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CASE REPORT

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Invasive oral aspergillosis in a patient with acute myeloid leukaemia

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ABSTRACT

Aspergillosis (a fungal infection by an organism of the *Aspergillus* species) of the oral cavity is an uncommon condition which most frequently occurs in immunocompromised patients, such as those with haematological malignancies. In such patients, prolonged neutropenia secondary to chemotherapeutic agents enables the spread of invasive aspergillosis, which is unaffected by anatomical barriers. Early detection and treatment of the condition is essential to avoid more serious complications, such as disseminated infection, which results in increased morbidity and mortality. This case report describes a patient with acute myeloid leukaemia who developed localized invasive *Aspergillus* flavus of the palate. High-dose antifungal therapy was instituted along with surgical removal of the involved tissues. Aspergillosis of the palate was successfully eradicated with no long-term ill effects from the treatment. Management of invasive aspergillosis includes early aggressive antifungal medication combined with surgical removal of the involved tissues.

Keywords: *Aspergillosis,* invasive, leukaemia, oral.

Abbreviations and acronyms: AML = acute myeloid leukaemia; CT = computed tomography; PAS = periodic acid-Schiff.

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INTRODUCTION

Aspergillus species (sp.) are a collection of around 200 soil-dwelling, airborne mould fungi that are ubiquitous throughout nature. They are commonplace among households and some species have important medical and commercial uses (Table 1). Only a small number of strains are pathogenic and cause disease in humans and animals. The most common of these are *Aspergillus* fumigatus and *Aspergillus* flavus.[1] In the hospital setting, construction activities, rotten leaves, or insufficient cleaning from dust can increase the risk of developing aspergillosis.[2] The fungal infection is contracted through spores that commonly colonize the upper and lower respiratory tracts causing rhinosinusitis and pulmonary infections. From here, the fungus may spread to the skin, orbits, nose and palate. However, primary invasive aspergillosis of the oral cavity is uncommon and only a few cases have been reported.[1,3–9]

Opportunistic fungal infection by *Aspergillus* sp. most often occurs in patients with haematological malignancies. Other at-risk patients include those receiving bone marrow or organ transplantation; chronic steroid users; or those with acquired immune deficiency syndrome; aplastic anaemia; chronic granulamatous diseases and burn victims. Once established, the fungus invades tissues rapidly, causing disseminated disease. Aspergillosis infection is associated with a high mortality rate in immunocompromised patients. Autopsies have revealed pulmonary aspergillosis in as many as 40% of patients who had died from acute leukaemia.[1] In a meta-analysis of 1941 cases, the overall fatality rate from invasive aspergillosis was found to be 58% (Table 2).[10] This highlights the mortality associated with aspergillosis and the fact that early diagnosis and treatment is necessary to enable survival.

Invasive oral aspergillosis usually occurs in the palate or tongue as a painful necrotic lesion which is not raised and has a yellow or grey slough.[11] Once inoculation of oral epithelium occurs, *Aspergillus* hyphae can invade host tissues through the release of toxins. These include various proteases, phospholipases, haemolysin, gliotoxin, aflatoxin, phthioic acid and other toxins.[12] Aspergillus spreads into blood vessel walls, resulting in secondary thrombosis and haemorrhage, leading to tissue necrosis and rapid systemic involvement.[13]

Table 1. List of common *Aspergillus* species, their distribution and uses

Species	Distribution and commercial usage
A. clavatus	Soil, animal manure
A. flavus	Carbohydrate-rich foods, mildew, damp carpets
A. fumigatus	Soil, compost
A. nidulans	Eurkaryotic research
A. niger	Carbohydrate-rich foods, fruit, vegetables Production of citric acid
A. oryzae	Fermentation of soybeans for soy sauce Fermentation of rice and potatoes to produce alcohol
A. terreus	Production of organic acids Production of cholesterol-lowering drugs

This article reports a case of invasive aspergillosis in the maxilla that was successfully treated at Waikato Hospital, Hamilton, New Zealand. This tertiary-base hospital, with 600 beds, offers specialist diagnostic treatment services to the whole of the Midland region – a population of 700 000 people.

CASE REPORT

A 64-year-old male patient was admitted to Waikato Hospital with a febrile neutropenia and a current diagnosis of acute myeloid leukaemia (AML). He had just completed his first cycle of cytarabine chemotherapy one day prior to his admission. The patient was pancytopenic with marked anaemia and thrombocytopenia (haemoglobin 75 g/L, white blood cells 1.4×10^9/L, platelets 19×10^9/L) (Table 3). No obvious cause for sepsis could be identified and the patient was immediately commenced on antimicrobial therapy consisting of amoxicillin and clavulanic acid, ciprofloxacin and oral fluconazole.

A referral was made to the Maxillofacial and Dental Department as the patient had complained of a painful mouth. On examination, a diffuse non-fluctuant swelling of the right cheek was noted but there was no palpable lymphadenopathy. Intraorally, there was a grey discolouration of the palatal gingivae associated with a periodontally compromised upper right second premolar and first and second molars. The initial diagnosis was periodontitis due to infection from bacterial pathogens. A decision was made to extract the teeth once the patient's haematological status had improved. Regular chlorhexidine mouthrinses and intravenous metronidazole were added to the antimicrobial regime. Despite parenteral therapy, fever persisted and teicoplanin, meropenem and aciclovir were added one week later. In addition, fluconazole was replaced by intravenous caspofungin (Table 4). Blood and urine cultures were negative for bacteria and fungi.

Table 3. Normal reference ranges for blood counts

Test	Reference Range	Units
Haemoglobin	130–175	g/L
White blood cells	4.0–11.0	$\times 10^9$/L
Platelets	150–400	$\times 10^9$/L

Three weeks later the patient's neutropenia had improved (haemoglobin 88 g/L, white blood cells 15.2×10^9/L, platelets 384×10^9/L) and he attended for extraction of the involved teeth. The cellulitis of the cheek had resolved but the intraoral lesion had increased markedly in size. On examination, a yellow/brown, painful necrotic wound measuring 3×2 cm was present on the palatal gingiva (Fig 1). This necrotic tissue was well demarcated from the surrounding soft tissues and there was minimal swelling associated with it.

An incisional biopsy was performed and the tissue sent for analysis. Histopathological examination with H & E stain revealed a characteristic appearance of septate hyphae typical for *Aspergillus* (Fig 2). Cultures on Sabouraud's dextrose agar yielded a fungus, which was identified as *Aspergillus* flavus based on the morphological characteristics of the colonies.

A computed tomography (CT) scan revealed abnormal soft tissue extending from the anterior aspect of the right lateral pterygoid muscle to the maxillary alveolus with no bony erosion. Due to the anatomical extension of the lesion, surgical excision was necessary to ensure clearance.

Table 2. Distribution of patients according to underlying conditions and site of aspergillosis (as determined from patient-level data)[10]

Site of aspergillosis	Underlying condition			Total no. (%)
	Bone marrow transplant	Haematological malignancy	AIDS or HIV infection	
Lungs	26	124	40	190 (56.9)
Sinuses	5	9	2	16 (4.8)
Upper airway	0	0	1	1 (0.3)
Multisite	9	3	4	16 (4.8)
Disseminated or CNS	48	56	2	106 (31.7)
Cutaneous or other	2	3	0	5 (1.5)
Total no. (%)	90 (26.9)	195 (58.4)	49 (14.7)	334 (100)

Table 4. Drugs uncommonly encountered in general dental practice

Drug	Class	Action	Notes
Caspofungin	Echinocandin antifungal	Inhibit beta-glucan synthesis disrupting cell wall	Limited resistance demonstrated by *Candida* albicans
Itraconazole	Triazole antifungal	Inhibit ergosterol synthesis disrupting cell wall	Broader spectrum than fluconazole
Voriconazole	Triazole antifungal	Inhibit ergosterol synthesis disrupting cell wall	Broader spectrum than itraconazole
Meropenem	Beta-lactam antibiotic	Inhibit cell wall synthesis	Broad spectrum, resistant to beta-lactamases
Teicoplanin	Glycopeptide antibiotic	Inhibit cell wall synthesis	Effective against gram positive bacteria including methicillin-resistant *Staphylococcus* aureus
Tranexamic acid	Antifibrinolytic	Inhibition of plasminogen activation	Prevent fibrin degradation in formed blood clot

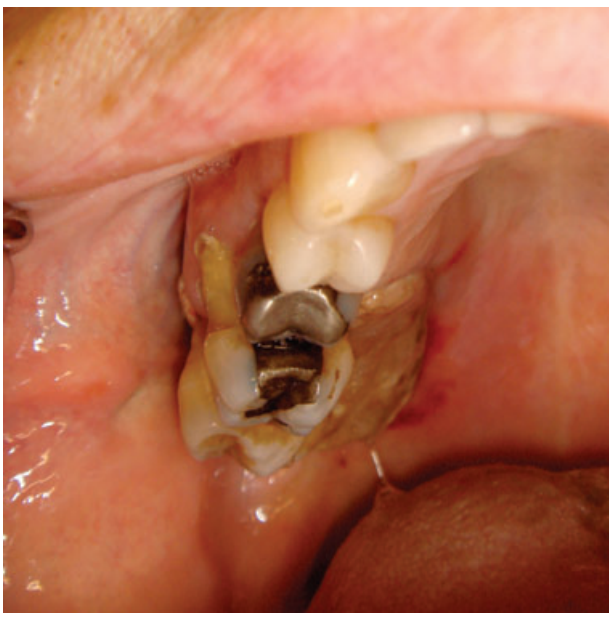

Fig 1. Clinical photograph of the well demarcated, necrotic lesion located on the palatal gingiva.

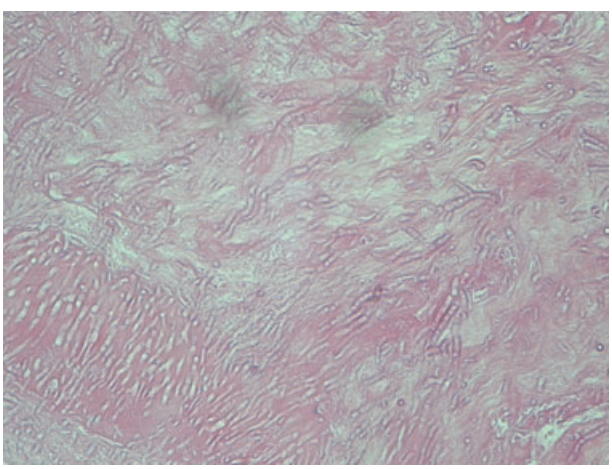

Fig 2. Photomicrograph demonstrating multiple *Aspergillus* flavus hyphae infiltrating connective tissue of the oral mucosa (haematoxylin & eosin).

A right posterior alveolectomy was performed, along with extraction of the involved teeth (15, 16, 17). A section of alveolar bone was removed with the necrotic

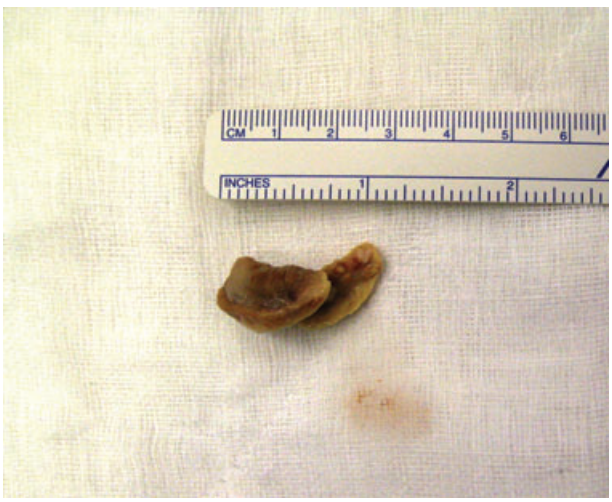

Fig 3. Clinical photograph of the resected right maxillary alveolus with teeth removed.

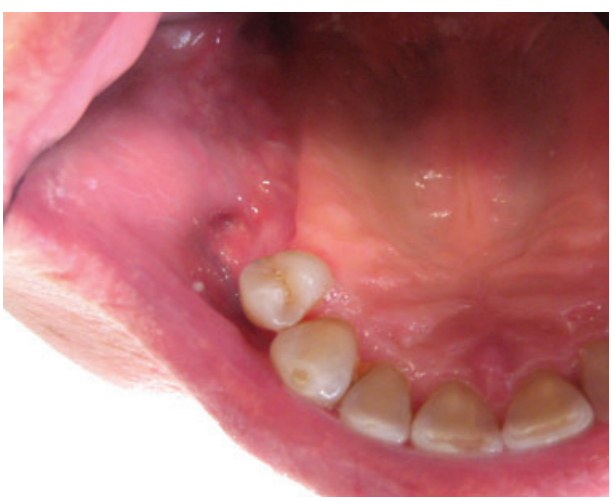

Fig 4. Clinical photograph demonstrating complete mucosal healing at a three-month post-operative review.

gingival tissue attached (Fig 3). The maxillary sinus lining remained intact and a buccal fat pad flap was mobilized to achieve primary closure. Immediately following this, a healing plate was constructed to cover the surgical site.

The patient was started on oral voriconazole, intravenous amphotericin B and nystatin. Eight days later the individual's fever had resolved. The surgical wound healed uneventfully with complete mucosal coverage and no evidence of oro-antral communication (Fig 4). There was no sign of recurrence at a three-month follow-up appointment. Shortly after this review, the patient suffered a relapse in AML. The patient was admitted for a further two rounds of chemotherapy carried out over four months. Despite this neutropenia did not resolve (haemoglobin 72 g/L, white blood cells 1.6×10^9/L, platelets 1×10^9/L). The patient passed away one month later with Staphylococcal septicaemia from a skin infection of the finger.

DISCUSSION

Diagnosis of an *Aspergillus* infection is generally based on tissue culture and histological examination. Clinical findings such as patient response to antifungal treatment may be helpful in diagnosis. Physical examination is an important factor in diagnosis and any unusual appearance of soft tissues in an immunocompromised patient should be suspected for aspergillosis. In particular, the characteristic yellow or grey colour of the gingiva may be an early indicator of disease. Differential diagnoses for an ulcer such as the one presented include bacterial infection (acute necrotizing ulcerative gingivitis), viral infection (herpes simplex), deep fungal infection, tuberculosis, actinomycosis, and malignant infiltration. Other clinical findings suggestive of invasive aspergillosis include fever refractory to broad-spectrum antibiotics and maxillary sinusitis in febrile neutropenic patients. Diagnosis may not be straightforward as it can be complicated by concomitant bacterial, viral, or other fungal infections. Patients with aspergillosis are also likely to have an underlying immune deficiency.

A definitive diagnosis requires biopsy of the lesion to obtain a tissue specimen for culture and histological examination with a periodic acid-Schiff (PAS) stained smear.[11] The histological appearance of aspergillosis in tissue is characterized by hyphae that are 3–8 μm in diameter, septate, and show repeated, dichotomous branching at an angle of about 45°.[1] In order to prevent bleeding in patients with thrombocytopenia, careful suturing of the wound is needed. Use of local haemostatic agents and mouthrinses with tranexamic acid can also be helpful (Table 4).

The initial oral presentation of aspergillosis in a leukaemic patient can be difficult to diagnose. In this case the condition of the periodontal tissues falsely led to the belief that the source of infection was from the gingival sulcus and that periodontal pathogens had colonized the oral cavity during immunosuppression. It was further confused by an improvement in the cellulitis, probably resulting from the broad-spectrum antibiotic therapy (meropenem and teicoplanin), which eradicated the secondary bacterial infection of the lesion. However, it is also possible that the bacterial infection was the primary one. Myoken *et al.* found that invasive aspergillosis of the oral region starts on the marginal gingiva and periodontal disease may partially contribute to the development of the disease.[13]

In the treatment of invasive aspergillosis, surgical excision of the involved tissue has been shown to provide a better outcome than antifungal therapy alone.[3] However, surgery should be carefully considered in the neutropenic patient and is generally not suited for patients with persistently low thrombocyte and neutrophil counts. Therefore, close consultation with the haematology and anaesthetic teams is required to prepare the patient for surgery.

Antifungal treatment should be commenced as soon as possible, as its efficacy depends upon how early in the course of infection the treatment has been instituted.[2] Traditionally, high-dose amphotericin B was considered the treatment of choice for aspergillosis infections.[11] In particular, there is support for its use with the triazole antifungal, itraconazole.[3,14] Maschmeyer and Ruhnke found that initial therapy with voriconazole improved survival with fewer side effects compared with the standard approach of initial therapy with amphotericin B[2]. Caspofungin in combination with amphotericin B or an azole has been recommended in refractory cases where front line antifungals have not worked.[15]

Side effects of antifungal therapy may include fever, chills, visual disturbances, dyspnea or skin reactions, and nephrotoxicity. In addition, there is the potential complication of interaction with other drugs metabolized by the cytochrome p450 isoenzyme. Despite the advent of new and improved antifungals, treatment may still be unsuccessful due to resistance, inadequate penetration of the drug into the fungal foci or patient intolerance of an effective antifungal dose. Alternatively, the patient may simply lack enough neutophils to amount an effective resistance against the infection.

In our case, the patient tolerated his therapy well. Initial response to oral fluconazole and intravenous caspofungin was poor. Following diagnosis of aspergillosis, amphotericin B and voriconazole was commenced which resulted in resolution of fever. However, this change may be attributed to surgical removal of the *Aspergillus* focus rather than the administration of antifungals alone. We believe this combined surgical and medical approach is required to eradicate the pathogen due to its invasive nature.

CONCLUSIONS

Oral aspergillosis is uncommon and may occur in immunocompromised patients with leukaemia and

granulocytopenia. It is a serious condition associated with a high morbidity and mortality if not diagnosed promptly. Preferred treatment is surgery combined with systemic antifungal therapy. Despite the availability of newer antifungal therapies and improved management of underlying diseases and conditions, the prognosis for invasive aspergillosis of the orofacial tissues remains poor. Successful treatment of oral invasive aspergillosis depends on a multidisciplinary approach, and the patient's medical and haematological profile is a key determining factor.

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