Sarcoidosis: Treatment with Cortisone, ACTH and Urethane

MICHAEL F. KOSZALKA, M.D. and ARTHUR C. FORTNEY, M.D.*

Fargo, North Dakota

Consistent results were not obtained from urethane, calciferol, nitrogen mustard and antibiotics in the treatment of sarcoidosis by Sones and his associates1 but they recently reported marked improvement in two patients with sarcoidosis treated with cortisone. Association of functional adrenal impairment with sarcoidosis was suggested by their report. The dramatic regression observed in their two patients was not attributed to spontaneous regression and striking changes occurred in the biopsied tissues after treatment. On the other hand, Thorn and his co-workers2 reported the use of ACTH without beneficial effect in one case of sarcoidosis.

Since no other effective or specific treatment for sarcoidosis is known, the results obtained from the use of all three drugs, cortisone, ACTH and urethane, in a patient with sarcoidosis is the occasion for the following report.

Case Report

A 32 year old white male, while en route home from the Letterman General Hospital, was admitted to the Fargo Veterans Administration Hospital, August 1, 1950 because of sudden onset of paroxysmal cough, extreme dyspnea, vomiting and semicoma.

Present Illness: Upon reenlistment in the U. S. Army on May 12, 1948 he was stationed in California. He remained in good health until July 1949 when he was hospitalized because of a persistent cough productive of a greenish-white mucoid sputum associated with exertional dyspnea. In August 1950, biopsy of a parasternal lymph node established the diagnosis of sarcoidosis. A study of this slide showed round masses of epithelioid cells with occasional Langhans giant cells but no central necrosis (Figure 1). Several skin biopsies and a sternal marrow puncture were normal. During army hospitalization he required or received many therapeutic measures, such as penicillin, sulfadiazine, aureomycin, potassium iodide, oxygen, diuretics and mercurial diuretics. At one time he appeared terminal, was comatose for 10 days, and had two Jacksonian epileptiform seizures but rallied and gradually improved sufficiently to receive a medical discharge on July 29, 1950.

Past history and family history were non-essential and non-contributory.

Physical examination on admission revealed a 32 year old fairly well developed but poorly nourished white male who appeared acutely and chronically ill with dyspnea, cyanosis, weakness and paroxysms of coughing. Facial expression of fright and marked anxiety were exhibited. His lungs were filled with inspiratory and expiratory moist rales and wheezes. A systolic apical murmur was present. Examination of the slightly protuberant abdomen revealed enlarged liver four finger breadths below the right costal margin. His color was ashen gray and his

*From the Medical Service, Veterans Administration Hospital, Fargo, N. Dakota. Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.
skin bore multiple, discrete, superficial and deep self-induced excoriations. There was no superficial lymphadenopathy.

**Laboratory Findings:** Red blood cell count was 4,750,000 per cubic millimeter. Hemoglobin 13.8 grams (Sahli). White blood cell count was 9,800 per cubic millimeter with the differential count showing 68 per cent polymorphonuclear cells, 30 per cent lymphocytes and 2 per cent monocytes. The sedimentation rate was 8 mm. (Wintrobe method). Hematocrit 50-55 per cent. Urinalysis and blood Kahn tests were negative. The total protein was 7.32 mg. per cent with an albumin-globulin ratio of 2.08-5.4. CO₂ volume per cent: 46. Blood NPN: 35-54.6 mg. per cent. Blood calcium: 9.7 mg. per cent; inorganic phosphorus: 4.3 mg. per cent. Blood chlorides: 500 mg. per cent. Repeated sputum studies were negative for acid fast bacilli. Spinal fluid findings were normal. Tuberculin P.P.D. skin tests with 1st and 2nd test strengths were negative. A Thorn eosinophile test on August 18, 1950 demonstrated a drop in the eosinophil count from 110 to 36 eosinophiles per cubic millimeter, with a 9.2 per cent increase in the urine uric acid:creatinine ratio. Repeated at weekly intervals throughout the entire hospital stay, the patient's hematologic findings, CO₂ combining power, blood chlorides, NPN and urinalyses remained within the limits of normal except for the appearance of albuminuria during the latter half of his hospital course. The electrocardiogram showed the characteristic findings of right ventricular hypertrophy. X-ray films of the hands and feet were negative. X-ray films of the chest showed enlargement of the heart with marked pulmonary infiltration bilaterally within the inner one-third and one-half of the lung fields and first and second interspaces (Figure 2).

**Course in the Hospital:** The course of this patient's illness is summarized in Figure 3. The outstanding features were right heart failure and terrifying paroxysms of cough and cyanosis. Upon admission to the hospital he appeared in a terminal state but gradually responded to oxygen, digitalis, ammonium chloride, mercurial diuretics and hormonal therapy. He was semi-ambulatory by the early part of September but required a maintenance daily dose of digitalis and weekly or bi-weekly mercurial diuretic parenterally for control of orthopnea, peripheral edema and weight. A total of 1,730 gm. of ACTH were administered from August 18, 1950 to October 19, 1950, when he developed a moon-face appearance and medication was discontinued. During this time there was marked improvement in his sense of well being, cessation of vomiting and improvement in appetite but there was no alternation in the degree of pulmonary infiltration roentgenographically. Both urethane and later cortisone were given as shown in Figure 3 for a total of 68 gm. and 1900 mg., respectively. Repeated electrocardiographic tracings showed no changes other than that of right ventricular hypertrophy. There was no significant change in pulse rate or blood pressure at any time except terminally. The patient frequently required narcotics (codeine, meperidin or methadon) for relief or control of episodes of paroxysmal coughing which occurred most frequently during the night. In the last two weeks of life, dyspnea, paroxysmal cough and cyanosis gradually increased progressively into shock and he expired quietly on March 14, 1951, approximately 20 months after onset of illness.

Necropsy was performed 24 hours after death. Lightly pigmented superficial scars and numerous fresh and healing excoriations of the skin were distributed over the entire body. No edema of the face or extremities was noted.

**Lungs:** Both lungs were bound down to the chest wall by adhesions. The left weighed 690 gm. and the right, 620 gm. Both were firm on palpation in general with extreme firmness in the apices. The upper half of the lungs on cut section showed a mottled grayish-white and black, honey-combed appearance while the lower halves presented a dark red mottled surface. A thrombus occluded the right pulmonary artery at the hilus of the right upper lobe. The hilar lymph nodes were enlarged, reddish-black in color and firm in consistency on cut section.

**Heart:** The heart was markedly enlarged and weighed 800 gm. The right auricle and ventricle were dilated and hypertrophied. The myocardium of the right ven-
Figure 1: Microscopic section (×150) of a lymph node biopsy made in August 1950, showing nodules of epithelioid cells without necrosis. Figure 5: Microscopic section (×100) of lymph node nineteen months after initial biopsy demonstrating fibrous tissue replacement. Note the absence of granulomatous.
tricle measured 8 mm. in thickness. Otherwise the musculature, valves and coronary arteries appeared normal.

Spleen: The spleen weighed 220 gm. It was firm in consistency and on cut section revealed a dark purplish surface which did not scrape easily.

Liver: The liver weighed 1,500 gm. On cut section it demonstrated a typical nutmeg appearance.

The remainder of the necropsy was not significant.

Anatomic Diagnosis: Sarcoidosis of the hilar lymph nodes, lungs, liver and spleen; thrombosis of the right pulmonary artery; chronic cor pulmonale; apical fibrocoseous tuberculosis?

Microscopic Examination (Reported by Dr. D. F. Gleason, Pathologist, and Dr. A. C. Aufderhiede, Resident in Pathology, Department of Pathology, Veterans Administration Hospital, Minneapolis, Minnesota):

“Lungs: Many sections of the lung reveal a similar picture in that most of the parenchyma has been replaced by a vast amount of scar tissue throughout which are scattered small foci of lymphocytes (Figure 4). No active tuberculosis is seen anywhere, and there is no evidence of granulomas or tubercles. In some sections scar is seen to be in pleural and subpleural positions, although in other areas the scar appears to be deep in the pulmonary tissue itself. Some of the other sections reveal simple hypostatic congestion.

“Liver: An extreme degree of chronic passive congestion is seen as manifested by markedly dilated sinusoids and atrophy of the liver cords in the central areas.

FIGURE 2: Roentgenogram of the chest, November 30, 1950, showing cardiac enlargement with marked pulmonary infiltration.
This is so marked as to involve the central and mid portions of the lobules in most areas and in some areas even the entire lobule. No tubercles or granulomas are seen.

"Pulmonary Artery: A relatively recent unorganized thrombus is found in the section of the pulmonary artery.

"Spleen: No granulomas or tubercles are seen. Small areas of scar are scattered throughout the section.

"Bone Marrow: The marrow is normocellular and without granulomas or tubercles.

"Lymph Nodes: Section of multiple nodes, most of which appear to be bronchial in origin, reveal a similar picture in that a large amount of scar is seen within these nodes. Some of the nodes are involved to only a mild degree, others to an extreme degree. The scar in most of the nodes is rather diffuse, although in others appears in small focal areas. No evidence of tuberculosis or active epithelioid cell formation is noted (Figure 5). The original biopsy of this patient made at Letterman General Hospital was obtained for review and study. The node is seen to be occupied by vast numbers of epithelioid cell granulomas without necrosis. An occasional Langhans type giant cell is found in association with these tubercles but these cells are without asteroid bodies (Figure 1).

**FIGURE 3:** Chart summarizing course and therapy during last eight months of illness.
Sections of the kidneys, heart, adrenals, pancreas, and prostate reveal no unusual changes.

Summary: The cause of death is obviously thrombosis of the pulmonary artery. That increased pressure in the venous system has existed for sometime is manifested by the marked congestive changes in the liver. Although the original biopsy reveals changes in the lymph node characteristic of the syndrome usually described as 'Boeck's sarcoid,' it is of striking interest that the necropsy fails to reveal a single granuloma in spite of an intensive search for such a lesion. The fibrotic changes seen in the lymph nodes, as well as the spleen and possibly the lungs, could be interpreted as fibrosis of pre-existing granulomas in these structures, although conclusive evidence of this is lacking in view of the absence of demonstrable active lesions. In spite of the gross protocol note that some suspicious caseous areas were seen in the lung at necropsy, no such lesions were found microscopically despite sectioning of all material submitted for examination. In summary, this appears to be a case of 'Boeck's sarcoid' treated extensively with ACTH in which death occurred from thrombosis of the pulmonary artery and in which the necropsy failed to reveal any residual evidence of the disease.

Microscopic Diagnosis: Thrombosis of the pulmonary artery; sarcoidosis?; chronic passive congestion of the liver.

Comment

This patient demonstrated the development of chronic cor pulmonale and severe paroxysms of coughing due to extensive sarcoidosis of the lungs. A fatal course appeared obvious, therefore treatment with adrenocorticotropic hormone (ACTH), cortisolone and urethane were added empirically to the symptomatic and supportive regimen with the hope of altering the course of the disease. Knowing that heart failure is a relative contraindication to the use of ACTH and cortisolone, and that sarcoidosis frequently shows active tuberculosis terminally, it was postulated that the possible therapeutic gain might outweigh the risk if the hormones were
administered with care. Outside of increasing the patient's sense of well
being, no improvement of the lung involvement could be detected roent-
genographically. Urethane also did not appear to alter the course. No
change in the normal hematologic picture during the administration of
urethane was noted. Impaired adrenal function associated with sarcoid-

osis as observed by Sones and his collaborators1 was not evident in this case.

Deaths almost always result from direct or indirect complications of
this enigmatic granulomatous disease. The relationship between sarcoidosis
and pulmonary tuberculosis is not completely understood but their existence
together is well known and need not be discussed.3-5 Although fibrocaseous
tuberculosis of the pulmonary apices was suspected on gross examination,
no such lesion was reported microscopically after a diligent search in this
case. Right heart failure secondary to extensive pulmonary involvement
in sarcoidosis, uncommon as it is, has also been mentioned in the litera-
ture5,4,6-8 but the occurrence of thrombosis of a pulmonary artery as a
complication of sarcoidosis is reportedly unknown. Heart failure from other
causes is recognized as a factor in the production of pulmonary thrombosis
in situ. It reasonably provided the background in this instance.

Spontaneous remissions are frequently observed in sarcoidosis and it is
generally considered a benign disease. The lesions may undergo fibrosis
and replacement by hyalinized connective tissue and this is taken to
indicate a healing or healed process.5-10 The residual changes may, how-
ever, produce respiratory distress and right heart failure.6,7 No recogn-
izable sarcoid structure was detectable in any of the organs in this case.
In its stead was a striking amount of scar tissue which presumably was
preceded by epitheloid granulomatous lesions present before treatment.
If the transformation occurred prior to therapy, it must be deduced that
hormonal therapy has no beneficial effect on the end stage of sarcoidosis.

SUMMARY

A case of sarcoidosis complicated by chronic cor pulmonale and throm-

bosis of a pulmonary artery with post mortem findings is presented.
Empirical trial with ACTH, cortisone and urethane clinically failed to
alter the fatal course but autopsy failed to reveal any active sarcoid
lesions. The presence of a large amount of scarring and collagen is taken
to indicate a healing or healed process that occurred spontaneously and
was not affected by the treatment or was induced by the hormonal or
urethane therapy without benefit. Further confirmatory studies with these
drugs in the earlier phase of this disease are necessary.

RESUMEN

Se presenta un caso de sarcoidosis complicado con cor pulmonale y
thrombosis de la arteria pulmonar, con los hallazgos post-mortem. El
tratamiento empírico con ACTH, cortisona y uretano clínicamente fracasó
en evitar la evolución fatal pero la autopsia no reveló ninguna lesion
activa de sarcoide. La presencia de gran cantidad de tejido cicatrizal y
colágeno se considera como proceso en curación o curado que aconteció
esponáneamente y no fue afectado por el tratamiento o inducido sin beneficio por la terapia hormonal o por uretano. Se necesitan estudios confirmativos con estas drogas en una fase temprana de la enfermedad.

RESUME

Les auteurs rapportent un cas de maladie de Besnier-Boeck-Schaumann, compliqué d'un coeur pulmonaire chronique et d'une thrombose de l'artère pulmonaire, avec les constatations faites à l'autopsie. Un traitement empirique à l'ACTH, cortisone et urethane ne permet pas de modifier l'évolution fatale. Mais il ne fut plus possible à l'autopsie de trouver la moindre lésion active de sarcoïdose. La présence d'une grande quantité de tissu cicatriciel et de tissu collagène indique qu'un processus de guérison spontanée n'a pas été affecté par le traitement. Il est nécessaire de confirmer ces études par la connaissance de l'action de ces produits dans la phase précoce de la maladie.

REFERENCES