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Sarcoidosis and Polyarthritis

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ABSTRACT

Polyarthritis is a well-recognized manifestation of sarcoidosis, but the various series of cases reported in the literature reveal considerable variation in its incidence as well as in its clinical manifestations. Three major types of sarcoid polyarthritis are defined, as distinguished by their clinical and pathological features. Two of these types are usually seen in conjunction with the subacute or transient form of sarcoidosis and, in most cases, are accompanied by erythema nodosum. They differ markedly in severity, but their prognosis is uniformly good. The third type, in contrast, is of a chronic nature and is often associated with permanent joint changes. Mild joint manifestations are a frequent finding in sarcoidosis, but more severe arthritis is relatively rare.

Two cases of sarcoidosis, presenting with severe polyarthritis, are reported in detail, and cases seen in Halifax hospitals during the period 1954 to 1964 are reviewed.

SOMMAIRE

La polyarthrite est une manifestation bien connue de la sarcoïdose, mais les divers groupes de cas qui ont été publiés dans la littérature médicale indiquent qu'il y a de fortes variations dans sa fréquence ainsi que dans ses manifestations cliniques. On définit trois types principaux de polyarthrite sarcoïdienne selon leurs caractéristiques cliniques et pathologiques. Deux de ces formes s'observent généralement concurremment avec la forme subaiguë ou transitoire de la sarcoïdose et, dans la plupart des cas, s'accompagnent d'érythème noueux. Leurs degrés de gravité diffèrent grandement, mais leur pronostic est toujours bon. Par contre, le troisième type est de caractère chronique et s'accompagne souvent de modifications articulaires permanentes. Les manifestations articulaires bénignes sont une observation fréquente de la sarcoïdose, mais l'arthrite de forme plus grave est relativement rare.

L'auteur rapporte en détail deux cas de sarcoïdose avec polyarthrite grave et passe en revue les cas qui ont été observés dans les hôpitaux de Halifax pendant la période de 1954 à 1964.

SINCE 1899 when Boeck[1] first described the clinical and pathological findings and named the syndrome "sarcoidosis", an increasing number of reports concerning this disorder have appeared in the literature each year. Although joint involvement was first described by Burman and Mayer[2] in 1936, this aspect of the disease at first attracted little attention. This communication will describe in detail two cases seen at the Canadian Forces Hospital, Halifax, in 1963,[3] will discuss the cases treated in other Halifax hospitals during the period 1954 to 1964, and will briefly review the literature on the subject.

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CASE REPORTS

CASE 1

A 27-year-old white Air Force corporal was admitted to the Canadian Forces Hospital, Halifax, with a history of a swollen, red, painful left foot of six days'

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duration. On the day of admission the process had spread to involve the ankle. There was soreness in both wrists as well. There was some accompanying malaise with a slight febrile reaction. The leukocyte count was slightly elevated and the Westergren sedimentation rate (ESR) was greatly increased.

Despite normal uric acid determinations, colchicine was given as a clinical trial but no response was obtained.

The day after admission, the patient had an obvious tenosynovitis of his left Achilles' and hamstring tendons. There was tenderness and swelling of the left gastrocnemius as well. By the third hospital day, he had a full-blown polyarthritis involving both ankles, both wrists, and the third metacarpophalangeal joint of his left hand. The patient was then very ill. Any movement in bed was painful and weight-bearing was out of the question.

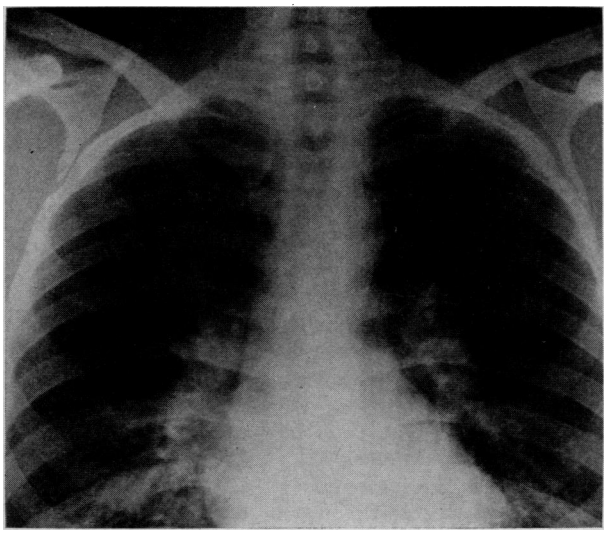

Fig. 1.—Case 1. Chest radiograph showing obvious bilateral hilar lymphadenopathy with no apparent parenchymal infiltration. (Reproduced with permission from the editor, *Med. Serv. J. Canada*, 20: 621, 1964.)

Three days later he developed red, tender lesions on his left forearm and the anterior aspects of both legs. These were typical of erythema nodosum, and with the appearance of these lesions the possibility of sarcoidosis was entertained. A chest radiograph revealed bilateral hilar lymphadenopathy (Fig. 1), and a presumptive diagnosis of sarcoidosis was made.

The eyes and parotid glands were normal. Electrocardiograms, serum uric acid, latex fixation, and Rose-Waaler tests were normal. Lupus erythematosus cells were sought but not found. Gamma globulins were normal, as was the serum calcium. Urinary calcium levels were not determined. Skin tests for histoplasmosis and tuberculosis (10 T.U.) were negative. Roentgenograms of hands and feet were normal. The ESR remained over 30 mm. per hour (Westergren) during the entire hospitalization.

During the most acute phase of his illness there was continuous fever with temperatures varying from 101° to 104° F.

The fever, rash, polyarthritis and tenosynovitis all subsided within the next 10 days. The patient was symptom-free three weeks from the onset of his illness.

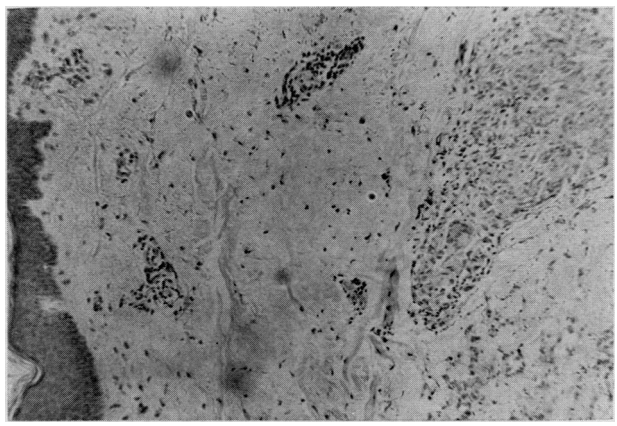

Fig. 2.—Case 1. Biopsy of Kveim test showing epitheloid cell granuloma with typical giant cells of the Langhans type. Note relationship in deeper skin layers. (Hematoxylin and eosin, × 180.) (Reproduced with permission from the editor, *Med. Serv. J. Canada*, 20: 621, 1964.)

The only treatment given, apart from the colchicine already mentioned, was salicylates and supportive therapy.

The patient was discharged to convalescence at his unit infirmary. Prior to discharge, Kveim antigen was injected. Four weeks later a nodule was present at the site. A biopsy was taken and sections showed a granulomatous reaction with Langhans' giant cells but no necrosis (Fig. 2). This positive Kveim test provided final confirmatory evidence for the diagnosis.

At this writing it is one year since his discharge from hospital. The patient has remained well. The ESR and chest radiograph are now normal.

CASE 2

A 30-year-old white Air Force corporal was admitted with an acute polyarthritis of two weeks' duration. The patient had been vacationing in Europe. Over the course of one day, while hiking, he developed swollen, red, painful ankles. This was accompanied by stiffness in his knees and hips but no real pain. On the second and third days of his illness, his elbows, wrists, and hands became stiff, slightly swollen, and painful. He consulted a physician in Stockholm. A diagnosis was not made, but his transportation to Canada was arranged.

He was admitted to the Canadian Forces Hospital, Halifax, 16 days after the onset of his illness.

The findings were as stated previously, but on examination a fairly discrete, reddened, tender, and somewhat indurated lesion was noted on the lateral aspect of his left leg. This had the typical appearance of erythema nodosum and on questioning he stated that it had appeared on the first day of his illness.

In contradistinction to the first case, there were only minimal constitutional symptoms and a very low grade fever. He was unable to walk or move about because of pain but was otherwise quite well.

Because of the symmetry of the lesions, the first diagnosis considered was rheumatoid arthritis. The erythema nodosum, however, provided the clue, and a chest radiograph, showing hilar lymphadenopathy (Fig. 3), supported the diagnosis of sarcoidosis.

As compared with the first case, this patient had already had a rather long illness. Nevertheless, he began to get worse. On the fifth hospital day his

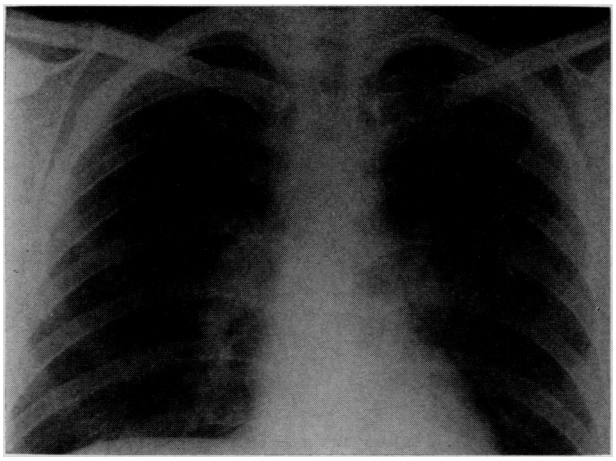

Fig. 3.—Case 2. Chest radiograph showing more unilateral hilar lymphadenopathy. (Reproduced with permission from the editor, *Med. Serv. J. Canada,* 20: 621, 1964.)

temperature rose to 101.5° F. and the pain and swelling in both knees and elbows increased although they were neither very red nor warm. This flare-up was accompanied by a new crop of erythema nodosum lesions on the anterior aspects of both legs.

This situation persisted for five days during which he was very ill, before he finally began to improve. There was continuous fever with temperatures fluctuating between 101° and 103° F. It was nearly six weeks from the onset of his illness before all objective evidence of arthritis and erythema nodosum had disappeared.

The same investigations were completed on this patient with exactly the same findings as in the first case. Skin tests were negative and blood chemistry was normal. The erythrocyte sedimentation rate remained in the vicinity of 30 mm. per hour (Westergren) during his hospital stay.

Prior to his discharge, Kveim antigen was injected and in four weeks a clinically positive papule was present. Biopsy (Fig. 4) confirmed the positive Kveim test.

For a few weeks after discharge this patient complained of some arthralgia. At this writing, however, one year after discharge, he is symptom-free and his chest radiograph and sedimentation rate are normal.

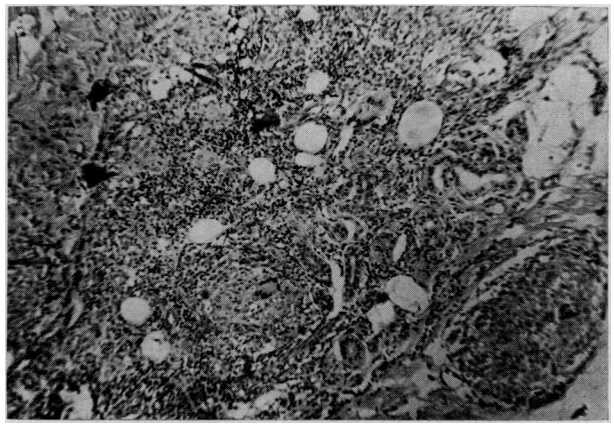

Fig. 4.—Case 2. Biopsy of Kveim test showing typical granulomatous reaction and Langhans' giant cells. (Hematoxylin and eosin, × 180.) (Reproduced with permission from the editor, *Med. Serv. J. Canada,* 20: 621, 1964.)

DISCUSSION

Hollander's textbook (6th edition)[4] states that: "Sarcoid arthritis has received little, if any, attention in the more exhaustive treatises on sarcoidosis. This may have been due to the fact that the arthritis is not a common manifestation; that joint involvement, when present, is frequently mild or evanescent; when prominent or protracted, is diagnosed as rheumatic fever or rheumatoid arthritis and when accompanied by erythema nodosum, is attributed to that disease. Since 1952, however, arthritis has been reported by some authors to occur in 10-25% of their cases; and during the last 25 years, since the first report of polyarthritis[2] was published, approximately 60 cases have appeared in the literature."

In fact, many more cases with joint involvement have been recorded; Löfgren[5] alone reported 101—an incidence of 43% in his series.

The literature on sarcoidosis is confusing with regard to both the incidence and character of the joint involvement. This is largely due to the lack of specific description. With few exceptions, reports list the incidence under headings of "Joint Manifestations" or "Joint Involvement", without clearly defining the clinical picture as it was seen in the patients or without describing the involved joints. Nevertheless the literature does indicate that at least three different types of joint involvement can be recognized. Such differentiation makes possible the determination of a more accurate incidence of polyarthritis in sarcoidosis.

The first type could be termed "mild acute". This is by far the most common form of joint involvement. It is usually associated with the "subacute" or transient type of sarcoidosis. Löfgren, in describing his cases, stated that the articular symptoms were mild in type, that the fever was of low grade, and that the slight swelling, affecting large joints (classically the ankles), was transitory or even "fleeting" in duration. The arthritis tends to be symmetrical and migratory, and does not respond readily to salicylate therapy.

There is a clear parallel in the incidence of erythema nodosum and acute polyarthritis, although either may be present without the other. In Löfgren's series of 212 cases, 117 had erythema nodosum, and of these 101 had articular symptoms. A similar relationship has been noted in reviews from both the United States and the United Kingdom.

It is well known, however, that the incidence of erythema nodosum is much lower in the United States than abroad, and this is equally true of polyarthritis. The incidence of both manifestations is approximately 5% in the U.S.A., as compared with 40-50% in Sweden. Certain smaller American series[6] have reported the incidence of polyarthritis as high as 25% as well. Figures from the U.K. seem to fall somewhere in between. James[7] reported the incidence of erythema nodosum in sarcoidosis as 23%.

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Because of the close relationship between the two, the sex incidence of polyarthritis naturally follows that of erythema nodosum: the majority of cases occur in females.

Case records from the four Halifax hospitals—the Victoria General Hospital, the Halifax Infirmary, Camp Hill Veterans Hospital, and the Canadian Forces Hospital—were reviewed, covering the period 1954-1964 inclusive. There were 61 proved cases of sarcoidosis. Of these, 10 had articular symptoms, an incidence of 16%. Except in three cases, all those with arthritis had erythema nodosum as well. Only two of the patients presented with erythema nodosum without mention of polyarthritis. With the exception of the two cases here presented, symptoms and clinical findings were minimal and would fall into this first classification.

The second type of sarcoid polyarthritis is the "severe acute". This is the type presented in the cases described in this report and is much the same as the "mild acute" type except that it is accompanied by much more pain, fever, swelling, and systemic disturbance. The large joints are primarily affected, and the relationship of this form of sarcoid arthritis to erythema nodosum, its resistance to salicylates and tendency to regression in a few weeks are similar to those of the "mild acute" type.

The articular symptoms regress concurrently with the erythema nodosum, and the appearance of new crops of the latter is usually accompanied by an exacerbation of the joint symptoms.

A search of the literature disclosed only 13 specific cases[6, 8-12] describing a clinical picture similar to the two presented here.

It is in this latter group that many cases are probably misdiagnosed because the symptoms and findings are so dramatic and so much like those in more common forms of arthritis. For example, Riley[13] reported five cases of sarcoidosis with coexistent rheumatic fever not affecting the myocardium. These were almost certainly cases of sarcoid polyarthritis. Castellanos and Galan[14] reported an arthritis resembling Still's disease in a 6-year-old patient with sarcoidosis. There are probably many more.

The only real distinction between the two types is the severity. The other major characteristics are the same.

Sokoloff and Bunim[8] have found granulomata in the synovium of a patient with this severe type of sarcoid arthritis. They interpreted the polyarthritis as an intrinsic manifestation of sarcoidosis, and not as a hypersensitivity reaction or a lesion secondary to bone involvement. This is to say, when sarcoid granulomata invade the synovia, arthritis develops.

In contrast, it has been suggested that the arthritis of the mild type, as described by various authors, is little different from the polyarthralgia that may accompany any generalized systemic disorder. This, however, is only supposition, as one is unable to find any reports of cases with mild joint symptoms in which biopsy of the synovium had been performed to confirm or disprove the presence of granulomata.

The prognosis is good with either type of acute sarcoid polyarthritis. In the majority of cases the patients have completely recovered in a few weeks. Occasionally there may be exacerbations or recurrences. Rarely there is progression to the more chronic type. As in the case of sarcoidosis generally, the presence of erythema nodosum is a good prognostic sign.[15, 16]

The third type of sarcoid polyarthritis is "chronic" or "recurrent" arthritis. This type is most uncommon. The first reported case of sarcoid polyarthritis, beautifully documented by Burman and Mayer,[2] belongs to this group, as does the case reported by Castellanos and Galan.[14] Sokoloff and Bunim[8] also reported three cases of this type, Kaplan[17] reported two, and another is described in Hollander's textbook.[4]

TABLE I.—SARCOID POLYARTHRITIS

	Acute		
	Mild	*Severe*	*Chronic*
Incidence	*Common*	*Uncommon*	*Rare*
Joints.....	Mild swelling and discomfort	Hot, painful, red, swollen	May be joint destruction
Duration....	Weeks	Weeks	Months or yrs.
Fever.....	Low	High	Variable with activity
Erythem. nod.	Present	Present	Not present
Prognosis....	Good	Good	Variable

The features are more varied, small points are often affected, the duration is much longer, and occasionally there are permanent joint changes. At times, particularly in the small joints, arthritis appears secondary to adjacent bone disease, but in other cases the joint lesions are independent of bone involvement. When biopsies have been taken, granulomata have been found in the synovia (Table I).

A different concept has been advanced by Kaplan and Klatskin,[18] who reported three cases of sarcoidosis, with no apparent renal involvement, in patients with gout. They postulated a relationship between these two diseases and presented some evidence in support of this concept. Later, Kaplan[17] reported two cases of apparent sarcoid polyarthritis successfully treated by colchicine. It will be noted that colchicine was tried in the first case described in this report, with no effect.

The diagnosis of sarcoid polyarthritis depends on the diagnosis of sarcoidosis. When the latter has been established and when diagnostic tests exclude the other more common types of arthritis, joint

changes with the characteristics described above can be designated as sarcoid polyarthritis. The serum chemistry is variable as it is in the case of sarcoidosis generally. The ESR is always elevated.

Treatment

With regard to treatment, most authorities feel that because the condition is so benign, only supportive therapy is indicated. Others advocate that corticosteroids should be used because they do give relief and the duration of symptoms is such that only a short course is required. In the presence of chronic progressive polyarthritis, the use of steroids would seem to be indicated. The use of colchicine has already been mentioned, and this drug is generally not of benefit.

It will be noted that tenosynovitis was present in our Case 1. This appears to be a rare feature. The only reference to it that could be found in recent literature was a mention of one case among 1245 patients reviewed by Mayock *et al.*[19] It is interesting that tenosynovitis was also a feature in the case described by Besnier[20] in his original monograph, and by Burman and Mayer[2] in their case report. In the latter, granulomata were demonstrated in the tendon sheath by biopsy, the only reported case in which this procedure was done. In retrospect, it seems likely that in our Case 1, sarcoid myopathy of the left gastrocnemius was present as well. The clinical findings were similar to those described by Harvey[21] in his article on sarcoid myopathy. It is regretted that synovial and muscle biopsies were not taken in both of our cases.

SUMMARY

Two cases of sarcoidosis and polyarthritis are presented. Tenosynovitis and possibly sarcoid myopathy were additional features in one case. Cases seen in Halifax hospitals in the period 1954-1964 are reported.

The literature is reviewed and an attempt is made to distinguish the various types of clinical presentation. It is evident that mild joint symptoms are a common manifestation of sarcoidosis but that more severe arthritis is a relatively rare feature of this disease.

The diagnosis, treatment and prognosis of sarcoid polyarthritis are briefly discussed.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

PHARMACOLOGY OF ANIMAL EXTRACTS

It would be both valueless and indeed impossible in a paper such as this to consider in detail the pharmacological actions which have been ascribed to all the various animal extracts which have been tested experimentally and clinically. We are, indeed, at once led into the bewildering labyrinth of facts and supposed facts relating to the physiology of the organs of internal secretion. Few, indeed, of the extracts upon the market have any proved pharmacological actions and fewer still have been sufficiently studied to justify their employment in medicine, and I would like to utter a word of protest against the credulity with which physicians listen to the statements of the manufacturers of animal extracts, and supposedly find these statements confirmed by the histories of the cases in which they employ them . . .

Pituitary extract has only of late years been fully studied. Its active principle has not been isolated. It is much less labile. The extract of the posterior lobe acts apparently upon gland and muscle tissue directly. On the heart it produces slowing with usually some increase in out-put, but its effect on the cardiac blood supply is bad and some authorities consider its entire cardiac action to be deleterious (Tigerstedt and Airila). The action of a second injection in animals often causes a fall in blood pressure. It causes a marked increase in the tone and movements of the intestine and hence is of value subsequent to abdominal operations, though if distension becomes extreme before it is displayed, it rarely has any effect. It also increases the tone and movements of the urinary bladder and again shows its value when employed after laparotomy or post partum (Jaschke). Its most important use is undoubtedly in the second stage of labour when the uterine movements cease or become weak. It then produces increase of movements with relatively little increase of uterine tone, so that a uterine tetanus is exceedingly rarely seen. Owing to its not producing an increase in tone it is of much less value post partum than ergot. In some cases it is successful in producing abortion or bringing on a labour at full term (for literature see Harrison and Watson). In certain animals the injection of pituitary extract causes a flow of urine, but it is by no means clear that this is not secondary to its action on the vascular system. Subcutaneous injection of pituitary extract also produces a marked flow of milk (MacKenzie, Ott and Scott) with a richer fat content, but this primary effect is compensated by a decrease in the milk produced subsequently (Hill and Simpson) and possibly in the fat content also (Hammond). There seems little reason for its employment clinically as a lactagogue though some observers think that they have used it with advantage (Reynolds). The hormone having this lactagogue action is probably distinct from that acting on muscle (Herring).

The connection between the activity of the pituitary gland and growth as instanced by acromegaly is well known, but this metabolic side of the gland's activity as yet presents no clear cut principles for treatment.—V. E. Henderson, *Canad. Med. Ass. J.*, 5: 661, 1915.