Musculoskeletal Sarcoidosis and Rheumatoid Factor*

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An extensive review of sarcoidosis in 1952, reported that one of the characteristics of the disease is the unaffected joints (8). However, a careful reading of this article reveals gross photographs and radiographs which are quite compatible with inflammatory arthritis. In that same year it was emphasized that sarcoidosis can present itself as arthritis (10). The association of sarcoidosis with hilar adenopathy, erythema nodosum, and polyarthritis was described in 1953 (Löfgren's Syndrome) (7). Five cases of sarcoid arthritis were reported by Sokoloff and Bunim in 1959, and synovial granulomata were noted in three of the five patients studied (12). Subsequently, a number of articles have appeared in the literature reporting the musculoskeletal involvement of sarcoidosis to vary between 2.2 and 38% (9, 13). Usually associated with hilar adenopathy and erythema nodosum, musculoskeletal sarcoidosis is less frequently linked with transient arthritis, arthralgia, or periarticular inflammation. Its relationship to destructive polyarthritis, myopathy, or tendinitis is relatively uncommon.

The discovery of the rheumatoid factor in sarcoidosis (6, 11), coupled with the observed musculoskeletal involvement, prompted a review of our experience at the Medical College of Virginia.

The charts of 224 patients with sarcoidosis were examined. Of the 224, those selected for our study were at the time being followed as outpatients because of their condition. Sixty such patients were available for personal observation and evaluation. These 60 patients had been followed at MCV from 1 to 372 months with an average of 46.8 months.

In making a histologic diagnosis of sarcoidosis, we rely primarily on peripheral lymph nodes. Excised palpable cervical, epitrochlear, and axillary nodes have been our first choice for biopsy material. In the absence of palpable lymph nodes, we usually perform a scalene node biopsy, and in about 90% of these cases, non-caseating granulomata have been revealed when the clinical findings suggested sarcoidosis. In a few patients, a skin lesion has been used as material for microscopic examination, but in most cases when the skin has been biopsied we have obtained a second source of material. A lung biopsy has been performed in about 5% of our patients; in most instances the clinical manifestations were atypical, and a lung biopsy was considered a better source of material for bacteriological as well as for histological studies. We generally have not relied on liver biopsies where the yield of granulomata is around 75% (1).

The following serologic procedures were employed.

1. Sensitized Sheep Cell (SSC): The SSC test used was the Heller (4) modification of the Waaler-Rose test. Test sera were absorbed with unsensitized sheep cells and diluted in saline. Sheep cells, from a constant source, were sensitized with 1/20 the basic agglutinin titer of rabbit anti-sheep cell serum. Titers of 1:20 and above were considered positive. The SSC test was standardized in this way in order to obtain relative specificity although it is not as

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sensitive a test as those used in other laboratories.

2. Sensitized Human Cell (SHC): A selected DCe/DCe test cell was sensitized with Ripley serum (high-titered anti-DC), diluted 1:10. The Rh positive cells were sensitized for 30 minutes at 37°C and then washed three times with saline. Test sera were titrated in saline in 0.1 ml volumes. Titers of 1:20 or above were considered positive. The SHC test was especially valuable in obtaining reproducible titers of rheumatoid factor in those individuals who were negative with the SSC test.
3. Latex Test: This test was performed with the commercial reagents supplied by the Hyland Laboratories, Los Angeles, California. Reactions with the sera diluted 1:20 were considered positive.

The results of our studies are illustrated in the accompanying tables. Table 1 lists the average age of the patients when sarcoidosis was first diagnosed. Of the 60 patients, 38 were Negro females (63.3%).

Table 2 lists the presenting symptoms or why a diagnosis of sarcoidosis was suspected. It is noted that 22 of the 60 patients (36.6%) were asymptomatic, but sarcoidosis was suspected from screening chest radiographs and was subsequently proved.

Table 3 lists the types of musculoskeletal involvement present in 19 patients. Nine of the 60 patients (15%) presented with arthritis as the initial manifestation of sarcoidosis. Five of these nine had the syndrome of migratory arthritis, erythema nodosum, and radiographic findings of hilar and right paratracheal lymphadenopathy. Two patients had arthritis and an abnormal chest radiograph but did not have erythema nodosum. One patient, a 20-year-old white female, had the recently described condition of periarticular ankle inflammation and bilateral hilar adenopathy (2). The arthritis and pulmonary radiographic findings cleared spontaneously within four weeks in eight of these nine patients. One patient progressed to destructive polyarthritis which spontaneously entered a permanent remission in two years.

Six of the remaining ten patients (32% of total) developed short-lived arthralgia during their course of follow-up. Four of the six progressed from Stage 1 pulmonary disease (hilar lymphadenopathy) to Stage 2 disease (hilar lymphadenopathy and pulmonary infiltration). Two patients had Stage 1 pulmonary disease which became normal in six months.

The other four patients (21% of total) developed either short-lived oligo- or polyarthritis. Three of these patients progressed from Stage 1 to Stage 2 pulmonary disease. One patient progressed from Stage 2 to Stage 3 (pulmonary infiltration and fibrosis).

Other Organs Involved. Liver function studies, other than serum protein determinations, were not routinely performed. Liver biopsy was carried out

TABLE 1. AGE, RACE, AND SEX OF 60 PATIENTS WITH SARCOIDOSIS

	NM	NF	WM	WF
	9	38	4	9
Ages:	(14-48)	(13-72*)	(27-61)	(24-50)
Av:	25	28	38	35

* Only 1 patient over 52

TABLE 2. PRESENTING SYMPTOMS OR WHY SARCOIDOSIS WAS SUSPECTED IN 60 PATIENTS

	No.
1. Routine chest film	22
2. Chronic cough	7
3. Fever of undetermined origin	6
4. Erythema nodosum and arthritis	5
5. Uveitis	5
6. Arthritis	4
7. Lymphadenopathy	4
8. Dyspnea	3
9. Hoarseness	2
10. Fatigue	2

TABLE 3. TYPES OF MUSCULOSKELETAL INVOLVEMENT PRESENT IN 19 OF 60 PATIENTS WITH SARCOIDOSIS

I.	Erythema nodosum, hilar adenopathy, arthritis				
	Total	NM	NF	WM	WF
	5	:	4	1	
II.	Transient arthritis				
	Total	NM	NF	WM	WF
	6	:	3	2	1
III.	Transient arthralgia				
	Total	NM	NF	WM	WF
	6	:	3	1	2
IV.	Periart. inflam. and hil. adenopathy				
	Total	NM	NF	WM	WF
	1	:			1
V.	Destructive polyarthritis				
	Total	NM	NF	WM	WF
	1	:	1		
Total:		0	11*	4	4

* The preponderance of Negro females is in accord with the observations of others.

in only one patient, and this revealed non-caseating granulomata. Marked hepatomegaly was noted in three patients. Six patients had uveitis. One patient had uveoparotid fever and one asymptomatic parotid swelling. Laryngeal involvement in two patients was manifested by hoarseness, and one required a tracheostomy. Skin involvement of our patients could not be evaluated since careful skin examination was not performed at each visit. Only three patients, however, were noted to have skin involvement initially.

Synovial Fluid. Synovial fluid examination was performed in only two patients. One patient was a 25-year-old Negro female who entered the hospital because of fever of unknown origin. Polyarthritis subsequently developed. Synovial fluid examination revealed a poor mucin clot; leukocyte count of 24,700/mm^3 with 87% polymorphonuclear cells and 13% mononuclear cells; sugar 30 mg per 100 ml; and protein 4.2 gms per 100 ml. No crystals were observed. Percutaneous synovial biopsy revealed a non-specific chronic synovitis.

The other patient, a 30-year-old white male, had Löfgren's syndrome. The mucin clot test was poor; leukocyte count 42,500/mm^3 with 90% polymorphonuclear cells and 10% mononuclear cells; and sugar 78 mg per 100 ml with simultaneous blood sugar of 102 mg per 100 ml. No crystals were observed. Synovial fluid protein was not done. In neither of these fluids was rheumatoid factor found.

Miscellaneous Blood Studies. Four of the 60 patients had peripheral leukocyte counts of less than 4,500/mm^3. In none of these was there peripheral lymphadenopathy or splenomegaly.

Serum calcium levels were determined in all 60 patients. In only one case was there an elevated level—12.4 mg per 100 ml.

Serum uric acid levels were performed in all 19 of the patients with articular symptoms and in 23 of the other patients. No elevations were found.

Rheumatoid Factor and Serum Proteins. Reactive slide latex flocculation tests with negative sensitized human cell tests were noted in only two of the 60 patients (3.3%). One of these patients was a 32-year-old Negro female with Stage 3 lung disease (pulmonary infiltration and fibrosis) of at least seven years' duration. Articular symptoms were denied. The serum gamma globulin was diffusely elevated. She was receiving long-term adrenocorticosteroids. The other patient was a 30-year-old Negro female who had similar history and laboratory findings.

Serum protein electrophoresis was performed on 47 of the 60 patients. An elevated gamma globulin of the diffuse type was noted in 35 (74%).

Conclusion. Articular manifestations of sarcoidosis were present in 19 of our 60 patients (32%). This correlates with previously reported studies. In all of our cases but one, the articular manifestations subsided in eight weeks. This fact and the absence of hyperuricemia are in contradistinction to other studies for which we have no adequate explanation (13, 5, 3).

The finding of reactive latex flocculation tests in only two of 60 patients is an interesting observation and deserves further comment.

It has become apparent that rheumatoid factors are not abnormal antibodies but rather normal serum components present in low titer in normal as well as diseased persons. These "heterophile" antiglobulin antibodies reach their highest titers in rheumatoid arthritis, and the diagnostic value of high titers of these antibodies may be compared with the diagnostic value of titers of another heterophile, the anti-sheep erythrocyte antibody and the associated disease, infectious mononucleosis.

Positive slide latex tests have very little diagnostic value except possibly in the negative sense. The percentage of positive tests in a non-rheumatic population is apparently related to the degree of hypergammaglobulinemia.

In our geographic area, the young Negro female, in accordance with our study, was most prone to sarcoidosis. This segment of the population is not characterized by an unusually high incidence of positive latex tests, and thus we were not surprised to find that our patients with sarcoidosis did not show an increased incidence of positive tests for rheumatoid factor. None of these patients showed positive SHC or SSC tests.

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