CASE REPORT

A 35-year-old Nigerian male was referred by a general dental practitioner to the oral medicine clinic for a painful, non-healing ulcer on the left side of the palate. The referring general practitioner had prescribed antibiotics and analgesics a week earlier, but without any relief to the patient. The patient reported that he first noticed the lesion approximately two weeks before and complained of extreme discomfort when either his tongue or food came into contact with it. On questioning, the patient mentioned that he had travelled beyond the borders of South Africa during the past year but was very vague about the countries he had visited. He reported no other health problems, was not using any chronic medication and claimed that he had tested negative for HIV-infection about six months previously. He admitted to smoking ±10 cigarettes per day and to drinking alcoholic beverages on social occasions.

Extra-oral examination revealed nothing of note and no regional lymph nodes could be palpated. Intra-orally, a well-defined erythematous ulcer of approximately 12x9 mm was seen on the palate adjacent to the 24 to 26 area. The ulcer had firm, rolled margins and its surface appeared red and granular (Figure 1). The patient had poor oral hygiene and calculus and plaque covered the surfaces of the teeth adjacent to the ulcer. No other intra-oral changes were noted.

Exfoliative cytologic smears were obtained from the lesion with an endocervical brush (Craig-Brush, Pharmaceutical Enterprises (Pty) Ltd). The slides were either spray-fixed or left dry and were submitted to the cytology laboratory (NHLS) for routine Papanicolaou (Pap) and Giemsa staining. The brush biopsy was immediately followed by an incisional biopsy under local anaesthesia. The histology specimen was fixed in 10% buffered formalin and sent to the histopathology laboratory for routine Haematoxylin...
and Eosin (H & E) staining. Sutures were placed and the patient was instructed to use an antibacterial mouthwash, 0.2% chlorhexidine digluconate, twice daily, and return to the clinic a week later for suture removal. At this follow-up visit the biopsy site had healed satisfactorily.

HISTOPATHOLOGICAL FINDINGS
Histopathological examination revealed a florid sub-mucosal histiocytic infiltrate. The histiocytes (macrophages) contained small, round intra-cytoplasmic organisms with a clear halo and a central dark nucleus. The organisms were positive for Gomori methanamine silver stain and periodic acid Schiff (PAS) stain (Figures 3 and 4).

DIAGNOSIS AND MANAGEMENT
On the basis of the clinical features alone, a differential diagnosis of oral squamous cell carcinoma, syphilis, tuberculosis, deep fungal infection, lymphoma, foreign body reaction and Wegener’s granulomatosis was listed. Based on the histopathological features gleaned from the incisional and brush biopsies, a final diagnosis of histoplasmosis was established. At the successive visit the patient’s sutures were removed and the final diagnosis discussed with the patient. He was advised to return to the referring clinic for further retroviral tests and then to return to the oral medicine clinic for management of the oral infection. Unfortunately the patient was not seen again despite concerted efforts to contact him directly or through the referring clinic.

DISCUSSION
Histoplasmosis was first described in 1906 by the American pathologist, Samuel Darling, and is also referred to as Darling’s disease. It is a relatively common systemic fungal infection that develops due to infection with either of the two Histoplasma species pathogenic to humans, i.e. Histoplasma capsulatum var capsulatum or Histoplasma capsulatum var duboisii. The latter is usually seen in Africa. These organisms are saprophytic and dimorphic fungi found globally in soil and especially in areas where the soil is contaminated with bird or bat droppings, such as may be found in chicken coops, attics, caves, uninhibited buildings, trees and the roosting areas of wild birds. The European starling is the main vector of Histoplasma capsulatum in North America. This bird was first introduced into Central and South America, Southern Europe, Africa and South-eastern Asia. It is endemic to the Ohio and Mississippi river valleys of the continental USA, and also to Central and South America. The bird was first introduced into Central and South America, Southern Europe, Africa and South-eastern Asia.

Human infection is caused by the inhalation of airborne spores that enter the terminal passages of the lungs where they germinate. The fungi are usually phagocytised by pulmonary macrophages within 24 to 48 hours after inhalation. Individuals with a competent immune system develop an antigen-specific CD4+ T lymphocyte-mediated cellular response with activation of macrophages and this usually controls the disease either by eliminating or confining the organism. In the latter instance, viable organisms may still be recovered several years after the initial infection. Therefore, individuals from endemic regions where they may have acquired the infection may later express the disease should they become immune-compromised, such as after chemotherapy or advanced HIV-infection. In such individuals, the organism may produce disseminated systemic and possibly fatal disease as the fungus, acting as an opportunistic agent, spreads through the reticulo-endothelial system. Infection depends on the size and nature of the inoculum and males are more frequently affected, probably because of a higher risk of exposure to the organism. Three variants of histoplasmosis have been described:

- Primary acute pulmonary histoplasmosis:
This form of histoplasmosis is usually asymptomatic as the majority of individuals who become exposed to the organism are healthy and do not inhale a large number of spores. In some cases patients suffer from a transient and mild flu-like illness lasting no longer than two weeks. The symptoms include fever, headache, myalgia and a non-productive cough. Hilar lymph node calcification may be detected on chest radiographs, incidentally, years later. In cases of inhalation of a large dose of spores, the patient may develop signs and symptoms of acute pneumonia and this clearly requires early and decisive therapy.
• Chronic pulmonary histoplasmosis:
  This form of the infection primarily affects the lungs and often occurs in the presence of an existing pulmonary disease. Its clinical features are similar to that of tuberculosis and patients present with weight loss, fever, dyspnea, chest pain, haemoptysis, weakness and fatigue. Upper-aerodigestive involvement can present as mucosal ulcerations that may cause hoarseness, pain on swallowing and dysphagia.¹

• Disseminated histoplasmosis:
  This variant is characterised by the progressive spread of the infection to extra-pulmonary sites. Disseminated forms are most frequently seen in infants younger than two years and elderly patients with a decreased cell-mediated immunity. Individuals who are immune-compromised, such as those with advanced HIV-infection, haematological malignancy or receiving chemotherapy may also present with disseminated histoplasmosis.²
  For this reason the Centres for Disease Control and Prevention consider extra-pulmonary histoplasmosis as an acquired immunodeficiency syndrome (AIDS)-defining illness.¹ Tissues that may be affected include the spleen, adrenal glands, liver, lymph nodes, gastro-intestinal tract, central nervous system, kidneys and Upper-aerodigestive tract (i.e. oral cavity, larynx, and oesophagus).³
  Patients with upper-aerodigestive involvement typically present with ulcer-like lesions of the mucosae, and it is usually covered by a pseudomembrane. In some patients histoplasmosis may present as nodules or vegetations on the relevant mucosae.⁴

Cytological evaluation is of great value in revealing the fine morphology of Histoplasma in superficially accessible oral lesions, such as oral malignancies and oral infections caused by viruses, bacteria and fungi, and it is a useful adjunct to surgical biopsy.⁵ Oral epithelial cells can be obtained with a cytology brush, using a rotary technique under mild pressure for ulcers. Necrotic areas of the lesion should be avoided as these will reveal little of note except inflammatory and degenerated cells. The Papanicolaou stain (for fixed preparations) is the most useful stain for the cytological evaluation of oral squamous cells; however, other staining techniques such as the Giemsa (for air-dried specimens) may be used. A cytological smear positive for histoplasmosis exhibits small, round, intra-histiocytic organisms surrounded by a narrow clear halo and faint dark nuclei (Figures 5a and 5b). Histological examination reveals a dense sub-mucosal infiltrate of histiocytes containing petite round organisms with a clear halo and central dark nuclei (Figure 3). Granulomatous inflammation may be present and the overlying epithelium can be hyperplastic.⁵

The treatment of oral histoplasmosis may differ according to the severity of the infection and the immune status of the patient. In immune-competent individuals, an acute infection does not merit specific treatment other than supportive care as it is a self-limiting process. However, in patients with chronic histoplasmosis, oral itraconazole is the drug of choice due to its fewer side-effects, but it requires a daily dose of 200 – 400mg for at least three months, taken immediately after a full meal for maximum absorption. Regular liver function tests should be requested during long-term therapy.⁶ In immune-compromised individuals with chronic or disseminated disease, and with progressive pulmonary damage, the treatment usually includes intravenous amphotericin B. It should be noted, however, that this may lead to significant kidney damage and such patients should be admitted and carefully monitored during therapy. Once the life-threatening phase of the disease is over, oral itraconazole is prescribed for a further period of six to 18 months.⁶ Typically, patients with acute or chronic histoplasmosis usually recover uneventfully but, in severe forms of the disease, a mortality rate of seven to 23% has been reported, despite active therapy.⁶

CONCLUSION AND DENTAL CONSIDERATIONS

The case presented here is of a foreign patient who was diagnosed with oral histoplasmosis, probably as part of the disseminated variant of the disease. It was assumed that the patient had acquired the organism during his travels in
Africa and that the oral lesion had developed due to reactivation of a latent infection after the patient’s immune system was compromised. As oral histoplasmosis is considered as an AIDS-defining lesion, it was assumed that the patient was probably HIV-positive, at least until proven otherwise. Although the patient reported that he had previously tested negative for HIV-infection, it was felt that further retroviral testing must be done. Unfortunately the patient absconded before his HIV-status could be confirmed and, sadly, the treatment could thus also not be completed.

Dental professionals should remain aware that oral histoplasmosis can and does occur in the oral cavity and should take this into consideration when faced with an unusual or unexplained chronic oral ulcer. In such cases, the brush biopsy provides a simple, non-invasive and inexpensive method of diagnosis and is a useful adjunct to surgical biopsy. Moreover, improvements in the analysis of cytology specimens (especially the introduction of liquid based cytology which allows application of molecular techniques) has increased the sensitivity and specificity of oral brush cytology making the technique extremely useful in cases of suspected malignancy, and in cases where an incisional biopsy of a lesion is difficult or impossible. Finally, it should also be kept in mind that oral histoplasmosis is an AIDS-defining condition and that patients with a positive diagnosis for oral histoplasmosis should always be referred for retroviral testing.

Declaration: No conflict of interest declared

References and *recommended reading