October 1994

Arthritis of leprosy

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British Journal of Rheumatology 1994;33:963–966

CLINICAL REVIEW

ARTHRITIS OF LEPROSY

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SUMMARY

An inflammatory polyarthritis has been previously described in leprosy but accounts of the clinical characteristics have varied. All patients with joint symptoms admitted to a leprosy centre over 5 months were examined by a rheumatologist. Of 48 acute admissions, 20 (42%) had a symmetrical polyarthritis affecting the wrists and fingers. This was strikingly similar to RA in appearance. The arthritis occurred exclusively in patients with reactions mainly during anti-mycobacterial treatment. The clinical features of the joint disorder were identical in Type I (associated with alterations in immune status) and Type II (erythema nodosum leprosum) reactions. Synovial tissue from one patient revealed no mycobacteria. Four of five hand X-rays suggested small erosions of the finger joints.

KEY WORDS: *Mycobacterium leprae*, Symmetrical polyarthritis, Leprosy reactions.

ONE by one the old infectious scourges of mankind have been contained or eliminated. At least one exception is leprosy. Its insidious onset makes early recognition and isolation difficult and its social stigma ensures that treatment may not be sought until late. In the developing countries of South Asia the prevalence is estimated to be 2/1000 [1]. The notorious deformity and disability of the disease are mainly due to destructive tissue invasion by *Mycobacterium leprae* and to peripheral neuropathy. Arthritis is a recognized feature, but its frequency and contribution to morbidity may be underestimated [2]. Arthritis occurring in Type 2 reactions (erythema nodosum leprosum) is described [3]. Both Type 1 and 2 reactions are associated with inflammation at sites of mycobacterial infection such as the skin and peripheral nerves and are often precipitated by treatment. The former is linked to downgrading or upgrading of cell-mediated immunity and a shift toward one or other clinical poles of the disease spectrum [4]. It tends to occur in borderline disease although not exclusively. The better known Type 2 reaction is characterized by the additional feature of painful red nodules over the face and limbs and is more often seen in lepromatous and borderline lepromatous disease. This study describes the pattern of arthritis amongst new admissions to a leprosy centre in Pakistan. The arthritis was invariably associated with either Type 1 or 2 reactions.

SUBJECTS AND METHODS

The Marie Adelaide Leprosy Centre in Karachi is a charity aided unit which has an inpatient facility for both acute admissions and elective procedures. It is the organizational focus for a network of leprosy control centres throughout Pakistan. Most of the in-patients are admitted from poor areas of Karachi, rural Sind and Baluchistan.

During a 5-month period in 1992, a rheumatologist (TG) visited the unit weekly and examined any new patient with joint symptoms. The history and distribution of joint pain, tenderness and swelling were recorded. Patterns of leprosy (lepromatous to tuberculoid) were identified clinically and by skin biopsy by two leprologists (QA, KH). Types of reaction were categorized clinically depending on the presence or absence of erythema nodosum leprosum and the systemic features of a Type 2 response (e.g. orchitis). Haemoglobin, ESR, RF (latex slide test, Laboratorios Knickerbocker, Barcelona) and X-rays of hands were performed where the cost could be justified clinically. Joint aspiration and needle synovial biopsy of an affected knee were performed on two patients but synovium was obtained in only one. This was stained by haematoxylin and eosin and by Wade-Site stain for *Mycobacterium leprae*.

RESULTS

There were 48 acute admission of which 31 (64%) were for reactional states. Of these, 20 (60%) had joint symptoms. Apart from three other patients with incidential OA of the knee or spine, no other patient had joint pain. Amongst the long-standing inpatients and elective admissions were some with peripheral neuropathy exhibiting digital atrophy, autoamputation, foot ulcers and Charcot joints. These were easily distinguished and were not part of this study.

Peripheral arthritis was seen in both types of reaction and details of the patients and the distribution of the joint disease are summarized in the tables according to their reaction patterns. Histories were not always easy to obtain because of cultural and linguistic difficulties. At least nine (75%) of those with Type 1 and three (40%) with Type 2 reactions recalled joint pain or swelling before or at the time that other clinical mani-

Submitted 14 March; revised version accepted 15 July 1994.

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0263-7103/94/100963 + 04 $08.00/0

TABLE I
Clinical features of leprosy in patients experiencing reactional states with arthritis

	Type 1	Type 2
Sex	8 M 4 F	6 M 2 F
Mean age (yr)	37	30
(range)	(16–68)	(20–41)
Class of leprosy:		
Lepromatous	3	4
Borderline lepromatous	5	4
Borderline	2	—
Borderline tuberculoid	1	—
Indeterminate	1	—
Other manifestations:		
Ear swelling	5	5
Nose swelling	4	5
Iritis/conjunctivitis	—	6
Orchitis	—	2
Treatment at time of reaction:		
*MDR	4	1
Dapsone	3	6
Clofazimine	3	1
None	2	—
Mean (range) duration of treatment (months)	10 (1–24)	49 (7–132)

*MDR, multiple drug regimen: dapsone, clofazimine, rifampicin.

festations of leprosy first appeared. In these cases, joint pain and swelling had worsened at the onset of the reaction. By the time of examination the associated acute arthritis had been evident for variable periods of days, weeks or months. Three patients claimed that acute joint swelling had been recurrent for several years. Similarly, of 10 patients with reactional swelling of nose, ears or both, seven had experienced milder swelling of these sites weeks or months beforehand. Other features of the Type 2 reaction were conjunctivitis or iritis in six and orchitis in two patients. The majority of those in reaction had been receiving treatment although two with Type 1 had not received any antimycobacterial therapy (Table I). It is noteworthy that the majority of patients with Type 1 reactions and arthritis were borderline cases whereas those with Type 2 reactions were toward the lepromatous end of the clinical and immunological spectrum. Males were represented more than twice as often as females.

The clinical picture of arthritis was strikingly similar to RA. Finger joints were the most commonly affected sites (Table II). The pattern of disease was the same in both Type 1 and 2 reactions. Swelling of the wrists, MCPs and PIPs in a symmetrical distribution was characteristic (Fig. 1).

SF examination in one case revealed white cell count $4.0 \times 10^9/l$ (90% lymphocytes). No acid-fast bacilli were seen and none was cultured. Synovial biopsy obtained from the knee of another patient revealed a modest perivascular lymphocyte infiltration but a careful search failed to reveal any mycobacteria.

Anaemia and elevation of ESR were common (Table II). The rheumatoid latex test was negative in all patients tested. X-rays of the hands were obtained in five patients. The quality of the films was poor but four of the five sets of hand films showed small erosions of PIP or MCP joints (Fig. 2).

DISCUSSION

The association of arthritis with leprosy does not receive emphasis in standard accounts of the illness [5]. Nevertheless, descriptions of joint involvement are numerous [6–11]. There is inconsistency in the documented picture of the joint disease. In one prospective study of 25 patients, arthritis was seen both with and without other features of Type 2 reactions [11]. It affected one, few or many joints; SF was non-inflammatory, inflammatory or purulent and acid-fast bacilli were seen in occasional samples. These observations imply that there may be more than one pattern of arthritis which in some cases is due to direct infection and in others to a different mechanism. There is confirmatory evidence that mycobacteria can be found in the synovium of some affected patients [12, 13]. Other accounts describe an inflammatory peripheral arthritis occurring in the absence of reactional states but in these reports there was no attempt to exclude direct infection of involved joints [14, 15].

Our own description of a peripheral arthritis resembling RA echoes earlier studies in which examination of SF and tissue failed to yield mycobacteria [3, 16]. Successful synovial biopsy was achieved in only one of our patients and that did not reveal acid-fast bacilli.

TABLE II
Distribution of joint inflammation and results of investigations in patients with reactional states and arthritis

	Type 1		Type 2	
	Tenderness	Swelling	Tenderness	Swelling
Shoulder	2	—	—	—
Elbow	5	3	5	1
Wrist	9	6	5	3
MCP	10	8	7	4
PIP	9	9	5	2
DIP	2	1	1	—
Knee	6	3	1	—
Ankle	9	5	7	3
MTP	8	2	4	2
Mean (range) haemoglobin (g/dl)	9.6 (8.2– 11.5)		9.4 (5.2– 11.6)	
Mean (range) ESR (mm/h)	57 (25–128)		73 (15–160)	
Rheumatoid latex positive	0/10		0/2	
X-ray erosions	3/3		1/2	

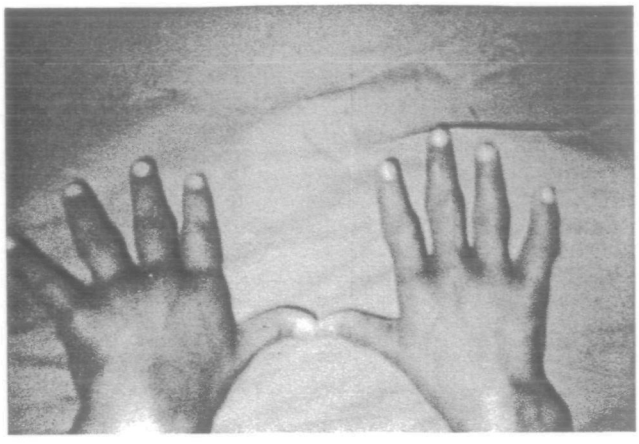

FIG. 1.—Symmetrical swelling of PIP, MCP and wrist joints in a patient with a leprosy reaction.

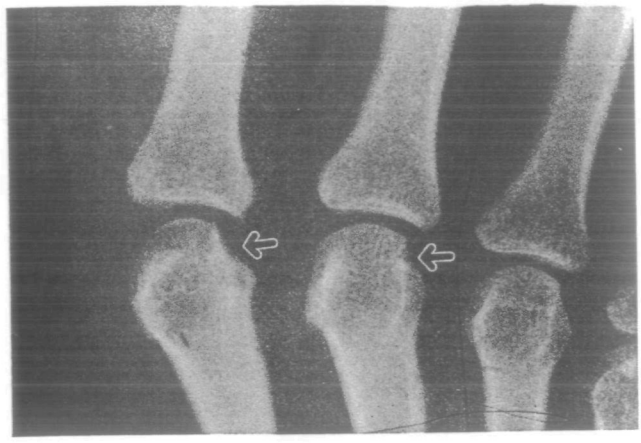

Fig. 2.—Minor erosions of MCP joints (arrows) in a patient with Type 1 reaction and associated arthritis.

Some earlier accounts of this clinical picture did not describe associated reactions although the onset of arthritis was considered by Bonvoisin *et al.* [17] to herald a reactional state. The relationship of peripheral arthritis with Type 2 reactions has been noted by others [18, 19] but we are the first to describe joint inflammation resembling RA occurring in both Type 1 and 2 reactions. The two reactional states are not always easily distinguishable and painful swelling of specific sites such as the ears and nose is common to both. The appearance of minor joint erosions in a small number of patients made the comparison with rheumatoid disease even more striking. Similar changes have been observed by others [20, 21]. None of our patients had a positive rheumatoid latex test which is surprising because leprosy is reputed to be one of the chronic non-rheumatoid diseases associated with RF [22]. The anaemia and high ESR are characteristic of reactional states which represent the paradox of acute inflammation and worsening of symptoms despite effective antimycobacterial infection [23].

Both Type 1 and 2 reactions, especially the latter, tend to occur during treatment when it is presumed an increased mycobacterial antigen load follows death of the organisms. However, as in the current series of patients, spontaneous reactions also occur in untreated patients. In both types, swelling and inflammation develop at sites where invasion by mycobacteria commonly occur, such as skin, nerves, eyes, ears and nose. By analogy the acute arthritis probably also arises in joints infiltrated by the organism. This would explain the disparities in the descriptions of arthritis in leprosy and accords with the histories of previous, but milder joint symptoms in many of our patients. Men seem to be more vulnerable than women to reactions and the predominance of males amongst our patients has already been noted. Although the two patterns of reactional states share some clinical characteristics each is thought to have a different immunopathogenesis. In Type 1 reactions, patients move toward either the lepromatous (severe) or tuberculoid (mild) pole of the disease. In the latter case at least, the cytokine profile in the skin is distinctive, with amongst other features a relatively reduced IL-4 [24]. It has been reported that in Type 2 reactions, there is immune complex deposition and IL-4 remains strongly expressed [24]. It thus seems that two different immune mechanisms may be operating. As in our patients, Type 2 reactions tend to be confined to lepromatous or borderline lepromatous patients, that is to those with the greater concentration of organisms and the least cell-mediated immunity against the mycobacterial antigen. Our observations suggest that the arthritis which accompanies these different reactions are identical. Much has yet to be learned about the immunological events which influence the clinical spectrum of leprosy and its complications. Whether or not the reactional states are as distinct as claimed, requires confirmation. The striking similarity of the associated arthritis with rheumatoid disease warrants emphasis especially since some autoimmune diseases may be induced by infection [25]. Closer examination of the immunological sequence and its relationship to the presence of *Mycobacterium leprae* within the joints could carry implications for the mechanism of other joint disorders.

ACKNOWLEDGEMENTS

The authors thank Dr Thomas Chiang and the staff at the Marie Adelaide Leprosy Centre for their assistance, and Dr Rabia Hussein for her help and encouragement. Dr Gibson was partly supported by the Arthritis and Rheumatism Council and the Special Trustees of Guy's Hospital.

REFERENCES

1. Cossermelli-Messina W. Leprosy: Statistics in the Americas. *J Rheumatol* 1993;**20**:893–6.
2. Chandrasekaran A. Infection and arthritis, our experiences, a retrospective and prospective study. *J Ind Rheum Ass* 1993;**1**:7–20.
3. Karat A, Karat S, Job C, Furness M. Acute exudative arthritis in leprosy—rheumatoid arthritis like syndrome in association with erythema nodosum leprosum. *BMJ* 1967;**3**:770–2.
4. Naafs B. Reactions in leprosy. *Biol Mycobacteria* 1989;**3**:359–94.
5. Bryceson A, Pflatzgraff R. *Leprosy*. Edinburgh: Churchill Livingston, 1990.

6. Iveson J, McDougall A, Leatham A, Harris H. Lepromatous leprosy presenting with polyarthritis, myositis and immune complex glomerulonephritis. *BMJ* 1975;**3:**619–21.
7. Berman L. Exudative arthritis in leprosy. *Arthritis Rheum* 1979;**22:**593.
8. Albert D, Weisman M, Kaplan R. The rheumatic manifestations of leprosy. *Medicine* 1980;**59:**442–8.
9. Markusse H, Smelt A, Teepe R. Unusual arthritis: be on the alert after leprosy. *Clinic Rheumatol* 1989; **8:**266–8.
10. Atkin S, El-Ghorbarey A, Kamel M, Owen J, Dick W. Clinical and laboratory studies of arthritis in leprosy. *BMJ* 1989;**298:**1423–5.
11. Pernambuco J, Opromolla D, Tolentino M, Fleury R. Arthritis in lepromatous Hansen's disease. *Int J Leprosy* 1979 **47** (Suppl. 2):353–4.
12. Modi T, Lele R. Acute joint manifestations in leprosy. *J Ass Phys India* 1969;**17:**247–54.
13. Holla V, Kenetkar M, Kolhatkar M, Kulkarin C. Leprous synovitis. A study of 50 cases. *Int J Leprosy* 1983;**51:**29–32.
14. Bank I. Arthritis in leprosy. *Arch Int Med* 1984; **144:**421.
15. Atkin S, Welbury R, Stanfield E, Beavis D, Iwais B, Dick W. Clinical and laboratory studies of inflammatory polyarthritis in patients with leprosy in Papua New Guinea. *Ann Rheum Dis* 1987;**46:**688–90.
16. Lele R, Sainani G, Sharma K. Leprosy presenting as rheumatoid arthritis. *J Ass Phys India* 1965;**13:**275–7.
17. Bonvoisin B, Martin J, Bouvier M, Bocquet B, Bouilliat J, Duivon J. Les manifestations articulaires de la lepre. *Sem Hop Paris* 1983;**59:**302–5.
18. Alcocer J, Herrera R, Lavalle C, Gudino J, Fraga A. Inflammatory arthropathies in leprosy. *Arthritis Rheum* 1979;**22:**587.
19. Chavez-Legaspi M, Gomez-Vazquez A, Garcia de la Torre I. Study of rheumatic manifestation and serologic abnormalities in patients in leprosy. *J Rheum* 1985;**12:**738–41.
20. Enna C, Jacobson R, Rausch R. Bone changes in leprosy: a correlation of clinical and radiographic features. *Radiology* 1971;**100:**295–306.
21. Morley K, Vickers H, Hughes G. An unusual cause of arthritis. *Postgrad Med J* 1983;**59:**522–4.
22. Garcia de la Torre I. Autoimmune phenomena in leprosy, particularly anti-nuclear antibodies and rheumatoid factor. *J Rheumatol* 1993;**20:**900–3.
23. Malin A, Waters M, Shehade S, Roberts M. Leprosy in reaction: a medical emergency. *BMJ* 1991;**302:**1324.
24. Yamamura M, Wang X, Ohmen J *et al.* Cytokine patterns of immunological mediated tissue damage. *J Immunol* 1992;**149:**1470–5.
25. Ehrenstein M, Isenberg D. Autoimmunity associated with infection: leprosy, acute rheumatic fever and Lyme disease. *Curr Opin Immunol* 1991;**3:**930–5.