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Histoplasmosis vs tuberculosis in the differential diagnosis of pulmonary calcifications

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HISTOPLASMOSIS vs TUBERCULOSIS IN THE DIFFERENTIAL DIAGNOSIS OF PULMONARY CALCIFICATIONS

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INTRODUCTION AND HISTORY

Prior to about 1930, the finding of intrathoracic calcification by roentgenography was nearly always attributed to tuberculous infection. However, studies involving the correlation of pulmonary calcifications with tuberculin skin testing revealed that many individuals with radiographically demonstrable intrathoracic calcifications were tuberculin-negative. Attempts were made to explain this inconsistency with accepted teachings on several grounds. Some suggested the possibility of reversal or loss of tuberculin sensitivity. It is known that certain infections (especially measles), extreme debility, and overwhelming tuberculous infection may suppress tuberculin sensitivity in known positive reactors. Also it has been pointed out that over 10 per cent of tuberculin positive individuals may revert to negative without presence of any of the above factors. In patients with roentgenographically recognizable lesions, however, only 0.72 per cent were observed to change from positive to negative during periods of observation as long as fifteen years.(20) In addition, when reversals do occur, they are observed primarily in children.

In certain areas of the United States, the number of individuals with intrathoracic calcification was too great to be explained by loss of tuberculin sensitivity. As might be expected, the value of tuberculin as a diagnostic agent was seriously questioned. For those who were unwilling to deny the value of tuberculin, an

explanation was afforded in the suggestion that agents other than the tubercle bacillus might be responsible for intrathoracic calcification. This premise was supported by evidence that Coccidioides immitis was capable of producing pulmonary calcification in individuals residing in a sharply localized region in California.

As early as 1940, Furcalow indicated that a fungus other than Coccidioides immitis was suspected as a cause of pulmonary calcification in tuberculin - negative children in Ohio.(13) He noted a surprising number of children reacting to coccidioidin in southwestern Ohio. This area is well out of the known endemic region for Coccidioidomycosis. Thus a cross reaction with other fungi became a possibility to be seriously considered. In 1943, Smith(21) tested thousands of soldiers with coccidioidin and found that many individuals from Missouri, Illinois, Indiana, Michigan, Tennessee, Kentucky, Ohio, West Virginia, Virginia, Pennsylvania and New York had borderline positive reactions while a few were undoubtedly positive. This area coincided with the area of pulmonary calcifications in tuberculin - negative individuals and is also the endemic area of histoplasmosis. Consequently, Histoplasma capsulatum was specifically suggested as a possible cross-reactant and etiological agent of non-tuberculous pulmonary calcifications.

In 1945 Christie and Peterson(3) undertook the testing of school children in Tennessee with histoplasmin antigen. Briefly, their results indicated that approximately three-fourths of the children examined showed a positive reaction to histoplasmin

while about one-fourth were positive to tuberculin. 43.6 per cent showed intrathoracic calcification on roentgen examination, and ten per cent of the individuals with calcifications were negative to both antigens. The number of children positive to histoplasmin and showing pulmonary calcification was more than three times that of those with pulmonary calcification and sensitive to tuberculin. The number of individuals with positive histoplasmin tests and with pulmonary calcification increased rapidly in relation to age. Pulmonary calcification followed very closely the incidence of positive histoplasmin tests. The incidence curve for tuberculin reactors did not show this close relationship.

In the same year, Palmer(17) screened 10,000 student nurses in sixty-five schools throughout the country with both histoplasmin and tuberculin. The geographical localization of non-tuberculous pulmonary calcification and sensitivity to histoplasmin was almost identical to the areas outlined previously by Smith (Eastern Central United States).

It is noteworthy to mention that up to this time, histoplasmosis had been considered a rare disease which was uniformly fatal. However, with such studies as these, it seemed likely that histoplasmosis was a fatal disease in only an extremely small percentage of persons infected. It was a logical inference, therefore, that subclinical forms of the disease exist or that mild forms occur which masquerade as other diseases, especially of the respiratory tract. These so affected individuals develop a positive histoplasmin

reaction, and, in roughly half of them, roentgen signs of pulmonary calcification are found.

Extensive studies were undertaken in the three years following 1945 to attempt to confirm the inference made by the coorelative studies of skin testing and pulmonary calcifications. Geographic distribution investigations revealed with monotonous regularity that eastern central United States is the location for individuals with positive histoplasmin skin tests and roentgen evidence of intrathoracic calcification.

The incidence of both increases with age. Males and females are equally affected until the end of the second decade, at which time the male begins to predominate. The incidence of positive histoplasmin reactors is significantly greater among rural residents than city dwellers, in distinct contrast to the distribution of tuberculin reactors. Intra-family studies reveal that if the oldest child is positive, the incidence of positive reactions in siblings is significantly greater than if the oldest child is negative. Racial factors appear to be less important than geographic factors with respect to incidence.

The most revealing data are those pertaining to positive skin tests in individuals with pulmonary calcification. In a study(13) of over 6,000 school children in Kansas City, Missouri, 37.6 per cent were histoplasmin positive and tuberculin negative. Approximately 16 per cent of the entire group had pulmonary calcification. Of the 828 children with calcification, 78.4 per cent of them were

positive reactors to histoplasmin. When only children with disseminated calcification were considered, the percentage with positive histoplasmin and negative tuberculin skin tests rose to 93.5 per cent.

The highest figures are obtained in studies within the geographical area of endemic histoplasmosis, but the close relationship between pulmonary calcification and histoplasmin sensitivity persists even in non-endemic areas. Individuals with pulmonary calcification who are negative to both histoplasmin and tuberculin skin tests vary from 3 - 38 per cent.(13) This discrepancy probably can be accounted for by an error both in performance and interpretation of skin testing. Retests of persons with calcification show a significantly higher percentage of reaction to either tuberculin or histoplasmin than do retests of persons whose chest films were negative.

It is evident, therefore, by this series of studies and findings, that a frontier had been established in a "new" disease, the etiological agent of which has been known since 1906, but the true pathogenic nature of which had not been accurately known until studies commenc- in 1945 began to reveal it. The disease at that time was considered rare and fatal. In fact, only 71 cases could be found in the literature in 1945. In 1949, 123 cases could be found. As testimony to the work done and results achieved, there were an estimated 30 million individuals infected with histoplasmosis in 1955.(12)

The belated recognition of histoplasmosis as a problem of importance to the medical profession may be ascribed to two causes:

(1) the clinical disease mimics other diseases, and (2) the prevalence of tuberculous infection led to the erroneous conclusion that almost all chronic chest lesions were tuberculous. Since histoplasmosis mimics other diseases even in its milder forms, it is obvious that until diagnostic tools were reliable and readily accessible, differentiation from such common illnesses such as typhoid fever, influenza, and even cavitary tuberculosis was not possible. Secondly, the assumption by clinicians and radiologists that all chronic chest lesions were due to tuberculosis was fostered by the high incidence of positive tuberculin skin tests. However, with the fall in the rate of tuberculin positives among the general population, more persons were found who had active or healed lesions in their chest x-rays and negative tuberculin skin tests. The time was thus ripe in 1945 for investigation to demonstrate that there was a relationship between non-tuberculous pulmonary calcification and sensitivity to histoplasmin. Subsequent studies previously mentioned, have confirmed this original concept and indicate that histoplasmosis is the most common cause of pulmonary calcification, even more common than tuberculosis itself.

DESCRIPTION OF ORGANISM

It would seem appropriate to digress from the historical aspects of this subject at this time to consider some of the characteristics of the organism with which we are dealing.

Histoplasmosis was first described by Darling in 1906, who

recognized it as a new disease, but who believed that the Leishmania-like organisms which he found in the tissues were a form of protozoa. He, therefore, gave the organism the name Histoplasma Capsulatum. Subsequent investigators noted cultural characteristics related to certain fungi and questioned this classification. It was not until 1934 that De Monbreun conclusively identified the organism as a fungus.(20)

The fungus occurs in two forms: a yeast-like form which is its pathogenic phase, and in which it is generally found in infected tissues; and a mycelial or filamentous form in which it is much more readily cultured, and which is presumed to be the form found in nature. Experimentally, the organism can be cultured in both phases.

The yeast form occurs as round or ovoid cells approximately three microns in long axis, both free and intracellularly. When stained with Gienesa or Wright's stains, a basophilic mass is observed within the cell, usually eccentrically located. A clear refractile capsule surrounds the organism in unstained specimens, accounting for the descriptive name. The yeast form is grown on sealed blood agar slants at 37 degrees C., and can be maintained if subcultures are made frequently (three to five day intervals). If subcultures are not made, or if cultures are made aerobically at room temperature, the mycelial form develops. It is probable that the humidity maintained by sealing the slant is more important than the relative anaerobiosis in the successful cultivation of the yeast phase. Serial studies of yeast form subcultures show budding

to take place at the pointed end opposite the basophilic mass. Transformation into the mycelial form occurs when buds remain attached to the parent cell and rapidly elongate to typical mycelia.

The mycelial form grossly demonstrates long filaments extending out from the massed colony. Attached to these are rounded spore forms up to ten microns in diameter. Initially the spores may be smooth; with the passage of time or after drying, characteristic tubercles project from the surface and produce an appearance which has been likened to an ancient Teutonic war club. The spores are relatively resistant to drying and heat. Single spores have been studied after subculture; tubercles are observed to enlarge and elongate and to develop into mycelia. These, in turn, give rise to more spores. Transformation into the yeast form occurs after inoculation of yeast-free mycelia into susceptible animals or by subculturing the mycelia on special media at 37 degrees C.

Since penicillin and streptomycin have no appreciable effect on pathogenic fungi (except for Actinomyces), the addition of 20 units per cubic milliliter of medium inhibits the growth of bacteria which, present as a contaminant or secondary invader, might overgrow the fungus.

Several stains have been used to demonstrate Histoplasma capsulatum in the tissues. The first of these special stains to be employed was the Periodic Acid Schiff (PAS). Later this was supplemented by the Gridley stain. At present the methenamine-silver nitrate method of Gomori is regarded as the best single

stain for the visualization of the fungi.(15)

In Gomori preparations, the fungal elements appear as sharply delineated black-staining structures on a background which remains largely unstained unless counter staining is employed. The essential chemical phenomena involved are the liberation of aldehyde groups as the result of pre-treatment with chromic acid and their subsequent detection by the reduction of an alkaline methenamine-silver nitrate complex.

The pathologic response visualized with this stain is that of a granuloma with giant cell formation and typical tubercles similar to those seen in tuberculosis. The organisms are fairly easy to demonstrate in disseminated lesions; however, in the old chronic fibrotic, or calcified lesions, they may be extremely difficult.

EPIDEMIOLOGY

Histoplasmosis is not a contagious disease by the ordinary definition, since it is not communicable from man to man or from animals to man.(12) The organism grows in the soil and is transmitted to man without intermediate hosts. Infection appears to be acquired by inhalation of spores either blown about by the wind or stirred up by some activity such as shoveling in an area where organisms are growing.

The organism appears to grow in localized areas where conditions of temperature and humidity are favorable for its growth. Such places are shady areas, particularly if covered, and areas which

have a high organic content of the soil, such as chicken coops, pigeon roosts, caves, storm cellars, and silos.

Visits to rural environments appear to be the most important single source of infection, even among city dwellers. It, therefore, appears that the most practical method of prevention of the disease would be avoidance of areas favorable for the growth of the organism. This is especially true for children. Also in rural areas or areas where the organism is suspected to grow, such as chicken coops, it would be well to dampen down the debris before cleaning to avoid dissemination of the organism in the air. There is considerable epidemiologic evidence to suggest that the degree of illness and number of chest lesions are directly corelated with the number of spores inhaled.

Prevalence of this disease in the middle west, in an area well staffed by physicians, leads to the generalization that it must simulate other diseases in its milder forms. This has been shown to be true. Even in the severe cavitary form, the patients are most commonly found in tuberculous sanatoriums. Moreover, some patients have the infection without any overt symptoms. However, it is becoming increasingly apparent that many persons who are infected have clinical symptoms.

CLINICAL FORMS AND ROENTGEN SIGNS

The symptoms in the mild form are chiefly malaise and fever, sometimes with a slight cough or chest pain. The picture is not

unlike influenza and lasts one to three days. Physical examination is usually negative. Not infrequently, however, x-ray studies of these patients reveal lesions in the lungs and also lesions can almost invariably be found at autopsy on such patients, should they die of some unrelated cause. Pulmonary calcification is found in about one-third of these persons with positive histoplasmin skin tests. The chest roentgenogram reveals one or more lesions, usually nodular, in one or both lung fields, and not necessarily restricted to a particular area of the lung. Enlargement of hilar lymph nodes is a common finding and calcification of both the parenchymal lesion and lymph nodes is not uncommon.

In moderately severe disease, malaise and fever are the predominant symptoms. Cough and chest pain are unusual but do occur. The illness as a whole is almost indistinguishable from a severe influenza lasting from five to fifteen days. Physical and laboratory examination are usually negative except for an elevated sedimentation rate. As in atypical pneumonia, the chest x-ray findings are more pronounced than one would expect from the clinical symptoms. Pulmonary lesions are common and usually consist of scattered pneumonic areas usually through both lung fields or perihilar infiltration characteristic of atypical pneumonia. Isolated nodular lesions also are not uncommon. Epidemiologic study of this type of moderately severe disease with x-ray findings indicates that it is more prevalent in the summer and that it is usually associated with visits to a rural area and particularly with inhalation of dust

from chicken coops or other sources of infection. Evidence is accumulating that much of the summer pneumonitis in the midwest is histoplasmosis.

A more severe type of illness occurs in epidemic form and occurs at any time of the year. Epidemics of pulmonary disease, which have been given titles such as "cave sickness", "atypical pneumonia", and "disseminated pulmonary disease", have since had Histoplasma capsulatum incriminated as the etiological agent. This type is characterized by the coincidental occurrence of a number of cases of severe pneumonitis having a common association with a single source of infection. The severity of the illness and the association of the source usually indicate the epidemic nature of the illness.

The onset of this type of disease or illness is usually acute and characterized by chills, high spiking fever, drenching sweats, cough, and chest pain. Most cases are severe, although there is an occasional patient with only moderate illness and fever who apparently has had less exposure to the point source. As has been mentioned previously, severity of illness and roentgen findings of pulmonary calcification appear to be directly proportional to the number of spores inhaled.

In this form of disease, there is usually an extreme degree of pulmonary involvement as seen by x-ray. The roentgen picture is one of marked scattered nodular infiltrations throughout both lung fields, usually accompanied by enlargement of hilar lymph nodes.

Less severe cases may show only occasional scattered infiltration or enlargement of the perihilar nodes. Illness is apt to be prolonged, especially with a more severe pulmonary involvement, and in several of the army epidemics it lasted as long as six months. Characteristically the lesions appear worse by x-ray a week or so after onset, apparently due to hardening and better visualization of the lesions.

Involvement in histoplasmosis is not limited to the pulmonary system. Acute disseminated histoplasmosis occurs and is characterized by blood-borne dissemination of the fungus with enlargement of the liver and spleen, high fever, and usually a fatal termination. It appears most commonly in those with some immunologic defect, such as Hodgkins' disease, or other disease such as cancer, or in young infants or in very old persons whose immunity appears to be deficient.

The disease is often fatal in a month to six weeks, however, it may be chronic and last for months especially in older persons. Nevertheless, the termination is usually fatal, often with adrenal involvement. In these chronic disseminated cases, the diagnosis is often first established by biopsy of an ulcer of the larynx or pharynx or following the development of Addison's disease.

Physical examination reveals a chronically ill patient with hepatosplenomegaly and a moderate degree of fever. Gastro-intestinal complaints may be present. It is significant to note that x-ray lesions of the lung may be mild or absent and when present usually

consist of fine granular infiltration which resembles miliary tuberculosis.

Recently recognized is a chronic progressive or cavitary type of histoplasmosis. It is noteworthy that only 11 cases were found in the literature in 1953. In 1958 more than 40 cases were found in one sanitorium.(12) The disease is very similar to chronic cavitary tuberculosis. Symptoms include low-grade fever, weight loss, profuse sputum, and a tendency to remissions and relapses.

X-rays of the chest reveal infiltration and usually cavitation, often bilateral and usually apical. The disease is progressive, tending to spread from one lung to the other. The onset of a relapse is characterized by an influenza-like illness accompanied by an increase in sputum and new areas of infiltration in the lungs by x-ray. These areas sometimes clear, although the majority progress to cavitation. The disease is usually fatal, often years after the appearance of the first cavitation. Extensive fibrosis and cavitation of the lung may result in death from cardiac failure rather than from histoplasmosis directly. For instance, where the disease itself kills the patient, there is usually blood-borne dissemination at the time of the fatal termination.

Regarding the specific pulmonary aspects of the disease, Furcolow in 1949(11) presented a classification of the pulmonary lesions as seen by x-ray. In group one there were <u>disseminated infiltrates</u> manifested by multiple lesions, ranging in size from millet seed to a few millimeters to larger patchy areas, scattered

throughout the lung fields. In some may be seen a central core of calcification. There may be marked increase in size of the hilar nodes, and in not a few cases minute calcific densities may be seen throughout the lung parenchyma.

In the second group there are pneumonic infiltrates, small areas of infiltration, poorly circumscribed, and irregular areas of calcification. Calcification may be scattered or present as a single lesion in the midst of a clear area.

Nodular lesions comprise the third and last group and are usually well-defined nodular shadows, 0.5 - 4 cm. in diameter. There may be a calcified central core or the entire lesion may be replaced by calcific deposits.

CASE STUDIES

The literature of late is revealing, in increasing numbers, cases of individuals confined to tuberculous sanatoria for granulomatous pulmonary disease diagnosed as tuberculosis, who subsequently, through skin testing, serologic tests, and special staining of tissue specimens, are found to have histoplasmosis. One of the most valuable diagnostic tools available is simply to suspect the presence of histoplasmosis when confronted with roentgenographs of pulmonary lesions and calcifications. In addition, there are undoubtedly countless numbers of individuals who have undergone resection of pulmonary lesions diagnosed as tuberculosis which were actually Histoplasma infections.

In 1960 a study[25] was undertaken at a local hospital to investigate the etiology of pulmonary lesions which were surgically resected. All cases involving resection of pulmonary granulomatous disease between the years 1949 and 1960 were collected and studied. Gomori staining methods were employed. An analysis of the results of a total of 30 cases is presented below.

Pathological Diagnosis	Cases
Histoplasmosis (original pathological diagnosis)	12
Histoplasmosis (corrected from tuberculosis)	8
Tuberculosis (original pathological diagnosis)	5
Unknown	4
Coccidioidomycosis	1
	30

Lesions, originally diagnosed as tuberculosis by gross and microscopic inspection, later revealed Histoplasma organisms by utilization of the Gomori stain. A significant number of cases fall into this category. It is of interest to examine one of these cases.

A 22-year-old white female was admitted to the hospital on October 13, 1954 with a history of a chest lesion found on routine x-ray examination two years previously. It was described as "thumb-tip" in size and located in the upper portion of the right middle lobe. Following discovery of the lesion gastric washings and tuberculin skin testing were done and both were negative. A subsequent histoplasmin test was positive. In May of 1953 this skin test lesion was the size of a half-dollar. After five months the chest lesion showed evidence of calcification and healing. In August

1954 a repeat chest film revealed an area of haziness around the periphery of the lesion which suggested extension of the disease process. Two months later the patient entered the hospital for elective resection.

The patient was placed on streptomycin, PAS, and bed rest. On October 27, 1954, x-ray of the chest revealed a triangular area of infiltration in the dorsal apical segment of the right lower lobe. She was given Procaine penicillin. On October 29, 1954, bronchoscopy was performed and no abnormality was found. Preparation for segmental resection of the posterior segment of the right upper lobe was made. A lesion of this segment was located which caused puckering of the pleural surface. There were also several subpleural nodules measuring two millimeters in diameter. The lesion was grossly described as typical of pulmonary tuberculosis. The lesions were removed which grossly revealed several large lesions measuring up to one cm. in diameter and the central portion of these contained a semi-caseous material.

Microscopic examination revealed numerous small nodules with central caseous necrosis. Surrounding this there was some fibrosis and scattered lymphocytes and a few epithelioid cells. Numerous Langhan's type giant cells were present. Some of the tubercles were composed almost completely of dense, hyalinized fibrous tissue and appeared inactive. A pathologic diagnosis of tuberculosis was made.

The patient experienced a satisfactory post-operative course

and was discharged on November 8, 1954. Re-examination of surgical specimens at the time of this study utilizing the Gomori stain revealed Histoplasma capsulatum organisms. This testifies to the fact that this organism is capable of producing pulmonary lesions so similar to those of tuberculosis that they defy differentiation unless specialized staining techniques are employed.

SUMMARY

As a result of correlative studies of skin testing and screening chest x-rays, it was found that a diagnosis of tuberculosis made from the presence of pulmonary lesions on x-ray, an almost universal practice in the past, is now not justified. In patients with pulmonary lesions, especially individuals living in endemic areas, histoplasmosis must be considered.

The disease is capable of producing clinical pictures ranging from mild pneumonic processes to chronic cavitary pulmonary lesions resembling in every aspect those of tuberculosis.

Special staining techniques have been employed to demonstrate the organism, the latest and most satisfactory method being that of Gomori.

CONCLUSION

Once thought to be a rare, uniformly fatal disease, histoplasmosis is now known to be frequent and widespread - to have a spectrum that ranges from asymptomatic infection to fulminant disease. Recognition of the many types is attributable to three factors: use of skin tests, serologic testing, and special stains for identification of the organism. Awareness of the disease is opportune because effective treatment is now available.

Every physician should be aware of this disease and consider it in any patient presenting with a radiographically demonstrable chest lesion, especially a patient residing in the eastern central portion of the United States.

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