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Tropical respiratory medicine · 3

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Histoplasmosis and pulmonary involvement in the tropics

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History and microbiology

Histoplasmosis was first described by Darling in 1905, in a postmortem specimen from the tropical country of Panama, although the greater part of subsequent published experience has been from the United States.[1] The name *Histoplasma capsulatum* reflects his hypothesis that the organism was an encapsulated protozoan. The organism was cultured and shown to be a dimorphic fungus in 1934.[2] The mycelial form produces spores which are readily airborne and able to reach the small bronchi and alveoli. The organism takes the yeast form at body temperature; in histological specimens it is found almost exclusively in macrophages. The "capsule" is an artefact of certain stains such as haematoxylin and eosin.

Histoplasma capsulatum var *duboisii*, a variant found only in Africa, was first reported in 1952.[3,4] It is characterised by yeast cells which are of larger size and with thicker walls in tissue section than those of *H capsulatum* var *capsulatum*.[5] Throughout this article the term *H capsulatum* will be used to include both variants unless otherwise specified.

Epidemiology

Histoplasma is found in soil in endemic areas and shows a striking association with sites which are heavily contaminated with bat or avian faeces. Disturbance of such sites – for example, by construction – can generate large numbers of airborne spores. Clusters of cases of acute histoplasmosis have been associated with these activities[6] and with visiting bat caves. Birds are not infected, probably because of their high body temperature, but bats may be infected and excrete the organism in their faeces. Other mammals are readily infected, but it is not known what part they play in the epidemiology of *Histoplasma* infection in humans.

Our understanding of the prevalence and distribution of the infection worldwide is based mainly on skin test surveys. These indicate widely varying rates of infection between and within countries. Infection is nearly universal in some areas of the east central United States. Central America and northern South America appear to have the next highest documented prevalences with rates of over 40% in certain populations of several countries.[7] Skin test positivity was found in 4–34% of several populations in Thailand with somewhat lower rates in Burma, India, and Malaysia. Information from Africa is more limited, but rates based on small samples range from 0% to 31% in Uganda, 9% to 49% in Ivory Coast, and 1% to 20% in Liberia, Mali, Sudan, Rwanda, Zaire, and South Africa. Findings in West Africa may reflect the presence of *H capsulatum* var *duboisii*. *Histoplasma capsulatum* infection is found in both temperate and tropical regions, although rarely in areas that are very dry or have no warm season.

Reports of clinical disease due to *H capsulatum* parallel, to some degree, the reported prevalence of skin test sensitivity. Outside the USA histoplasmosis is best documented in Latin America and the Caribbean. The number of reported cases remains relatively small. Up to 1978 only 34 cases of progressive forms of histoplasmosis had been reported in Brazil, of which only four had mainly pulmonary disease.[8] Five epidemics of acute histoplasmosis (four involving caves) had also been described at that time, as had infections in several animal species. A review of 162 cases of deep mycoses from 6152 postmortem examinations and 85 386 biopsies and surgical specimens in Columbia revealed only a single case of histoplasmosis.[9] Small numbers of cases have been reported from Mexico[10] as have cave-associated epidemics of acute histoplasmosis from Costa Rica, Belize, and Panama.[11–13] Three cases of acute histoplasmosis and two of chronic disease were found in Trinidad in a study which also included Barbados and Guyana.[14]

Small numbers of scattered cases only have been reported from south east Asia and Oceania.[15–18] In New Caledonia, for example, a total of five cases have been described, all with pulmonary involvement. A 1970 review described only 30 cases of human histoplasmosis from Asia.[19] Among these lung disease was identified in only six, although seven others were considered "disseminated".

Histoplasma capsulatum var *capsulatum* has been reported from several countries in Africa including some which overlap with the geographical range of *H capsulatum* var *duboisii*.[20–28] Calcifications on chest radiography were associated with histoplasmin reactivity in both tuberculin positive and negative Kenyans.[29] Cave-related acute pulmonary

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histoplasmosis has been described in Tanzania, Zimbabwe, and South Africa.[30-33]

Disease due to *H capsulatum* var *duboisii* has been recognised only in Africa (if Madagascar is included) or in individuals who have lived in Africa. A review in 1986 found 206 reported cases.[34] While reported primarily from West Africa[35-38] it has been found in patients from as far apart as Sudan,[39] Ethiopia,[40] Malawi,[41] South Africa,[42] and Madagascar.[43] The organism has been identified in a small number of African animals, but little is known of its ecology or the source of human infection.[44]

Clinical features

The clinical spectrum of infection with *H capsulatum* has been well documented, particularly in the USA. No recognisable illness occurs in approximately 99% of infections following low level exposure to the organism; it is presumed to have been contained by cell mediated immunity. Late reactivation of disease can occur if the individual becomes immunosuppressed. Persisting calcification in the lung, lymph nodes, or spleen is common. Most symptomatic histoplasmosis falls into one of three categories: acute, chronic pulmonary, or disseminated disease.

Acute pulmonary histoplasmosis is a self-limited illness characterised by fever with headache, cough, or both, sometimes with chest pain and occasionally accompanied by erythema nodosum or multiforme. Following high level point source exposure, the incidence of symptomatic illness may be over 50%. The incubation period in non-immune hosts is approximately two weeks. The chest radiograph is usually normal, but may show pulmonary infiltrates or hilar adenopathy in more severe cases. The diagnosis is usually made when a cluster of cases occurs in the appropriate epidemiological setting – for example, after visiting a bat cave. Cultures are rarely positive, but serological examination can confirm the diagnosis. The illness almost always resolves without treatment.

Chronic pulmonary histoplasmosis is a relatively well defined clinical syndrome in histoplasmosis endemic areas. Even in populations where *H capsulatum* infection is nearly universal, the incidence of chronic pulmonary histoplasmosis is estimated to be only one per 100 000 per year.[45] In a series of 118 patients with chronic pulmonary histoplasmosis almost all were smokers and most had evidence of chronic obstructive airway disease or emphysema.[45] It is thought that underlying lung disease is a usual, if not a necessary, precondition for the development of chronic pulmonary histoplasmosis. The clinical presentation is similar in many ways to tuberculosis although chest pain was more common and night sweats less frequent in the series reported by Goodwin *et al.*[45] Histoplasmosis shares with tuberculosis a predilection for apical and posterior segments of the lung as well as for slowly progressive fibrotic lesions and calcification on chest radiography. "Early" non-cavitating pulmonary lesions associated with an acute or subacute clinical presentation usually resolve spontaneously but with scarring, some loss of lung tissue, and a risk of recurrence. The development of cavities, particularly with thick walls, is an indicator of progressive disease. In *H capsulatum* endemic areas of the USA it is estimated that 2–3% of patients diagnosed as having tuberculosis actually have histoplasmosis, a diagnostic problem of particular concern in tropical and developing countries where tuberculosis is common and often diagnosed without microbiological confirmation. Furthermore, tuberculosis and histoplasmosis occasionally coexist.[45] A definitive diagnosis may not always be possible, even where fungal culture facilities are available, as the sensitivity of sputum culture is only about 60% in chronic pulmonary histoplasmosis.[6 45] Serological tests are positive in most patients with chronic pulmonary histoplasmosis, and may support a clinical and epidemiological diagnosis, but cross reactions with other fungal infections can cause false positives.[46] The clinical course, particularly when thick walled cavities are present, is usually one of slowly progressive destruction of pulmonary parenchyma. Antifungal treatment is usually indicated, but some patients with chronic pulmonary histoplasmosis have a poor response to chemotherapy.

Disseminated histoplasmosis in children is characteristically a fulminant illness which may or may not have clinically apparent pulmonary involvement. Less rapidly progressive disseminated disease, often with localised organ involvement – for example, the meninges, adrenal glands, gastrointestinal tract, pericardium, liver, spleen, and occasionally the lungs – may be seen in adults who often have some degree of underlying deficiency in cell mediated immunity.

A distinct clinical syndrome has been associated with *H capsulatum* var *duboisii*. The clinical picture is characterised by a high frequency of skin, bone, and lymph node lesions with occasional mucous membrane and gastrointestinal involvement.[37 38] Several authors have commented on the relative rarity of pulmonary disease in *H capsulatum* var *duboisii* infection.[36 37] No clinical or radiological evidence of pulmonary disease was found in one series of 56 cases.[37] Clark and Greenwood, however, reported 12 cases with some evidence of pulmonary involvement and a number of reports have described cases with either localised pulmonary involvement, or involvement as part of a disseminated process, or at post-mortem examination.[20-38 47-52] If pulmonary disease is indeed less frequent in infections with *H capsulatum* var *duboisii* than with *H capsulatum* var *capsulatum*, it is not clear whether this is because of differences between the two organisms or because of a lower prevalence in Africa of the emphysematous changes which predispose to chronic pulmonary histoplasmosis. Host characteristics could also play a part as chronic pulmonary histoplasmosis occurs more frequently in white than black subjects in the USA.[45]

Treatment

Amphotericin B is the established treatment for patients who are seriously ill with histoplasmosis. Ketoconazole, usually for at least six months, is effective in most of those with less acute forms of disease. The response of *H capsulatum* var *duboisii* to drug treatment appears to be similar to that of *H capsulatum* var *capsulatum*.[53 54] Early experience in *H capsulatum* var *capsulatum* infection with triazole drugs, particularly itraconazole, suggests that it is likely to be at least as effective as ketoconazole and may be better tolerated.[55]

Histoplasmosis and HIV infection

Histoplasmosis was not added to the list of AIDS-defining conditions until 1987, yet in histoplasmosis endemic areas of the USA it may be the leading opportunistic infection in AIDS.[5 6] *Histoplasma capsulatum* var *capsulatum* associated with HIV infection has now been reported from tropical co-endemic regions such as the Caribbean, Africa, and South America.[57–59] There are also a few reports of disseminated *H capsulatum* var *duboisii* associated with HIV infection.[60–63]

Histoplasmosis was the AIDS-defining illness in just under half of the patients in two series,[64 65] suggesting that it can occur earlier in the course of HIV-related immunosuppression than is the case with such opportunistic infections as *Mycobacterium avium*. Fever and weight loss are almost invariably present. Respiratory symptoms are present in more than half of the cases. A reticulonodular pattern is seen on the chest radiograph in more than half,[65] while mediastinal lymphadenopathy was noted in only 2·8–4·5% of cases.[64] Calcification in the lung or mediastinum was present in only 2·5% of American patients. Hepatomegaly or splenomegaly are seen in a substantial minority, and skin or gastrointestinal tract involvement in a few. A septic shock-like picture with coagulopathy has also been described.

In HIV-infected patients the diagnosis of histoplasmosis is usually made by isolation of the organism from blood or tissue. Wheat *et al* found the rate of positive cultures of both blood and bone marrow to be >90% when a lysis centrifugation technique was used.[64] Culture of respiratory secretions or lung biopsy, urine, lymph node tissue or biopsy of other clinically involved tissue may be diagnostic. An immediate diagnosis can sometimes be made from microscopic examination of bone marrow or even peripheral blood. Antigen detection shows promise as a tool for diagnosis and following response to treatment.[66] Depending on the technique and the laboratory, serological tests for histoplasmosis may be positive in >70% of patients with HIV infection and histoplasmosis,[64] but there is little experience in relying on this as a primary diagnostic method in this patient population.

Amphotericin B is considered the standard treatment for HIV-associated histoplasmosis and has been associated with a response rate of at least 80%. Two recent reports suggest that itraconazole alone is often effective, even in HIV-infected patients.[59 67]

Relapse is very common unless suppressive treatment with either intermittent amphotericin[68] or daily oral itraconazole[69] is continued indefinitely. Ketoconazole appears not to be adequate either for initial treatment or suppression of relapse in HIV-infected patients. Achlorhydria, which is common in patients with AIDS, significantly reduces absorption of this drug.

Conclusions

Although histoplasmosis is not likely to be a common cause of lung disease anywhere in the tropics, it is probably underdiagnosed because of the technical difficulties of microbiological diagnosis and the likelihood of confusion with tuberculosis. *Histoplasma capsulatum* var *duboisii* is a pathogen unique to Africa; it is not yet clear whether this organism is truly less likely to cause pulmonary involvement than is *H capsulatum* var *capsulatum* in Africa. Histoplasmosis as an opportunistic infection in HIV-infected patients is likely to be recognised increasingly in the tropics. These observations may add to our understanding of the geographical distribution of histoplasmosis by demonstrating previously unrecognised endemic areas. While histoplasmosis is a relatively treatable complication of HIV infection, the limited availability of sophisticated diagnostic facilities and the present high cost of treatment are likely to limit the possible benefits of treatment for many affected patients in the tropics.

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