Residual Cavities in Pulmonary Coccidioidomycosis: Follow Up Studies*

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In an article published elsewhere1 we reported observations on 20 cases of residual lesions of pulmonary coccidioidomycosis in veterans of World War II now residing in New York City. Thirteen cases were described in detail. Twelve were of the form known as the initial or primary infection, and one was the progressive or disseminated (coccidioidal granuloma) form of infection. The need for a careful distinction between these two forms has been stressed most recently by Smith, Beard and Saito.2 The primary form of infection follows the inhalation of the chlamydospores of the fungus coccidioides immitis, and results in self-limited, usually benign, pulmonary lesions. The disseminated form of infection, which is relatively rare, arises from lymphohematogenous spread of the primary infection, and it is fatal in up to 50 per cent of the cases. The high incidence,3 (estimated 25 per cent), of coccidioidal infection in military personnel who were exposed in the Southwest desert endemic area is reflected in the veterans now coming under medical observation. A significant number of cases of residual pulmonary lesions have been encountered.

A series of cases with coccidioidal pulmonary cavitation has been studied. The four representative case reports which follow are limited to patients with pulmonary cavities, residuals of the primary infection. Emphasis is placed on the residual cavity, as distinguished from residual nodular densities, because of the importance of its differentiation from other pulmonary conditions, particularly tuberculosis. From five to seven years have elapsed since these patients were exposed in the Southwest endemic area. They are generally asymptomatic and the roentgenographic appearance shows little or no change during the period of observation. The question of therapy, which has recently been mentioned prominently in the literature,3,4 will be discussed following the case reports.

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CASE REPORTS

Case 1. Cavity Mistaken for Tuberculosis: A routine roentgenogram of the chest taken prior to separation from military service in March 1946 showed "an infiltrative lesion with cavity in the apex of the right upper lobe." The patient was entirely asymptomatic. Numerous sputum and gastric examinations for acid-fast bacilli and for coccidioides immitis were negative. The intracutaneous skin test with tuberculin was positive; negative with coccidioidin and histoplasmin. The patient was discharged to his home in October 1946 with a diagnosis of pulmonary tuberculosis.

On May 11, 1948 the patient was examined on a disability compensation claim. Because he had continued in excellent subjective general health, and in view of the history of intermittent service in the New Mexico and Texas desert from 1943 to 1946, it was felt that the diagnosis should be re-evaluated. A chest roentgenogram showed an infiltration in the right upper lobe, and a cavity 2.5 cm. in diameter in the periphery of the right first intercostal space, anteriorly. Physical signs were negative except for slightly diminished breath sounds over the involved area. Smears and cultures of the sputum were negative for tubercle bacilli and for fungi. The coccidioidin test of the skin (Fig. 1) was negative in a dilution of 1:100, but it was 4 plus in a dilution of 1:10. The complement fixation test for coccidioidal infection was positive. A roentgenogram of the chest on November 8, 1948 (Fig. 2) shows no change.

FIGURE 1: Coccidioidin skin test. Four plus reaction 24 hours following intracutaneous injection of 0.1 cc. coccidioidin, dilution 1:10 (scale in inches).
Case 2. Solitary Cavity: In February 1945, two years after he was discharged from the Army, the patient applied for disability compensation for rheumatic heart disease. A roentgenogram of the chest disclosed a thin walled cavity, with no surrounding disease, in the upper lobe of the right lung. He was hospitalized with a tentative diagnosis of pulmonary tuberculosis. The only complaint was moderate fatigue. Sputum and gastric washings failed to reveal tubercle bacilli and he was discharged in six months.

On March 18, 1946 a chest roentgenogram demonstrated persistence of the cavity and the patient was admitted to a Veterans Administration tuberculosis hospital. Additional history of several months military service in 1942 in the Western Texas desert was noted, at which time he suffered a febrile illness accompanied by a skin eruption described as erythema nodosum. Tuberculin and coccidioidin tests of the skin gave positive reactions. Smears and cultures of gastric washings were again found negative for tubercle bacilli and fungi. Right phreniclasia was performed in March 1947 with failure to obliterate the cavity. The patient was discharged with a final diagnosis of pulmonary coccidioidomycosis "based on the characteristic x-ray appearance, negative findings for tubercle bacilli and positive coccidioidin skin test."

The chest roentgenogram on November 29, 1948 (Fig. 3), shows the cavity to be still present, almost four years since its original demonstration, with the cavity wall slightly thicker and more irregular. The coccidioidin skin test is still positive. The patient has no complaints.

Case 3. Isolated Thin Walled Cavity: In March 1948, upon learning that his sister-in-law had pulmonary tuberculosis, the patient had a roentgenogram of his chest. He had no symptom other than a mild, dry morning cough. The roentgenogram revealed a cavity in the upper lobe of the right lung, and rest in bed was advised. Gastric washings were found negative for acid-fast bacilli.

The patient was asymptomatic when he entered a Veterans hospital in July 1948. There was a history of service in the Mohave desert for three months in 1943, but no recollection of illness during that period. Examination of the chest was negative, and the remainder of the physical examination was noncontributory. Sputum and gastric washings, and also bronchoscopic washings of the right upper lobe bronchus, were negative for acid-fast bacilli and for coccidioides immitis on smear and culture. The tuberculin skin test was negative in both first and second strengths. The coccidioidin skin test gave a positive reaction. The pulmonary cavity was unchanged in September 1948, when the patient was discharged from the hospital.

A service chest roentgenogram taken on October 30, 1944 was secured from the War Department and was reviewed, and the isolated cavity, a little smaller in diameter, was found to be present. A roentgenogram on January 24, 1949 (Fig. 4), reveals a cavity 2 cm. in diameter, with no surrounding infiltration, in the right first interspace, anteriorly.

Case 4. Cavity and Small Calcific Deposits: Initial hospitalization occurred in December 1944 for minor combat wounds of the back. Following a roentgenogram of the chest a diagnosis of "ill defined disease of the lungs" was made, and the patient was evacuated to a general hospital in the United States. He was afebrile and asymptomatic. A history of four months training in the Mohave desert in 1942 was obtained. The
chest roentgenogram in May 1945 showed linear infiltrations in the left first interspace and a cavity 1 cm. in diameter in the left second interspace, anteriorly. Numerous examinations of the sputum and gastric washings were negative for acid-fast bacilli. The tuberculin and the coccidioidin skin tests gave positive reactions. Serological (complement fixation and precipitin) tests for coccidioidal infection were negative. In November 1945 a growth of coccidioides immitis was cultured out of a gastric washing. The patient received a medical discharge from service. Serial roentgenograms of the chest during the one year period of hospitalization had shown no change.

At present the patient has no complaints and he has regular full time employment as a clerk. The coccidioidin skin test still gives a positive reaction. The roentgenogram of the chest on October 5, 1948 (Fig. 5), shows some thickening of the wall of the cavity, with several tiny neighboring calcific deposits; also several small calcifications in the left hilar region.

Comment

Diagnostic Criteria: A characteristic triad is common to all the cases; (1) history of residence in the endemic area, (2) a positive

FIGURE 5: Cavity in left second intercostal space, anteriorly. Neighboring small calcific deposits.
coccidioidin skin test, and (3) persistence of residual pulmonary lesions, showing little or no change. Recovery of the etiologic fungus is not essential to the diagnosis. In only one instance (Case 4) was coccidioides immitis found. This paucity of demonstration of the etiologic agent is consistent with the fact that the majority of cases do not come under observation until several years after the onset of the infection. Worthy of note is a report by Smith in which intensive efforts were made to recover the fungus in 225 cases. These cases were studied in the early stages of infection, when the fungus is more readily demonstrable, however, it was found in only 42 per cent.

Most of our cases had positive tuberculin skin tests. We do not share the reluctance of others to accept the diagnosis of coccidioidomycosis in the presence of a positive tuberculin test. The benign clinical course of our patients and the practically stationary roentgen appearance of the pulmonary cavities throughout several years of observation, together with the absence of tubercle bacilli, militate against the possibility of tuberculous etiology. Coexisting pulmonary tuberculosis and coccidioidomycosis occurs occasionally; less than a dozen cases have been reported. We are at present treating with artificial pneumoperitoneum a patient who developed cavitary tuberculosis subsequent to surgical resection of an upper lobe containing a coccidioidal cavity.

_Therapy_: Knowledge of the nature of the residual pulmonary coccidioidal lesions is essential to the intelligent application of therapeutic principles. One is at once impressed by their benignity. The lesions consist in the main of two types: (1) nodular fibrotic density and (2) cavity. Accurate figures on the overall incidence of residual cavitation are not available, but it is definitely less common than the nodule. Unlike tuberculosis, spread of the disease to the remainder of the lung fields or dissemination to distant organs rarely if ever occurs. In our patients the roentgen appearance has shown little or no change over a two to five year period of observation. The majority of cases show no symptom of illness at any time, many being discovered only on routine chest roentgenogram.

Also important in the approach to therapy is the improbability of contagion. It is generally believed that man becomes infected with coccidioidomycosis as a result of the inhalation of desert dust contaminated with chlamydospires of coccidioides immitis. A parasitic stage in the life cycle of the fungus then occurs, the fungus appearing in the human sputum as endospores. It is believed that the saprophytic stage in the soil must then occur again before the fungus can be infectious to man. Recently, however, Rosenthal and Routlen concluded from experiments with guinea
pigs that active primary or progressive coccidioidomycosis in humans may be contagious. In an article to be published elsewhere we have reported the results of a study of 11 intimate family contacts of six patients with cavitary pulmonary coccidioidomycosis, also a contact of a patient with disseminated coccidioidomycosis. Chest roentgenograms and coccidiolin skin tests were performed after periods of two or more years of exposure. None of the contacts had become infected. The latter study, we believe, constitutes additional evidence of the noncontagousness of the disease.

Nonintervention, therefore, should be the keystone of the therapy of these residual lung lesions. With only an occasional exception the condition is benign and the patient has few if any symptoms. Medicinal treatment is of no specific value. Collapse therapy and pulmonary resection have been and are still being performed for coccidioidal cavity. We wish to emphasize that pneumothorax or other surgical intervention is not indicated, except in the infrequent case where there is significant hemorrhage from a cavity.

SUMMARY

1) Observations on four cases with residual cavities of pulmonary coccidioidomycosis are made.
2) Diagnostic criteria and differentiation from pulmonary tuberculosis are discussed.
3) The generally benign nature of the lesions is stressed and conservative therapy is recommended.

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RESUMEN

1) Se presentan las observaciones de cuatro casos de cavidades residuales en coccidiolomicos pulmonar.
2) Se discute el criterio diagnóstico y la diferenciación de la tuberculosis.
3) La naturaleza generalmente benigna de la lesión se recalca y se recomienda el tratamiento conservador.

REFERENCES

4 Krapin, D. and Lovelock, F. J.: "Recurrence of Coccidioidal Cavities
Discussion
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The paper presented by Dr. Berke and associates is a timely one and is a challenge to us to be on the alert for similar cases. The reported high incidence (25 per cent) of coccidioidal infection in military personnel, exposed in the southwest endemic area, does not refer to the severe forms of the disease. Most infections are relatively mild and recover promptly. Coccidioidal granuloma is infrequent, as is indicated by the health bulletins in San Joaquin Valley of California, which report an average incidence of only 46 cases of coccidioidal granuloma each year in their valley of 750,000 population.

The essayers here stressed the benignity of most of the cases. This is quite true, except for the granulomatous, progressive form, which usually occurs soon after the primary infection is acquired. Although most of the acute cases recover spontaneously, some progress into the subacute stage, wherein the bronchial and mediastinal lymph nodes frequently become involved. Beck, Traum and Harrington have observed that in infected cattle the bronchial and mediastinal lymph nodes, and these only, were involved. It seems likely that in the prolonged acute cases in the human the hilar lymph nodes are infected, may remain dormant and inactive for years, and, in some cases, be the cause of dissemination in later years.

The four cases reported today bring out some interesting facts:
1) The paucity of physical findings of the chest, although we may find depressed breath sounds, dullness and rales.
2) Erythema nodosum appearing within 5 to 21 days after the onset of the infection.
3) The tendency for the pathologic picture in the lungs to show:
   (a) Nodular lesions,
   (b) Thin-walled, cyst-like cavities,
   (c) Hilar adenopathy,
   (d) Pleural involvement, fibrosis, effusion.
There is no proof of direct man to man, or animal to man transmission of the disease. Therefore, the history of residence in a known endemic area, should suggest the possibility of coccidioidal disease in every puzzling illness. The patients do not appear to be ill. There are few subjective and objective signs. They may give a history of erythema nodosum with a concomitant arthritis, appearing some days after having a respiratory infection, usually mild, but in some cases a severe respiratory infection, frequently with some pleural pain; recovery taking place within a few weeks at the most. A latent, dormant state may persist for years, the patient may harbor a low grade, asymptomatic infection in the bronchial or mediastinal lymph nodes for many years, only to become disseminated at a later date. The clinical picture at this time is one of mild subjective complaints. The physical examination of the chest may reveal no distinctive, characteristic findings, but the negativity of evidence of tuberculosis, syphilis, tumors, other fungus diseases, should alert one to the likelihood of coccidioidal granuloma. The roentgenogram may show in individual cases only hilar enlargement, single or multiple nodular lesions of varying size within the lungs, or the characteristic thin-walled, cyst-like, cavitation. It is my opinion that persons whose past clinical histories point to previous residence for a few months in an endemic area, with negative findings of other disease, who are not seriously ill, the roentgenogram revealing a thin-walled, cyst-like cavity with little, if any, surrounding infiltration in the lungs, with a positive coccidioidin skin test and negative tuberculin, even though the mold coccidioides immitis is not isolated, should be classified as cases of coccidioidal granuloma until proved otherwise. The presence of positive tuberculin reactions does cloud the diagnosis, but even so, one might be correct if the above stated symptom-complex is present, in making a tentative diagnosis of C. granuloma. The main point I wish to stress is that the diagnosis in these cases is not difficult if the physician is cognizant of its possibility.

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This fungus has two phases, the saprophytic and the parasitic. Coccidioides immitis affects animals and humans by the inhalation of the chlamydospores and the arthrospores of the fungus, from dust of infected soil, and, as far as we know, is not transmitted from man to man, although in the recent work by Rosenthal of Chicago, there is an attempt to prove otherwise.
During the war many soldiers were known to have become infected in some of the endemic areas in which they were stationed, and their wide dispersal since has presented this disease to many localities and clinics where differentiation between it and tuberculosis is essential in selecting therapy. Sixty per cent of the cases infected in the endemic areas are asymptomatic. It is more prevalent in men than women. Women are more apt to show erythema nodosum.

The frequency of cavitation in asymptomatic coccidioidomycosis is not known. The incidence in hospital cases in the U. S. Army has been given as 2 to 8 per cent and the etiology in 274 pulmonary cavities was verified by recovery of fungus in 40 per cent and by serological tests in 49 per cent. They further report that coccidioidomycosis was not found progressive. The relatively benign nature of the cavities is indicated by the fact that in the military patients three-fifths of them were discovered incidentally. They also report that 90 per cent of the cavities were single and 70 per cent located in the upper portion of the lungs.

In diagnosing these lesions the coccidioidin skin test was the first step. The complement fixation test shows a lower titer in the pulmonary cavitations and a higher titer in the disseminated or granuloma type of disease. Dr. C. E. Smith feels that this can be used as a guide in the prognosis.

In his studies Dr. William A. Winn reported a series of cavities and he feels we should be conservative in our approach toward consideration of cavities.

I have observed a number of cases over considerable periods in the last 30 years. In the early years they were not always diagnosed and were frequently classified as cases of pulmonary tuberculosis, without finding tubercle bacilli. Prior to a proper diagnosis, and later, these cases were many times treated with pneumothorax and phrenic paralysis; also specific vaccine was used, and occasionally, where cavitation existed, pneumothorax succeeded in closure, but complications were encountered when the lesions were near the periphery, with resulting bronchopleural fistulae. Following an incident of this kind I have not continued pneumothorax treatment, except as might be indicated by specific reasons, namely, hemorrhage.

I have had no occasion to resort to any treatment, surgically or otherwise, during the last 10 years. Most of these cavities are thin-walled and found to fluctuate, becoming larger, receding, possibly disappearing, only to reappear again. Occasionally one is seen that becomes thickened with considerable fibrosis. I watched a case of this type for years, eventually to hear of her dying from pneumonia.
I feel that therapy should be divided into two groups, prophylactic and indicative, and that cavities per se, unless of such size as to encroach upon the pulmonary function or endangering the individual by hemoptysis, should be left alone. Therefore, I would stress that in the presence of cavitation of the lung, with absence of acid fast bacilli, great diligence should be observed in eliminating possibility of coccidioidomycosis.