Histoplasmosis:

Another Endemic Mycosis in Our Neighbourhood

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In North America alone, it is believed that over fifty million individuals have been infected with *Histoplasma capsulatum*. *H. capsulatum* is endemic in certain areas of the US and Canada. Since infection of human hosts can lead to several different clinical presentations of histoplasmosis, *H. capsulatum* is this month's **Bug of the Month**.

The history of histoplasmosis

First described by Samuel Darling in 1905, histoplasmosis is a fungal infection caused by *Histoplasma capsulatum*, a dimorphic fungus endemic in the Ohio and Mississippi River Valleys. Infection is also frequent in the St. Lawrence River Valley. *H. capsulatum* can lead to a variety of clinical presentations from mild respiratory illness to a disseminated disease state. In a damp, acidic environment, often inhabited by birds and bats, *H. capsulatum* exists as a mycelium in the soil. While bats may become infected, transmitting disease through defecation, birds do not become infected. However, bird excrement serves to enrich the soil for fungal growth.

Stirring up the dirt

Infection can occur from occupational exposure or other recreational activities which result in disruption of the soil and aerosolization of the spores which are then inhaled. Once in the lungs, the spores germinate into yeast. Lung macrophages phagocytose the yeast which continue to proliferate intracellularly. The oval budding yeast is able to raise the pH within the macrophage and inactivate the digestive enzymes. Dissemination is possible through lymphatic spread. Approximately two weeks after infection, a cellular immune response is mounted. Immunocompromised individuals may be unable to mount an appropriate immune response, thus leading to an often fatal, progressive disseminated disease. Factors such as underlying lung disease, immune status and degree of exposure determine severity of symptoms. Only about 5% of individuals become symptomatic after a low-level exposure with variety of non-specific symptomology. However, a high-dose exposure can lead to the rate of disease being 75% in healthy individuals.

How does it present?

The spectrum of presentations with histoplasmosis is as follows:

- Asymptomatic primary infection: This presentation is common in immunocompetent individuals. A chest radiograph often results in a solitary pulmonary nodule. Enlargement of the mediastinal and hilar lymph nodes may also be observed
- Acute pulmonary histoplasmosis: The severity of this self-limiting disease presentation is often related to an overt exposure to spores. Clinical presentation can encompass fevers, headaches, sweats and malaise. Physical examination is often non-contributory, although some signs such as adenopathy, erythema multiforme and hepatosplenomegaly may be seen. A chest radiograph may reveal a patchy pneumonia or diffuse small lung nodules. Enlargement of the mediastinal lymph nodes may also occur. They may become large enough to lead to obstruction of airway or blood vessels. The clinical course can be varied and may lead to dyspnea, cough and hemoptysis. Pleuritic chest pain may be a result of pericarditis stemming from local lymph node inflammation. Up to 10% of individuals with acute pulmonary histoplasmosis will develop a spectrum of arthralgias, erythema nodosum, erythema multiforme and arthritis

- Chronic pulmonary histoplasmosis: Patients with underlying lung pathology, such as chronic obstructive pulmonary disease, may develop chronic pulmonary histoplasmosis. Symptoms are similar to pulmonary TB. If untreated, it is progressive and can affect contiguous lung tissue leading to cavity formation. Lung necrosis is often due to a hyperimmune reaction to fungal antigens
- Progressive disseminated histoplasmosis: This is an infrequently encountered disease that usually occurs in those individuals with disorders of cell-mediated immunity, such as those individuals who have AIDS, on immunosuppressive therapy, or even immunocompetent individuals who have had a profound exposure to *H. capsulatum*. It can present with fevers along with other constitutional symptoms. Spread to the liver and spleen can lead to hepatosplenomegaly and lymphadenopathy. It is common to see oral ulcerating lesions in patients with AIDS. Disseminated disease can result in elevated liver function tests and pancytopenia, reflecting liver and bone marrow involvement respectively. Adrenal involvement can be found in up to 90% of patients while meningitis can be seen in 10%. Adenopathy and diffuse airspace disease are rare; however, diffuse interstitial infiltrates are often seen
- Other clinical presentations: Histoplasmosis may affect the central nervous system and could also cause broncholithiasis, mediastinal granuloma and fibrosis. Ocular involvement has also been reported

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How is it diagnosed?

The standard for diagnosis is culture of *H. capsulatum*. However, the long incubation period of up to six weeks has made investigators strive for a more rapid means for diagnosis. Other methods for diagnosis include tissue biopsy for histological analysis; skin testing, which is unfortunately non-diagnostic due to the high rate of positive tests in endemic regions; serological antibody tests which are rapid but may have frequent false-negative (in immunocompromised individuals with disseminated disease) and false-positive results (due to cross-reactivity with other fungal infections); complement fixation and immunodiffusion assays may be used but the diagnosis is made on observing a four-fold increase in the complement fixation antibody titer and thus it may be difficult to differentiate active infection from inactive infection as titers remain elevated for several years. Antibody assays are useful for chronic forms of histoplasmosis. Ultimately, although culture is slow, it may well be the most appropriate investigation to definitively establish the diagnosis of histoplasmosis.

Treatment

There are several treatment recommendations available for the management of histoplasmosis and they depend upon the immunological and clinical status of the patient. It may be prudent to consult with a specialist in infectious diseases before embarking upon treatment of a patient in whom histoplasmosis has been diagnosed, as therapy may not be required. The disease is often self-limiting in immunocompetent patients and no specific therapy beyond symptomatic control is often necessary. Antifungal therapy is indicated for those patients who have severe or prolonged acute pulmonary histoplasmosis, chronic pulmonary histoplasmosis and progressive disseminated histoplasmosis. Often corticosteroids are a useful adjuvant therapy for immunocompetent patients who have respiratory compromise and acute pulmonary histoplasmosis. Suppressive therapy is required to prevent relapse for patients with AIDS.

Other suggestions

Previous infection has been shown in > 80% of young adults in the endemic areas surrounding the Ohio and Mississippi Rivers. Although exposure is common, the clinical manifestations are uncommon. Still, several recommendations can be made to avoid infection. Patients at risk should be educated to avoid high exposure areas, especially those heavily populated by birds and bats. This is especially true where disruption of soil is expected. Extra care should be exercised if the individual is immunocompromised. Difficulty is faced by the physician when making a diagnosis, especially given the array of clinical presentations. Travel, occupational and exposure history-taking is vital as well as contributing factors to immune status when a clinician is involved with a possible diagnosis of histoplasmosis.

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