Histoplasmosis on a Small Tuberculosis Service in a General Hospital

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The recognition of mycotic infections of the lungs is particularly desirable on a Tuberculosis Service so that patients with mycotic infections alone may avoid unnecessary exposure to tuberculosis. When pulmonary mycosis and pulmonary tuberculosis are present at the same time and are recognized, appropriate therapy for the mycotic infection may be added to the anti-tuberculosis treatment.

Pulmonary histoplasmosis, like pulmonary tuberculosis, may occur either as a primary type with little or no symptomatology, or as a re-infection type which may result in progressive disease with fibrosis and cavity formation. As in tuberculosis, the primary infection results in hypersensitivity which may be demonstrated by the histoplasmin test. The hypersensitivity may remain for many years or possibly for life. The complement fixation test becomes positive, but is transitory and reverts in a period of months. There is an excellent discussion of the diagnostic significance of these findings by Smith. A chronic progressive form of pulmonary histoplasmosis with cavity formation has been described by Furcolow and Brasher. In this form of the disease positive sputum cultures for the fungus usually are obtained without difficulty. This type of pulmonary histoplasmosis resembles the fibrocaceous re-infection type of pulmonary tuberculosis. There is no present satisfactory specific treatment for histoplasmosis and the treatment of the chronic progressive form of the disease is similar in many ways to that of tuberculosis before the discovery of anti-tuberculosis drugs. Furcolow and Brasher found 7.2 per cent of 600 patients at a tuberculosis sanatorium had positive serology (complement fixation or precipitin) for histoplasmosis. Thirty-three per cent of these cases with positive serology had either a positive culture for *H. capsulatum* or organisms typical of *H. capsulatum* in tissues removed surgically or at autopsy.

The coexistence of pulmonary mycosis and pulmonary tuberculosis has been reported many times. Meloney presented a series of cases in which pulmonary histoplasmosis and tuberculosis were present and active simultaneously. Three cases of pulmonary tuberculosis were reported by Larkin and Phillips with a different coexisting pulmonary mycosis in each case. *Cryptococcus hominis* was present in one, *Coccidioides immitis* in the second and histoplasmosis in the third. All three ended

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fatally. Roger, Terry and Binford reported two cases in which tuberculosis and histoplasmosis were associated with Hodgkin's disease. Six cases of coexisting active infection with *Coccidioides immitis* and *M. tuberculosis* were described by Stein. A case of Addison's disease associated with disseminated histoplasmosis and pulmonary tuberculosis was recently reported by Fitzpatrick and Reuber. A case which was admitted to the tuberculosis service at the Veteran's Administration Hospital, Wadsworth, Kansas in September 1954 was diagnosed as pulmonary tuberculosis when a chest x-ray film showed bilateral fibrocavernous disease and sputum cultures were reported positive for *M. tuberculosis*. Three and one-half months later a postmortem examination showed coexisting disseminated histoplasmosis with involvement of the adrenals, kidneys, trachea, lungs, spleen, liver, bone marrow, and pancreas. Two other patients admitted to the tuberculosis service during 1955 were found to have pulmonary mycosis without tuberculosis. Only of these had cavitary histoplasmosis of the lungs and the other had sporotrichosis. This case will be the subject of a separate report at a later date.

**Case 1:** W. Y., a 66 year old white male gas welder, was admitted to the tuberculosis service at Wadsworth, Kansas on September 21, 1954. Pulmonary tuberculosis had been diagnosed early in September with acid fast bacilli in sputum smears and extensive disease revealed by x-ray film. This was confirmed by repeatedly positive sputum cultures for tuberculosis. There was a history of progressive weakness, anorexia and loss of about 30 pounds during the eight months preceding hospitalization. There had been slight hoarseness for six weeks preceding admission. He had syphilis and was treated in 1927 and in 1964.

![FIGURE 1A: Admission film (November 24, 1954) showing extensive bilateral, fibrocavernous disease.](image-url)
Figure 1B: Lung section through a tuberculous cavity. Figure 1C: Lung section showing acid fast bacilli but no histoplasma. Figure 1D: Lung section resembling solid organ due to reticulum cells filled with histoplasma. Figure 1E: Higher magnification showing masses of histoplasma but no tubercle bacilli.
He was emaciated and appeared acutely ill. He weighed 100 pounds compared with a normal weight of 130 pounds. His temperature was 97.2°F; pulse 80; respiration 22 and blood pressure 100/74. The chest expansion was bilaterally limited. There was diminished vocal fremitus over both lungs and moist rales over all portions of both lungs. The liver was somewhat enlarged and there was mild edema of the ankles. The electrocardiogram and cardiac examinations were consistent with cor pulmonale and mild pulmonary hypertension.

The x-ray film of November 24, 1954 showed far advanced bilateral pulmonary disease involving all portions of both lungs with cavities on both sides. The base of the left lung was emphysematous (Figure 1A). A frontal planigram on December 7, 1954 confirmed the presence of cavitation in the upper portions of both lungs.

Six sputum smears and three cultures were reported positive for M. tuberculosis. The organisms obtained on September 23, 1954 were sensitive to streptomycin and isoniazid but resistant to para-aminosalicylic acid. Blood serology (VDRL and Kolmer) were positive on admission. Skin tests using intermediate strength PPD and histoplasmin 1:500 were negative. Blood cultures were sterile. The blood hemoglobin decreased from 9.7 grams in September 1954 to 7 grams in December 1954. The red blood count fluctuated around 5,600,000. The white blood cell count on admission was 11,400, decreasing and leveling off at 4,000 during the latter part of November 1954. The erythrocyte sedimentation rate gradually fell from 28 mm. per hour in September 1954 to 20 mm. per hour in December 1954. At various times the urine contained from a trace to 1 plus albumin. In December 1954 the urine showed a clumping of white cells and granular casts. The blood urea nitrogen gradually increased from 27 mg. per cent in October 1954 to 42 mg. per cent in December 1954.

Streptomycin one gram twice weekly, isoniazid 300 mgm. daily and para-aminosalicylic acid 12 grams daily were started on October 1, 1954 and continued with the exception of short interruptions until death. Penicillin 9,600,000 units was given because of the positive blood serology. After the first week of hospitalization he remained afebrile except for occasional temperature elevations to 99. Although there was slight improvement by chest x-ray film, he remained clinically unimproved and died three and one-half months after admission.

**Necropsy:** The body was that of a moderately well developed, poorly nourished, white man. A few small petechiae were present over both forearms. The mesenteric nodes were small and somewhat shotty. Enlarged para-aortic nodes measuring as much as 3 cm. in the long axis were located along side each renal artery. Extensive pleural adhesions were present bilaterally, particularly over the spines and upper lobes.

The right lung weighed 580 and the left, 680 grams. The most extensive pathology was found in the right upper and middle lobes which were markedly distended as a result of extensive fibrosis. Small caseous lesions and cavitation were demonstrated. Cavities were present in the right upper and lower lobes, and left upper lobe. There were multiple superficial ulcerated zones in the lower portion of the trachea.

Both adrenal glands were plump and enlarged. The combined weight was estimated at 40 to 50 grams. Cut section showed almost complete replacement by pale, yellowish-gray tissue in which a few necrotic markings were observed.

The right kidney weighed 150 and the left 170 grams. The cut surface showed an ulcerative lesion involving several papillae in each kidney with extension of yellowish-gray tissue into the adjacent parenchyma. There were a few pale gray zones located just beneath the capsule of the left kidney. The cortico-medullary junction was distinct for the most part, although the cortex was pale and the glomeruli were not well visualized. The pelvis and ureters were not dilated.

The spleen weighed 240 and the liver, 1,650 grams. Neither organ was remarkable grossly.

Sections taken from the two largest cavities (Figure 1B) showed evidence of tuberculosis with a ragged lining of granulocytic tissue in which epithelioid cells were prominent along with a few scattered giant cells. Acid-fast bacilli were demonstrated, but the periodic acid Schiff stain failed to color Histoplasma capsulatum. Sections from the small caseous lesions (Figure 1C) showed characteristic, well delineated tubercles with little evidence of activity at the periphery. Appropriate stains again demonstrated acid-fast bacilli but failed to stain Histoplasma. A single lung section resembled a solid organ (Figure 1D) due to the presence of innumerable reticulum cells whose cytoplasm was filled with histoplasma. At the periphery, the infected macrophages were seen to invade the wall of a small bronchiole and also to lie free within the lumen. The fibrosis with the PAS stain, and acid-fast organisms could not be demonstrated here (Figure 1E). Sections from the ulcerated trachea were filled with masses of histoplasma, and no tubercle bacilli could be found.

There was massive necrosis of the renal papillae with heavy infestation by Histoplasma capsulatum which also involved the peripelvic fat and extended into the cortex. Sections stained by the PAS method were colored deep red to the naked eye. A few fungi were demonstrated in the glomeruli, and in some instances were present in the tubules.
Figure 2A. The earliest available film (September 17, 1955) showing disease in the upper right and in the lower left lung.

Figure 2B: Dense infiltrate in upper right lung (January 4, 1956) resulting in the diagnosis of pulmonary tuberculosis.

Figure 2C: Admission film (June 23, 1956) showing 6 cm. cavity in upper left lung.
Sections from each adrenal gland showed massive necrosis of the parenchyma. Histoplasma laden macrophages were so numerous that a slide stained by the PAS method appeared red to the naked eye. Small granulomatous lesions showing epithelioid-like giant cells without necrosis were found in the spleen, liver, lymph nodes, pancreas, and a coronary artery. The bone marrow showed minimal involvement. The periodic acid Schiff stain demonstrated Histoplasma capsulatum in each of the above organs. Tubercle bacilli could not be found. Histoplasma capsulatum was cultured from an adenral and from a kidney removed at the time of autopsy. The lung was not submitted for bacteriological examination.

Case 2: W. C., a 60 year old white, male, barber was admitted to this hospital on June 22, 1955 for treatment of lacerations resulting from a fall while under the influence of intoxicants. A routine chest x-ray film showed extensive bilateral pulmonary disease and a giant cavity in the upper left lung. When a history of previous treatment for pulmonary tuberculosis was elicited, he was transferred to the tuberculosis service. Pulmonary tuberculosis was first diagnosed on January 4, 1954. Four sputum and three gastric cultures obtained at that time were subsequently reported negative for acid fast bacilli.

There were several lacerations over the forehead. The temperature was 98.4° F., pulse 76 and blood pressure 112/68. He weighed 114 lbs. compared with his average weight of 140 lbs. The right pupil reacted sluggishly to direct light and there was a central lens opacity. Coarse rales were present over both hilar regions and over the upper left chest. No enlargement of the liver, spleen, or kidneys was detected.

The earliest available x-ray film of September 17, 1953 (Figure 2A) showed disease in the upper half of the right and in the base of the left lung. There was progression of the disease, shown on the x-ray film of October 26, 1953, throughout the remainder of the right and into the lower two-thirds of the left lung. There was a dense infiltrate in the upper right lung on January 4, 1954 (Figure 2B) when the diagnosis of pulmonary tuberculosis was made. No film was available between January 4, 1954 and June 23, 1955. During this interval the disease in the upper right lung became dense and more scattered in appearance. Fibrocaseous disease appeared in the upper part of the left lung where an annular shadow measuring 6 cm. in diameter was visible (Figure 2C). A left lateral view taken on July 19, 1955 showed that the cavity was located somewhat anteriorly. Subsequently the annular shadow previously seen had decreased to a slit with a maximum diameter of 1 cm. before he left the hospital against medical advice.

Eleven sputum cultures were reported negative for tuberculosis. Eleven other sputum cultures were reported positive for Histoplasma capsulatum. Skin tests showed no hypersensitivity to PPD 1, coccidioidin 1:500 or blastomycin 1:100. Skin tests using PPD 2 and histoplasmin 1:500 did show hypersensitivity to both. Complement fixation tests for histoplasmosis were reported negative on four occasions. The red blood count increased from 3,600,000 on June 23, 1955 to 4,400,000 on January 18, 1956. The hemoglobin gradually increased from 10.5 gms. on June 23, 1955 to 12.6 gms. on February 20, 1956 just before discharge. The hematocrit changed from 38 VPC on June 23, 1955 to 43 on February 20, 1956. The erythrocyte sedimentation rate also gradually increased from 29 mm. per hour on June 23, 1955 to 37 mm. per hour on February 20, 1956. The serum albumin on admission was 2.6 gms. per cent and at discharge 3.7 gms. per cent. The serum globulin varied within the range of normal (2.6 gms. per cent to 3.4 gms. per cent). Blood serology for syphilis (VDRL) was negative.

Mycostatin was administered intravenously. The total dose was 3,577,500 units during a 6 month period between December 27, 1953 and February 2, 1956. Chillingness, substernal burning sensations, nausea, and transitory febrile reactions were frequent during and immediately following these intravenous injections. The drug was discontinued when he declined further intravenous therapy. He gained from 114 to 120 pounds during the eight months of hospitalization. At the completion of mycostatin therapy the only noticeable difference in the chest x-ray films was that the large annular cavity 6 cm. in diameter had changed to a narrow slit varying in width from 0.5 to 1 cm.

Discussion

We have found serological screening tests for histoplasmosis helpful in selecting cases whose sputum should be cultured for fungi. Since November 1955 we have participated in a serological survey conducted by Michael L. Furcolow for the United States Health Service in several hospitals in this area. Complement fixation tests for histoplasmosis have been done on 111 patients on the tuberculosis service at Veterans Administration Hospital, Wadsworth, Kansas. One hundred and seven of these
were reported negative, three were positive and one was anti-complementary. The sputum from one of the patients with positive serology for histoplasmosis yielded cultures positive for sporothrix. Sputum from the other two were negative for fungi but positive for M. tuberculosis. It is possible that these two patients may have active histoplasmosis together with tuberculosis, but are not expectorating sufficient quantities of fungi to yield positive cultures. Complement fixation tests for histoplasmosis have been done routinely on each new admission to the tuberculosis service since we began our participation in the survey.

The diagnosis of pulmonary mycotic infection rests upon the demonstration of the etiologic organism. There are no characteristic radiologic findings which differentiate pulmonary mycotic infections from pulmonary tuberculosis. In an individual where the diagnosis of tuberculosis has not been definitely established, the differential diagnosis should include neoplasm and lung abscess, as well as mycotic disease.

**SUMMARY**

1. Since mycotic pulmonary infections are now relatively more frequent, their differential diagnosis is especially important on tuberculosis services because of their clinical and radiologic similarity to pulmonary tuberculosis.

2. Two cases with histoplasmosis are reported. One had repeatedly positive sputum cultures for Mycobacterium tuberculosis, and histoplasmosis was diagnosed only at postmortem by microscopic tissue examination with PAS stain and culture of Histoplasma capsulatum from autopsy material. The other had a giant cavity on admission and progressive disease on serial chest x-rays films over a period of nearly two years. Sputum cultures were positive for Histoplasma capsulatum and negative for Mycobacterium tuberculosis. Intradermal sensitivity tests were positive with both tuberculin and histoplasmin. Complement fixation tests were negative for histoplasmosis.

**RESUMEN**

1. Ya que las infecciones micóticas pulmonares son ahora relativamente más frecuentes, su diagnóstico diferencial es especialmente importante en los servicios de tuberculosis debido a su similitud clínica y radiológica con la tuberculosis pulmonar.

2. Se reportan dos casos de histoplasmosis. Uno tuvo cultivos positivos para Mycobacterium tuberculosis repetidos, y la histoplasmosis fue diagnosticada únicamente post-mortem mediante el examen microscópico histológico con tinción de PAS y cultivo de Histoplasma capsulatum del material de autopsia. El otro tenía una cavera gigante a la admisión y enfermedad progresiva evidenciada por el estudio radiológico seriado durante un período de cerca de dos años. Los cultivos de esputo fueron positivos para Histoplasma capsulatum y negativos para Mycobacterium tuberculosis. Las pruebas intradérmicas de sensibilidad fueron positivas tanto con tuberculina como con histoplasmina. Las pruebas de fijación del complemento fueron negativas para la histoplasmosis.
RESUME

1. Depuis que les mycoses pulmonaires sont devenues plus fréquentes, leur diagnostic différentiel est particulièrement important dans les services de tuberculose, à cause de leur ressemblance clinique et radiologique avec la tuberculose pulmonaire.


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REFERENCES