

# Oral Histoplasmosis Associated with HIV Disease: Report of two Cases from Thailand

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**Introduction:** Histoplasmosis caused by *Histoplasma capsulatum* (*Hc*) rarely affects the oral mucosa. Oral histoplasmosis (OH) may occur both in the immunocompetent individual as well as in patients with HIV-infection and AIDS. The majority of cases has been observed in the United States and South America. In South and Southeast Asia OH seems to be rare.

**Patients and Methods:** Two cases of OH in two Thai male patients (aged 30 and 43 years) are described. Clinically, ulcerated lesions with indurated borders were seen, which had persisted for some time. Biopsies revealed the *Hc* organism. Therapy consisted of administration of ketoconazole, itraconazole and/or amphotericin B. One patient was lost to follow-up, in the other complete healing of the oral lesions occurred.

**Conclusions:** Oral histoplasmosis in HIV-infected patients in Thailand is rare. The diagnosis is made on histopathologic and serologic parameters. Patients with active antiretroviral therapy or highly active antiretroviral therapy are unlikely to develop OH due to immunoreconstitution.

**Key words:** histoplasmosis, oral, HIV infection, Thailand

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## INTRODUCTION

Lesions of the facial skin and the oral cavity caused by systemic mycoses are most commonly seen as a consequence of disseminated disease, particularly when involving the respiratory tract. Isolated oral lesions are more rare (Scully et al, 1992; Samaranayake, 1992). Deep mycoses, including histoplasmosis, may complicate HIV disease and produce orofacial lesions (Hodgson and Rachanis, 2002). Histoplasmosis is caused by *Histoplasma capsulatum* (*Hc*), a dimorphic fungus that assumes yeast form in host tissues. In soil it develops into a branching hyphal form (Ng and Siar, 1996). Infection occurs by inhalation of airborne spores. Lungs are the primary portal route of entry. Histoplasmosis is endemic in the Mississippi and Ohio river valleys of the United States (Goodwin and Des Pres, 1978). Moist temperature, areas of bird droppings, and soil high in nitrogen content pro-

vide an ideal environment for *Hc*. In other parts of the world *Hc* is uncommon. However, it occurs in Latin America, India, East Asia and Australia. *Histoplasma capsulatum* var. *duboisii* is predominantly found in Central and Southern Africa (Hodgson and Rachanis, 2002). The disseminated form of histoplasmosis is most common (Ng and Siar, 1996; Cole and Grossman, 1995; Souza Filho et al, 1995) and primarily occurs in individuals over the age of 54 years and those who exhibit some form of immunosuppression (Davies et al, 1978; Wheat et al, 1982). In recent years histoplasmosis has been described in association with HIV infection and AIDS (Kurtin et al, 1990; Eisig et al, 1991). Oral lesions are rare and present as ulcers, granulomas or verrucous and plaque-like lesions (Prabhu et al, 1992). Oral lesions have been detected in up to 50 % of individuals with disseminated histoplasmosis and HIV-infection (Fowler et al, 1998; Huber et al, 1998; Oda et al, 1990). Diagnosis is confirmed



histopathologically. Granulomas with periodic acid-Schiff positive spores with a narrow halo in macrophages, microabscesses and necrosis are characteristic. Culture on Sabouraud's agar is confirmatory. Complement fixation test may be of value, with a titre greater than 1:32 being indicative of histoplasmosis infection.

Oral manifestations of histoplasmosis associated with HIV disease in Thai patients have rarely been reported (Nittayananta and Chungpanich, 1997; Nittayananta et al, 1997). Since oral manifestations of histoplasmosis seem to be rare among HIV-infected and AIDS patients in Thailand, the purpose of this article is to present two patients with this type of oral complication of HIV-infection.

### CASE 1

In November 1995, a 30-year-old Thai man came to the Oral Diagnosis Section, Faculty of Dentistry, Chiang Mai University, with a one-month history of a painful lesion of the buccal mucosa of the lower right second molar. On physical examination, the patient appeared well, with dark skin and scaling rashes. He gave a history of a productive cough with yellowish-white sputum and fever for a period of two months. Oral examination revealed poor oral hygiene and generalised gingivitis especially on the right side. There were large ulcerated, granulomatous, cauliflower-like lesions covered with a yellowish-white pseudomembrane on the buccal mucosa and gingiva of the lower right second molar, extending to the retromolar area and the buccal and lingual gingiva of lower right premolar area (Fig 1a). The margins and surface of the ulcers were irregular and very painful. Lymphadenopathy of the right submandibular lymphnodes and partial trismus were observed. White patches were found on the gingival area of the right side, the sublingual space and dorsum of tongue (Fig 1b). The lower right second molar showed severe mobility; the third molar was partially erupted with pericoronitis. The first and second premolars were clinically missing. Widening of the periodontal space and some degree of alveolar bone loss of the lower right second molar were seen on the panoramic radiograph. Review of the social history revealed that the patient had been married five years ago and had a four-year-old daughter. Before getting married he regularly had sex with commercial sex workers. His house was next to a chicken-raising farm. No systemic disease was reported, except weight loss of 5 kg and persistent productive cough for three months. A blood test for antibody to HIV was found to be positive. His complete blood count showed low hemoglobin (9.8 gm%), low hematocrit (31%), a low white blood cell count (4,600 cells/mm<sup>3</sup>), a normal platelet count and normal blood coagulation parameters.

A biopsy from the ulcerated lesion was taken under local anesthesia. The histologic examination revealed the presence of spores representative of *Hc* in granulomas (Fig 1c).

The following medications were prescribed: tetracycline hydrochloride 1.5 gm/day for 10 days, ketoconazole 200 mg/day taken orally daily and chlorhexidine gluconate 0.2% as a mouth rinse. Consultation for testing for pulmonary TB and histoplasmosis was requested at a hospital specialising in pulmonary diseases. AFB test from sputum was negative. Organisms of *Hc* were not demonstrable.

After two weeks of follow-up, some improvement of the oral lesion had occurred, demonstrated by less pain, more shallow ulcerations and less swelling of the right side of the face. Ketoconazole 200 mg/day taken orally and chlorhexidine 0.2% as a mouth rinse were continued. A week later, the patient reported less coughing and less pain on the ulcerated lesions, but clinically these had spread to the soft palate and uvula. Unfortunately, the patient was lost to follow-up.

### CASE 2

In December 2003, a 43-year-old Thai man was referred by his general dentist to the Oral Diagnosis Section, Faculty of Dentistry, Chiang Mai University, for evaluation and treatment of a painful, ulcerated lesion on the gingival area of the lower left second and third molar. The lesion had been present for three months. No other information was given from the referring dentist, except that the patient reported to have been treated for tuberculosis for seven months.

Oral examination showed poor oral hygiene, generalised gingivitis with heavy calculus and tobacco stain. There was a destructive granulomatous reddish ulcer with an irregular and slightly indurated margin at the lower left second and third molar, involving the buccal and lingual gingiva of an approximate size of 2 x 3.5 cm in diameter. The ulcer was very painful, and there was swelling of the left side of the cheek with submandibular lymphadenopathy. Tooth mobility of the second and third molar was observed.

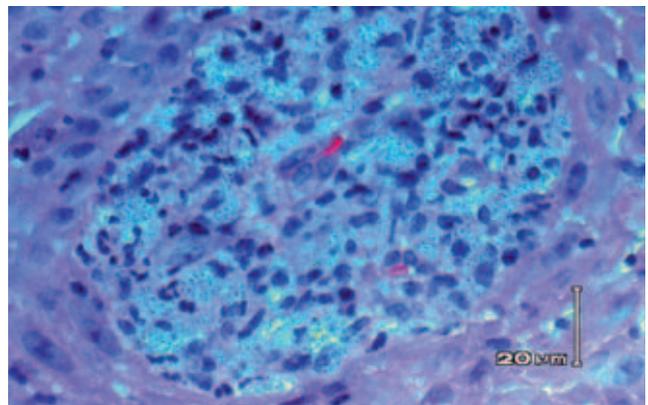
On physical examination the patient appeared fatigued and emaciated. His skin was dark and showed erythematous rashes all over the body. On admission, serologic testing for anti-HIV was positive. Complete blood count was within normal limits (hemoglobin 13.74 gm%, hematocrit 39.2%), except for a low white blood cell count of 3.750 cells/mm<sup>3</sup>. Blood chemistry was within normal limits (AST 13U/L, ALT 12 U/L, alkaline phosphatase 26 U/L, and total bilirubin 0.3 mg/dL). Review of the medical history revealed that the patient had been diagnosed with pulmonary tuberculosis (TB)



**Fig 1a** (Case 1) Extensive ulceration with irregular borders involving the soft palate and fauces of the right side demonstrating the extent of the lesion caused by histoplasmosis.



**Fig 1b** Histoplasmosis of the alveolar ridge involving the buccal and lingual gingiva.

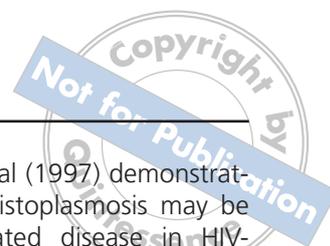


**Fig 1c** Micrograph showing granuloma with multiple spores of *Hc* (bar represents 20  $\mu$ m).

and HIV-infection since April 2003 with the symptoms of productive cough, skin rashes and itching. He received anti-TB drugs but developed side-effects of nausea, vomiting and dizziness. An AFB test from sputum was negative. Review of the social history revealed alcohol abuse and heavy smoking. The patient's wife had died of AIDS four years earlier. He lived in a village where chickens were raised, including in his house.

A biopsy was taken under local anesthesia from the margin of the oral ulceration. Histologically, an ulceration was seen, with granulomatous inflammatory changes and foci of necrosis. Numerous organisms of *Hc* were seen intracellularly, as demonstrated in H&E and methenamine silver stains. Oral histoplasmosis was diagnosed. For treatment of histoplasmosis, ketoconazole 800 mg/day was given orally, together with clotrimazole lozenges 10mg, applied three times per day. Oral amoxicillin 2g daily for seven days was administered for controlling infection of the buccal space. The lower left second molar was extracted by the patient's dentist two weeks after admission. The oral lesion improved within five weeks. Three weeks later

the patient came back with pain in the area of the previous oral lesion. The oral lesion had recurred and extended to the retromolar area, involving the buccal and lingual gingiva of the first molar. When being asked whether he had taken the medicine regularly, the patient admitted that he had stopped taking all medicine a week earlier because his mother had died. The same regimens were started again. A week later, the lesion became worse and extended to the gingiva of the second premolar. Itraconazole 400mg/day was given instead of ketoconazole. The oral lesion responded well with less pain. However, the lesions of the skin became more severe. The CD4 count decreased to 6 cell/mm<sup>3</sup> and the CD8 count was 352 cell/mm<sup>3</sup> (CD4/CD8 ratio = 0.02). The WBC was reduced to 2,700 cell/mm<sup>3</sup>. Due to disseminated histoplasmosis, amphotericin B was given 25 mg/day intravenously together with oral itraconazole 400 mg/day for 14 days. After one week of follow-up, the oral lesion had completely healed. In that week the patient was given the following antiretroviral therapy: D4T (stavudine) 80mg/day, 3TC (lamivudine) 300mg/day and EFV (efavirenz)



600mg/day, together with itraconazole 800mg/day and multivitamin. After eight months of follow-up, there were no oral or skin lesions, except that the skin was very dark. By this time the CD4 cell count had increased to 170 cell/mm<sup>3</sup>. The patient had gained 5kg of bodyweight and was in good condition.

## DISCUSSION

The occurrence of oral manifestations of histoplasmosis in non-HIV-infected patients has been demonstrated in several case reports (Yusuf et al, 1979; Toth and Frame, 1983; Loh et al, 1989; Rahman et al, 2004) and in case series. Ng et al (1996) reviewed 37 cases of OH, which had been collected between 1967 and 1994 in Malaysia. Padhye et al (1994) described OH cases from India. From 1968 to 1992 a total of 29 cases with oral involvement of histoplasmosis was recorded. Both studies demonstrate the extremely low prevalence of OH in this part of the world.

Until 1997 only 15 cases of OH in HIV-infected and AIDS patients were reported (Scully et al, 1997; Werber, 1988, Fowler et al, 1989; Huber et al, 1989, Oda et al 1990; Cohen et al, 1990; Eisig et al, 1991; Jones et al, 1992; Heinic et al, 1992; Lucartorto and Eversole, 1993; Swindells et al, 1994; Souza Filho et al, 1995; Cole and Grossman, 1995; Chinn et al, 1995). The majority of these cases were reported from the United States. In 1997, Warnakulasuriya et al reported a case of localised OH associated with HIV infection. Two cases of OH in Thai HIV-infected patients were reported by Nittayananta et al (1997). In another study, by Nittayananta and Chungpanich (1997), five patients with OH were observed among 102 HIV-infected patients with oral lesions. Larger groups with OH in patients with HIV-infection or AIDS were reported from Argentina (Casariego et al 1997 (n=21); Hernández et al 2004 (n=21)) and from Brazil (Ferreira et al, 2002 (n=8)). In another study, by Borges et al (1997), three patients of 17 with HIV infection or AIDS revealed oral mucosal involvement. Involvement of the tongue was recorded by De Faria et al (2005) and by Piluso et al (1996) in one case, respectively. Vargas et al (2003) observed two cases of parotid gland involvement in advanced AIDS cases.

The spectrum of clinical appearances of OH in HIV disease and AIDS varies. However, ulceration is most commonly seen. Often these ulcerations show an indurated border. Single or multiple nodular or vegetative oral lesions may also be observed. Lesions showing necrosis or ulceration with severe inflammation may occur on the tongue, floor of the mouth, hard and soft palate, oro-nasal mucosa, gingiva and mandible (Casariego et al, 1997). Oral lesions are most often seen in cases of disseminated disease (Loh et al, 1989;

Young et al, 1972). Casariego et al (1997) demonstrated that oral manifestations of histoplasmosis may be observed in 66% of disseminated disease in HIV-seropositive patients. It was concluded that histoplasmosis in HIV-infected patients is not rare in South America. This is in contrast to Southeast Asia, particularly Thailand, from where only very few cases have been reported up to date.

Generally, histoplasmosis in HIV-infected patients may be a primary diagnostic manifestation of underlying AIDS and should be suspected in an immunocompromised patient with unexplained symptoms of infectious disease and skin and other lesions.

Diagnosis of OH is confirmed microscopically, revealing granulomas with periodic acid – Schiff – positive spores with a narrow halo in macrophages, micro-abcesses and necrosis. Culture on Sabouraud's agar is confirmatory. The histoplasmin skin test is of little importance diagnostically (Scully et al, 1997).

Treatment of OH has generally been based on the use of amphotericin B (Ferreira et al, 2002). In the cases described patients were treated with ketoconazole (case 1) and ketoconazole, itraconazole and amphotericin B (case 2). In the latter immunoreconstitution was also achieved by antiretroviral therapy. In this case oral lesions of histoplasmosis healed completely. Some have recommended continuous lifelong treatment with itraconazole for patients with HIV-infection and AIDS (Ferreira et al, 2002).

In conclusion, histoplasmosis, in particular OH, seems to be rare in HIV-negative individuals of the south and southeast region of Asia. Few patients with OH and HIV-infection or AIDS have so far been reported from Thailand and southeast Asia. This is in contrast to reports from South America, where the number of patients with oral manifestations of histoplasmosis seems to be higher. The spectrum of differential diagnoses includes other granulomatous diseases of the oral mucosa including oral squamous cell carcinoma. Diagnosis is confirmed histopathologically by culture or by chemiluminescent DNA-probe assay and exoantigen test. Therapy is achieved by administration of azoles, in particular ketoconazole, itraconazole or amphotericin B.

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