Arthritis in leprosy

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Abstract

Leprosy, a chronic granulomatous infection caused by Mycobacterium leprae, classically presents with cutaneous and neurological manifestations. Musculoskeletal involvement though third most common is underdiagnosed and underreported. It may manifest in the form of Charcot’s arthropathy, acute symmetrical polyarthritis or swollen hands and feet syndrome during lepra reactions, insidious-onset chronic symmetrical polyarthritis mimicking RA or as isolated tenosynovitis or tenosynovitis associated with arthritis or neuropathy. At times, articular involvement may be the sole presenting manifestation even without cutaneous lesions. Other rheumatological manifestations occasionally reported are enthesitis, sacroiliitis, cryoglobulinaemic vasculitis and DM. With increasing travel of population between tropical and temperate zones, it is likely that rheumatology clinics in countries free of leprosy may come across cases of leprosy with rheumatological manifestations. Delay in diagnosis and management may be detrimental and may result in deformities and loss of function. Not only this, but recent reports of leprosy being diagnosed in native white populations following anti-TNF-α therapy should alert rheumatologists across the globe to be more familiar with this disease. This review is aimed at presenting a comprehensive clinical scenario of various rheumatological manifestations of leprosy to sensitize rheumatologists and physicians across the continents.

Key words: Hansen’s disease, Arthritis, Neuropathy, Lepra bacilli, Tenosynovitis, Charcot’s arthropathy, Swollen hand and feet syndrome, Lepra reactions.

Introduction

In this era of increased travel and migration, especially of people from the developing world to the developed world, there is need to understand those diseases that were hitherto confined to the developing world or tropical countries [1]. Leprosy is one such disease. Recently, a few cases of leprosy have been reported among native white Americans after treatment with infliximab or adalimumab [2, 3]. Since anti-TNF-α mAbs are increasingly being used for the management of various rheumatological conditions, these cases highlight the importance of awareness of leprosy and its various presentations even in the geographical regions believed to be free of this disease.

Leprosy has been recognized for millennia and it develops insidiously over months and years. The word leprosy is derived from the ancient Greek word lêpéra, which means ‘a disease which makes the skin scaly’. Leprosy is a chronic granulomatous infectious disease caused by Mycobacterium leprae. The causative agent M. leprae was first reported by G. H. Armauer Hansen in Norway in 1873 [4]. Its mode of transmission is still uncertain and despite advances in diagnosis and treatment, it is a major cause of morbidity in many developing countries even today. The first mention of leprosy dates back to the 6th century BC in a medical treatise, Sushruta Samhita, by the surgeon Sushruta who flourished in India at that time. It later spread to Europe with the armies of Alexander the Great. Norway and Iceland were the most affected countries in the 17th century.

Its clinical manifestations are primarily confined to skin and peripheral nerves. However, musculoskeletal involvement including inflammatory arthritis, though underreported, is quite common. Rheumatologists should be aware of this disease since joint involvement occurs in ~75% of cases of leprosy and at times, is the only presenting manifestation.

Epidemiology

Data from the World Health Organization (WHO) in 1985 estimated that leprosy was endemic in 122 countries with
a global prevalence of 12 cases per 10,000 people and considered it to be one of the world’s major public health problems. It aimed to eliminate the disease (at least reduce the prevalence rate to fewer than one case per 10,000 persons) by 2000 AD. With the introduction of multidrug therapy (MDT), the disease burden has diminished dramatically and leprosy is being eliminated from most countries [5]. However, it remains a major problem in some of the developing countries in Asia, Africa and South America. India, one of the world’s fastest growing economies, alone accounts for 80% of prevalence and 88% of newly detected cases in the South East Asia Region. The global registered prevalence of leprosy at the beginning of the year 2009 stood at 213,036 cases, whereas the number of new cases detected during 2008 was 249,007 (this number excluded the few cases in Europe). Pockets of high prevalence were identified in Angola, Brazil, Central African Republic, Democratic Republic of Congo, India, Madagascar, Mozambique, Nepal and the United Republic of Tanzania. The number of new cases detected globally has fallen by 9126, a 4% decrease, during 2008 compared with 2007 [6].

The epidemiological data concerning the prevalence of arthritis in leprosy vary depending upon geographical area and the reporting centre or leprosarium. Various studies have reported it to range from 1 to 78% [7–9]. In one of the largest and earliest studies from India, only 27 out of 2500 patients with leprosy had articular involvement amounting to just over 1% [10]. Other authors have described varying prevalence. Cossermelli-Messina et al. [11] from South America reported arthritis in 12 out of his 44 patients with leprosy. Gibson et al. [12] reported arthritis in 12 out of 31 patients from Pakistan. Surprisingly, Alcocer et al. [13] observed a very high prevalence rate in his series of leprosy patients. In his series of 18 patients, 14 [78%] had articular involvement [13]. Nearly one-third of the 66 consecutive leprosy outpatients seen by Atkin et al. [8] had an inflammatory arthritis. Two recent Indian studies observed the prevalence rates for arthritis in leprosy at 61.4 and 10%, respectively [14, 15]. Thirteen out of 30 patients in the latter study presented initially to a rheumatology clinic and were subsequently detected to have leprosy. A recent study from South America reported a prevalence rate of 6.3% in a cohort of 1257 patients with leprosy [16].

Pathogenesis

The pathogenesis of articular involvement in leprosy is still not fully clear. Proposed mechanisms include reactional states (Types I and II lepra reaction), direct infiltration of the synovium and peripheral sensory neuropathy (Charcot’s or neuropathic joints) leading to joint destruction.

The immune response to M. leprae is dynamic with either increase or decrease of T-cell reactivity from time to time, which are termed reactional states. Reactions may occur spontaneously or may be precipitated by inter-current infections (viral, malaria, etc.), anaemia, mental or physical stress, puberty, pregnancy, parturition or surgical interventions or at times spontaneously [17]. There are two types of reaction: Types I and II. Type I reaction occurs in almost a third of leprosy patients and is characterized by spontaneous change in reactivity and infiltration of IFN-γ and TNF-α secreting CD4+ T-cells in the skin, nerves, joints and other tissues. It may be a downgrading reaction (suppression of cell-mediated immunity) or a reversal reaction (upgradation of cell-mediated immunity). Reversal reactions often occur in the first months or years after the initiation of therapy. The cytokine profile of Type I lepra reaction, increased TNF-α, IFN-γ, IL-2 and IL-4, is suggestive of Th1 type whether downgrading or reversal [18].

Type II (Gell and Coombs Type III hypersensitivity) reaction commonly known as erythema nodosum leprosum (ENL), is an immune complex-mediated reaction seen predominantly in patients with borderline lepromatous or polar lepromatous leprosy. It causes neutrophil infiltration and complement cascade activation leading to an intense inflammatory response. Although ENL may precede the diagnosis of leprosy and initiation of therapy (sometimes, in fact, prompting the diagnosis), in 90% of cases it follows the institution of chemotherapy, generally within 2 years. Skin biopsy of ENL papules reveals vasculitis or panniculitis, sometimes with many lymphocytes but characteristically with polymorphonuclear leucocytes as well. Elevated levels of circulating TNF-α have been demonstrated in ENL which plays a central role in the pathogenesis of this syndrome. Further, ENL is thought to be a consequence of immune complex deposition, given its Th2 cytokine profile, high levels of IL-6, IL-8 and IL-10.

Clinical features

Leprosy typically affects the skin (macules, plaques, papules or nodules, which are hypopigmented and anaesthetic; Figs 1 and 2) and the peripheral nervous system (mononeuropathy, mononeuritis multiplex or peripheral neuropahty; Fig. 3). Involvement of the musculoskeletal

![Fig. 1 Hyperpigmented hypoaesthetic macules over forearm and hand in a middle-aged male with Type II lepra reaction.](image-url)
system though often ignored, is the third most common manifestation.

To date, there has been no formal classification of arthritis in leprosy. However, arthritis in leprosy can be divided into the following groups: (i) Charcot’s joints, (ii) septic arthritis, (iii) acute polyarthritis of lepra reaction and (iv) chronic arthritis (Table 1).

Charcot’s joints, also known as neuropathic arthropathy, is characterized by joint dislocations, pathological fractures and debilitating deformities usually involving the weight-bearing joints of the lower limbs, i.e. ankles and the knees. Diabetes mellitus, tabes dorsalis (syphilis), chronic alcoholism, meningomyelocele, spinal cord injury and syringomyelia are some of the common conditions resulting in neuropathic joints. Despite the advent of effective anti-microbial therapy, leprosy is still one of the major aetiological causes of neuropathic joints in the developing world. The exact incidence and prevalence of neuropathic joints in leprosy remain to be defined, but according to a rough estimate, up to 10% of leprosy patients will have Charcot’s arthropathy as a result of long-standing peripheral neuropathy [19].

Fever, worsening of cutaneous lesions and paraesthesia dominate the clinical picture in both Types I and II lepra reactions. The arthritis of lepra reactions is acute in onset, symmetrical inflammatory polyarthritis affecting small joints of the hands and feet, resembling RA (Fig. 4). Rarely, knees, ankles, shoulders and elbows may be affected. The arthritis settles down within a few weeks. Lele et al. [10] in 1964 documented 13 cases of leprosy that had developed acute painful symmetrical polyarthritis involving hand joints. Seven years later, Modi and Lele [20] presented their data of 21 cases with lepra reaction associated with arthritis. Non-specific synovitis (n = 10), healed scarred lesions (n = 9) and _M. leprae_ infiltration (n = 4) were seen on synovial biopsies [20]. Gibson et al. [12] reported the presence of arthritis in 20 (65%) out of 31 patients with lepra reaction; Atkin et al. [8] reported predominantly Type I lepra reaction-associated arthritis in 19 (50%) patients in his series of 38 patients. Arthritis predominantly involved the small joints of hands and resolved by 4 weeks in most of the patients [20].

Albert et al. [9] described three cases of acute-onset painful oedema over the dorsum of the hands with marked restriction of movement and nodules along the extensor tendons. The underlying pathogenesis was lepra reaction in all these cases. Biopsy of the nodules showed a granulomatous reaction with _M. leprae_ infiltration. All responded to anti-leprosy and glucocorticoid therapy [9]. Occasionally, lepra reactions may manifest as insidious-onset chronic symmetrical or relapsing polyarthritis, mimicking RA.

Atkin et al. [21] were the first to describe chronic symmetrical polyarthritis identical to RA, not associated with lepra reactions in leprosy patients. They reported 31 patients of leprosy with chronic symmetrical polyarthritis [21] who do not have any evidence of reactional states. Cossermelli-Messina et al. [11] described 39 cases of leprosy with arthritis not associated with lepra reaction. Arthritis in most of the patients was chronic (mean duration 11 years) and RA-like in distribution. Leprosy had been present for >10 years in most of their patients and was currently inactive in 19 of them. Although these patients had considerable relief with anti-leprosy therapy, their arthritis never resolved completely. Permanent joint damage had occurred in some, most notably in the hands, leading to boutonnière and swan neck deformities, as well as mallet finger and ulnar drift: highly suggestive of RA.

Sacroiliitis, albeit rare, has been described. Cossermelli-Messina et al. [11], surprisingly, found a very high incidence of sacroiliitis (seen in 64%) in their cohort of leprosy patients.
patients long after their leprosy was cured. However, none of the other series has reported sacroiliitis.

Tenosynovitis in leprosy has been the subject of anecdotal reports [22, 23]. Agarwal et al. [23] recently described five cases of pure neuritic leprosy confirmed by nerve biopsy, presenting with tenosynovitis and arthritis (Fig. 5). Two of these had only tenosynovitis at presentation. Four of these patients were classified as RA, unclassifiable arthritis or primary SS [23]. A combination of arthritis, tenosynovitis with or without paraesthesia or thickened nerves is highly suggestive of leprosy. Cryoglobulinaemic vasculitis, DM and enthesitis [24, 25] and isolated tenosynovitis [22] are some of the other uncommon but well-described manifestations of leprosy.

**Diagnosis**

A high index of suspicion is required to diagnose arthritis due to leprosy even in a patient with characteristic neuro-cutaneous lesions. Lepra bacilli are difficult to demonstrate in the joint and other rheumatological problems may coexist in the same patient. Therefore, the diagnosis depends upon exclusion of all other causes of arthritis before attributing it to leprosy itself. The situation gets more complicated when rheumatological manifestations are the first or predominant presentation or where skin involvement is minimal or absent especially in cases with pure neuritic leprosy. Adding to this confusion is often positivity for RF, LE cell and ANAs. However, anti-CCP antibodies are negative in leprosy and thus may serve as useful serological marker to differentiate it from RA. A careful examination for skin lesions (hypo/anaesthetic macules or patches or erythematous macules, nodules), history of paraesthesia, thickened and tender peripheral nerves and sensory and motor neuropathy would be the clues to look for in the case of unexplained rheumatological symptoms, especially if belonging to an endemic area.

Radiological abnormalities in patients of arthritis due to leprosy can range from normal joints to joint subluxations and complete destruction. Juxta-articular erosions were seen in 12 (43%) out of 28 available radiographs, quite similar to those in RA [8]. Modi and Lele [20] even described erosions in three patients with acute arthritis and leprosy. Periostitis, bone resorption, sacroiliitis and deformed joints have all been described in arthritis associated with leprosy [11, 19].

Histopathologically, the synovium in chronic polyarthritis patients may demonstrate non-specific granulomatous

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**Table 1** Characteristics of different forms of articular involvement in leprosy

<table>
<thead>
<tr>
<th>Onset</th>
<th>Symmetrical</th>
<th>Poliarthritis</th>
<th>Joints involved</th>
<th>M. leprae in synovium</th>
<th>Response to MDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lepra reaction</td>
<td>Acute</td>
<td>Yes</td>
<td>Yes</td>
<td>Wrist, MCP, PIP, ankle, MTP</td>
<td>±</td>
</tr>
<tr>
<td>Swollen hands and foot syndrome</td>
<td>Acute</td>
<td>Yes</td>
<td>Yes</td>
<td>Ankle, wrist, feet, MCP, PIP</td>
<td>No</td>
</tr>
<tr>
<td>Chronic arthritis</td>
<td>Insidious</td>
<td>Yes</td>
<td>Yes</td>
<td>Wrists, MCP, PIP, Knee, MTP</td>
<td>+</td>
</tr>
<tr>
<td>Charcot’s arthropathy</td>
<td>Insidious</td>
<td>No</td>
<td>Mono to polyarticular</td>
<td>Hand and foot joints, ankle, knee, wrist</td>
<td>+</td>
</tr>
<tr>
<td>Tenosynovitis</td>
<td>Insidious</td>
<td>±</td>
<td>–</td>
<td>Extensor tendons of hands and feet</td>
<td>–</td>
</tr>
</tbody>
</table>

*Requires glucocorticoid therapy in addition to MDT.

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**Fig. 4** Arthritis of the hands mimicking RA in a young female.

**Fig. 5** Arthritis of the wrist and extensor tenosynovitis in a middle-aged male with Type I lepra reaction.
synovitis, epithelioid cells or even *M. leprae* bacilli. From 25 cases of arthritis due to leprosy, 32 SF samples along with 20 synovial and 3 bone biopsy samples were examined. The spectrum ranged from non-inflammatory to turbid effusions with an inflamed synovium. Nine of these samples showed the presence of *M. leprae* [26].

The gold standard remains the demonstration of *M. leprae* bacilli in the joint. As the bacilli are difficult to demonstrate and often not found in the SF or synovial biopsy specimen, diagnosis often depends on circumstantial evidence based on good clinical judgement. Recently, a new serological test for detection of antibodies to the *M. leprae*-specific phosphoglycolipid-1 has been added to the armamentarium. These antibodies are present in 90% of patients with untreated lepromatous disease, but only in 40–50% of patients with paucibacillary disease and 1–5% of healthy controls [27]. PCR for detection of *M. leprae* DNA-encoding-specific genes or repeat sequences is potentially highly sensitive and specific, since it detects *M. leprae* DNA in 95% of multibacillary and 55% of paucibacillary patients [28]. Currently, PCR is not used in clinical practice.

**Treatment**

The first-line drugs against leprosy are rifampicin, clofazimine and dapsone. According to the WHO, all patients should receive a multidrug combination with monthly supervision. For paucibacillary disease, rifampicin 600 mg/month and dapsone 100 mg/day for 6 months are effective and recommended by WHO. For multibacillary disease, rifampicin 600 mg and clofazimine 300 mg/month along with clofazimine 50 mg and dapsone 100 mg for 24 months will suffice [27].

In lepra reactions associated with arthritis, the immediate goal is to control acute inflammation, ease pain and reverse nerve damage. CS along with MDT form the backbone of management of lepra reactions. The starting dose of prednisolone is 1 mg/kg/day. Thereafter, the dose of prednisolone is gradually decreased by 5 mg every 2–4 weeks. The duration for which steroids are given depends upon the clinical response and usually varies between 4 and 6 months. For severe Type II reaction (ENL), MDT and prednisolone will not be enough to control inflammation and more potent drugs may be required. Under such circumstances, clofazimine (300 mg/day) or thalidomide (400 mg/day) is the drug of choice [27]. Recently, TNF-α blocker therapy has been reported to have efficacy in Type II lepra reaction and is emerging as a potential new therapy.

**Conclusion**

Leprosy is a great mimicker (can mimic RA, seronegative SpA or systemic necrotizing vasculitis) as far as the musculoskeletal manifestations are concerned. In patients with rheumatological complaints, a diagnosis of leprosy may be considered in the presence of neurocutaneous lesions. Moreover, leprosy should be diligently searched for, in patients with unexplained articular manifestations, as these may be the first and only presenting complaint. The startling truth is that even in areas of the world where leprosy is endemic, inflammatory arthritis due to leprosy is not appreciated and often overlooked. To conclude, inflammatory joint manifestations are among the many facets of leprosy and should be considered in patients from endemic areas even in the Western world.

**Rheumatology key messages**

- Arthritis in leprosy is common but under-recognized.
- Articular manifestations of leprosy can mimic RA or SpAs.
- Thickened or tender nerves with or without tenosynovitis or characteristic skin lesions, if present, are diagnostic clues of leprosy.

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