Steroid Induced Disseminated Coccidioidomycosis
Report of Two Cases

BERNARD M. LIPSCHELTZ, M.D.* AND HOWARD E. LISTON, M.D.*

Phoenix, Arizona

The increased use of antibiotic and steroid therapy has made us more aware of complicating fungal infections. Aspergillus, Mucor and Candida are the most common saprophytic organisms abundant in most environments. These saprophytes have been responsible for the increase of secondary pulmonary infections, which are generally believed to result from the extensive administration of cortisone and related steroids with antibiotics. Other predisposing factors are generalized debilitative states, diabetes mellitus, and malignant diseases including leukemia, Hodgkin's disease and allied lymphomas.

The most common fungus infections are those resulting from *Candida albicans*. Moniliasis, as a complication of antibiotic or steroid therapy, is usually manifested as a superficial skin or mucous membrane disease, but more severe monilial infections have resulted in pulmonary or intestinal involvement. However, the combination of steroids and antibiotics seems to predispose to disseminated disease, especially the Candida, Aspergillus and Mucor infections and, to a lesser degree, Cryptococcus and Histoplasma infections.

*Coccidioides immitis*, a diphasic fungus, occurs in nature in the hyphal or so-called "saprophytic form," but in man may become a primary infecting agent. Coccidioidomycosis is a disease of endemic geographic area, including the San Joaquin Valley in California and other areas of the southwest, including Arizona, New Mexico and west Texas. The disease is primarily a self-limited pulmonary infection which may be asymptomatic. Negroes and Filipinos are more prone than Caucasians to have severe primary illnesses and to suffer dissemination.

Following are two case reports of disseminated coccidioidomycosis, apparently induced by the administration of steroid therapy.

**CASE 1**

A 41-year-old white man was admitted to the Phoenix VA Hospital on July 24, 1961, because of fever, nonproductive cough, right-sided chest pain and weakness of five days duration. Past history included a diagnosis of chronic lymphocytic leukemia made in 1958 at the U. S. Naval Hospital, San Diego, California. He moved to Phoenix, Arizona in May, 1960, and remained relatively asymptomatic until his present illness.

Physical examination revealed a chronically ill white man with a temperature of 101.4°F.; pulse 90 and blood pressure were 150/86. Firm, non-tender, discrete lymph nodes, 1 cm. in diameter, were palpable in both axillae and inguinal areas; the spleen was slightly tender and enlarged to 6 cm. below the left costal margin; and the lungs were clear to auscultation and percussion. The remainder of the physical examination was not remarkable.

The admission white blood count was 7200 per cmm. with 82 per cent lymphocytes and 18 per cent neutrophils; hemoglobin was 10 grams; hematocrit was 32 per cent; and the erythrocyte sedimentation rate was 30 mm. per hour (Wintrobe). Sputum culture revealed anhemolytic streptococcus sensitive to all the common antibiotics. Chest x-ray film showed an infiltrative process in the right upper lobe (Fig. 1). Skin tests with PPD No. 2 and coccidioidin 1:100 were negative at 48 hours, and sputum examination was negative for acid-fast bacilli and *C. immitis*.

The initial diagnosis was bronchopneumonia, and he was treated first with tetracycline and then chloramphenicol over a 14-day period. Followup chest x-ray film then revealed a nodular infiltration involving the right upper lobe. With no clinical response to antibiotics, leukemic infiltration of the right upper lobe was considered, and the patient was started on prednisone 40 mg. daily. There was a prompt decline in fever and enough symptomatic improvement for him to
leave the hospital August 11 on prednisone 40 mg. daily. A chest x-ray film on August 16 showed a decrease in the size of the apical shadow and some clearing of the nodular infiltration, but the right upper mediastinum had enlarged. The patient returned to the hospital on September 2, 1961, with a recurrence of fever, cough and weakness. Chest x-ray film then showed the right apical infiltration to have decreased further and the right upper mediastinal shadow to have become more discrete. A repeat coccidioidin skin test in the 1:10 dilution was positive. Coccidioidal serologic studies were positive with a 4+ precipitin test in the 1:10 dilution and a 2+ positive complement fixation in the 1:2 dilution. This indicated a focalized primary coccidioidomycosis, and with this diagnosis established, steroids were discontinued.

He became progressively ill with fever ranging between 104° and 105°F., weakness, sweats and cough. Followup coccidioidal serologic studies revealed a negative complement fixation test although the precipitin test continued positive in a 1:10 dilution. Amphotericin-B therapy was started September 8, 1961, with an initial dose of 15 mg. intravenously. Because of severe nausea and vomiting, he refused further treatment. He continued to be extremely toxic with chills, a daily temperature up to 105°F., cough and weakness. A followup chest x-ray film September 12, 1961, showed an additional infiltration in the right lower lung and in the left upper lung peripherally. Disseminated coccidioidomycosis was strongly considered even though repeat serologic studies were not diagnostic. Dissemination was proved by the growth of Coccidioides immitis from a routine blood culture. His condition continued to deteriorate and he expired ten weeks after the onset of illness.

Necropsy findings disclosed granulomatous lesions containing the spherules of C. immitis which had involved the lungs, lymph nodes, liver and spleen. The bone marrow contained predominantly mature lymphocytic cells compatible with the diagnosis of chronic lymphocytic leukemia.

Case Summary: This case represents disseminated coccidioidal infection complicating steroid and antibiotic therapy in a patient with chronic lymphocytic leukemia. Immunologic response was so poor that the increased enhancement of growth and spread of C. immitis resulted in a coccidioidocemia, which is rare to obtain even in hematogenous dissemination.

Case 2

A 30-year-old white man was admitted to the Phoenix VA hospital on June 7, 1961, with chills, fever and general malaise of two weeks' duration. In 1951, he developed cervical and inguinal lymphadenopathy, and on the basis of lymph node biopsies, a diagnosis of sarcoidosis was made. He remained well, without treatment, except for a period of chills and fever during 1954. Prior to admission, he had lived in Phoenix 18 months, remained symptom-free and continued working.

Physical examination revealed a poorly nourished and chronically ill white man with a temperature of 101°F., pulse of 100 and blood pressure of 100/70. There was no lymphadenopathy or skin lesion, and the liver and spleen were both enlarged 6 cm. below the right and left costal margins, respectively. The remainder of the physical findings were normal.

The admission white blood count was 7900 per cemm. with a normal differential count, hemoglobin was 10 grams, hematocrit was 32 per cent and the erythrocyte sedimentation rate 30 mm. per hour (Wintrobe). Urinalysis showed 2+ albumin. The blood urea nitrogen was 10 mg. per cent; serum albumin 3.45 gram per cent; and globulin 3.86 gram per cent. Liver function tests were normal. Serum calcium was 10.3 mg. per cent and serum phosphorus 4.1 mg. per cent. The intermediate PPD, coccidioidin 1:100 and histoplasmin skin tests were all negative, and the chest x-ray film was normal. A liver biopsy specimen showed non-caseating granulomatous lesions compatible with hepatic sarcoidosis.

The diagnosis of sarcoidosis was reconfirmed. With continuing symptoms of chills, fever and malaise, prednisone was started June 29, 1961, in a dose of 40 mg. daily. There was prompt clinical improvement, and he was allowed to leave the hospital on a maintenance dose of 20 mg. prednisone daily. He was followed at fre-
quent intervals and remained asymptomatic for four months.

When readmitted to the hospital November 6, 1961, he had been acutely ill for one week with recurring chills, fever, malaise, non-productive cough and right-sided pleuritic chest pain. His temperature was 104°F, and there were medium crepitant rales heard throughout both lungs. The hepatosplenomegaly was unchanged, as was the remainder of findings on physical examination. A chest x-ray film then showed bilateral parenchymal, nodular and productive infiltrations (Fig. 2). Repeat routine laboratory tests were unchanged and the skin tests remained negative. Sputum smear and culture examinations for *C. immitis* and acid-fast bacilli were likewise negative. Serologic tests for coccidioidal infection revealed, on the first specimen of November 16, 1961, a positive precipitin test in the 1:40 dilution. This indicated the patient had acquired a primary coccidioidal infection and prednisone therapy was discontinued. By November 27, 1961, the complement fixation test was positive in the 1:8 dilution and the precipitin test remained unchanged. X-ray bone survey disclosed a punched-out lesion in the distal right femur (Fig. 3), which suggested dissemination. Follow-up coccidioidal serologic studies on December 27, 1961, showed a rising complement fixation titer to the 1:16 dilution and a continuing precipitin titer in the 1:40 dilution. This was considered compatible with a single extrapulmonary lesion.

Because of the strong suspicion of coccidioidal dissemination, intravenous amphotericin-B was started January 2, 1962. After 450 mg. had been given over a one month period, the chest x-ray film showed some clearing. The precipitin titer was then positive only to the 1:10 dilution, and the complement fixation titer to 1:8 dilution. Five weeks later, on March 6, 1962, a total of 2000 mg. of amphotericin-B had been given, and there was further resolution of the pulmonary lesions. The coccidioidal precipitin test had become negative, while the complement fixation titer remained positive at 1:8 dilution. By April 4, 1962, after the patient had received 2850 mg. of amphotericin-B, the chest x-ray film revealed complete clearing of the pulmonary lesions although the lytic lesion in the right femur was slightly larger. The complement fixation titer had decreased to 1:4, and the precipitin test remained negative. Treatment was discontinued April 24, 1962, after a total dose of 3200 mg. of amphotericin-B had been given.

During treatment, the patient's cough subsided,
but he continued to have intermittent chills and fever. Nausea and vomiting were present early in the course of amphotericin-B treatment, but were not a great problem. The blood urea nitrogen did not rise above 26 mg. per cent. A chest x-ray film May 1, 1962, was unchanged, and the complement fixation titer decreased to 1:2 while the precipitin test remained negative. At the time the patient was discharged on June 14, 1962, he was asymptomatic and planned to return to his former home in New Jersey.

**Case Summary:** This case represents a systemic disease, sarcoidosis, treated with prednisone, complicated by primary pulmonary coccidioidomycosis with a localized disseminated spread to the femur. The disseminated coccidioidal infection was successfully treated with amphotericin-B.

**Discussion**

Disseminated coccidioidomycosis is not ordinarily considered one of the “lower form” or “opportunistic” fungal infections, complicating steroid therapy. In fact, steroids have been used effectively in the treatment of erythema multiforme and/or erythema nodosum associated with primary coccidioidomycosis. Levan and Einstein treated 19 such patients over a four to six day period, with a total dose of 350 to 775 mg. of cortisone. This short course of steroids cleared up the allergic skin manifestations of coccidioidomycosis with no resulting dissemination. However, it has been observed that primary coccidioidomycosis with hypersensitivity and the allergic manifestations of erythema multiforme and/or erythema nodosum rarely disseminates and have an excellent prognosis. Steroids have been used in treating disseminated coccidioidomycosis in conjunction with amphotericin-B therapy with some success, primarily to counteract the side effects of amphotericin-B. The direct effects of the steroids in conjunction with amphotericin-B have not been definitely established as the ideal treatment to date. Experimentally, cortisone usually enhances fungal infections, especially Candida infections, to a far greater degree than infections due to *Histoplasma capsulatum* or *Cryptococcus neoformans.* On experimental coccidioidomycosis, cortisone appeared to produce earlier maturation and multiplication of the fungus, with an adverse effect on longevity of mice infected with *C. immitis.* Other factors influencing spread of the disease are inhibition of the inflammatory reaction and probably alteration in immunologic responses.

Chronically ill individuals have a diminished resistance against many types of infections. This diminished host resistance is an important factor in complicating bacterial and fungus infections, especially in patients with lymphoma, leukemia and other blood disorders. Treatment of these blood disorders with steroids is known to reduce host resistance to many bacterial infections, and for this reason antibiotics are often administered in conjunction with these steroids. While the combination of these drugs may influence preventive secondary bacterial infection, it is apparent that susceptibility to infection with fungi that are ordinarily non-pathogenic for man is thus enhanced.

Zimmerman states that in contrast, coccidioidomycosis shows little or no tendency to occur in patients already afflicted by another primary condition. However, by the experimental evidence mentioned previously, there is apparently some predisposition to primary and disseminated coccidioidomycosis in the endemic areas previously mentioned.

Castellot et al. reported the first case of disseminated coccidioidomycosis associated with adrenocortical steroid therapy in a patient with a seven year history of myelofibrosis. The patient developed, during therapy, an undiagnosed febrile illness with faint miliary densities on chest x-ray films. It was only at necropsy that disseminated coccidioidomycosis was discovered.

**Acknowledgment:** We wish to thank Dr. Charles E. Smith, Professor of Medicine of the University of California School of Public Health, Berkeley, California for his assistance in performing and interpreting the serologic studies for coccidioidomycosis, and for his helpful suggestions in reviewing this article.

**References**

STERIOD INDUCED DISSEMINATED COCCIDIOIDOMYCOSIS


For reprints, please write Dr. Lipschultz, VA Hospital, Phoenix.

CURRENT CONCEPTS OF BRONCHOCYTIC CARCINOMA

Five hundred forty-one cases of bronchogenic carcinoma have been reviewed at Emory University Hospital and the Atlanta VA Hospital. General data are comparable to other series and show possible increase in the younger age group and in the female after menopause. Cystic lesions, particularly in anterior segments, and the so-called static lesions are strongly suspect of carcinoma. Pulmonary angiography as a diagnostic and prognostic tool is discussed. Resection in cases with no lymph node involvement yielded 35 per cent survival with evidence of recurrence. The increase in the operability and possible cure rate with preoperative radiation is discussed.


BALLISTOCARDIOGRAMS

Two hundred twenty-one hospital patients studied by the high-frequency force BCG have been followed up until death or, if still alive, for five years or longer. These data have been studied to determine the relationship between longevity and the degree of abnormality of force BCG's. No evidence has been secured that force BCG's slightly abnormal in form (Class II) have a clinical significance different from that associated with a normal record (Class I). Force BCG's moderately abnormal in form (Class III) were followed by greatly reduced duration of life. When paired with those with Class IV records, patients having Class III records showed significantly greater average longevity. Force BCG's extremely abnormal in form (Class IV) were clearly associated with a markedly diminished life duration and most of the patients with such records died of heart disease within a few years. One must conclude that the incoordinate myocardial contractions identified by force BCG's moderately or extremely abnormal in form are accompanied by a great reduction in life expectancy.


CARBON DIOXIDE ANGIOCARDIOGRAPHY

The technique of CO2 angiocardiography has several advantages which recommend its use in preference to previously utilized radio-opaque substances which are used in intravenous and selective angiography. These latter procedures are technically more difficult and time consuming than CO2 angiocardiography and carry greater hazards with occasional equivocal or unsatisfactory results. The procedure of CO2 angiocardiography is technically much simpler than conventional angiography; it is faster, utilizes conventional x-ray equipment. It is also possible to repeat the entire procedure within a few minutes if the first result is unsatisfactory. It must be stressed, however, that only medically pure CO2 be used and that all air be flushed from the tubing system before the injection is made. After the injection of CO2 is completed, the patient should be maintained in the left lateral decubitus position until the CO2 is entirely absorbed. This is usually complete within ten minutes after injection.