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Pulmonary Histoplasmosis: A Review of 50 Cases

SUMMARY

Histoplasmosis is a systemic fungal infection caused by Histoplasma capsulatum. Infection, identified by skin testing, has been found in more than 50 countries. In Canada the disease is endemic in the St. Lawrence River Valley. Fifty patients with positive reaction to histoplasmin skin tests were reviewed at the Provincial Chest Clinic in Windsor, Ontario. All were asymptomatic; 27 had a history of present or previous involvement in farming or poultry rearing. (Can Fam Physician 26:225-230, 1980).

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HISTOPLASMOSIS is a systemic fungal infection caused by Histoplasma capsulatum. The organism is inhaled, invading the lung where it characteristically involves the body's reticuloendothelial system, producing a granulomatous reaction. The majority of infections are benign and self limited.

The organism was first identified by Darling in Panama in 1905 in three patients at autopsy.[1] As late as 1945 most reported cases proved fatal.[6, 7] In 1955 Billings and Couch[8] described two patients with pericardial calcification and a histoplasmin sensitivity, suggesting that Histoplasma capsulatum might be the cause of the pericardial disease. In 1976 Bilgi and Slesar[9] reported two cases of constrictive pericarditis and pericardial calcification with a positive histoplasmin skin test.

Materials and Methods

Ninety-eight patients had histoplasmin skin tests at the Provincial Chest Clinic, Windsor, Ontario in the period Oct. 1, 1978 to Sept. 30, 1979. Patients showing a positive reaction (five mm or greater induration) to histoplasmin skin test (intradermal injection of 0.1 ml of histoplasmin, diluted stabilized solution, clinically equivalent in potency to the U.S. Reference Standard, Lot H-42 (1:100), of the U.S. Public Health Service, National Centre for Disease Control), were included in the present study. Patients also had a tuberculin skin test. Histoplasmin complement fixation tests were obtained in 20 patients. Patients also had P/A and lateral chest X-rays; tomograms were obtained when necessary.

Results

Fifty patients showed a positive reaction to histoplasmin skin test, size of induration varying from five mm to 25 mm. Patients showing less than five mm of induration were excluded from the present study. Seven patients also showed a positive reaction to tuberculin skin test, i.e. more than ten mm of induration. Sputum culture for acid-fast bacilli were obtained from these patients; none of them showed positive culture for acid-fast bacilli. Out of 20 patients who had histoplasmin complement fixation test, nine patients were reactive with variable titer from 1:2 to 1:16 dilution. Eleven patients were non-reactive.

There were 29 male and 21 female patients. The age range was 14-82 years, with average age 49.5 years.

Seventeen patients were chronic smokers with an average smoking history of 33 pack years. Twenty-nine patients were residents of rural areas in Essex and Kent County and 21 patients were residents of the Metropolitan Windsor area. Ten residents of a rural area were involved with farming and nine were associated with the poultry business. Eight out of 21 urban residents gave a previous history of involvement with either farming or poultry.

Thirteen patients showed unilateral hilar calcification, seven patients showed multiple bilateral hilar calcification and solitary parenchymal calcification was noted in 15 patients. Solitary parenchymal calcification and hilar calcification were seen in 14 patients.

All 50 patients were asymptomatic at the time of the study.

Epidemiology

The spores of H. capsulatum, a soil saprophyte, are inhaled as 'droplet nuclei' by man and animals; invasion then takes place in the alveolar walls. The respiratory tract is almost invariably the route of infection. Occasional cases may result from direct mucosal invasion of the oral pharynx or gastrointestinal tract. Rare cases of percutaneous inoculation have been reported.[10] For all practical purposes, man-to-man or animal-to-man transmission does not occur. Thus, while the route of infection is essentially identical to disease resulting from M. tuberculosis, the absence of man-to-man transmission is distinctly different.

Geographic Distribution

Histoplasmosis occurs worldwide. Infection, as identified by skin testing, has been found in more than 50 countries. On the basis of skin test surveys, 18-20% of the U.S. population, some 50 million or more people, have been infected.[11, 12] Areas with the highest infection rates in the U.S. centre about

the Mississippi River Valley and its major tributaries, the Ohio, Missouri, and Tennessee River Valleys. In Canada the disease is endemic in the St. Lawrence River Valley. Even within highly endemic areas, infection rates may vary two-to-ten-fold within relatively short distances.[13]

The histoplasma organism appears to thrive best in red-yellow podzolic soil with relatively high humidity and moderate temperatures. Its growth is enhanced in the presence of bird droppings, especially chickens and starlings or bat guano mixed with soil, or in decaying matter such as wood. Starling roosts in urban areas have repeatedly been identified as a point source for epidemics.[14]

Pathogenesis and Pathology

Studies in man indicate a striking similarity between the pathogenesis of histoplasmosis and tuberculosis. Following an incubation period of five to 18 days, the initial site of invasion is almost invariably the lung. This is followed by extension to adjacent lymphatics, lymph nodes, and the bloodstream.[15] Hematogenous dissemination with the initial infection appears to be almost invariable. Mycobacteria and Histoplasma grow relatively slowly. However, there are some apparent differences. Especially in the so-called epidemic form of histoplasmosis there are multiple airborne foci of pulmonary infection, manifested as multiple nodular densities, which is extraordinarily rare in tuberculosis. Histoplasmosis in the lung and other organs, especially the spleen, calcify more frequently and to a greater extent. Histoplasmosis tends to have greater lymphatic involvement; mediastinal lymphatic involvement may produce fibrosing mediastinitis and obstruction of blood vessels, leading to the superior vena cava syndrome and marked narrowing of the tracheobronchial tree. It also involves the adrenal glands, more commonly resulting in adrenal insufficiency.[16]

Histoplasma capsulatum, when present in large numbers may be seen in tissues with hematoxylin and eosin stains. However, they are more readily identified with periodic acid-schiff, Gridley or Gomori methenamine-silver stains. The organism is usually three to five microns and almost always intracellular. However, there can be considerable variation in size, even up to 15-20 microns. They may appear to be growing by budding, and occasionally there is evidence of hyphae formation.[16] The organism is particularly difficult to identify in solitary pulmonary nodules, but careful study can be quite successful.[17]

Clinical Patterns of Histoplasmosis

Subclinical Infection

The most common form of infection is subclinical. Infection is documented subsequently by a positive histoplasmin skin test with or without other evidence of infection, such as parenchymal scarring, a pulmonary nodule, or mediastinal node enlargement, any of which may have calcification on chest X-rays.

Acute Pulmonary (Benign) Infection

This form of the disease most often presents as a respiratory tract infection of varying severity or an influenza-like illness. The individual may have a cough with little or no sputum production, chest pain (subpleural location of lesion), and systemic manifestations of fever, malaise, headache, anorexia and myalgia.

Examination of chest may be normal; there may be some localized rales or rarely an area of consolidation. Chest X-ray may show a localized infiltrate, a picture similar to any number of pneumonias. There may also be hilar or mediastinal node enlargement. If a larger number of organisms has been inhaled, there may be multiple nodular infiltrates. Over a period of time these nodules coalesce and may calcify. Some cannot, producing multiple tiny discrete calcifications. Some patients presenting with pulmonary calcifications cannot recall even a severe respiratory or influenza-like illness.[18]

Acute Pulmonary (Severe) Infection

This presentation is due to inhalation of a large number of organisms, usually from a source that can be subsequently identified (e.g., cleaning out an old feces-laden chicken coop, spelunking in a cave with bat guano). The individual appears acutely ill and quite toxic with a high fever, cough, commonly paroxysmal with little sputum production, marked tachypnea and dyspnea; cyanosis may be present. The chest X-ray discloses multiple nodular lesions varying from small and discrete to larger, fluffy lesions that tend to coalesce.[19]

Chronic Cavitary Infection

This presentation is clinically and radiologically indistinguishable from tuberculosis. The individual has a productive cough and may have some hemoptysis. He may relate coughing up small bits of gravel or sandy, gritty material (i.e. broncholithiasis) with specific questioning. Non-specific symptoms of anorexia, weight loss, and malaise are common. With extensive parenchymal involvement there may be dyspnea. There is fibronodular disease usually with cavities and volume loss, particularly in the upper lobes or the superior segment of the lower lobes on the chest roentgenogram. Co-existing tuberculosis and histoplasmosis have frequently been identified, especially in tuberculosis sanatoria.[20, 21, 22]

Disseminated Infection

Disseminated infection commonly affects infants or older men. Its presentation is reticuloendothelial or systemic rather than pulmonary. It is very rare, probably occurring in less than 0.1% of acute infections. The individual has fever, malaise, weight loss, and anorexia. There may be generalized lymph node enlargement which is more prominent in adults. The individual may complain of pharyngeal pain, hoarseness or dysphagia; ulceration of the tongue, palate, epiglottis or larynx occurs in up to one-third of adults. Gastrointestinal involvement may be manifested by nausea, vomiting, diarrhea, and abdominal pain. Commonly there is hepatosplenomegaly. Marked anemia and leukopenia are associated with bone marrow invasion. The most commonly involved organs are the adrenals, meninges, and brain; less commonly involved are the endocardium, pericardium, kidney, testes, prostate, esophagus, and pleura. Bone involvement is less frequent than in other systemic fungal infections. Pulmonary parenchymal or mediastinal involvement is not usually a prominent manifestation. Nodular or ulcerative skin lesions are also frequent. Direct smears of the lesion using potassium hydroxide or one of the blue stains (e.g., cotton methylphenyl blue) may immediately provide a diagnosis; a biopsy of the lesion wall for histology and culture should also be obtained.[23, 24]

Specific Organ Involvement

Some patients with extrapulmonary

disease present with primary manifestations related to a single organ. Patients may present with lymphadenopathy, hepatosplenomegaly, jaundice, anemia, fever, or evidence of a coagulopathy simulating a primary reticuloendothelial disease. A patient with meningeal involvement may relate slowly progressive symptoms of headache, altered mentation, psychologic changes, and may have minimal meningismus. Some will present with chronic diarrhea, melena, or hematochezia. Rarely the presenting problem is that of pleural effusion, empyema or bronchopleural fistula.[25, 26]

Pericardial involvement with histoplasmosis is another uncommon entity seen more often in children and young adults. Identification or isolation of the organism in the pericardium or fluid is uncommon. Full recovery is often slow; there may be episodes of recurrent pericarditis.

The mediastinum may be involved with histoplasmosis in two forms: a lymph node may enlarge and impinge on a vital structure, or extensive fibrosis may extend throughout large areas of the mediastinum. Symptoms result from impingement on a vital structure. Histologic specimens may disclose organisms only with extensive scarring.

Diagnosis

The absolute diagnosis of Histoplasmosis requires cultural identification of the organism. Its identification in histologic preparation is often satisfactory. At times such proof may not be obtainable and a clinical diagnosis can be made on the basis of the clinical and X-ray findings, exclusion of other disease processes by careful study, and serologic evidence of infection.

Skin Test

Skin testing material for Histoplasmosis (histoplasmin) is made from a broth filtrate of the mycelial phase of H. capsulatum. The usual test dose is 0.1 ml of a 1:1000 solution. The reaction is read at 48-72 hours; a reaction of five mm of induration is considered positive. The actual measured induration should be recorded. A positive skin test indicates infection with H. capsulatum at some time, whether remote or recent. The reaction tends to wane over many years. There is frequent cross-reactivity with blastomycosis and occasionally with coccidioidomycosis. A false-negative reaction occurs in about five percent of patients with active pulmonary histoplasmosis and in one-third to two-thirds of patients with disseminated histoplasmosis. Most importantly, a histoplasmin skin test may falsely elevate serologic studies to either mycelial or yeast phase antigens in 25% or more of reactors.[27, 28] This elevation is usually evident within 15 days and may remain for three or more months. Thus in an adult being evaluated for active disease which might be histoplasmosis, the histoplasmin skin test should not be used. The skin test may be quite helpful in an infant with possible active histoplasmosis, since a positive reaction even in an endemic area strongly supports the diagnosis.

Serologic Tests

The standard serologic study is the complement fixation technique using a mycelial phase antigen (MF), histoplasmin, and a yeast phase antigen (YF). The YF is usually elevated first after initial infection, while the MF rises later but tends to remain elevated with chronic disease for extended periods. After acute infection one or the other is elevated in 14% at two weeks, 67% at three weeks, 86% at four weeks, and almost all after four weeks.[29] Thus it is important to repeat serologic studies at two to four week intervals. This will avoid missing a titer which is in the rising phase. Unfortunately, in disseminated disease, false-negative results have occurred in 45-80%.[30, 31]

The height of titers does not appear to correlate with the severity of disease or ultimate prognosis. Some authors consider the continued elevation of titers of 1:32 or greater, or titers that vary from zero to 1:8 or 1:16, as indications of continued activity and potential difficulty. Low-grade titers have been documented for many months without evidence of disease activity. A histoplasmin latex agglutination test is frequently positive in acute infections but in only about 50% of chronic active infections.

Identification

Direct preparations of sputum or

Fig. 1.
Histoplasmosis: dense left hilar calcification.

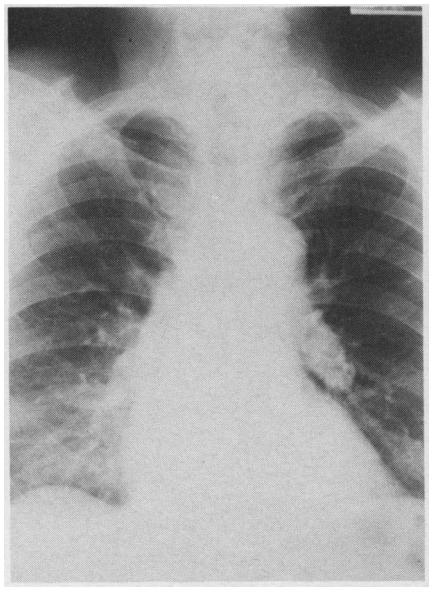


Fig. 2.
Histoplasmosis: bilateral multiple calcifications of varying size.

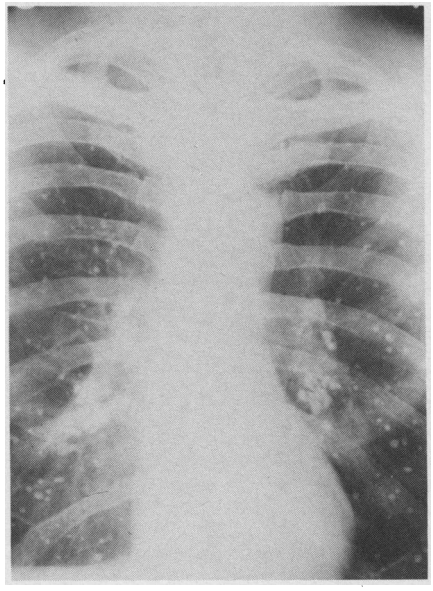
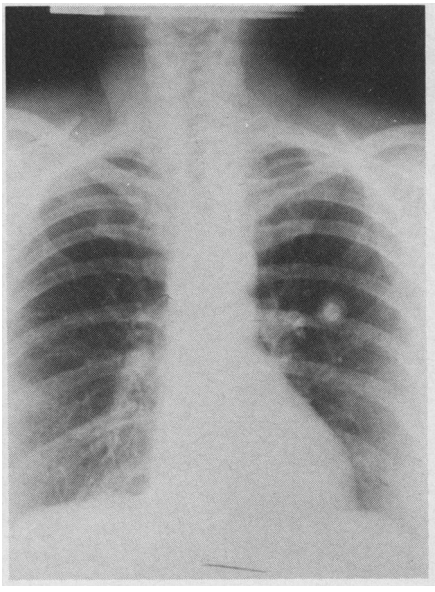


Fig. 3.
Histoplasmosis: a solitary nodule in the left lung.



other material stained with Wright or Giemsa stain will demonstrate the organism as an oval two to four microns in size, with a large vacuole; buds with a narrow attachment may be seen at the smaller end of the cell. Surrounding each organism is a pale capsule-like area (hence the name capsulatum) which represents an artifact due to protoplasmic shrinkage rather than a true capsule.

Culture

Histoplasma capsulatum has been most difficult to grow in many laboratories even when an appropriate specimen is provided. The organism will grow on brain-heart infusion glucose blood agar and Sabouraud's glucose agar at room temperature and 37°C with antibiotics added to prevent bacterial overgrowth. It can also be grown in laboratory animals such as mice.

Management

The vast majority of patients who develop histoplasmosis do not require treatment and with subclinical disease do not even seek medical attention. Patients with acute benign pulmonary histoplasmosis have a self-limited illness requiring nothing more than symptomatic and supportive therapy for a short period. In the presence of severe symptoms, clinical toxicity, and extensive, usually multinodular, infiltrate on chest X-ray, one should seriously consider specific therapy, namely amphotericin B. Since the drug must be given intravenously over an extended period, its morbidity must be weighed against that of the primary illness.

Chronic pulmonary histoplasmosis that is progressive, or radiographically cavitary, or symptomatic, requires a full course of amphotericin B.

The usual current recommended total dose of amphotericin B is 2-2.5 g or a minimum of 35 mg/kg body weight. The drug must be given intravenously in a daily dose not exceeding one mg/kg.

Discussion

Histoplasmosis infection is not a new entity, but it has probably often been overlooked. It is frequently difficult to differentiate from other types of calcification without histoplasmin skin testing.[32] Brodsky and colleagues[33] reported that skin tests were positive in 70-79% of residents in Delaware County, Ohio, during an outbreak of histoplasmosis. While the majority of cases arise in endemic areas, many occur in areas where the skin test reaction rate is as low as two to three percent. Thus the possibility of histoplasmosis should be considered in a patient with a clinically compatible history, even when there has been no contact with an endemic area.

Epidemics occur in nonendemic areas or in groups who visit an endemic area. They have provided immensely valuable information about point sources, incubation time and the spectrum of disease. The following point sources have been identified: chicken coops (particularly cleaning old ones); starling roosts; bats both in caves and buildings; dismantling old buildings (especially old schools); cleaning old buildings (barns, water towers, bridges, silos, church belfries); hollow trees; mycology laboratories; old storm cellars; building fires with old decaying wood; peat moss; digging for worms in woods; construction sites; major clean-up efforts; and compost heaps.[34, 35]

In the present study history of present and previous occupation revealed that ten residents of a rural area were involved with farming and nine were associated with the poultry business. Eight of the 21 residents in the urban region gave a previous history of involvement with either farming or chicken breeding. There appears to be high prevalence of skin-test sensitivity in Essex and Kent Counties; similarly, the Ottawa Valley has a high prevalence of histoplasmosis infection.[9]

In endemic areas, 80-95% of the population may have a positive histoplasmin skin test. A parenchymal lymph node complex has been identified in 67% of routine autopsies in an endemic area;[36] postmortem X-ray studies of spleens have found 67% with calcifications and 40% with multiple calcifications characteristic of histoplasmosis.[37]

In a study of a small endemic focus in Milan, Michigan, 25% of five year olds and 95% of 19 year olds had positive histoplasmin skin tests, as compared to an eight percent rate for the rest of the county.[38] In evaluating 750 chest X-rays from this population, 185 were abnormal. Two-thirds of these had calcification, 40% unilateral hilar, 30% solitary parenchymal and 30% both. Other abnormalities were less common: only two children showed clinical evidence of disease.[39] Among

the 50 patients with positive histoplasmin skin test in our study, 49 showed pulmonary calcification. Twenty-six percent showed unilateral hilar calcification (Fig. 1), 14% showed multiple bilateral hilar calcification (Fig. 2), while 30% of the patients showed solitary parenchymal calcification (Fig. 3). In a patient with a pulmonary nodule or parenchymal or lymph node calcification, a positive or negative histoplasmin skin test should not be considered as definitive of a specific etiology for the lesion.

While it is useful to consider the presenting patterns of histoplasmosis individually, it is important to recognize that they often blend into one another. The data available would indicate that hematogenous dissemination at the time of initial infection occurs in essentially all individuals. All 50 patients in our study were asymptomatic. In evaluating the course of 90 patients without chemotherapy, there were nine deaths due to the pulmonary disease (four others after pulmonary surgery) and X-ray progression in 79% of those followed for three years.[18]

In the United States Public Health Cooperative Mycoses Study, 27 of 84 patients with untreated chronic pulmonary disease died at a fairly constant rate of six to nine percent per year: there was X-ray progression each year, increasing from 23% in the first to 64% in the sixth year. These individuals had extensive bilateral, usually cavitary disease.[40] A subsequent study comparing treated vs. untreated patients clearly documented the efficacy of amphotericin B at a total dose of 25 mg/kg body weight or greater.[41]

Disseminated histoplasmosis affects the very young as well as those beyond the fifth decade, and is often associated with other underlying severe disease. It has a mortality of over 80% if not treated. In one series, 20 of 22 patients not treated died two weeks to 67 months from the time of diagnosis—16 within four months. In a group of 22 patients receiving an adequate course of therapy, all were alive at three months; 13 died between three and 107 months after starting treatment, but none died from active histoplasmosis. Relapses requiring treatment occur. Patients have been reported as cured with total doses as low as 460 mg, although most physicians recommend a total initial dose of two g or 35-40 mg/kg body weight.[42]

In conclusion, histoplasmin skin testing continues to be a very valuable epidemiologic tool in population surveys identifying endemic areas. ◉

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