

Histoplasmosis in the Head and Neck

L Chee,**FRCS (Edin)*

Abstract

Histoplasmosis is a fungal infection which when disseminated can be potentially fatal, especially in the immunocompromised patient. Disseminated histoplasmosis can present with orolaryngeal manifestations which often mimic carcinoma or tuberculosis. A high index of suspicion and diagnosis with biopsy is needed. Two recent cases are presented and the literature reviewed. As the number of immunocompromised patients increases, more cases of histoplasmosis in the head and neck will be encountered. Early treatment can reduce morbidity and mortality.

Ann Acad Med Singapore 1997; 26:510-3

Key words: *Dissemination, Immune compromised, Investigations, Mimic, Orolaryngeal*

Introduction

Histoplasma fungal infections in most immune competent persons are largely asymptomatic and benign. Endemic areas include not only the central United States but also Malaysia and Indonesia, of which Singapore is in close proximity. Infection in the elderly and the immunocompromised can be severe and potentially fatal.^{1,2}

Disseminated histoplasmosis can present with head and neck manifestation and may be the only presenting symptom. A high index of suspicion together with appropriate stains and culture, is needed to make a diagnosis. Two cases of orolaryngeal histoplasmosis were encountered which prompted a review of local experience and literature.

Case Reports

Case 1

A 70-year-old Chinese gentleman presented with a painful mouth and hoarseness for three months. He migrated from Fujian, China sixty years ago and is a chronic smoker. Six months ago he travelled to Medan, Indonesia for a holiday.

Clinically there was a nodular, ulcerating growth at the frenulum of the tongue. Flexible endoscopy revealed fleshy lesions in the larynx as seen in Figure 1. Provisional diagnosis was squamous cell carcinoma of the larynx. Biopsy confirmed the presence of histoplasmosis. The patient was subsequently referred to a respira-

tory physician but defaulted follow up. Five months later he was admitted to the Communicable Disease Centre, still symptomatic and in adrenal failure. Additional signs detected included hyperpigmentation, a multinodular goitre and hepatomegaly. Computed tomographic (CT) scan of the abdomen (Fig. 2) showed adrenal masses and CT scan of the neck (Fig. 3) showed cystic nodular thyroid. Fine needle aspirate of the thyroid nodule again demonstrated histoplasmosis. Laryngeal swab, blood histoplasma antibodies and blood cultures were all negative.

He was treated with prednisone and itraconazole with good response. He is now asymptomatic and has gained weight from 37 kg to 44 kg.

Case 2

A 47-year-old Chinese male had renal transplant in 1979 for end-stage renal failure. He was on prednisone when he presented with a painful tongue ulcer for six months. A provisional diagnosis of carcinoma was made and a punch biopsy taken. Histoplasmosis was reported.

Out of fifteen cases treated by various public institutions in Singapore since 1980, three patients presented with head and neck manifestations and all were detected in 1995. The third case was not reviewed because only part of the notes could be traced. The male preponderance is supported by other studies. Histology was diagnostic in all the cases, while sputum culture and

* Registrar

Department of Otolaryngology

Singapore General Hospital

Address for Reprints: Dr Lincoln Chee, Department of Otolaryngology, Singapore General Hospital, 1 Hospital Drive, Singapore 169608.



Fig. 1. Endoscopic view of the larynx showing lesions, granulomatous lesions of the vocal cords.



Fig. 3. Computed tomographic scan of the neck with a cystic thyroid nodule. Aspirate showing histoplasmosis.

serology for anti-histoplasma antibodies were all negative. Both patients, though human immunodeficiency virus (HIV) negative, were to some degree immune-suppressed: case 1 had adrenal failure while case 2 had renal transplant. This is similar to findings by Gerber et al.³

Multisystem involvement was present in case 1 with pulmonary, adrenals, thyroid and liver involvement. No dissemination was found in case 2 presumably because treatment was started early.

Discussion

Histoplasma capsulatum is a dimorphic soil fungus in areas where there is accumulation of bat or avian excrement. People working in construction, caves and farms in endemic areas may be at higher risk of developing histoplasmosis.⁴ Singapore's accelerated urbanisation, lack of agricultural land, relatively small population and possible under diagnosis may be reasons for the scarcity of cases. Both our patients in the series had a travel

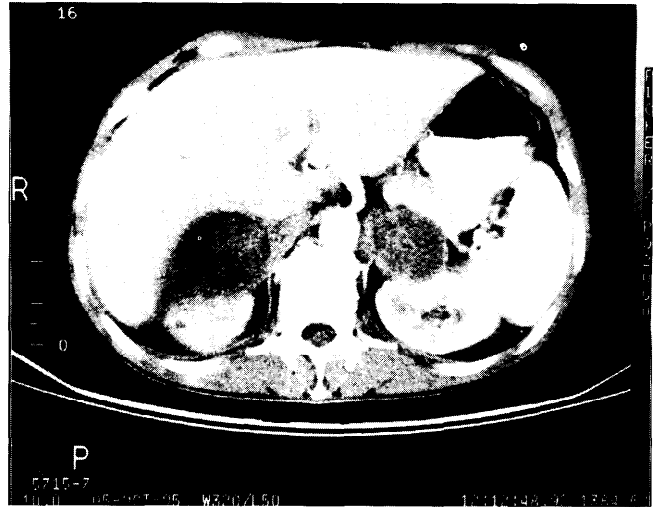


Fig. 2. Computed tomographic scan of the abdomen showing adrenal masses.

history to endemic areas. In the soil, the fungus exists in a mycelial form but converts to a yeast in the human. It was named by Samuel Darling, a US Army pathologist because he found it in histiocytes, thought it was a protozoan and believed it to be encapsulated." This has been proven not to be so but the name has persisted.⁶

Human infection can be classified as asymptomatic, pulmonary and disseminated histoplasmosis depending on the size of the inoculum and the immunocompetence of the host.² In endemic regions most infections are asymptomatic and spontaneous resolution occurs. Reinfection is common. When the inoculum is large in a normal host, acute pulmonary histoplasmosis with influenza-like symptoms such as fever, malaise and cough can result. This is usually self limiting and requires no specific treatment. On rare occasions a vigorous host reaction can produce mediastinal fibrosis with tracheal and oesophageal obstruction.^{7,8}

Dissemination occurs when the macrophage is unable to demonstrate intracellular fungal destruction. This leads not only to persistence of viable fungi but also to intracellular multiplication.^{9,10} This inability to kill a low virulence organism implies an immune system that is compromised. In both our cases, the patients had evidence of an immune compromise state (Addison's disease and renal transplant). The degree of parasitization will determine the constitutional symptoms and the anatomical and functional disturbance within the organs. This can be acute, subacute or chronic.

In acute disseminated histoplasmosis, the clinical course is progressive with unrelenting fever, weight loss, hepatosplenomegaly lymphadenopathy, interstitial pneumonia and haematologic disorder. Histopathologically there is diffuse histiocytosis of various organ systems (e.g. liver, spleen, lymph nodes and marrow adrenals). If untreated the mortality is high.¹¹

In subacute dissemination, the constitutional symptoms differed from the acute group primarily in degree and the duration of illness was considerably longer. More focal lesions were reported to involve the digestive tract, heart, oropharynx and central nervous systems.¹⁰ Most HIV-associated infections are of the subacute type and constitute an acquired immune deficiency syndrome (AIDS)-defining illness.¹²

Chronic disseminated histoplasmosis is often the characteristic form of the disease in adults. Destructive focal lesions especially of the head and neck predominate." The clinical course can be indolent and patients can survive for years if left untreated. The 2 patients presented with subacute or chronic disease. Microscopically there was less mononuclear parasitization and pleomorphic inflammatory infiltration was seen with tuberculoid granuloma formation. Low fungal loads are best detected with methanamine silver¹³ or with periodic acid shift (PAS) stain.

Diagnostic Studies

Disseminated histoplasmosis is diagnosed when organisms are demonstrated in extrapulmonary tissue. Peripheral blood smears and marrow biopsy may only be positive in 50% of subacute and negligible in chronic disseminated disease. Blood cultures may be positive in about 57% of cases.¹⁴ Though complement fixation (>1:8) is positive in two-thirds of disseminated cases, cross reactivity with other fungi can occur. Anti-histoplasma antibody serology for M bands and H bands are positive in 58.3% and 2.8% respectively in AIDS patients.¹⁴ Certainly radioimmunoassay for histoplasma polysaccharide antigen (HPA) in blood, urine or cerebrospinal fluid is more sensitive and specific but is not readily available.

Biopsy with silver stains, such as gomori methenamine silver (GMS) or with PAS stains is most useful in demonstrating intracellular fungi against a contrasting back-

ground (Figs. 4 & 5). Therefore biopsy and culture complement each other and are necessary for maximum diagnostic accuracy.

Significance

As many as two-thirds of chronic disseminated histoplasmosis can present with orolaryngeal manifestation." The larynx and tongue are the sites of predilection but multiple foci are common. Both the ulcerated and nodular lesions are most often diagnosed as epidermoid carcinoma. The clinical appearance of these lesions is in no way diagnostic and the fact that nearly 40% of patients in one series who were biopsied did not have the specimen cultured proved that granulomatous infection was often not suspected.¹³ These lesions can be easily mistaken for carcinoma or tuberculosis unless appropriately stained and looked for. The frequency with which these apparently localised lesions later disseminated is well documented in the literature¹³ and also seen in Case 1. If left untreated, it is almost always fatal. Both adrenal involvement and Addison's disease may be major factors in causing the death of patients.¹⁰

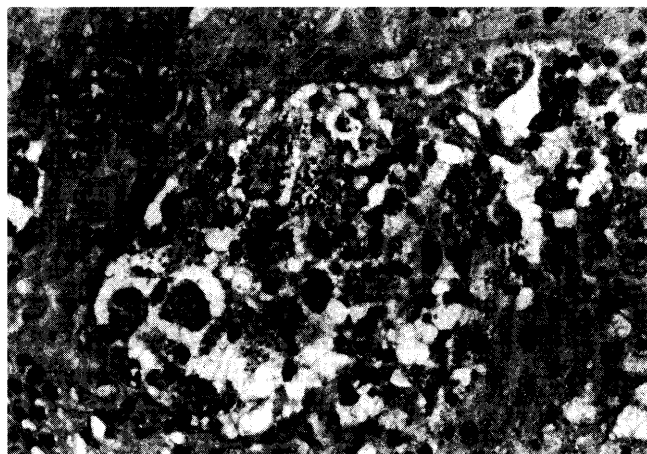


Fig. 5. PAS stain showing intracellular yeast form of histoplasmosis. High magnification x100 (Slide courtesy of Dr G Chiang).



Fig. 6. Tongue ulcer — histoplasmosis.



Fig. 4. PAS stain showing laryngeal biopsy (Case 1). Low magnification x40 (Slide courtesy of Dr G Chiang).

Treatment

All cases of disseminated histoplasmosis, regardless of severity, are considered potentially fatal and require systemic anti-fungal therapy. Treatment is divided into an "induction" phase to obtain clinical remission and a "maintenance" phase to prevent relapse. The rate of recurrence is high in those in immunocompromised state, especially in HIV infection. Amphotericin B at a dose of 35 mg/kg is the traditional drug used for induction.^{12,14,15} Newer azole drugs such as itraconazole and fluconazole have less toxicity but variable response ranging from 40% to 86%. In both our patients, they were successfully managed and maintained on itraconazole.

Conclusion

In summary, it is interesting to note that both our cases of head and neck manifestation of histoplasmosis were diagnosed in the past one year (1995). A high index of suspicion is necessary to make the diagnosis especially in immunocompromised patients. Although Singapore is not an endemic area, increased travel, regional referrals and increasing numbers of immunocompromised patients will result in histoplasmosis becoming more common. An appreciation of its manifestation in the head and neck is important to the otolaryngologist to avoid the morbidity and mortality that would result if it was unrecognised.

Acknowledgements

The author would like to thank Dr Wong Sin Yew and Dr Brenda Ang for making available the case records of the patients. These physicians have an interest in histoplasmosis and have participated in the care of the patients in this study.

REFERENCES

1. Davies SF, Kahn M, Sarosi G A. Disseminated histoplasmosis in immunologically suppressed patients. Occurrence in a non endemic area. *Am J Med* 1978; 64:94.
2. Loyd J E, Des Prez R M, Goodwin R A Jr. *Histoplasma capsulatum*. In: Mandell G L, Douglas R G, Bennett JE, editors. *Principles and Practice of Infectious Diseases*. 3rd ed. New York: Churchill Livingstone, 1990.
3. Gerber ME, Rosdeutscher J D, Seiden A M, Tami T A. Histoplasmosis: the otolaryngologist's perspective. *Laryngoscope* 1995; 105:919-23.
4. Huang C T H, McGarry T, Cooper S, Saunders R, Andavolu R. Disseminated histoplasmosis in the acquired immunodeficiency syndrome. *Arch Intern Med* 1987; 147:1181-4.
5. Darling S T. A protozoan general infection producing pseudotubercles in the lungs and focal necrosis in the liver, spleen and lymph nodes. *JAMA* 1906; 46:1283.
6. Ribi E, Salvin S B. Antigens from the yeast phase of *histoplasma capsulatum*: I. Morphology of the cue as revealed by electron microscopy. *Exp Cell Res* 1956; 10:394.
7. Mathisen D J, Grillo H C. Clinical manifestations of mediastinal fibrosis and histoplasmosis. *Ann Thorac Surg* 1992; 54:1046-52.
8. Loyd J E, Tillman B F, Atkinson J B. Mediastinal fibrosis complicating histoplasmosis. *Medicine* 1988; 67:295-310.
9. Schulz D M. Histoplasmosis: A statistical morphologic study. *Am J Clin Pathol* 1954; 24:11.
10. Binford C H. Histoplasmosis: Tissue reactions and morphologic variations of the fungus. *Am J Clin Pathol* 1955; 25:25.
11. Goodwin R A, Shapiro J L, Thurman G H, Thurman S S, Prez R M. Disseminated histoplasmosis: Clinical and pathologic correlations. *Medicine* 1980; 59:1-33.
12. Drew R H. Pharmacotherapy of disseminated histoplasmosis in patients with AIDS. *Ann Pharmacother* 1993; 27:1510-8.
13. Bennett DE. Histoplasmosis of the oral cavity and larynx: A clinicopathologic study. *Arch Intern Med* 1967; 120:417-27.
14. Wheat L J, Stringfield P A C, Baker R L, Curfman M F, Eads M E, Israel K S, et al. Disseminated histoplasmosis in acquired immune deficiency syndrome: Clinical findings, diagnosis and treatment, and review of the literature. *Medicine* 1990; 69:361-74.
15. Johnson P C, Hamill R J, Sarosi G A. Clinical review: Progressive disseminated histoplasmosis in the AIDS patient. *Semin Respir Infect* 1989; 4:139-46.