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Benign and malignant histoplasmosis

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BENIGN AND MALIGNANT HISTOPLASMOSIS

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Ziegler (1), in 1946, defined Histoplasmosis as follows: "Histoplasmosis is an acute, subacute, or chronic; localized or systemic; sporadic, granulomatous, infectious, fatal disease, caused by the fungus, Histplasma capsulatum. It is spreading more rapidly or being recognized more frequently or both."

A review of the literature concerning histoplasmosis fails to reveal a more comprehensive concept of this disease than that quoted above. However, in the same year and in those immediately following, up until the present time, there has appeared evidence which leads one to dispute the validity of a universal concept as to the fatality of histoplasmosis, despite the fact that the majority of authorities maintain such an opinion. The time appears to be at hand to establish a wider viewpoint. As is recorded many times in medical literature, a "new" disease is fast becoming recognized as a common bedfellow of man in his struggle for survival. We all have seen one such example in the transplantation of amebiasis from the mythical sphere of tropical medicine to a force to be dealt with by most every practitioner in the fold. It is to be feared that fungi may someday establish such a foothold.

There is a slight discrepancy in the literature, as to who first described the disease, histoplas-

mosis. In 1906, Richard P. Strong (2)(1) published descriptions by Wright, Rheil, Cunningham, and others concerning organisms found in chronic, granulomatous skin lesions. The description of these organisms resembles that of Histoplasma capsulatum. Samuel T. Darling, in his publications from 1906 to 1909 (3) (4) (5) (6) (1), gave this disease its name and called the organism, Histoplasma capsulatum. He well described the clinical picture and pathological material; although, he was unable to appreciate the protean nature of his discovery. He initiated the concept of the uniform mortality of Histoplasmosis. da Rocha-Lima (7) (1) established Histoplasma capsulatum as a fungus and not a protozoon.

The recording of the works of H. capsulatum faded from the literature until 1926, when, Watson and Riley (8) reported cases occuring in Minnesota. The record then becomes one of rapid advance. Dodd and Tompkins (9) in 1934, reported the first case, diagnosed during life. They demonstrated the organisms in monocytes, circulating in the peripheral blood.
De Monbreun (10) (11), reported the cultural characteristics of H. capsulatum; reproduced the disease in laboratory animals and was impressed with the possibility of a reservoir in dogs. In 1940, Meleney (12) publish-

ed the first comprehensive review, bringing the total reported cases, at that time, to thirty-two. He reported the transmission of the disease to young dogs, per ora and parenterally, via culture material obtained from a case occuring, naturally, in a dog. At that time, the disease was known to occur, naturally, in mice and ferretts. There is no known reservoir, outside of animal hosts.

The pathology of the fatal, or malignant form of histoplasmosis, is indeed, protean. As reported by Ziegler (1) and Meleney (12), granulomatous lesions have been seen, involving the skin, mucous membranes, lymph nodes, liver, spleen, lungs, bone (marrow and periosteum) adrenal glands, kidney, brain, prostate, heart, pleura, endocardium, joints, large and small bowel, ear, nose, and larynx. The skin, mucosae, lymph nodes, liver, spleen, and lungs are the common sites.

The lesions are grossly minute or massive and necrotic; with, or without hemorrhage. They vary in color, from whitish to gray, or black. Surface lesions have been seen, both, as undermined ulcers, and as nodules. Necrosis is prominent, usually of the focal type. Lesions in the lung have been those of non-tuberculous cavitation. Fibrinous or fibrino-purulent pleurisy is

not uncommon. Involvement of the lymph nodes, spleen and liver are, of course, manifest by adenopathy and megaly.

Microscopically, one sees large numbers of reticulo-endothelial cells, containing phagocytosed parasites. Plasma cells, lymphocytes, monocytes, eosinophiles and fibrocytes are also present in the meshes of the granulation tissue. Giant cells of the Langhans type, may be encountered. There is no true lymphocytic circumscription. The center of the lesion is necrotic, often caseous. Thus, the lesions are, as Darling (3) termed them, pseudo-tubercles.

Parasites have been demonstrated in the pathological material in circulating monocytes, reticulo-endothelial cells (especially in those adjacent to necrotic tissue), endothelial cells, alveolar epithelium, mucous and glandular epithelium, and rarely in the intercellular spaces.

On the basis of the general picture, Meleney(12) has listed four clinical types of malignant histoplasmosis. I) A systemic form of febrile disease, similar to kala-azar, with septic temperature curve, anemia and leukopenia. Rarely, in this type, no gross lesions are demonstrable at autopsy. Cases which fit into this group are reported, in which the onset was characterized by

gastro-intestinal disturbances, in the form of pain and diarrhea. Most of these showed extensive ulcerous involvement of the bowel at post-mortem. II) A type which is predominated by lymphadenopathy and simulating Hodgkins disease, leukemia, lymphosarcoma and aplastic anemia. III) One with the picture, predominated by pulmonary symptons. This type is often complicated by, or superimposed upon pulmonary or miliary tuberculosis. IV) The picture may be predominated by a skin lesion which can progress to a generalized, ulcerative, cutaneous involvement, or a nasopharangeal lesion may present. These cases often manifest adrenal insufficiency, resultant from massive necrosis of the adrenal glands.

Parsons and Zarofenetis (13) 1945, in a review of seventy-one cases, stated that the most common signs and symptons of the acute disseminated or fatal type of histoplasmosis, were fever, hypochromic anemia, hepatomegaly, splenomegaly, and lymphadenopathy. Weight loss is also characteristic.

Diagnostic procedures are designed to demonstrate the organisms in the involved tissues, bone marrow and blood stream. These are, of course, aspiration biopsy of marrow, spleen, liver, lymph nodes and blood smear. Organisms can be found in scrapings from cutan-

eous and mucosal lesions. The demonstration, as in the case of other such work, seems to depend on the searcher being aware of the possibility of histoplasmosis as a diagnosis. Meleney (12), states that only positive cultural evidence is absolutely diagnostic.

H. capsulatum grows readily on ordinary media, including Sabouraud's agar, potato-dextrose agar, blood agar, etc. It grows well in incubation at thirty-seven degrees C., and slower at room temperature. The organism cultures as the mycelial form; and can be transformed to the budding yeast form by cultivation on sealed blood agar slants at thirty-seven degrees C. It is aerobic and resistant to drying.

A consideration of the pathological and clinical picture of the fatal form of histoplasmosis, which we have considered so far, shows a definite resemblance to tuberculosis of the reinfection type. It is not surprising, in this light, that a second or benign form of histoplasmosis, has entered the picture.

The work of Gifford, Dickson and Smith (14) on Coccioidomycosis, plus the correlation of tuberculin and chest xrays surveys, in the problem of pulmonary calcification, led Smith (14) to point the way to the discovery of benign histoplasmosis. He pointed out that, in the

area including Missouri, Illinois, Michigan, Indiana, Tennessee, Kentucky, Ohio, West Virginia and certain parts of Virginia, Pennsylvania and New York, many persons are tuberculin negative and at the same time, show pulmonary calcification. In view of the fact, that most cases of fatal histoplasmosis had occured in the same area, Smith suspected a relationship between pulmonary calcification and H. capsulatum.

Although the majority of physicians had associated pulmonary calcification with resolved primary complex tuberculosis, there was awareness that all such lesions did not have this basis. This had been demonstrated, especially, in regards to miliary pulmonary calcific lesions in non-reactors to tuberculin (15). Causes varying from "healed miliary tuberculosis" to pneumoconiosis, have in the past, been submitted as etiological theories in such cases (16 through 22).

The high incidence of pulmonary calcification was brought out by Long and Stearns (23). They reported on the examination of inductees in an area, roughly bounded by Fort Oglethorpe, Georgia; Jefferson Barracks, Missouri; Little Rock, Arkansas; and Columbus, Ohio. Fifteen percent of inductees, showed pulmonary calcification on chest xray with the miliary picture predominating over the non-miliary.

Further advance in the study of histoplasmosis has come from a group, working for the United States Public Health Service (24 through 35). This group attacked the problem by survey investigations, in which they correlated chest xray findings, with tuberculin and histoplasmin sensitivity. The histoplasmin used was a filtered extract from cultures of H. capsulatum on synthetic broth medium. This medium is said to be practically non-antigenic..

Palmer (28) reported that in the Central United States, non-tuberculous pulmonary calcification occured most often in positive histoplasmin reactors. This finding was corraborated by Zwerling and Palmer (32), as well as Christie and Peterson (24 through 27). The latter group found further, that the incidence of pulmonary calcification paralleled that of histoplasmin sensitivity in different groups, up until the age of fifteen years.

After this age, they found a decrease in calcification, which was interpreted as possible absorption of calcified lesions. The possibility of H. capsulatum, as an etiological agent, was also brought out by the early appearance of histoplasmin sensitivity; whereas, tuberculin sensitivity lagged considerably behind the development of demonstrable calcification.

Palmer(28), found the highest incidence of histoplasmin sensitivity to be in the area of Kansas City, Missouri, and Kansas City, Kansas. He also pointed out (29) that the incidence decreased with increasing distance from this area. An incidental finding, in this study, indicated the possibility, that splenic and hepatic calcifications may be related to histoplasmin sensitivity.

High, Zwerling and Furcolow (33), substantiated the work of Christie and Peterson. They also found a greater incidence among Whites than among Negroes, as well as a definite familial relationship. These authors also, pointed out that the incidence of histoplasmin sensitivity increased proportionately with age and that it is more prevalent in the adult male than in the adult female. They concluded that the disseminated type of pulmonary calcification is not often due to tuberculosis; but, that it is caused by an agent bestowing sensitivity to histoplasmin.

Ferebee and Furcolow (36), in a statistical analysis of the Kansas City survey, found a prevalence of histoplasmin sensitivity among siblings. They did not, however, demonstrate a familial or environmental factor to account for this. They are of the opinion that this finding has a broader basis.

Sontag and Allen (31) studied the radiographic findings in a group of histoplasmin sensitive children. They found that pulmonary calcification, associated with histoplasmin sensitivity, differed from that found with tuberculin sensitivity, in that calcification preceeded the development of sensitivity. In the majority of cases, calcification had occured, prior to the fourth year. Some pictures showed pneumonic infiltration preceeding calcification. These lesions progressed from fussy fan-shaped densities and exaggerated linear markings to definite rounded areas of calcification. Most of the lesions occured at the bases; however, apical lesions were not uncommon. They were unable to establish a definite difference between histoplasmin sensitivity and tuberculin sensitivity on the basis of xray picture alone. They did state that a multiple calcific tendency predominates in those showing histoplasmin sensitivity. The picture of disseminated or miliary punctate calcifications is characteristic of fungus infection in the lung.

Emmons and his group (34), and Howell (35), found cross reactions between histoplasmin, blastomycin, and coccidioidin.

In conclusion, as stated by Christie and Peterson (27), a direct causal relationship between histo-

plasmosis and pulmonary calcification, has not been proven. Such a relationship to fungus infection has been established; even though, H. capsulatum is not definitely the etiological agent in all such cases. At any rate, evidence presumptive of the widespread occurence of a benign form of histoplasmosis, is circumstantially indicative; and we must alter the old concept of fungus disease; in general, being open minded toward the elucidation of a new clinical picture. The resemblance to tuberculosis on a primary and reinfection basis is striking; however, discrepancies are already evident, so as to make such a conclusion hazardous.

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