
SARCIOIDOSIS WITH ARTHRITIS

BY

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"Sarcoidosis is a systemic granulomatous disease of undetermined aetiology and pathogenesis. Mediastinal and peripheral lymph nodes, lungs, liver, spleen, skin, eyes, phalangeal bones, and parotid glands are most often involved, but other organs or tissues may be affected. The Kveim reaction is frequently positive, and tuberculin-type hypersensitivities are frequently depressed. Other important laboratory findings are hypercaluria and increased serum globulins. The characteristic histologic appearance of epithelioid tubercles with little or no necrosis is not pathognomonic, and tuberculosis, fungal infections, beryllium disease, and local sarcoid reactions must be excluded. The diagnosis should be regarded as established for clinical purposes in patients who have consistent clinical features, together with biopsy evidence of epithelioid tubercles or a positive Kveim test."

(Definition prepared by the 1960 International Conference on Sarcoidosis, held in Washington, D.C.)

The twelve patients (all Negroes), who are discussed below, were seen in a rheumatology clinic within a period of 18 months. At least nine of the twelve were first diagnosed as cases of arthritis, so that a detailed report of the tests carried out and of the eventual diagnosis would appear to be worth while.

Clinical Findings

The clinical impressions on admission, as well as the clinical features confirming an eventual diagnosis of sarcoidosis, are summarized in the Table (overleaf). Ten of the twelve patients presented with objective arthritis in two or more joints, and the remaining two (Cases 2 and 4) gave a history of polyarthritis at the onset of symptoms, although no objective joint changes were present on admission to hospital. Fever was present on admission in five cases (1, 5, 7, 9, 12), but the response to salicylate therapy was only partial. No patient had splenomegaly, but hepatomegaly was found in Cases 9 and 10. The liver biopsy from Case 9 was compatible with sarcoidosis.

Skin.—Five patients (Cases 3, 5, 6, 8, 9) had cutaneous lesions compatible clinically and histologically with sarcoidosis (Fig. 1), and one (Case 10) had subcutaneous nodules shown microscopically to be of Darier-Roussy type. In Case 3 skin biopsies were taken from three different sites: one confirmed the widespread clinical ichthyosis, and the other two revealed a sarcoid reaction with the ichthyosiform pattern. Erythema nodosum occurred at the onset with polyarthritis in two patients (6, 7), and Case 6 also had histologically proven cutaneous sarcoid.

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Fig. 1.—Case 5, showing nodular cutaneous sarcoidosis involving nares, bridge of nose, inner canthi, and eyelids.
ANNALS OF THE RHEUMATIC DISEASES

Table 1

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Age at Onset (yrs)</th>
<th>Duration of Disease (yrs)</th>
<th>Initial Impression</th>
<th>History</th>
<th>Joint Involvement</th>
<th>Objective Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>F</td>
<td>25</td>
<td>1/2</td>
<td>Acute rheumatic fever</td>
<td>Arthritis following sore throat</td>
<td>Knees,* wrists</td>
<td>Swelling right wrist and both knees with effusions</td>
</tr>
<tr>
<td>2</td>
<td>26</td>
<td>F</td>
<td>26</td>
<td>1/2</td>
<td>For investigation</td>
<td>Polyarthralgia followed by painful lump right side of neck</td>
<td>Knees, ankles, elbows, wrists</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>27</td>
<td>M</td>
<td>18</td>
<td>10</td>
<td>Acute rheumatoid arthritis</td>
<td>Acute polyarthritis for 6 mths, involving hands and wrists</td>
<td>Wrist,* fingers</td>
<td>Hot, swollen metacarpophalangeal joints resembling rheumatoid arthritis</td>
</tr>
<tr>
<td>4</td>
<td>27</td>
<td>F</td>
<td>26</td>
<td>6</td>
<td>Tuberculosis</td>
<td>Admitted to hospital for pulmonary tuberculosis</td>
<td>Wrist, knees, ankles</td>
<td>History of swollen joints</td>
</tr>
<tr>
<td>5</td>
<td>43</td>
<td>F</td>
<td>36</td>
<td>8</td>
<td>Acute rheumatic fever</td>
<td>Initially diagnosed as rheumatic fever in 1954 Recurrent similar episodes of acute polyarthritis</td>
<td>Wrist,* knees, ankles</td>
<td>History of recurrent swelling for 8 yrs, resembling rheumatic fever</td>
</tr>
<tr>
<td>6</td>
<td>26</td>
<td>F</td>
<td>25</td>
<td>1/2</td>
<td>Possible sarcoid arthritis</td>
<td>Three attacks polyarthritis with erythema nodosum and cutaneous sarcoidosis</td>
<td>Elbow,* knees, ankles</td>
<td>History of two episodes acute joints and erythema nodosum</td>
</tr>
<tr>
<td>7</td>
<td>25</td>
<td>F</td>
<td>25</td>
<td>1/2</td>
<td>Acute rheumatic fever</td>
<td>Recurrent sore throat. Migratory polyarthritis. Erythema nodosum</td>
<td>Knees,* ankles, wrists</td>
<td>Swollen left ankle</td>
</tr>
<tr>
<td>8</td>
<td>33</td>
<td>F</td>
<td>26</td>
<td>8</td>
<td>Possible sarcoid arthritis</td>
<td>1955: Diagnosis established 1962: Polyarthritis and bilateral knee effusions</td>
<td>Knees,* elbows, right wrist</td>
<td>Effusions both knees 1961 and 1962</td>
</tr>
<tr>
<td>9</td>
<td>27</td>
<td>M</td>
<td>27</td>
<td>1/2</td>
<td>Rheumatic fever or rheumatoid arthritis</td>
<td>Arthritis in knees and ankles for 2 weeks</td>
<td>Knees,* ankles</td>
<td>Swollen ankles, Effusions both knees</td>
</tr>
<tr>
<td>10</td>
<td>58</td>
<td>M</td>
<td>58</td>
<td>1/2</td>
<td>Possible rheumatoid arthritis</td>
<td>Arthritis 4 mths with eye involvement</td>
<td>Ankles*</td>
<td>Swollen ankles</td>
</tr>
<tr>
<td>11</td>
<td>32</td>
<td>F</td>
<td>32</td>
<td>1/2</td>
<td>Acute rheumatoid arthritis</td>
<td>Acute polyarthritis for 2 mths, involving hands and wrists</td>
<td>Hands,* wrists, elbows, shoulders, knees, temporomandibular, sternoclavicular</td>
<td>Effusions both knees. Swollen wrists, two proximal interphalangeal joints and three metacarpophalangeal joints, resembling acute rheumatoid arthritis</td>
</tr>
<tr>
<td>12</td>
<td>44</td>
<td>M</td>
<td>44</td>
<td>1/2</td>
<td>Atypical infectious arthritis</td>
<td>3 wks before admission fever, chills, and cough 2 wks before admission symptoms of bilateral sciatica 1 wk before admission acute arthritis left elbow and right knee with effusions</td>
<td>Hands,* wrists, elbows, shoulders, knees</td>
<td>Effusions right knee and left elbow</td>
</tr>
</tbody>
</table>

* Arthritis was the presenting symptom. † All fungal tests negative. ‡ Parotids and lacrimal also involved. ND = Not done.

All patients tested for histoplasmosis, blastomycosis, and coccidioidomycosis had negative skin reactions. The tuberculin skin test was negative in all cases initially, but in Cases 4 and 8 it converted to positive several years after the onset of the disease. Case 12 was positive to PPD No. 1, the area of induration measuring 7 mm. one week after injection.

Kveim antigen was kindly supplied by Dr. Oscar A. Ross, who read the biopsy results 4 to 5 weeks after the intradermal injection without knowing any clinical details. As the antigen was not available when most of the patients were first seen, only Cases 7, 10, 11, and 12 were so tested. Case 7 was in clinical remission by the time she was injected and Case 10 was taking 40 mg. prednisolone daily because of ocular and pulmonary involvement; both gave negative results. Case 11 was in an acute episode with polyarthritis resembling acute rheumatoid arthritis, and Case 12 presented with acute infectious arthritis, but investigation revealed features compatible with both sarcoidosis and tuberculosis (see below).

Glands.—Generalized lymphadenopathy was found in eight patients, but only Case 10 had involvement of the parotid and lacrimal glands, which was associated with severe bilateral ocular sarcoidosis, acute anterior uveitis, cataracts, and finally glaucoma. Hilar adenopathy was found in nine of the twelve cases when first seen and Case 9 had huge subcarinal nodes. Case 7 exhibited
### Negro Patients and Results of Tests

<table>
<thead>
<tr>
<th>Biopsies</th>
<th>Skin Tests†</th>
<th>Non-pulmonary Adenopathy</th>
<th>X-ray Bone</th>
<th>Ocular Sarcoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td>Result</td>
<td>Old Tuberculin**</td>
<td>Kveim</td>
<td></td>
</tr>
<tr>
<td>Perisynovial nodules left knee</td>
<td>+</td>
<td>-</td>
<td>ND</td>
<td>+</td>
</tr>
<tr>
<td>Cervical node</td>
<td>+</td>
<td>-</td>
<td>ND</td>
<td>-</td>
</tr>
<tr>
<td>Skin</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
<td>+</td>
</tr>
<tr>
<td>Right scalene node</td>
<td>+</td>
<td>1956 - 1960+</td>
<td>ND</td>
<td>-</td>
</tr>
<tr>
<td>Skin of face</td>
<td>-</td>
<td></td>
<td>ND</td>
<td>-</td>
</tr>
<tr>
<td>Synovium of left wrist</td>
<td>+</td>
<td></td>
<td>ND</td>
<td>-</td>
</tr>
<tr>
<td>Skin of right arm</td>
<td>+</td>
<td></td>
<td>ND</td>
<td>+</td>
</tr>
<tr>
<td>Liver</td>
<td>+</td>
<td></td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Right scalene node</td>
<td>-</td>
<td></td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Muscle</td>
<td>+</td>
<td></td>
<td>1957 - 1962+</td>
<td>Refused</td>
</tr>
<tr>
<td>Synovium right knee</td>
<td>+</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Skin of left arm</td>
<td>+</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Liver</td>
<td>+</td>
<td></td>
<td>March 20</td>
<td>+</td>
</tr>
<tr>
<td>Right scalene node</td>
<td>+</td>
<td></td>
<td>ND</td>
<td>-</td>
</tr>
<tr>
<td>Synovium left ankle</td>
<td>+</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Muscle</td>
<td>+</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Conjonctiva</td>
<td>-</td>
<td></td>
<td>March 22</td>
<td>+</td>
</tr>
<tr>
<td>Skin nodule</td>
<td>+</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Scalene node</td>
<td>-</td>
<td></td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Right scalene node</td>
<td>+</td>
<td></td>
<td>+</td>
<td>April 12</td>
</tr>
<tr>
<td>Synovium right knee</td>
<td>+</td>
<td></td>
<td>+</td>
<td>May 10</td>
</tr>
<tr>
<td>Left axillary node</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Synovium right knee</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

§ First strength = 0·00002 mg. ** = 0·01 mg.

Complete regression of hilar adenopathy between July, 1962, and April, 1963, and became symptom-free.

**Eyes.**—Complete ophthalmic examinations were done in eleven cases. Case 10 is described above and Case 6 had no abnormality apart from diminished tear formation. Case 8 was treated for ocular sarcoid for years; the lesion started as a retinal detachment and progressed to cataract and phthisis bulbi in the left eye. The right eye remained normal.

**Skeletal Changes.**—Bone surveys and serial radiological examinations were done in all cases. Special attention was paid to the bone ends adjacent to affected joints but, apart from soft-tissue evidence of joint effusions, no articular abnormalities were found except in Case 5. This patient had cutaneous sarcoid of the face and bilateral radiological changes in both wrists that remained unchanged over 4 years. Both joint spaces were narrowed with marked sclerosis of the radial articulating surfaces which appeared to be flattened. Clinically, there was bilateral limitation of dorsiflexion with radial deviation of both wrists, presumed to be due to the flattened lower ends of the radii. During our period of observation these joints were never acutely inflamed, and a synovial biopsy of the left wrist revealed a non-specific, chronic synovitis with no evidence of granulomatous inflammation.
Apart from a small radiolucent area in the left capitate (Case 3) and a cystic area in each femoral neck (Case 12) no bony abnormalities were found except in Case 8. This patient showed bilateral knee effusions with quadriceps wasting and bilateral soft tissue thickening of both ankles. There was slight synovial thickening and limitation of dorsiflexion in the right wrist and bilateral clubbing of fingers and toes, but in each extremity the 4th and 5th digits were normal. Surgical biopsy of the right knee 6 months after the onset of arthritis revealed that the synovial membrane had a reddish, villous surface macroscopically. Microscopy revealed a marked synovitis with granulomata consistent with sarcoidosis (Fig. 2). These granulomata were surrounded by proliferating fibroblasts. Special stains and cultures of the fluid did not reveal any infectious cause for the granulomata.

Bone x-rays a year previously were normal, but on this occasion there were bilateral, symmetrical periosteal reactions by the ankles (Fig. 3, opposite), the lower medial aspects of the femora, the lower ends of both ulnae and radii, and effusions in both knee and ankle joints. The bones were otherwise normal.

**Laboratory Investigations.**—These included Kline, R.A. latex, and L.E. agglutination tests, eosinophil counts, and estimation of serum albumin, globulin, calcium, phosphorus, and uric acid.

The R.A. Hyland latex slide test was negative in ten of the twelve, the two positive cases exhibiting hyperglobulinaemia.

The range of eosinophil counts in the peripheral blood showed slightly raised counts on admission which soon became normal.

The Kline test was negative in all except Case 8, and serum uric acid levels were normal in the eight cases tested.

The L.E. agglutination test was repeatedly negative in the nine patients examined.

Seven patients had a raised serum globulin level.

The levels of serum calcium and phosphorus were normal on admission in ten of the eleven tested, slightly raised values being found in Case 10, who was the

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**Fig. 2(a).**—Synovial biopsy from right knee 6 months after onset of arthritis (Case 8). There is a granulomatous synovitis with multiple, discrete, non-caseating epithelioid tubercles within the villous processes. Special stains did not reveal any micro-organisms. ×14.

**Fig. 2(b).**—High-power view, showing tubercles surrounded by proliferating fibroblasts. Haematoxylin and eosin ×90.
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Fig. 3.—X-ray of ankles in 1962 (Case 8) to demonstrate periosteal reactions at lower ends of both tibiae and fibulae, and effusions into the joints.

Fig. 4.—Synovium of right knee 11 weeks after onset of arthritis (Case 11). Histological sections revealed a markedly thickened surface epithelium consisting of mononuclear cells and granulation type tissue. Several small, sub-synovial, non-caseating granulomata containing giant cells were seen. Haematoxylin and eosin × 90.

oldest member of the group and had widespread organ involvement. Three weeks later the serum calcium was normal after starting prednisolone 30 mg. daily. Case 6 had a low level on admission that rose to 6.7 mEq/litre 4 weeks later. A month after starting prednisolone 40 mg. daily, three estimations were within 4.5 mEq/litre.

Electrocardiography.—This was performed on all patients and revealed incomplete right bundle branch block in Cases 6 and 10.

Biopsies.—The sites and results are listed in the Table. Four of 24 specimens examined gave negative histological findings, one of these being from the conjunctiva (Case 10). Twenty different tissue samples contained non-caseating granulomata compatible with sarcoidosis, for which special stains and cultures revealed no infectious cause. In the lymph nodes foreign-body type giant cells were frequent and some contained inclusions (Schaumann bodies). Five of the six surgical synovial biopsies exhibited typical nodules in addition to a marked synovitis with hypertrophy of the lining cells (Fig. 2 and Figs 4 to 7). The single nonspecific synovial biopsy from the left wrist (Case 5) was from a chronically affected, uninflamed joint.
Fig. 5(a).—Synovium of left ankle (Case 9), containing several non-caseating granulomata. Haematoxylin and eosin × 18.

Fig. 5(b).—High-power view of area marked with arrow, showing hypertrophic synovitis. Haematoxylin and eosin × 185.

Pulmonary Function.—The data and criteria for classification will be published elsewhere (Martin and Lewis, in press; Adhikari, Bianchi, Boushy, Sakamoto, and Lewis, 1962). Hilar adenopathy was present in nine of the twelve cases, and six had bilateral interstitial lung infiltrates compatible radiologically with sarcoidosis; three of the six had florid alveolar-capillary block (Cases 4, 6, and 10), and Case 2 gave measurements at the lower limits of normal. Cases 5 and 9 had no pulmonary infiltrate but also gave borderline values. Case 7 had bilateral hilar adenopathy during her acute episode in 1962, but 9 months later these nodes had completely regressed, her respiratory function studies were normal, and she was symptom free.

Case 12 had two tissue biopsies compatible with sarcoidosis, and the chest laminograms on May 23, 1963, showed multiple, multi-sized, calcium-free nodular densities irregularly scattered throughout both lung fields, predominantly in the right upper lobe. No
Sarcoïdosis with arthritis

Fig. 6(a).—Synovium of right knee 5 weeks after onset of arthritis (Case 12). This is section (a) from the thick flat plaque with a red edge situated on the medial femoral condyle. No synovial lining cells are seen and the tissue is extensively occupied by discrete and confluent epithelioid tubercles containing numerous multinucleated giant cells and surrounded by lymphocytes. Occasional inconspicuous areas of central necrosis were noted. Haematoxylin and eosin ×8.

Fig. 6(b).—High-power view of area marked with arrow. Haematoxylin and eosin ×30.
abnormal hilar masses were seen. On May 13 the pulmonary diffusion capacity was definitely impaired, and on May 12 the purified protein derivative No. 1 was positive. Kveim antigen injected on May 10 gave a positive though atypical histological picture. Three samples of synovial fluid aspirated on May 6, 14, and 17, eventually grew acid fast bacilli. A repeat chest x-ray on June 26 revealed increasing size of the lung densities compatible with tuberculosis.

In Case 8, in whom the diagnosis was confirmed at autopsy, there was obstruction to air flow. Pulmonary function tests revealed a moderately severe reduction in vital capacity and maximum breathing capacity, but no diffusion studies were done. The chest x-ray showed large hilar nodes and bilateral lung infiltrate. Lamino-grams demonstrated that some of the large nodules in the
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upper lobes were radiolucent but contained radiodense material; they were termed "fungus balls" by the radiologists* (Fig. 8).

Synovium

Macroscopic and Microscopic Findings (Fig. 2 and Figs 4 to 7). Surgical joint biopsies were performed on Cases 1, 5, 8, 9, 11, and 12. Case 5 (left wrist) is described above and the synovial membrane was not visualized.

Case 1 had a normal, smooth synovial membrane of the left knee but several small nodules in the perisynovial fat lateral to the patella proved to be compatible histologically with sarcoidosis (Fig. 9). These had been palpated and marked before operation and each felt like a single, small nodule.

Case 8 had bilateral knee effusions in 1961 and 1962 with marked swelling, and in 1962 the surgeon noted that the right knee had a reddish villous synovial surface. Microscopy confirmed a marked synovitis with sub-synovial granulomata compatible with sarcoidosis (Fig. 2).

Case 11 also had bilateral knee effusions which were aspirated on several occasions, when the thickened synovium was easily palpated. Clinically, this patient presented as a case of acute rheumatoid arthritis with

* The term "fungus ball" is used by radiologists for a rounded, mobile filling defect within a cavity in the lung parenchyma. This radiodense material may be composed of masses of fungal mycelia, but, in this patient, repeated tests for fungi over 8 years were negative.
acute involvement of the finger, wrist, elbow, and knee joints and persistent dorsal sheath swellings over both wrists. At operation the synovium of the right knee was found to be thickened and injected, but there were no villous changes or pannus formation. The menisci and cartilage were normal. Microscopy revealed a chronic synovitis with a subsynovial granulomatous reaction consistent with sarcoidosis (Fig. 4).

In Case 9 the synovium from the ankle exhibited areas of fibrosis, several non-caseating granulomata, and hypertrophic synovitis (Fig. 5).

Case 12 had recurrent effusions of the right knee and surgical biopsy over the medial aspect revealed a greatly thickened, oedematous synovium, with a thick flat plaque with a red edge on the medial femoral condyle. The underlying cartilage and the menisci were normal, and there was no villous formation. Samples for histology were taken from (a) the vascular edge of the plaque, (b) the outer synovium, and (c) the synovium from behind the patella. Microscopy revealed complete absence of synovial lining cells in all three specimens, so that the multiple synovial granulomata formed the joint surface, and were covered by a few strands of fibrin (Figs 6 and 7). Giant cells were numerous in (a) and (b) and moderately so in specimen (c).

Synovial Fluids.—Unfortunately, these were not well studied except in Cases 11 and 12.

Cases 1 and 8 had negative aerobic and anaerobic cultures and no acid-fast bacilli were seen in the centrifuged deposit.

Case 11 had bilateral and Case 12 unilateral knee effusions. In both patients these effusions were recurrent and required repeated aspirations, and the fluid always contained many red and white blood cells. However, the initial synovial fluid on admission to hospital from each of the three knees was yellowish and watery, with a very low viscosity. Employing the Sink test, Case 11 gave strings only 3 to 5 mm. long (normal = several inches) and Case 12 yielded drops only. All these initial samples had high red and white cell counts and raised protein values (4 to 6 g. per cent.). No acid-fast bacilli were seen in the centrifuged deposits in either patient. Repeated cultures on serial aspirates for aerobic and anaerobic organisms and fungi were all negative in both. Case 11 had negative cultures for acid-fast bacilli from both knees, but Case 12 later grew acid-fast bacilli from three separate samples of synovial fluid aspirated on May 6, 14, and 17. In Case 12 cultures from the spinal fluid, from two samples of joint fluid, and from knee and axillary lymph node tissue, were all negative for fungi.

Comment on Case 8.—This patient died and an autopsy was obtained. This young Negro female presented with "arthritis", and a muscle biopsy and chest x ray supported the diagnosis of sarcoidosis. She also had congenital syphilis, treated when she was 13 years old. She was observed for 8 years and exhibited (a) progressive lung changes, (b) ocular sarcoidosis with left retinal detachment, cataract, and phthisis bulbi, (c) multiple joint involvement, bilateral knee effusions, and a synovial
biopsy consistent with sarcoidosis, (d) during the final year hypertrophic osteo-arthropathy of all extremities presumably secondary to the pulmonary lesions.

Autopsy revealed widespread sarcoidosis of the lungs, heart (Fig. 10), liver, spleen, and lymph nodes. Particles that were brilliantly anisotropic under polarized light were seen within the cytoplasm and between the cells in the lungs (Fig. 11, and Figs 12-14, overleaf, p. 474).

The wall of one of the so-called "fungus balls" in the lung was lined by stratified transitional-like epithelium (Fig. 15, overleaf, p. 475).

The question of pulmonary tuberculosis had been repeatedly raised over the years, but no evidence was found. The tuberculin test, originally negative, became positive so she was given a short course of antituberculous therapy by the chest department.

A left staghorn calculus and calcified uterine myomata were demonstrated radiologically in 1959 and at autopsy in 1963.

Repeated estimations of the serum calcium and phosphorus from 1958 to 1962 revealed no hypercalcaemia, but throughout this period she was taking prednisolone 5 to 10 mg. daily. The eosinophils in the peripheral blood were increased on only one occasion (9 per cent.). However, there was a persistent hyper-
Fig. 12.—Small, needle-shaped, refractile, crystalline body within the cytoplasm of an epithelioid cell (arrow) which is situated in a fibrous, non-caseating tubercle. \( \times 270. \)

Fig. 13.—Small, irregular, anisotropic, intracellular body in cytoplasm of an epithelioid cell (arrow). \( \times 425. \)

Fig. 14(a, b, c).—Series of exposures in non-polarized, partially-polarized, and fully-polarized light. In non-polarized light (Fig. 14a), the irregular intracytoplasmic body in the foreign body giant cell was brown in colour. \( \times 730. \)

globulinaemia from 1958 to 1962, ranging from 3.7 to 5.8 g. per cent., and accompanied by a progressive lowering of the serum albumin. Serum electrophoresis in 1962 (albumin = 2.46; \( \alpha_1 = 0.33; \alpha_2 = 0.73; \beta = 1.04; \gamma = 3.24 \) g. per cent.) demonstrated that this was mainly a hypergammaglobulinaemia.
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Muscle.—Working with the same patient population in this hospital 12 years ago, Myers, Gottlieb, Mattman, Eckley, and Chason (1952) emphasized the value of random muscle biopsy as a diagnostic tool in sarcoid arthritis; 6 years later Wallace, Lattes, Malia, and Ragan (1958) found 23 out of 42 sarcoid patients with positive muscle biopsies and illustrated the paravascular situation of sarcoid granulomata. Sokoloff and Bunim (1959) also noted this paravascular situation in the perisynovial fatty tissue of the knee. Our Case 1 was almost identical; at operation the synovium of the knee appeared normal but the nodules previously palpated clinically, were found in the perisynovial fat (Fig. 9).

Synovium.—Few synovial biopsies have been described in sarcoidosis. Sokoloff and Bunim (1959) gave detailed reports on five cases, another was published by Ferguson and Paris (1958), and brief reference to two more was made by Kaplan (1960). Our findings are in agreement with those of Sokoloff and Bunim (1959), and like them, we found varying degrees of granulomatous formation, and special investigations revealed no infectious cause. A biopsy of their Case 5, taken during a remission of the acute arthritis, showed microscopically a subacute to chronic inflammatory reaction. Our Case 5 had chronic involvement of both wrists for many years and biopsy revealed a non-specific, chronic synovitis with no evidence of granulomatous inflammation. In contrast, the acute cases in both series of patients were the same. Our Fig. 2 and Figs 4 to 7 demonstrate the marked synovitis with increase in the number and hypertrophy of the lining cells, but no villous formation. Subsynovial, well-formed, non-caseating, discrete granulomata were seen in Cases 8, 9, and 11, with varying numbers of giant cells, inflammatory infiltrate, and surrounding proliferation of fibroblasts. Our Case 12, who was the only one initially considered to be a case of infectious arthritis, had the shortest interval between onset and biopsy (5 weeks) and had by far the most severe granulomatous involvement of the synovium (Figs 6 and 7). The synovial lining cells had completely disappeared from three specimens from widely-separated areas of the joint, and the multiple granulomata were covered by a few strands of fibrin and formed the joint surface. Presumably this rapid progression into the joint accounted for the clinical recurrent effusions with increased cells and protein.

The data were analysed to see if there was any correlation between the histology and the length of time the joint had been inflamed, but none was found. Case 8 had a 6-month history of effusion before biopsy, and in Cases 11 and 12* the interval was 11 and 5 weeks respectively. Thus, it appears to be the rate and severity and not the length of time that is responsible for the histological picture.

Other Tissues.—Tissue biopsy clinched the diagnosis in most of our cases. The value of open surgical biopsy of the affected joint is to further the understanding of this ill-understood disease during

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* An additional feature in Case 12 was the culture of acid-fast bacilli from three separate samples of synovial fluid. This patient had some of the features of sarcoidosis (lymph node biopsy, positive yet atypical Kveim reaction, chest x ray, and impaired pulmonary diffusion) and tuberculosis (positive purified protein derivative No. 1, synovial fluid culture, and histology that could be sarcoidosis, but gave a more virulent picture than the synovial biopsies from the other cases). (Compare Fig. 4 and Figs 6 and 7). A careful search for a fungal or other bacterial cause for the condition was unsuccessful. All the tests mentioned and the node biopsy were performed, in the acute phase, within 2 weeks. It would appear that this patient could well represent the transition between sarcoidosis and tuberculosis recorded by Lees (1956), and Bunim, Kimberg, Thomas, Van Scott, and Klatskin (1962).
the acute phase in the area most involved. Inspection of the synovium, bone ends, cartilage, and menisci, as reported above, revealed changes confined to the synovium. This was thickened, oedematous, and vascular without pannus formation; some villous formation was seen in Case 8 only where the joint effusion had been present for 6 months. Histologically, the synovial lining cells were increased in number and hypertrophic, the synovitis matching the macroscopic picture. Non-caseating granulomata of varying size and number were found in the subsynovial tissue, but multinucleated giant cells were few in comparison with their abundance in the lymph nodes, liver, or skin of the same patients. As pointed out recently by Bunim and others (1962), non-caseating granulomata can occur in primary disorders of the liver, but are commonly found in systemic granulomatous disease. Only three of our patients had liver biopsies and in two of these other tissue histology supported the diagnosis of sarcoidosis.

Arthritic Symptoms.—Israel and Sones (1958), in their excellent analysis of 160 cases of sarcoidosis, cite only nine with arthralgia and myalgia, and do not mention arthritis, joint effusions, synovial biopsies, or pulmonary function studies. James (1956) analysed 150 cases of sarcoidosis and tabulated “the widespread clinical manifestations that may embrace any branch of medicine”. James, Thomson, and Willcox (1956) list seventeen out of 27 patients with sarcoidosis and erythema nodosum as having associated polyarthritis. This association has been noted by several authors. A recent paper (Edwards, Sproule, and Mason, 1962) reports three cases with hilar adenopathy and erythema nodosum (one with a normal pulmonary function test) with subsequent complete regression of all signs of the disease, as we found in our Case 7. Williams (1961) reported seven cases of sarcoidosis presenting with polyarthritis. Acute arthritis was the presenting symptom in ten of our twelve patients, but as time passed, it became evident that the initial impression was incorrect, and that the case was atypical for that particular category. For example, those thought to be cases of rheumatic fever responded only partially to salicylate therapy, a feature noted by other observers (Myers and others, 1952; Williams, 1961). Frequently the routine chest x-ray was responsible for bringing to mind the fact that enlarged hilar nodes and arthritis could occur in sarcoidosis.

It has been pointed out that erythema nodosum is usually associated with a transient form of the disease, whereas subcutaneous nodules are associated with the persistent, chronic form (Kaplan, 1963). Our Case 5 had nodular skin lesions (Fig. 1) which partially responded to chloroquine therapy (Morse, Cohn, Hirsch, and Schaedler, 1961; Hirsch, Cohn, Morse, Schaedler, Siltzbach, Ellis, and Chase, 1961). Case 10 had subcutaneous nodules of the Darier-Roussy type associated with severe ocular and pulmonary involvement. The two patients with arthralgia but no objective joint changes on admission (Cases 2 and 4) had lymph node biopsies compatible with sarcoidosis and impaired pulmonary function.

Laboratory Investigations.—The routine tests proved to be of little aid in diagnosis except by excluding other aetiologies. The electrocardiograms of two patients showed incomplete right bundle branch block. This is consistent with a diagnosis of sarcoid heart disease, in which conduction disturbances are the most common cardiac manifestation (Porter, 1960; Chamovitz, Culley, and Carlson, 1962). A slight increase in eosinophils in the peripheral blood and a moderate or mild hypergammaglobulinaemia can occur in many disease states, especially those involving the joints. However, false positive latex-fixation tests (Cases 3 and 6) have been reported in cases of sarcoidosis, due to a gamma globulin of high molecular weight indistinguishable in physical properties from the rheumatoid factor (Kunkel, Simon, and Fudenberg, 1958). Serum electrophoresis in Case 6 showed the gamma globulin fraction to be 3.27 g. per cent. (normal = 0.6-0.9). The two negative Kveim tests were believed due to (a) remission (Case 7) and (b) corticosteroid therapy (Case 10) (James and Thomson, 1959).

Only our Case 10 showed raised serum calcium and phosphorus levels (cf. David, Verner, and Engel, 1962). Mather (1957) found only four with hypercalcaemia in 86 untreated cases of sarcoidosis, and concluded that the condition occurs so infrequently in patients not receiving vitamin D, that routine estimation of the serum calcium was unnecessary. In Case 10 the serum calcium and phosphorus became normal within 4 weeks, after corticosteroid treatment of the severe ocular and pulmonary involvement. Similarly, in Case 6, the raised serum calcium became normal after starting prednisolone 40 mg. daily. The fall in serum calcium has been observed after treatment with corticosteroids by many authors (Anderson, Dent, Harper, and Philpot, 1954; Dent, Flynn, and Nabarro, 1953; Lovelock and Stone, 1951;
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McSwiney and Mills, 1956; Gleckler, 1956; Henneeman, Carroll, and Dempsey, 1954; Henneeman, Dempsey, Carroll, and Albright, 1956; Shulman, Schoenrich, and Harvey, 1952; Snapper, Yarvis, Freund, and Goldberg, 1958; Goetz, 1960). In Case 8 x rays showed a staghorn calculus and calcified uterine myomata in 1959, but six estimations of serum calcium and phosphorus from 1958 to 1962, while she was taking 5 to 10 mg. prednisolone daily, were all within normal limits.

Radiology.—Now that mass radiological surveys are disclosing more cases of early sarcoidosis, the frequency of bone involvement has been over-emphasized (Teirstein, Wolf, and Siltzbach, 1961). Löfgren (1953) saw only three examples of bone lesions in 212 early cases of sarcoidosis. Similarly, Mather (1957) found only nine in 120 cases and concluded that bone radiographs were of little value in diagnosis. Bone involvement is more frequent in chronic cases, the percentage ranging from 6 to 20 per cent. (Reisner, 1944; Holt and Owens, 1949; Nitter, 1953). Only two of our patients had radiolucent areas considered to be typical of sarcoidosis. Case 5 had unusual radiological joint changes in both wrists and bilateral limitation of dorsiflexion, clinically accompanied by radial deviation; this patient had been diagnosed as a case of rheumatic fever in 1954 and gave a history of recurrent similar episodes of polyarthritis. Both the clinical and radiological findings (described above) are atypical for rheumatoid arthritis, the major feature being the cutaneous sarcoid lesions of the face (Fig. 1).

Pulmonary Function.—Impairment of lung function matched the severity of the radiological changes in the lung parenchyma. The presence or absence of hilar glands appeared to be unrelated to the degree of impaired diffusion. Each of the three cases of florid alveolar-capillary block had severe bilateral radiological changes compatible with sarcoidosis.

The lungs were the main site of attack in Case 8 and autopsy confirmed the widespread involvement of the lung, the confluent nodules producing considerable areas of consolidation. Since the publication of the widely-quoted paper by Rakov and Taylor (1942), which states “that the individual sarcoids do not fuse to produce the conglomerate tubercle”, numerous authors have noted that confluence of the nodules can indeed occur in severe cases of proven sarcoidosis. This autopsy is an excellent example. It also demonstrates that a lung cavity, thought to be tuberculous by both clinicians and radiologists, was lined by stratified transitional-like epithelium. This excluded both tubercle bacilli and fungi as the causative agent. The prolonged course, the widespread involvement of so many different systems (eye, lungs, heart, liver, spleen, nodes, muscle, synovium, and skin), and the changes of hypertrophic osteo-arthritis occurring during the final year of her life, made this case unusual and informative. The osteo-arthritis of all the extremities was assumed to be secondary to the cardio-pulmonary condition and distinct from, though due to, the underlying sarcoidosis. The lungs contained needle-shaped particles that were brilliantly anisotropic under polarized light. These particles are believed to consist of calcium carbonate (Dr. D. G. James, personal communication), whereas Johnson and Pani (1962) identified them as calcium oxalate histochemically.

In conclusion, it would appear that definite joint involvement is a more frequent presenting feature than is generally supposed. Reports on the macro- and microscopic appearance of the synovium were obtained from the six open surgical biopsies which were performed. In the acute stage the inflammatory process was distinguishable from that of acute rheumatoid arthritis by the absence of villous formation and pannus, the intact normal cartilage covering the bone ends, and normal menisci. The microsponge showed an acute synovitis with subsynovial, non-caseating granuloma. The acute nature of the process was attested by the hot, swollen, tender joints, and the recurrent blood-stained effusions. The chronically affected joints showed mild non-specific synovitis. In Case 12, with features of both sarcoidosis and tuberculosis, the fact that the disease process in the knee had reached the joint surface itself, no synovial lining cells being seen, may be the reason that this was the only one thought on admission to hospital to be a case of acute infectious arthritis (Table). In addition, this patient had severe involvement of the left elbow persisting for several weeks, and the corresponding axillary gland contained numerous granulomata consistent with sarcoidosis which proved to be the first clue to the diagnosis. The Kveim test, though positive, gave an atypical histological picture compared with the typical sarcoid reaction.

As pointed out by Bunim and others (1962), multiple biopsy and other evidence is required before a diagnosis of sarcoidosis can be made; an isolated histological lesion, without evidence of dissemination to other tissues, does not constitute sarcoidosis. This is also emphasized by Anderson, James, Peters, and Thomson (1962), who described
36 patients with isolated granulomata from a variety of tissues, in whom the diagnosis could not be substantiated; they distinguished local granulomatous reactions from sarcoidosis by physical examination, chest radiography, and the Kveim test, the Mantoux reaction and serum globulin determinations being of little help.

Finally, the clinician does well to divide cases of sarcoidosis into the three groups described by Hoyle (1961): (1) benign with spontaneous resolution, (2) chronic but non-progressive, (3) chronic and progressive.

Summary

The clinical, pathological, and radiological findings in twelve cases of sarcoidosis with arthritis are described. Pulmonary function studies, six surgical synovial biopsies, eighteen tissue biopsies, and one autopsy report are included.

Each case presented with arthropathy, usually acute. The protean modes of presentation may mimic acute rheumatic fever, acute rheumatoid arthritis, infectious arthritis, or tuberculosis.

Case 12 appeared to be one of acute infectious arthritis; two biopsies showed non-caseating granulomata, the Kveim test was positive yet atypical, and the purified protein derivative No. I was positive; the chest x-ray was compatible with sarcoidosis and the pulmonary diffusion capacity was impaired; the synovium differed at operation and microscopically from the other cases, and culture of the synovial fluid grew acid-fast bacilli.

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REFERENCES

SARCOIDOSIS WITH ARTHRITIS


Sarcoïdose avec arthrite

RÉSUMÉ

Douze cas de sarcoïdose avec arthrite sont décrit du point de vue clinique, pathologique et radiologique, y compris des études de la fonction pulmonaire, de six biopsies chirurgicales de la synoviale, de dix-huit biopsies tissulaires et un rapport d'autopsie.

Tous les cas se présentèrent par une arthropathie, généralement aiguë. L'allure protéiforme de la présentation peut faire penser à la maladie de Bouillaud, l'arthrite rhumatoïde aiguë, l'arthrite infectieuse ou à la tuberculose.

Le cas numéro 12 ressembla à une arthrite infectieuse aiguë; deux biopsies montrèrent des granulomes non-caseux, le test de Kveim fut positif mais atypique, le dérivé de protéine purifiée No. 1 fut positif; la radiographie de la poitrine fut compatible avec une sarcoïdose et la capacité pulmonaire de diffusion fut diminuée; à l'opération et microscopiquement la synoviale fut différente de celle des autres cas et à la culture du liquide synovial on obtint des bacilles acido-résistants.

Sarcoidosis con artritis

SUMARIO

Se describen doce casos de sarcoidosis con artritis desde el punto de vista clínico, patológico y radiológico y se añaden a la descripción estudios de la función pulmonar, de seis biopsias quirúrgicas de la sinovia, de dieciocho biopsias de tejido y un informe de autopsia.

Todos los casos se presentaron con una artropatía, generalmente aguda. El modo protéiforme de la presentación puede imitar la enfermedad de Bouillaud, la artritis reumatoide aguda, la artritis infecciosa o la tuberculosis.

El caso No. 12 se pareció a una artritis infecciosa aguda; dos biopsias revelaron granulomas sin caseificación, el test de Kveim fue positivo pero no típico, la el derivado de proteina purificada fue positivo; la radiografía del pecho fue compatible con sarcoidosis y la capacidad pulmonar de difusión fue reducida; en la operación y microscópicamente la sinovia fue diferente de la observada en los demás casos y la cultura del líquido sinovial produjo bacilos ácido-resistentes.
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