Pulmonary Histoplasmosis: Report of a Case
Long Considered Tuberculous
Improved by Acti-Dione*

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Histoplasmosis in endemic areas such as the Mississippi Valley
is now considered to be the cause of many instances of pulmonary
calcification formerly thought to be tuberculous.1-5 We wish to
report a case who had a pulmonary infection in 1918-19 which
from 1925 to 1949 was considered to be tuberculous although
tubercle bacilli were never demonstrated. Skin test and comple-
ment fixation were positive for histoplasmosis. Histoplasma caps-
sulatum was cultured from sputum and lung tissue and was
demonstrated in lung tissue removed by lobectomy. He improved
clinically and the sputum no longer showed histoplasma after
intensive treatment with Acti-dione.

Case Report

This 51 year old white male was admitted October 29, 1949, for treat-
ment of pulmonary tuberculosis. Following an attack of influenza in
France in 1918, he had a severe productive cough and remained in
quarters for three months. He was discharged from the army March 20,
1919, apparently well. His first hospitalization here began July 24, 1925.
He complained of chest pain, weakness and cough intermittently since
three weeks after discharge from the army. Stereoscopic roentgenograms
of the chest in July showed a slight deviation of the trachea to the right,
increased hilar densities, and slight haziness in the right apex, first and
second interspaces. Stereoscopic views in December showed decrease of
the haziness in the right apex, persistence of the hilar shadows and the
presence of a filmy infiltration of the entire left upper lobe. Physical
findings were not remarkable except for constant medium rales over the
right apex. He weighed 140 lbs. and stood 5 ft. 10 in. Urinalyses, serology
and blood counts were normal. Fourteen sputum examinations were
negative for acid fast bacilli. There is no record of sputum culture or
animal inoculation. He was discharged against medical advice January
21, 1926, because his wife and son allegedly were ill with tuberculosis.
The discharge diagnoses were: arrested pulmonary tuberculosis and
chronic fibrous pleurisy.

On July 17, 1926, he was readmitted with the previous complaints of

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pain in the chest. X-ray examination still showed increased hilar shadows. The pleura appeared to be thickened in both apices. Physical examination was negative. He weighed 143½ lbs. Leucocytes were 10,960 c. mm. with 60 per cent polymorphonuclears, 32 per cent lymphocytes and 8 per cent large mononuclears. Ten sputum samples were negative for acid fast bacilli. He produced 3 cc. sputum per 24 hours. He was discharged July 31, 1926, with the previous diagnoses and not considered in need of treatment.

From 1926 to 1949 he had been able to work as a blacksmith, although the cough persisted and he was frequently seen by his family doctor. A chest x-ray film taken in a Veterans Administration Regional Office June 21, 1949, was fairly normal (Figure 1). In August he noted temperature elevations from 99 to 100 degrees F. daily. In September he experienced sharp pains in both sides of the chest, fever rose to 104 degrees F. and "hovered around 102 degrees F. for two weeks," and he was treated with a sulfa preparation and penicillin for "pneumonia." A follow-up chest x-ray film revealed pathology in the right lung and his physician advised hospitalization. He was admitted to the tuberculosis service October 29, 1949.

Physical examination showed a well developed, poorly nourished, 51 year old white male who appeared chronically ill. Temperature: 99.5 degrees F. Pulse: 78 per minute. Respiration: 18 per minute. Weight: 129 lbs. Blood pressure: 102/62 mm. Hg. Most of the teeth were missing, those remaining were carious and pyorrhea was present. There was mild bilateral deafness. Chest expansion was poor. The liver and spleen were not palpable. There were external hemorrhoids. Otherwise the physical examination was within normal limits.

Laboratory findings: On admission: erythrocytes 4,850,000, hemoglobin 13.5 gms., leucocytes 11,200 of which 69 per cent were neutrophils, 20 per cent lymphocytes, 7 per cent monocytes, and 4 per cent eosinophils. Cutler sedimentation rate was 22 mm./hr. Specific gravity of the urine was 1.010. Albumen, sugar and casts were absent. Kahn was negative. Twenty cc. of mucopurulent sputum was produced per 24 hrs. Daily sputum specimens were negative for acid fast bacilli and many cultures were likewise negative for tubercle bacilli. On December 12, 1949, Histoplasma capsulatum was identified in culture from a sputum specimen of November 25.* Four other samples were subsequently positive. Several cultures for acid-fast bacilli from sputum, gastric and bronchial washings were discarded as negative after 90 days incubation. Skin test with histoplasmin (1:100 dilution) produced an area of induration 20 mm. in diameter without erythema in 48 hrs. Complement fixation for histoplasmosis was reported positive 1/32 on two samples a month apart.† The leucocytes reached a maximum of 26,100 c. mm. The highest Cutler sedimentation rate was 30 mm./hr. X-ray film inspection of the chest on admission showed evidence of cavitary disease in the right upper lobe with infiltration of a mixed character extending downward to the level of the fourth anterior interspace. The left lung was essentially clear. Chest x-ray film taken January 10, 1950, showed a fluid level in the cavity and some spread to the left pericardiac area (Figure 2).

*Identification of the culture was confirmed by Arden Howell, Jr., Ph.D., Chief, United States Public Health Service, Medical Mycology Laboratory, Duke University.
†By United States Public Health Service, Chamblee, Georgia.
Figure 1: Relatively normal roentgenogram taken June 21, 1940, showing a fluid filled cavity and mixed infiltration in the right upper lobe and early spread to the left periarcadic area.

Figure 2: Roentgenogram taken January 10, 1950, showing a fluid filled cavity and mixed infiltration in the right upper lobe and early spread to the left periarcadic area.

Figure 3: Roentgenogram typical of recovery phase. Taken January 9, 1951.
After Histoplasma capsulatum was recovered the patient was transferred to the medical service. Sulfadiazine gm. 1 q. 4 hr. was given for one week without effect on the daily temperature elevation to 100-100.8 degrees F. No endobronchial disease was demonstrated by bronchoscopy.

Before the diagnosis was established, exploratory thoracotomy had been considered. Finally it was decided that since most of the detectable disease was in the right upper lobe, lobectomy would remove this and afford a better chance for the bodily defense mechanisms to overcome what remained. There was no evidence of generalized histoplasmosis. Accordingly therefore, the right upper lobe was removed by Dr. Louis F. Knoepp on January 27, 1950. The apical and posterior segments of the lobe were so densely adherent that they had to be literally excised from the parietal structures. Small nodules could be felt in the middle lobe and superior segment of the lower lobe but these were not disturbed because of the x-ray evidence of involvement of the left lung. Histoplasma capsulatum was cultured from the removed lung as well as demonstrated in sections of it as shown in Figure 4. The post-operative course was uneventful. On the 19th post-operative day he went home for a 14 day visit.

On February 5 the temperature suddenly rose to 103.2 degrees F. and he was returned to us for treatment. He weighed 132 lbs. Two days later the temperature spiked to 104 degrees F. Chest x-ray film showed an increase in pathology in the left upper lobe. Two hundred seventy five cc. of dark gray-green sputum was produced in 24 hours. Intramuscular penicillin 50,000 units every three hours was begun March 9 with a
prompt decline in temperature to 99-100 degrees F. and decrease in the volume of sputum to 120 cc. although its character remained unchanged. Therapy with Acti-dione* 60 mg. intravenously daily was begun March 13. Sputum obtained that day grew H. capsulatum. Within 24 hours the temperature was normal and the volume of sputum reduced by one half. On March 16 penicillin was discontinued. He remained afebrile thereafter and the sputum became thinner and averaged only 15-20 cc. per 24 hours. Only one specimen (March 24) during this period was positive. This was the last time histoplasma could be recovered from the sputum. The daily administration of Acti-dione was continued through May 18 at which time he went home without medication. He returned May 23 with chest pain, temperature of 103.4 degrees F. and respirations of 32 per minute. The day before he had had a chill. Sputum was increased. Acti-dione was resumed with prompt improvement. Bone marrow culture started June 1 was negative. On July 4 the dose of Acti-dione was reduced to 40 mg. daily. On August 9 he weighed 141 lbs., brought up 3 cc. clear sputum, and Acti-dione was discontinued. All was well until August 20 when he experienced chills with fever to 101 degrees F., and the next day sputum increased to 45 cc. Acti-dione 40 mg. daily was resumed. After five days he was afebrile and sputum was reduced to 5 cc. per 24 hours. On September 23 the dose was reduced to 20 mg. and on September 30 it was discontinued. Daily sputum cultures from October 2 through 6 were negative. He remained afebrile, sputum was scanty and weight was 145 lbs. so he was sent home on leave. Random specimens collected October 11, 12, 18, 19, 24 and 25 were negative. October 18 he returned with a history of chills, temperature was 100.2 degrees F., sputum was 15 cc. daily, and he had lost 7 lbs. He was then started on Acti-dione 25 mg. orally daily.* On October 30 the dose was increased to 25 mg. b.i.d.

This medication was not discontinued until January 5, 1951. There was no exacerbation and he was discharged from the hospital January 25, 1951, feeling "the best I have in years" and weighing 144 lbs. Leucocytes were 5,850 c. mm. with 44 per cent neutrophils, 44 per cent lymphocytes, 8 per cent monocytes and 2 per cent eosinophils. Erythrocytes were 4,820,000 c. mm. Hemoglobin was 14.8 gm. Cutler sedimentation rate was 8 mm. per hour. There had been no essential change in the chest x-ray film since September 1950. An x-ray film representative of this period is shown in figure 3. Sputums obtained January 8, 9 and 24 were sterile. The last one was held until March 3, 1951, without growth.

Six weeks after discharge he advised us by letter that he was still asymptomatic and afebrile.

Discussion

Although this patient's wife and son were thought to have pulmonary tuberculosis in 1925, neither that nor histoplasmosis was proved. The son served in the army in World War II and is clinically healthy. The wife has been under a physician's care

*Furnished by Dr. H. F. Hallman, the Upjohn Company, Kalamazoo, Michigan.

*Supplied by Dr. J. W. Frost, Eli Lilly and Company, Indianapolis 6, Indiana.
for frequent respiratory infections without the demonstration of an etiologic agent.

Histoplasmosis and tuberculosis have been reported in the same individuals.\(^6,7\)

Furcolow\(^7\) has emphasized that histoplasma may be found in a wide variety of clinical conditions in some of which it seemed to be an incidental finding of academic rather than practical importance. We believe the diagnosis of histoplasmosis is clearly established in our case and that the diagnosis of pulmonary tuberculosis was never proved. If we are to assume that pulmonary histoplasmosis existed from 1918-19, why was it relatively mild for so long? Why did it become more active with higher temperature and more sputum production in 1949-50? The chest x-ray film was relatively normal in June 1949 so that “pneumonia” in September may have been the initial infection with Histoplasma. However, the possibility of a fungous infection was not considered until November 1949.

The portal of entry of the fungus in man is not clearly established. The organisms have been demonstrated in the lungs of experimental animals inoculated intranasally and in the livers and spleens of animals infected orally.\(^8\) It would seem, then, that our patient was infected through the respiratory tract.

The histoplasmin skin test in either 1:1000 or 1:100 dilution is reportedly of value if induration and not erythema is considered a positive test.\(^4\) Many persons who are positive to histoplasmin and negative to tuberculin show other evidence of histoplasmosis. The skin test, however, may be negative in histoplasmosis. It is only suggestive, not diagnostic.

The complement fixation test has been positive in many proved cases but cross reactions with other fungi have been demonstrated. So it, too, must not be relied upon when unsupported by other findings.

The best diagnostic feature, therefore, is the repeated isolation of the fungus from cultures of blood,\(^8\) sputum, gastric washings, bone marrow, or tissue.

Either recovery or death may occur. Many of the recovered cases were exclusively pulmonary in location while the fatal cases often showed infection of lymph nodes, liver, lungs, spleen, adrenal glands, intestines, bone marrow, kidneys and oropharynx\(^10,11\) in order of decreasing frequency.

No effective method of treatment has been established. Lobectomy has been performed by others.\(^10,11\) We were unable to inhibit this patient’s strain of Histoplasma capsulatum in vitro with various concentrations of Actidione. No animal experiments were conducted.
The patient's sputum was reduced in quantity, his fever disappeared, weight and sense of well being improved, and H. capsulatum could no longer be cultured from the sputum after a prolonged course of Acti-dione. Several febrile exacerbations were promptly controlled by re-administration of the drug. We believe the improvement was more than coincidental and therefore Acti-dione merits further study in cases of histoplasmosis.

SUMMARY

A case* is presented who had a chronic cough following “influenza” in 1918-19 and was considered to have arrested pulmonary tuberculosis from 1925 to 1949 although acid fast bacilli were never recovered. In 1949, during the severest exacerbation he had experienced, Histoplasma capsulatum was repeatedly recovered in sputum cultures. Histoplasmin skin test was positive and coccidioidin and blastomycin were negative. The complement fixation test for histoplasmosis was positive. Right upper lobectomy was performed, although the pulmonary involvement was not entirely in this lobe.

Improvement with negative sputum and gain in weight followed prolonged treatment with Acti-dione which was effective when administered either intravenously (Upjohn) or orally (Lilly). Further investigation of Acti-dione in cases of histoplasmosis is indicated.

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RESUMEN

Se presenta un caso que tenía tos crónica después de “influenza” en 1918-19 y que era considerado como de tuberculosis detenida de 1925 a 1949 aunque nunca se encontraron bacilos ácido-resistentes. En 1949 durante la más severa de sus exacerbaciones se encontró histoplasma capsulatum en repetidos cultivos de esputos. La reacción cutánea de la histoplasmina fue positiva y la de la coccidioidina fue negativa. La reacción de fijación del complemento para la histoplasmosis fue positiva. Se llevó a cabo lobectomía superior derecha aunque la afección no estaba toda en ese lóbulo.

En seguida hubo mejoría con negativación del esputo y aumento de peso tras el uso de Acti-diona que fue efectiva administrada ya por vía intravenosa (Upjohn) u oral (Lilly). Está indicada la observación ulterior de casos de histoplasmosis tratados con Acti-diona.

*This patient was briefly referred to in the discussion of a recently published paper.
RESUME

Les auteurs rapportent l'observation d'un cas de toux chronique à la suite "d'influenza" en 1918-19 qui fut considéré comme une tuberculose pulmonaire de 1925 à 1949, quoique des bacilles acido-résistants n'aient jamais été trouvés. En 1949, pendant l'évolution la plus grave que le malade ait éprouvée, on découvrit plusieurs fois par les cultures de crachats "l'histoplasma capsulatum." Le test à l'histoplasmine fut positif, et ceux à la coccidioidine et à la blastomyicine furent négatifs. La réaction de fixation du complément pour l'histoplasmose fut positive. Une lobectomie supérieure droite fut pratiquée, malgré que l'atteinte pulmonaire ne s'étendit pas entièrement à ce lobe.

Un traitement prolongé à l'actidione fut suivi d'amélioration avec négativation des crachats, et gain du poids. Ce produit se montre efficace, aussi bien par voie intraveineuse (Upjohn) que par voie buccale. Les auteurs rapportent d'autres investigations sur l'action de l'actidione dans des cas d'histoplasmose.

REFERENCES