous epithelium (arrow A), with numerous non-necrotizing granuloma formations beneath (arrow B) (Magnification power 4x).

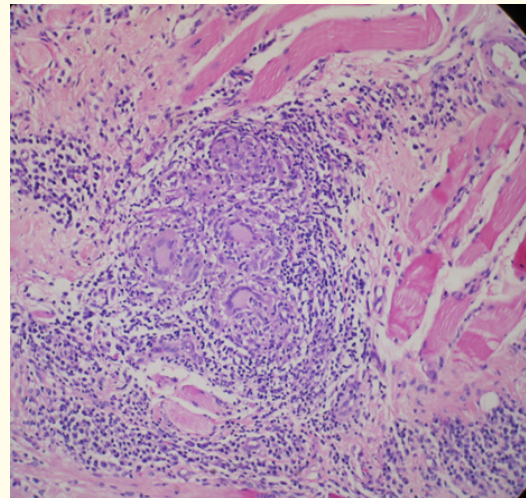


Figure 3: Haematoxylin and eosin (H&E) staining shows granulomatous inflammation extending deeply into the muscle layer (Magnification power 20x).

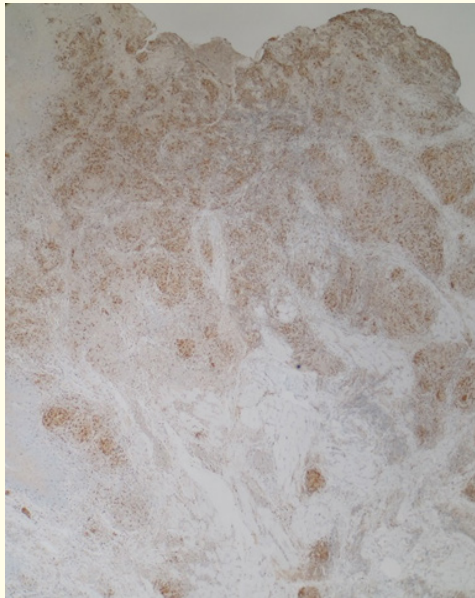


Figure 4: Immunohistochemistry of CD68 expression highlights the epithelioid histiocytes that form the granulomas (Magnification power 4x).

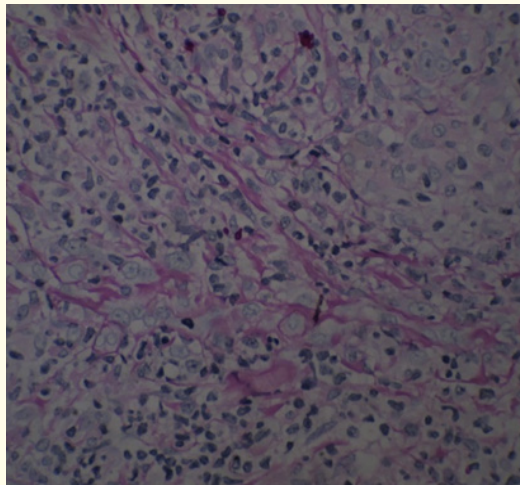


Figure 5: PAS staining shows fungal yeasts with occasional single to multiple chain buds (Magnification power 60x).

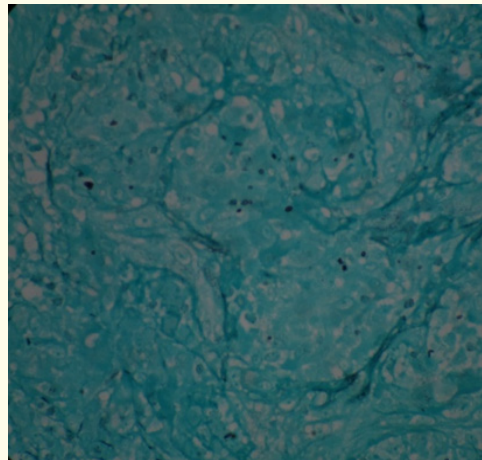


Figure 6: GMS staining shows fungal yeasts with occasional single to multiple chain buds (Magnification power 60x).

Infectious screenings including human immunodeficiency virus (HIV) serology, were negative. His full blood count, renal profile, and liver function tests were all within normal range. He was seen by the infectious disease team and was started on oral fluconazole 200 mg daily. The tongue lesion showed a favourable response to the treatment during outpatient review at two weeks, hence the oral fluconazole was continued. The tongue ulcer showed complete resolution at three months follow-up without other systemic manifestation of fungal infection.

Discussion

The most common pathogen in an invasive fungal infection is *Candida albicans*, followed by *Cryptococcus neoformans*, *Aspergillus fumigatus*, *Histoplasma capsulatum* and *Pneumocystis* species [3]. To cause invasive disease, fungus must grow at human body temperature, breach host tissue barriers, digest and absorb tissues, and defeat the host’s immune system [1].

Patients with an invasive fungal infection might present with a wide range of symptoms, depending on the organ system involved. Oral fungal infection commonly presents as oral soreness, burning pain, non-healing ulcer, parageusia and an aversion to eating [4]. Presentation varies with different fungal organism. Invasive aspergillosis in oral cavity frequently manifests as a painful necrotic lesion that is coated with a yellow slough. Oral histoplasmosis presents with vegetative, granulomatous, or plaque-like lesions. Ulcerations with induration, nodules or granuloma formation can be manifestations of oral cryptococcosis [4]. Oral candidiasis is classified into pseudomembranous, erythematous, and hyperplastic forms. Pseudomembranous candidiasis commonly presents as white or yellow scrapable plaques on the oral mucosa; the erythematous type frequently involves the palate and dorsum of the tongue and usually present as atrophied areas of the oral mucosa; chronic hyperplastic candidiasis presents as a white plaque on the commissural region which cannot be scraped off [4].

While invasive fungal infections are usually associated with patients who are immunosuppressed, they should be considered as a differential diagnosis in cases of non-healing ulcers, even in an

immunocompetent patient. While the exact cause of invasiveness in immunocompetent hosts is undetermined, it may result from an undetected or subclinical qualitative cellular or subcellular immunodeficiency [5]. Innate immunity of the host has a major role in controlling fungal infections. Innate immune cells such as macrophages, neutrophils, and dendritic cells contain pattern recognition receptors (PRRs), which recognise a number of pathogen-associated molecular patterns (PAMPs), such as the fungal cell wall β -1,3-glucan. They phagocytose, generate inflammatory cytokine compounds, and activate further immune cells to ward off fungal infection [6]. The mechanisms of infection in immunocompetent hosts can be explained by fungal evasion of the host immune mechanism through several ways. For instance, when *Candida albicans* forms hyphal structures, β -glucans are hidden by their surface mannoproteins and are not detectable by Dectin-1, thus shielding them from the immune system, whereas *Aspergillus* hinders host detection by secreting proteases that break down complements and their receptor CR3 [6].

The patient in this case report was a chronic smoker. Smoking alters the immune system through several avenues. In addition to reducing circulating immunoglobulin, T-cell and neutrophil activity, and the suppression of inflammatory cytokines, cigarette smoking also reduces the interferon response [7]. A systematic review and meta-analysis identified an increased risk of invasive fungal diseases (IFD) among smokers compared to non-smokers, and the risk of IFD was higher for invasive dimorphic fungal disease than for other IFD [7]. In the present literature, there is no study on the synergistic effect of cigarette smoking and kratom abuse, and hence, their association with an IFD in an immunocompetent patient is unknown. Neither studies nor case reports exist that relate kratom use to invasive fungal infection or weakening of the immune system.

There are a few differential diagnoses for chronic solitary tongue ulcer, which include squamous cell carcinoma, ulcer caused by cytomegalovirus, syphilis (chancre), tuberculous ulcer, eosinophilic ulcer, and invasive fungal ulcer [8]. A timely diagnosis of invasive fungal infection is of the utmost importance due to its high morbidity and mortality. To establish a diagnosis of invasive fungal infection, a positive microbiological culture from body fluid and/or a positive histopathological finding from a tissue biopsy is necessary [9]. Special stains for fungi such as Gomori's methenamine silver (GMS) and periodic acid-Schiff (PAS) stains are used to assess the morphology of a fungus [9]. Another diagnostic technique with excellent sensitivity and specificity is serological testing utilising a 1,3- β -d-glucan (BDG) assay, such as the Fungitell Assay [3], while

advancement in fungal polymerase chain reaction (PCR) test identifies antifungal drug resistance and cryptic/non-culturable species [3].

Treatment should be started promptly once the diagnosis of invasive fungal infection is established and should be targeted to the specific fungal species isolated from a tissue culture. However, the shortfall in the investigation of this case is the lack of a fungal culture and sensitivity test due to patient's refusal for a second tissue biopsy. Based on the histopathological fungal morphology, three possible fungal species were listed: *Candida* spp., *Histoplasma* spp., and *Cryptococcus* spp., and thereafter fluconazole was prescribed to him. Fluconazole is an FDA-approved drug to treat oropharyngeal and oesophageal candidiasis, as well as systemic *Candida* infections and cryptococcal meningitis [10]. Non-FDA-approved uses for fluconazole include blastomycosis, histoplasmosis, and coccidioidomycosis [10]. Fluconazole exhibits good microbiologic action against species of *Candida* and *Cryptococcus*, as well as moderate therapeutic efficacy against *Histoplasma*, hence providing coverage for all the differential fungal pathogens listed in the histopathological examination in this case.

Conclusion

The current case report highlighted the importance of considering invasive fungal infection as a differential diagnosis in immunocompetent individuals presenting with a non-healing tongue ulcer. Timely investigations and treatments can improve the outcome and avoid the devastating impact of invasive fungal infections.

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