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Pneumonia due to *Histoplasma capsulatum* in a bone marrow transplant recipient

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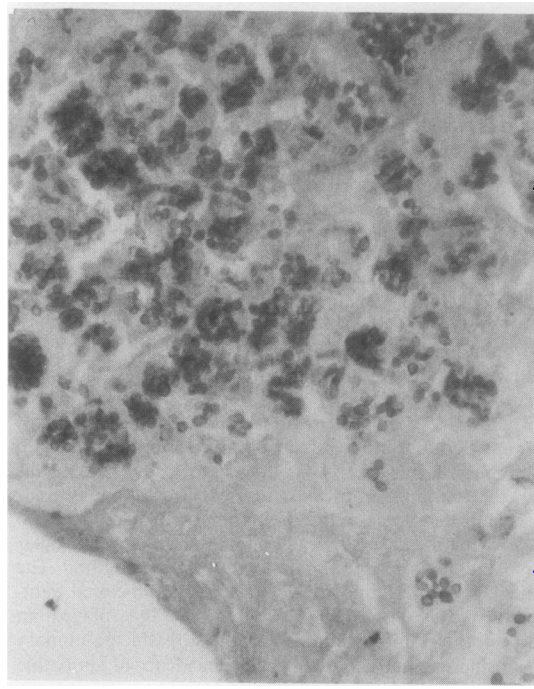
Allogeneic bone marrow transplantation has been used successfully in the treatment of leukaemia, aplastic anaemia, and immunodeficiency states.[1] Pulmonary infections remain a major impediment to the success of bone marrow transplantation.[2] An appreciable number of these cases of pneumonia are caused by fungi, but *Histoplasma capsulatum* has never been reported to cause pneumonia and has been reported only once as a cause of infection in these patients.[3] We report here the case of a recipient of a bone marrow transplant who developed histoplasma pneumonia.

Case report

A 20 year old college student, who was first seen in September 1983 for aplastic anaemia resistant to treatment with prednisone and antilymphocyte globulin, was admitted to hospital in April 1984 for allogenic bone marrow transplantation. She received cyclophosphamide and total body irradiation in preparation for transplantation, and after transplantation she received weekly methotrexate and daily methylprednisolone as prophylaxis against the development of graft versus host disease. On day 18 she developed a rash consistent with graft versus host disease and the dose of methylprednisolone was increased to 80 mg daily. Her course was further complicated by pseudomembranous colitis, *Staphylococcus epidermidis* bacteraemia and graft versus host disease affecting her gastrointestinal tract.

On day 35 she became febrile, and the chest radiograph showed new bilateral generalised reticulonodular shadowing. She had no lymphadenopathy, no new skin lesions, no abnormalities in the fundi, no oral lesions, no splenomegaly, and no cardiac murmurs. At this time she showed signs of marrow engraftment with a white blood cell count of 7000, and, because of the new pulmonary infiltrates, she underwent open lung biopsy. The surgical specimens showed budding yeast on silver stain and intracellular organisms consistent with *Histoplasma capsulatum* (figure). The result of a complement fixation test for *H capsulatum* was negative and H and M precipitation bands specific for *H capsulatum* were absent in an immunodiffusion test. After the open lung biopsy treatment was begun with amphotericin B 50 mg daily and after eight days on this regimen the patient became afebrile. Cultures of lung biopsy material subsequently grew *Histoplasma capsulatum* and, after eight days, *Chlamydia tracheomata*. Intravenous erythromycin was then added.



Histological section prepared from a lung biopsy specimen stained with Gomori methanamine-silver, showing abundant Histoplasma capsulatum.

After open lung biopsy she developed diffuse alveolar infiltrates and severe hypoxaemia. Swan-Ganz catheter measurements indicated a pulmonary arterial pressure of 39/10 cm H_2O, a pulmonary capillary wedge pressure of 12 cm H_2O, and a cardiac output of 8·45 l/min. Initially her condition became stable with ventilatory support; but after two weeks of illness she developed progressive respiratory failure with decreasing lung compliance, and she died on the 60th day. She had received a total dose of 1350 mg of amphotericin B. No necropsy was performed.

The bone marrow donor was the patient's father, a 46 year old farmer with no medical history of note. His chest radiograph was clear at the time of transplantation, and he had no recent history of systemic or respiratory illness.

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Discussion

Infections, especially pneumonias, remain a common impediment to the successes of allogeneic bone marrow transplantation. Despite the reported incidence of fungal pneumonia in such cases and the well known ability of *H capsulatum* to cause pneumonia in immunocompromised patients, *H capsulatum* has been reported only once as a pathogen in a recipient of a bone marrow transplant. Our case allowed us to observe the clinical presentation and course of disease, serological response, and response to treatment in this unusual group of immunocompromised patients.

In contrast to immunocompetent patients, where infection with *H capsulatum* is rarely symptomatic and is without sequelae, infection with the organism in the immunosuppressed host is usually disseminated and often fatal.[4-6] In the Indianapolis outbreak disseminated disease developed in 73·8% of immunocompromised patients infected with *H capsulatum* but in only 6·5% of immunocompetent patients. The reported mortality from histoplasmosis in the immunocompromised population ranges from zero[4] to 73%[5] with an overall mortality in four series of 60%. All of the patients who survived received at least 1·4 g of amphotericin B and had begun to improve by the 14th day of treatment. After an initial stable period our patient deteriorated steadily, even though she started treatment early in her course and received nearly 1·4 g of amphotericin. We cannot be sure if her progressive respiratory failure was the result of progressive infection, but early full dose treatment for her fungal infection clearly did not prevent respiratory deterioration.

The diagnosis of histoplasmosis requires either positive cultures, histological evidence of tissue invasion, or serological conversion. Serology, although useful in immunocompetent patients, may be less useful in immunosuppressed patients.[7] In three previous series of immunosuppressed patients with histoplasmosis complement fixing antibodies to *H capsulatum* were absent in 54%, but Wheat *et al* reported that all recipients of renal transplants infected with *H capsulatum* had complement fixation titres greater than 1:8.[4] The reconstitution of the immune system in recipients of bone marrow transplants occurs at variable rates but appears to be delayed by the development of graft versus host disease. Despite evidence of infection with large numbers of *H capsulatum* organisms in our patient there was no detectable serological response.

Although in most cases of histoplasmosis each episode represents a new infection with the organism, in immunosuppressed patients there have been cases of histoplasmosis that appear to represent reactivation of latent infection.[8] We had no evidence of either new infection or transmission of infection from the marrow donor to our patient, so our patient may have had reactivation of a latent infection. Like the patients with reactivated disease reported by Davies,[8] our patient was receiving high dose corticosteroids at the time she developed pneumonia. She also had evidence of graft versus host disease, which delays the reconstitution of the immune system and is associated with a higher incidence of infections.[1]

This case extends the recorded range of diseases seen among recipients of bone marrow transplants and suggests that reactivation of latent infection with *H capsulatum* may occur in this group. Patients having high dose corticosteroid treatment for graft versus host disease may represent a particularly high risk group.

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