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HISTOPLASMOSIS[1)]

By Nikodem Nikiel
Second Division of Internal Diseases
Institute for Improved Training and Specialization
of Medical Cadres, Warsaw

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Definition. Histoplasmosis is a systemic disease caused by the fungus Histoplasma capsulatum affecting all of the reticuloendothelial system or only part of it. It settles in the lungs, liver, spleen, alimentary tract, lymphatic glands, bone marrow, adrenal glands, skin, and mucosa.

History and Geography

Histoplasmosis was described for the first time by Darling in 1906 in Panama. This author believed that the etiological agent belonged to the phylum Protozoa. It was only in 1912 that Da Roche Lima proved that Histoplasma capsulatum is a fungus. Histoplasmosis is also known in the literature as Darling's disease or under the name of Cytomycosis reticuloendotheliatis (Humphrey).

In 1934, de Mombreun succeeded in obtaining, on artificial medium, cultures of Histoplasma capsulatum from the blood and spleen of a sick child. This marked the beginning of experimental studies on animals. Histoplasmosis was a little-known disease. According to Parson and Zarofonetis, up to 1945 only 71 cases of histoplasmosis were reported in the world literature. In Europe, Derry first reported the occurrence of histoplasmosis in England in 1942. Wohlwill and Maurais described in 1943 a case in Portugal. Tevfik Saglam reported a

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1) Read in April 1955.

case in Istanbul in 1946. Studies by Christie, Peterson, Furcolow, High, and Allen during the past few years revealed that histoplasmosis occurs much more frequently than originally assumed. It is most prevalent in the USA, especially in the Midwestern states. It also occurs among the populations of South America, south Africa, the Philippine Islands, Java, and in England. In 1945, Christie and Peterson, in conducting mass tests of the population, especially children, in the East Central states of the USA, noted that many of them had calcified foci in the lungs. In the majority of these persons the tuberculin test was negative whereas the histoplasmosis reaction was positive, indicating a history of histoplasmosis. Arenson, Saylor, and Parr reached a similar conclusion in their studies on the Indian population in Arizona. Collie and de la Fuenta observed the incidence of histoplasmosis in birds, mammals, insects, and the native population of South America. Tests with histoplasmin on 831 persons gave positive findings in 43.1 percent of the cases, and for children below 10 in -- 16.9 percent. Histoplasmin tests on recruits in Switzerland (555 cases) did not yield one positive case, proving that the disease is not prevalent in Switzerland. Koller and Kunn administered histoplasmin tests to 180 patients with radiologically established calcification foci in the lungs at the clinic in Zurich; a positive reaction was obtained in two cases, both of which had spent considerable time outside Europe, one in America and the other on Java. We, therefore, draw the practical conclusion, that, in view of the increased migration of people after the last few wars, a history of histoplasmosis must be considered in cases of radiologically established calcification foci in the lungs.

Etiology. Histoplasmosis is caused by the fungus Histoplasma capsulatum (Fig. 1). The route of infection is the respiratory tract, and presumably also the alimentary tract and the skin. The fungus can be cultivated on artificial media, and is pathogenic in laboratory animals. At room temperature, it grows in the form of a loose mycelium with spores. At a temperature of 37°C, cells similar to yeast are formed, about 1--5 micron in width and with a distinct capsule (capsula), which are morphologically identical to Histoplasma capsulatum found in the tissues of the diseased human. According to Conant, Histoplasma capsulatum belongs to the group Moniliaceae. The fungi which cause the disease are caught up by the cells of the reticulcendothelial system. They can be found in the blood, in the macrophages, and in the reticular cells of the liver, spleen, lymphatic glands, and bone marrow. These cells become filled with the fungus, which is rarely found outside the cells. In addition, the Histoplasma can be histologically determined in sections from skin ulcerations and mucous membranes. Its cultures from the marrow are rarely successful,

and are therefore of little diagnostic value. This observation is confirmed by Schwartz and Barsky, who succeeded in growing only one culture out of 193 from the marrow of histoplasmosis patients. The fungus can sometimes be identified in sputum slides stained by the Wilson, Wright, or Giemsa method. It is most frequently found inside the macrophages in the form of a small oval cell resembling that of yeast. It can also be grown from the sputum on Sabouraud's agar. Usual sources of infection are dogs and rodents (Kirsch, Fressel, Freijo, de Mombreun, and Anderson), and the fungus may also be found in the earth. Infection can occur by contact with animals, by means of ticks, or from the earth via inhaled dust.

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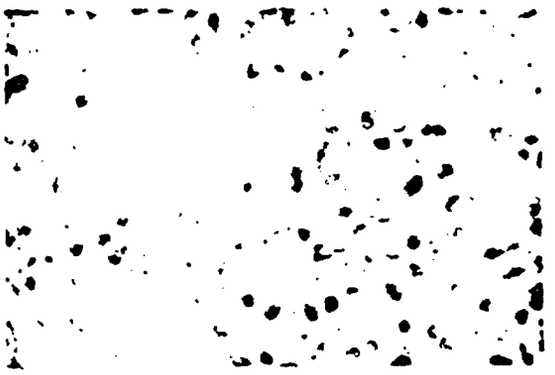

Figure 1. Histoplasma

Histological section of the bone marrow with Giemsa stain. Visible cells -- Histoplasma capsulatum -- with white rim corresponding to the capsule (capsula). Reproduced from: R.Philip and Custer, Atlas of the Blood and Bone Marrow, p 224.

Pathogenesis. Histoplasmosis is an infection damaging the reticuloendothelial system. It settles in the liver, spleen, alimentary tract, lymphatic glands, bone marrow, lungs, adrenals, skin, or mucosa, particularly of the mouth, and more rarely in the kidneys, heart, pancreas, or thymus. In the pulmonary form, the spores of the fungus reach, by means of the respiratory passages, the lungs, where they transform into H. capsulatum, multiply, and create granular foci of inflammation, which undergo caseous decomposition, and eventually become saturated with calcium salts, just like in tuberculosis. The granular infiltration caused by the fungus is indistinguishable from the similar tubercular nodules.

Pathologic Anatomy and Histopathology

Anatomic changes in the diseased organs resemble changes in sarcoid or tuberculosis (Pinkerton, Iverson), and particularly noticeable are the smaller or larger cavities filled with caseous matter. The histological picture of the granular infiltration includes phagocytes, fibroblasts, lymphocytes, plasma cells, and sometimes even Langhans's giant cells. In the lymphatic gland, one can frequently note complete alteration of the tissue, with an increased number of lymphocytes and few giant cells, likely to lead to a diagnosis of "maligne Lymphom mit Tuberkulose" (Murray, Brandt).

In the tissues of the system, H. capsulatum evokes apparent tubercles with a focus of necrosis in the center and surrounded by macrophages and granular tissue. Individual tubercles may merge to form a larger necrotic focus or ulceration. On the slide, H. capsulatum can most frequently be found on the borderline of the dead tissue (Pinkerton, Iverson) as round or oval shapes, with a diameter of 1--5 microns and more or less encased, located inside the cells. The parasite stains well with hematoxylin and eosin dye, but the casing does not.

Symptomatology

In the clinical course, we can differentiate two forms of histoplasmosis:

1. Malignant form, progressive, and nearly always fatal.

2. Benign form, with a mild and chronic course, frequently passing under cover of pulmonary changes.

Malignant Form. The clinical picture varies.

In a case described by Kirsch and Frassel, concerning a male 62 years old and recently returned from Indochina, the disease started slowly with subfebrility, increasing weakness, and emaciation. Later abdominal pains and diarrhea were added. Physical examination disclosed enlargement of the liver, spleen, and lymphatic glands, hypotonia, hypochromic anemia, and leukopenia. Thrombocytopenia may also frequently occur. The patient died amidst symptoms of adrenal failure, like in Addison's disease. Postmortem revealed a fist-size cavity filled with caseous-necrotic mass in the place of the two adrenals. Numerous caseous foci were found also in the spleen and kidneys. The macroscopic picture suggested tuberculosis. Microscopic examination revealed numerous H. capsulatum, which were most distinict on the periphery of the necrotic foci and in the mononuclear cells.

Pinkerton and Iverson, in describing three fatal cases, also considered adrenal failure to be the cause of death in view of the extensive necrosis of these glands. In the course of histoplasmosis we frequently encounter ulceration of the skin and the mucous membrane of the mouth, palate, and larynx. Enlargement of the lymph nodes and splenomegaly may lead to an erroneous diagnosis of chronic lymphatic leukemia or granulosis. Only the examination of the marrow and peripheral blood, a biopsy of the lymph nodes, confirmation in them of the presence of the fungus, and a positive histoplasmin test permit an exclusion of the above diseases.

The Benign Form is mild and settles most frequently in the lungs, with its course secretive and chronic, and lasting from a few months to several years. There is a tendency, in this form, for recession of pathologic changes and self-cure, with resultant remaining foci of calcification (Fig. 2). Clinical symptoms are similar to those of primary or atypical chronic pneumonia. There is a condition of subfebrility, general debility, and cough. Children may vomit, with overall emaciation added later. Physical manifestations in the lungs are frequently difficult to discern, or they may be completely absent, or may sometimes resemble focal changes in the lungs.

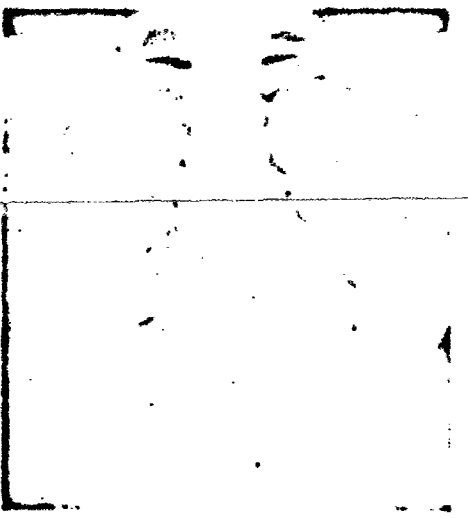

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Figure 2. Histoplasmosis of Lungs
Calcified foci in lung areas. Packet of calcified lymph nodes in the right hilus. Tuberculin tests negative. Histoplasmin reaction positive. After Palmer from textbook of T. Smith Dawid "Fungus Diseases of the Lungs," p. 38.

Christie and Peterson presented in 1945 several varying cases of the pulmonary form of histoplasmosis in children.

The disease manifested itself in enlarged lymph nodes in the pulmonary hila, peribronchial inflammation, lympho-pulmonary syndromes, infiltration, and atelectasis in connection with the increased lymph nodes or miliary changes. There was no enlargement of the liver or spleen, or of the peripheral lymph nodes in these children. Tuberculin reactions were always negative, whereas the histoplasmin ones always positive. The illness was chronic and lasted 2--5 months. Following recovery from the benign form of histoplasmosis, x rays of the lungs revealed single or numerous foci of calcification in the lungs or hila. The changes were sometimes symmetrical for both hila. Tuberculin reaction was always negative. First to call attention to this phenomenon was Opré in 1929. This was confirmed by Bernard, Crabtree, and Nelson.

In the last few years Peterson and Christie have sought to determine signs of a history of the benign form of histoplasmosis in persons with foci of calcification in the lungs. In these persons the histoplasmin test is more frequently positive than the tuberculin reaction. Particularly characteristic for histoplasmosis -- though not necessarily the rule -- are the numerous tiny calcification foci disseminated in the lungs or localized in the hilus (High, Zwerling, and Furcolow). Such a picture was once considered as cured "miliary tuberculosis." In addition to the calcified foci in the lungs, High found also such calcifications in the liver and in the spleen. Zwerling and Palmer observed patients with partially localized and partially disseminated foci of infection in the lungs, and with enlarged hila. These spots became calcified after recovery. During the course of the illness, the tuberculin test was constantly negative, and the histoplasmin reaction positive.

The x ray picture of the lungs may vary. Silverman noted in one case a strong reaction in the lymph nodes of the hila, in another -- a picture of diffuse inflammation, in a third -- reaction of hilus lymph nodes and the lungs, with simultaneous atelectasis, and in a fourth case -- delicate pulmonary miliaria.

Other authors classify histoplasmosis differently:

1. Form affecting alimentary tract. Appears mostly in children in the form of erosion of the mucosa of the mouth, larynx, and intestines, particularly of the lower end of the small intestines. Clinically, there are manifestations of lack of appetite, nausea, abdominal pains, diarrhea, and emaciation. The fungus H. casulatum may sometimes be detected in the stool.

2. Form affecting skin -- appearing both in children and in adults. It is characterized by eruptions of different kinds, varying from roseola up to ulcerations. Most frequently these are located around the nose and mouth.

3. Cardio-articular form, with symptoms resembling rheumatism.

4. Visceral form -- with damage to the lymph nodes in the mesentery, liver, spleen, and lungs.

In 20 per cent of histoplasmosis patients x rays reveal changes in the lungs. The pulmonary form manifests itself clinically in pulmonary infiltration, fever, and perspiration at night -- hence symptoms similar to pulmonary tuberculosis. In other cases, x rays of the lungs revealed calcification, pneumatic shadows, and sometimes the formation of pulmonary abcesses. In some cases the coexistence of histoplasmosis and tuberculosis was established. Histoplasmosis may occur in a small child, as well as in an aged person, but the greatest incidence is among children, and it occurs more frequently in the rural population. The problem of histoplasmosis is becoming particularly important in view of the rapid development of thoracic surgery. Histoplasmosis mainly comes to light only after the incision into the lung tissue, made due to erroneous diagnosis of tuberculosis. Puckett lists 22 cases of histoplasmosis diagnosed on histological examination of cut lung tissue. Zimmerman notes 35 cases in which granulomas were removed surgically after they were diagnosed both macro- and microscopically as "pulmonary tuberculomas." These cases were carefully examined for acid-fast bacteria and for fungi. The author used the Ziehl-Neelsen method to detect the acid-fast bacilli. To detect H. capsulatum and Coccidioides immitis the author employed the method of Gridley, Schiff, staining with hematoxylin and eosin, and also the inoculation of cultures. Of the above 35 cases, acid-fast bacteria were found in 6 (six), H. capsulatum -- in 19, Coccidioides immitis -- in three (3), and in seven (7) cases -- none of these three etiological factors were found.

Single, delicately encased granulomas of the lungs, considered to be the result of tubercular infection are commonly called by clinicists, radiologists, and pathological anatomists tuberculomas. The so-called "tuberculomas" are usually detected accidentally during x ray examinations of healthy persons. When x rays show calcification of a more or less laminar structure, an infectious state is frequently diagnosed. Other changes, probably of shorter duration, may appear on the x ray as a uniform shadow and may be erroneously diagnosed as a primary or metastatic neoplasm. Most frequently, a single, round, coin-like shadow is considered as a so-called "tuberculoma."

According to Hodgeson and McDonald, no granuloma in the lungs can be considered tubercular, unless it is so proven bacteriologically. It has been established several years ago that the Coccidioides immitis may also cause similar, delicate and encased granulomas, which are difficult to distinguish from the tuberculomas, if the etiological factor is not detected. More recent studies revealed that a considerable proportion of pulmonary granulomas are caused by the H. capsulatum. Prior to Puckett's studies, histoplasmosis was considered a benign state, causing calcification in the lungs of persons living close to the Mississippi river. It was also established that histoplasmosis may cause chronic pulmonary illness, with or without pulmonary cavitation. Thanks to improved techniques, detection of mycoses is now considerably easier by histological means than by inoculation of cultures. It should be added that inoculations give a negative result in 75 percent of the cases. In the USA, pathological anatomy institutions perform, as a matter of routine, histological tests for mycoses in all cases forwarded to them as "pulmonary tuberculomas" or "pulmonary granulomas suspected of being tubercular."

According to Zimmerman, both acid-fast bacilli and fungi can be detected histologically with greater ease from sections taken from the central portion of the necrotic focus. He recommends the preparation and careful examination of several sections. Practice has revealed that the search for fungi in the peripheral part of the granuloma is useless. Detection of H. capsulatum for an experienced person is not difficult. The C. immitis fungus can be detected in sections stained with hematoxylin and eosin, whereas detection of acid-fast bacilli and H. capsulatum requires special methods.

On the basis of the cited cases, the author concludes that H. capsulatum is the most frequent etiological factor behind the changes heretofore described as "pulmonary tuberculoma." They constitutednearly 75 percent of all these cases. This explains the frequent negative tuberculin reactions in the so-called tuberculomas.

Diagnosis is based on the detection of H. capsulatum in smears from ulcerations, lymphatic nodes, blood, or sputum -- or else on the basis of cultures grown on artificial media. Clinical manifestations include subfebrility; a chronic course of the illness; general debility and loss of weight; enlargement of the liver, spleen, and lymphatic nodes; and ulceration of the skin or mucous membranes of the mouth, throat, larynx, and nose. In the lungs -- disseminated foci, with a tendency for caseation, and hilar lymphadenopathy. These, on curing, form foci of calcification visible on x rays, like in tuberculosis; these persons, however, have a negative reaction to the tuberculin test, and frequently react positively to histoplasmin.

Differential Diagnosis

In making a differential diagnosis one must consider sarcoidosis, lymphatic and pulmonary tuberculosis, chronic lymphatic leukemia, malignant granulosis, reticulosis, leishmaniasis, tularemia, coccidioidmycosis, and toxoplasmosis.

Histoplasmosis is determined on the basis of the detection of the H. capsulatum fungus and positive histoplasmin reaction -- calcified foci in the lungs frequently simultaneously with a positive histoplasmin and negative tuberculin tests.

Prognosis in the malignant form is bad, since the outcome is nearly always fatal. In the mild benign form, the disease is cured by itself in the majority of cases.

Therapy. According to Freijo, sulfonamides should play a large role in the treatment of histoplasmosis. Other authors disagree. Iodine preparations, x-ray irradiation, extracts of bone marrow and of liver, and neoarsphenamine have been administered unsuccessfully. Streptomycin and other antibiotics arrest the growth of the fungi in vitro, but have no effect in vivo. Palmer, Amolsch, and Schaffer used antimony chloride. Christie reports that the ethyl ester of vanillic acid has a certain therapeutic effect. According to the latest reports of Robert and Nejedly, antimony compounds give good results in the treatment of histoplasmosis. The authors cured a case of histoplasmosis with 2-hydroxystilbamidine.

This case involved a 55 year old male patient with ulcerated hard palate and gingiva, from which H. capsulatum was isolated. The histoplasmin reaction was positive. The patient received daily an intravenous administration of 150 mg of 2-hydroxystilbamidine in 200 ml of physiological saline for 30 minutes. The treatment lasted about four (4) months, and the total amount of the administered drug was 20.0 g. No side effects were observed. A complete cure of the ulceration of the hard palate and gums was attained.

Methods of Detecting Histoplasmosis

(1) Preparation from blood, bone marrow, sputum, or intestinal rinsings, stained with Giemsa.

2. Biopsy: ~~a)~~ of lymphatic gland, ~~b)~~ spleen, ~~c)~~ liver, ~~d)~~ marrow.

Histological examination of ~~a)~~ section of ulcerated skin, mucous membrane, and material obtained during broncho-

scopy, or b) section of granuloma of excised lung tissue.

3. Culture: H. capsulatum on Sabouraud's medium or on blood agar, where it forms a mycelium with characteristic spores.

Material for culture: a) blood; b) puncture of lymphatic gland, spleen, liver, or bone marrow; c) sputum; d) stool.

Authors recommend running parallel bacteriological and histological determinations.

4. Biological test: Inoculation of infectious material in experimental animals: mice, rabbits, rats, guinea pigs, where the fungus can be determined in the cells of the reticulo-endothelial organs.

5. Histoplasmin reaction.

Histoplasmin (Lilly) is a specific antigen obtained from the filtrate of the fungus culture. Manner of administration: 0.1 ml solution of histoplasmin in a 1 : 100 or 1 : 1000 dilution is administered intracutaneously on the forearm. The result is read after 48--72 hours. A reaction is considered positive if if at the point of injection there appears an erythema on a hard, nodular, raised background, at least 5 mm in diameter, and surrounded by an edematous zona of the skin. The histoplasmin test has no side effects.

6. Serological reactions.

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Author's address: Wagrowiec, ul. Jednosc 8, m. 1.