

Disseminated histoplasmosis in an 'immunocompetent' child

J D Daubenton, D W Beatty

A rare case of severe disseminated histoplasmosis in a 7-year-old boy with apparently normal immune function is described. Current recommendations for diagnostic investigations, monitoring and the treatment of this disease with amphotericin B and itraconazole are reviewed.

S Afr Med J 1998; 88: 270-271.

Histoplasma capsulatum is a dimorphic fungus, the yeast form of which parasitises mammalian macrophages. The organism is more prevalent where heavy accumulations of bat or avian excrement are found. Pigeon roosts, chicken houses and sites frequented by bats such as caves, attics and hollow trees in endemic areas, are therefore most apt to be point sources.¹ In South Africa, this infection is rare and most reported cases have been related to cave exposure.²⁻⁵

Human infection has a number of different clinical pictures: acute pulmonary histoplasmosis (the most common form), chronic pulmonary histoplasmosis and disseminated histoplasmosis. The disseminated form is relatively uncommon. Two groups of susceptible hosts are recognised: infants with immature immunity and immunosuppressed individuals. Very rarely, infection occurs in patients with apparently normal immune function.^{1,6} Disseminated histoplasmosis is included among the opportunistic infections that can occur in AIDS and in recent years most reported cases have been AIDS-related.^{7,8} Few cases of disseminated histoplasmosis have been reported in southern Africa and only 2 of these were in children.⁹⁻¹³ The first was a 13-year-old boy from Zimbabwe in 1951 and the second a successfully treated 10-year-old boy from KwaZulu-Natal in 1976.

This report presents a third paediatric case and reviews the current diagnostic tests and management.

Case report

A 7-year-old black African boy presented at Frere Hospital in East London with fever, lassitude and weight loss. He had been a healthy child prior to the onset of this illness with no

previous history of recurrent infections or major illness. There was no history of exposure to caves. He lived on a rural farm and had been exposed to a large number of chickens. Examination showed him to be wasted and pale with diffuse lymphadenopathy and splenomegaly. The blood count showed anaemia and thrombocytopenia and he underwent a bone marrow biopsy and aspiration to exclude a possible underlying haematological malignancy. This showed a heavy infiltration of *Histoplasma capsulatum*. This finding was confirmed on cultures done at the South African Institute for Medical Research in Johannesburg and the organism was reported to be sensitive to amphotericin B. An enzyme-linked immunosorbent assay for HIV was negative. A Mantoux skin test was negative and a chest radiograph showed bilateral parahilar infiltrates.

The patient underwent 3 weeks of treatment with amphotericin B and was then put on ketoconazole. Two months later he deteriorated and was re-started on amphotericin B. After a further period of treatment he was referred to Red Cross Children's Hospital because of marked deterioration and the development of septic arthritis. At the time of transfer he had received a total of 22 mg/kg amphotericin B.

On admission he was extremely ill with severe wasting and diffuse septic arthritis affecting the ankles, knees, elbows, wrists and the costochondral junctions. Radiographs showed evidence of severe widespread osteitis. His skin, especially on his face, showed numerous raised, umbilicated lesions. He was anaemic with mild disseminated intravascular coagulation (DIC), and had significantly impaired renal function (serum creatinine concentration 192 µmol/l) and hypokalaemia (2.9 mmol/l). A repeat bone marrow examination confirmed histoplasmosis on microscopy and culture. Blood culture grew a *Staphylococcus aureus* resistant to cloxacillin and erythromycin. HIV tests were again negative.

No evidence of immune deficiency could be found on investigation. The patient had a polyclonal hypergammaglobulinaemia with normal antibody response to tetanus immunisation. T-cell response to mitogen and antigens and T-cell subset distribution were normal. The results of bactericidal assays for candida and staphylococcus, chemotaxis studies and complement assays were all normal.

He underwent surgical drainage procedures of the right wrist, right elbow, both ankles and the right tibia. Material drained from the joints cultured both *Histoplasma capsulatum* and *Staphylococcus aureus* and biopsy material from all sites (synovium and bone) showed many histoplasma organisms on methenamine silver stain. He was started on liposomal amphotericin and vancomycin. Liposomal amphotericin 3 mg/kg/day for 40 days was followed by 6 mg/kg/day for a further week; this regimen was chosen because of deteriorating renal function. Vancomycin was chosen because the staphylococcus was resistant to cloxacillin. His renal function and hypokalaemia returned to normal within a week on the above treatment.

The patient's general condition showed a slow but steady improvement with his fever settling and good weight gain. Repeat bone marrow examination after 14 days of liposomal amphotericin still showed a heavy fungal infiltrate and the organism was cultured after about 10 days. Repeat bone

Department of Paediatrics and Child Health, University of Cape Town, and Institute of Child Health, Red Cross War Memorial Children's Hospital, Cape Town

J D Daubenton, MD, FCP (SA) (Paed), DCH (SA)

D W Beatty, MD, FCP (SA) (Paed)

marrow examination after 34 days of treatment showed the same picture and prompted the increase of the liposomal amphotericin dose.

At this point, on the advice of Professor L J Wheat of Indiana University Medical School, treatment was changed to oral itraconazole 5 mg/kg/day with monitoring of the disease by means of histoplasma antigen levels, done by the histoplasma reference laboratory at Indiana University School of Medicine. The initial antigen levels were markedly raised in both urine (9.8 units) and serum (8.7 units). The patient progressed very well on itraconazole treatment and was discharged (nearly 9 months from his initial diagnosis) for outpatient treatment and follow-up. It was planned to give itraconazole 5 mg/kg/day until the histoplasma antigen levels were below 2 units. Repeat immune function tests prior to discharge were again normal.

Repeat measurement of histoplasma antigen levels over the next 18 months showed them to be persistently elevated, despite a significant decline in the first few months. Repeat bone marrow aspiration after 1 year on treatment showed a persistence of yeasts. The patient has been continued on long-term itraconazole and remains clinically well on treatment.

Discussion

The known risk factors for disseminated histoplasmosis include immunosuppression and extremes of age (infants and the elderly).^{1,14} In this patient, none of the known risk factors could be identified and immune function tests showed no abnormality. Goodwin *et al.*⁶ in a report of 102 cases of disseminated histoplasmosis, described 20 patients who had no demonstrable immune defect and remained well following treatment. He postulated a 'temporary impairment of immunological control'. Kurita *et al.*¹⁵ have shown a resistance of the yeast form of *Histoplasma capsulatum* to killing by human neutrophils, possibly as a result of evasion of the toxic products of the oxidative burst by an ill-defined mechanism.

The source of this patient's infection is not known, a history of any cave exposure being denied, but he does have a history of exposure to chickens. A limited number of non-cave-related infections are being recognised in specimens from patients in the Eastern Cape (K Klugman, SAIMR, Johannesburg — personal communication).

Two of the clinical features in this case, the skin lesions and particularly the severe bone and joint involvement, are also unusual although the concomitant staphylococcal infection contributed to the severe skeletal changes. The patient's inability to clear the infection could be due to dysfunction of his immune system that our tests failed to identify.

Disseminated histoplasmosis can be diagnosed by histological appearance, fungal culture of blood or bone marrow, serology or antigen detection.^{1,16} Histoplasma antigen levels, done every 3 - 4 months, are useful in monitoring both the initial response to treatment and relapse, especially in immunocompromised patients.^{6,17,18}

Treatment with antifungal therapy is indicated in all patients with disseminated histoplasmosis. Amphotericin B is the drug of choice in severely ill patients and the

recommended total dose is 35 mg/kg.¹ The main problem is drug toxicity. Goodwin *et al.*⁶ in a series of patients treated with amphotericin B reported that 40% failed to complete the treatment course because of drug toxicity. Standard amphotericin B is a colloidal complex with desoxycholate. In patients unable to complete a course of treatment because of toxicity a liposomal encapsulated preparation of amphotericin is an alternative. This preparation carries much lower toxicity but has two disadvantages: the extremely high cost (relative to the standard preparation) and the fact that larger doses may be necessary to achieve a biologically equivalent effect.¹⁹ Our patient tolerated a dose three times the standard amphotericin B dose without toxicity, but the response to treatment was very slow. It is impossible to say whether this was caused by resistant disease or lower biological activity of the liposomal amphotericin.

Following initial treatment with amphotericin B or, alternatively, as a first-line drug in less ill patients, ongoing treatment with itraconazole in a dose of 5 mg/kg/day orally has been recommended.^{20,21} Prolonged treatment, for a year or more, may be necessary and the resolution or relapse of the infection should be monitored with histoplasma antigen levels. Ketoconazole has also been used but appears to be less effective than itraconazole.^{15,20}

In conclusion, a very rare case of disseminated histoplasmosis has been described and the current diagnostic tests and management have been reviewed.

REFERENCES

- Loyd JE, Des Prez RM, Goodwin RA. *Histoplasma capsulatum*. In: Mandell GL, Douglas RG, Bennet JE, eds. *Principles and Practice of Infectious Diseases*. 3rd ed. New York: Churchill Livingstone, 1990.
- Murray JF, Lurie HI, Kaye J, et al. Benign pulmonary histoplasmosis in South Africa. *S Afr Med J* 1957; **31**: 245-253.
- Wolpowitz A, Van Eden J. Histoplasmosis — cave disease. *S Afr Med J* 1963; **37**: 1002-1005.
- Craven SA, Benatar SR. Histoplasmosis in the Cape Province. A report of the second known outbreak. *S Afr Med J* 1979; **55**: 89-92.
- Craven SA. Acute benign pulmonary histoplasmosis — the third known outbreak in the Cape Province (Letter). *S Afr Med J* 1990; **77**: 376.
- Goodwin RA, Shapiro JL, Thurman SS, et al. Disseminated histoplasmosis: Clinical and pathological correlations. *Medicine* 1980; **59**: 1-33.
- Sarosi GA, Johnson PC. Disseminated histoplasmosis in patients infected with human immunodeficiency virus. *Clin Infect Dis* 1992; **14**: suppl 1, S60-S67.
- Wheat LJ, Connolly-Stringfield P, Baker RL, et al. Disseminated histoplasmosis in the acquired immune deficiency syndrome: Clinical findings, diagnosis and treatment, and review of the literature. *Medicine* 1990; **69**: 361-374.
- Simson FW, Barnetson J. Histoplasmosis: Report of a case. *J Pathol Bacteriol* 1942; **54**: 299-305.
- Murray JF, Brandt FA. Histoplasmosis and malignant lymphoma. *Am J Pathol* 1951; **27**: 783-795.
- Klugman HB, Lurie HI. Systemic histoplasmosis in South Africa. *S Afr Med J* 1963; **37**: 29-31.
- Leibowitz MC, Berson SD, Martin PM. Disseminated histoplasmosis associated with disseminated tuberculosis: a case report. *S Afr Med J* 1977; **51**: 315-317.
- Mackenzie MK, Coovadia HM. Histoplasmosis treated with a sulphonamide. A case report. *S Afr Med J* 1976; **50**: 2015-2016.
- Wheat LJ, Slama TG, Norton JA, et al. Risk factors for disseminated or fatal histoplasmosis. *Ann Intern Med* 1982; **96**: 159-163.
- Kurita N, Terao K, Brummer E, et al. Resistance of *Histoplasma capsulatum* to killing by human neutrophils. *Mycopathologia* 1991; **115**: 207-213.
- Wheat LJ, Kohler RB, Tewari RP. Diagnosis of disseminated histoplasmosis by detection of *Histoplasma capsulatum* antigen in serum and urine specimens. *N Engl J Med* 1986; **314**: 83-88.
- Wheat LJ, Connolly-Stringfield P, Blair R, et al. Effect of successful treatment with amphotericin B on *Histoplasma capsulatum* variety capsulatum polysaccharide antigen levels in patients with AIDS and histoplasmosis. *Am J Med* 1992; **92**: 153-160.
- Wheat LJ, Connolly-Stringfield P, Blair R, et al. Histoplasmosis relapse in patients with AIDS: Detection using *Histoplasma capsulatum* variety capsulatum antigen levels. *Ann Intern Med* 1991; **115**: 936-941.
- Bennett JE. Antifungal agents. In: Mandell GL, Douglas RG, Bennet JE, eds. *Principles and Practice of Infectious Diseases*. 3rd ed. New York: Churchill Livingstone, 1990.
- Wheat LJ, Hafner R, Wulfsohn M, et al. Prevention of relapse of histoplasmosis with itraconazole in patients with acquired immunodeficiency syndrome. *Ann Intern Med* 1993; **118**: 610-616.
- Tobon AM, Franco L, Espinal D, et al. Disseminated histoplasmosis in children: the role of itraconazole therapy. *Pediatr Infect Dis J* 1996; **15**: 1002-1008.

Accepted 25 Apr 1997.