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Original Article

Rheumatological Manifestations of Leprosy- An Observational Study in a Tertiary Care Centre in North-Western India

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Leprosy commonly affects the skin and nerves but rheumatological manifestations in leprosy are not uncommon. Usually, the musculoskeletal manifestations of leprosy may remain under-diagnosed, especially when the patients present without any cardinal signs of leprosy. This study aims at evaluating the rheumatological manifestations presenting in biopsy proven cases of leprosy. This observational study was done in Department of Dermatology and Department of Rheumatology in Sawai Man Singh Medical College, Jaipur over a period of 2 years from January 2018 till January 2020. One hundred biopsy proven cases of leprosy were evaluated for rheumatological manifestations. Demographic profile, clinical features and type of leprosy were documented. Out of these 100 patients, 71(71%) were males and 29 (29%) were females. The most common type of leprosy in this study population was borderline tuberculoid leprosy (BT) (25%) followed by borderline lepromatous leprosy (BL) (22%). Type 2 reaction was diagnosed in 21(21%) cases. Arthritis was seen in 62 patients (62%) which was observed to be symmetric polyarthritis most commonly involving the knee, elbow joints and small joints of hands in 37(37%) patients while asymmetric oligoarthritis in 25(25%) patients. Arthritis was acute in onset in 26 patients (26%) while chronic, relapsing, symmetrical, peripheral polyarthritis affecting primarily the wrists, metacarpal and proximal interphalangeal joints of the hands were seen in 36(36%) cases. Arthritis, arthralgia, enthesitis were thus common rheumatological manifestations in leprosy seen in our study which may be the presenting complaint in the patients. Therefore, it is of utmost importance to recognize these manifestations early to prevent any error in diagnosis and treatment.

Keywords : Hansen's Disease, Arthritis, Arthralgia, Enthesitis, Rheumatic Manifestations, India

Introduction

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae*. After widespread use of multi-drug treatment (MDT) 1982 onwards, number of cases has been drastically reduced. Most countries including India had achieved the goal of elimination at public health level by 2005. However, several countries including India, Brazil and Indonesia continue to report occurrence of new cases in significant numbers. In 2021, 135 WHO Member States shared information on leprosy, accounting for a registered prevalence of 133 781 cases and 140 546 new cases (WHO 2022).

The morbidity in leprosy is low because a large portion of the population is naturally resistant to this disease (Lastoria & Abreu 2014).

The disease mainly affects the skin, peripheral

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nerves, mucosa of the upper respiratory tract and the eyes. Cutaneous and neurological manifestations are common and are the classical presentations of leprosy. Musculoskeletal involvement is the third most common manifestation but is less frequently reported (Alam & Emadi 2014, Albert et al 1980).

At times, leprosy cases may present with musculoskeletal manifestations directly to a rheumatology clinic where these cases are often misdiagnosed as various/ inflammatory rheumatological disorders. Since musculoskeletal symptoms may be the presenting manifestation of leprosy, it is important to recognize them for early diagnosis and treatment. Alternatively, the rheumatological manifestations may occur later in the course of the disease with varied presentations particularly in leprosy reactions. Various rheumatological manifestations ranging from arthralgia, polyarthritis, spondyloarthropathies, vasculitis has been reported with prevalence rates varying from 1% to 78% in different studies across the world (Atkin et al 1989, Henriques et al 2012, Vengadakrishnan et al 2004).

Actual data from different settings would be useful to clinicians and public health personnel for teaching, training, and management of leprosy cases. This study aims to study the rheumatological manifestations that may be present in leprosy cases which may need to be treated with a muti-disciplinary approach.

Materials and Methods

This cross-sectional observational study was carried out in the in Department of Dermatology and Department of Rheumatology in Sawai Man Singh Medical College, Jaipur over a period of 2 years from January 2018 till January 2020 after Institutional Ethical clearance (4033/MC/EC/2018). Sample size was calculated as 100 as per previous studies for 80% power and 0.05 alpha error.100 patients who presented in the leprosy clinic were included in the study after obtaining informed consent.

All the patients were evaluated thoroughly which included cutaneous examination, sensory examination and peripheral nerves examination for nerve thickening and neuritis by the dermatologist and examination of joints was further done by rheumatologist. Smear examination of ear lobule for acid fast bacilli (AFB) by the Ziehl–Neelson (ZN) staining method was done in all the cases. Morphological index and Bacteriological index were calculated after visualizing the smear. Skin biopsy from the lesions was done in all cases for histopathological confirmation using Hematoxylin and Eosin stain. Clinical diagnosis, classification and management of leprosy was based on commonly used national and international methods and guidelines (Ridley & Jopling 1966, IAL 1982, NLEP 2013, WHO 2012).

All the patients were evaluated for anti-nuclear antibody - ANA (by immunofluorescence assay - IFA), rheumatoid factor, erythrocyte sedimentation rate, C- reactive protein and X-ray of the affected joint.

Besides the treatment of leprosy and lepra reactions, rheumatological manifestations were managed by addition of NSAIDS etc. as and when required.

Statistical Analysis: All the observations were recorded, and statistical analysis was performed with the SPSS, version 21 for Windows statistical software package (SPSS Inc., Chicago, IL, USA.) in the form of absolute numbers, percentages, mean and standard deviation.

Results

In the study, among 100 cases, 71 (71%) were males and 29 (29%) were females and their age ranged between 17 to 70 years. The mean age at presentation was 36 ± 12.2 years, and the mean duration of disease was 18 ± 10.4 months.

The most common leprosy in this study population was borderline tuberculoid leprosy (BT), comprising of 25 patients (25%). Other

types of leprosy observed in decreasing order were Borderline Lepromatous (BL) in 22 (22%) patients, lepromatous leprosy (LL) in 19 (19%) patients, borderline borderline leprosy (BB) in 13 (13%) patients, tuberculoid leprosy (TT) in 10 (10%) patients, indeterminate in 6 (6%) cases, pure neuritic type in 4 cases (4%) and a single case with histoid leprosy (Fig. 1).

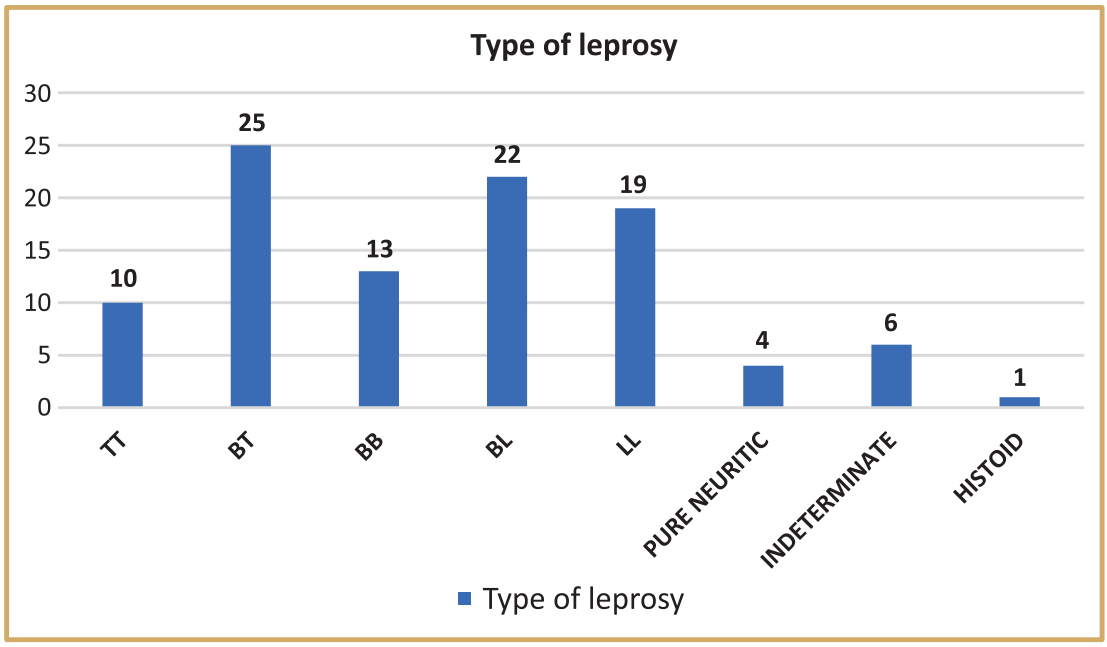

Fig. 1 : Type of leprosy in the study group.
(TT: Tuberculoid leprosy; BT: Borderline tuberculoid leprosy; BB: Mid borderline leprosy; BL: Borderline lepromatous leprosy; LL: Lepromatous leprosy)

Table 1 : Rheumatological manifestations and inflammatory/immunity markers in different types of leprosy cases.

Rheumatological manifestations of Leprosy/inflammatory/immune markers	TT	BT	BB	BL	LL
Arthralgia	2	21	12	21	19
Arthritis	2	11	10	20	19
Enthesitis	0	0	0	2	2
SHFS	0	1	0	3	2
Elevated C-reactive proteins (CRP)	1	15	10	20	19
Elevated ESR	7	23	12	17	18
Rheumatoid factor	1	7	7	8	9
Anti-nuclear antibodies -ANA	1	2	0	1	1

Most of the patients presented with a plaque with or without sensory loss (n= 48) followed by macule on the body in 20 cases. Patients also presented with combined plaques and nodules, nodules with ulcers and isolated sensory loss in pure neuritic leprosy cases. Type 2 reaction i.e. erythema nodosum leprosum (ENL) was seen in 21 cases out of which 2 cases presented with de novo ENL. Nine patients presented with deformity with most of them having claw hand deformity (n=8) and resorption of fingers was seen in 1 patient (Fig. 2).

Musculoskeletal manifestations were as follows: arthritis was seen in 62 patients (62%) which was observed to be symmetric polyarthritis most commonly involving the knee, elbow joints and small joints of hands in 37(37%) patients while asymmetric oligoarthritis in the rest of the cases (25%). Arthritis was acute in onset in 26 patients (26%) while chronic, relapsing, symmetrical, peripheral polyarthritis affecting primarily the wrists, metacarpal and proximal interphalangeal joints of the hands were seen in 36 cases (36%). These manifestations were seen mostin lepromatous leprosy cases followed by borderline lepromatous cases. Enthesitis was seen in 4 patients (4%) while swollen hand and foot syndrome was seen in 6 cases (6%) (Fig. 3, Table 1)

C-Reactive protein was elevated in 68 patients of leprosy (68%) while rheumatoid factor was positive in 32 cases (32%) of which 18 had

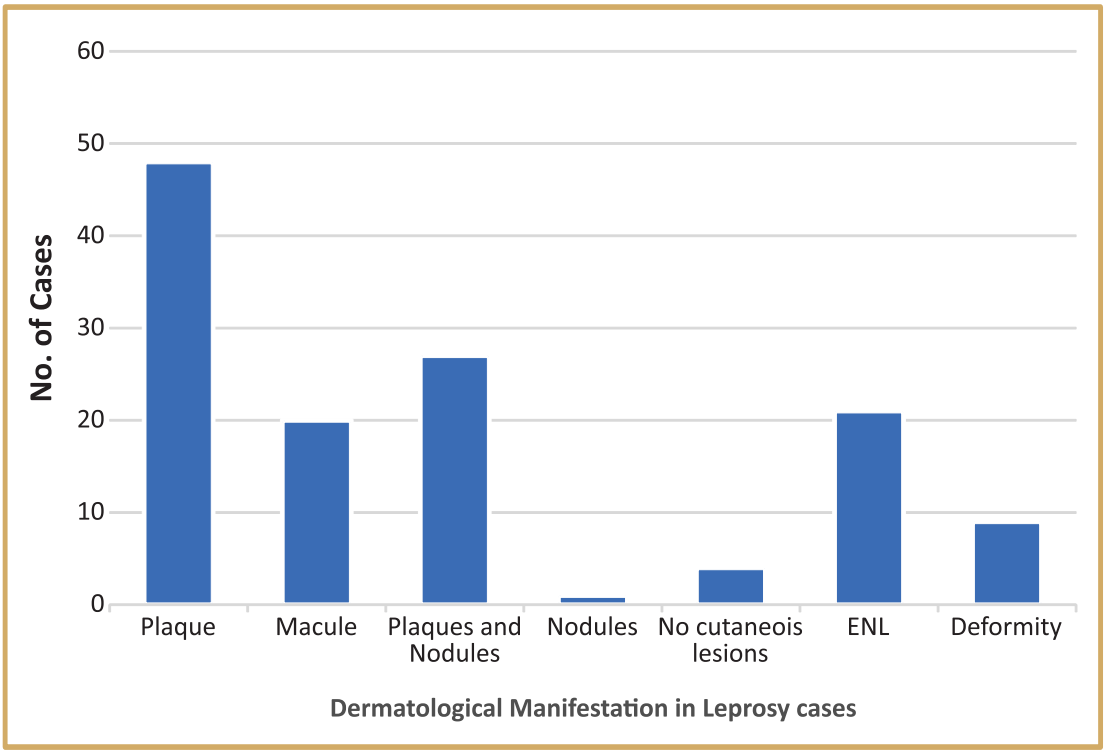

Fig. 2 : Dermatological manifestations and deformities seen in leprosy cases included in the study.

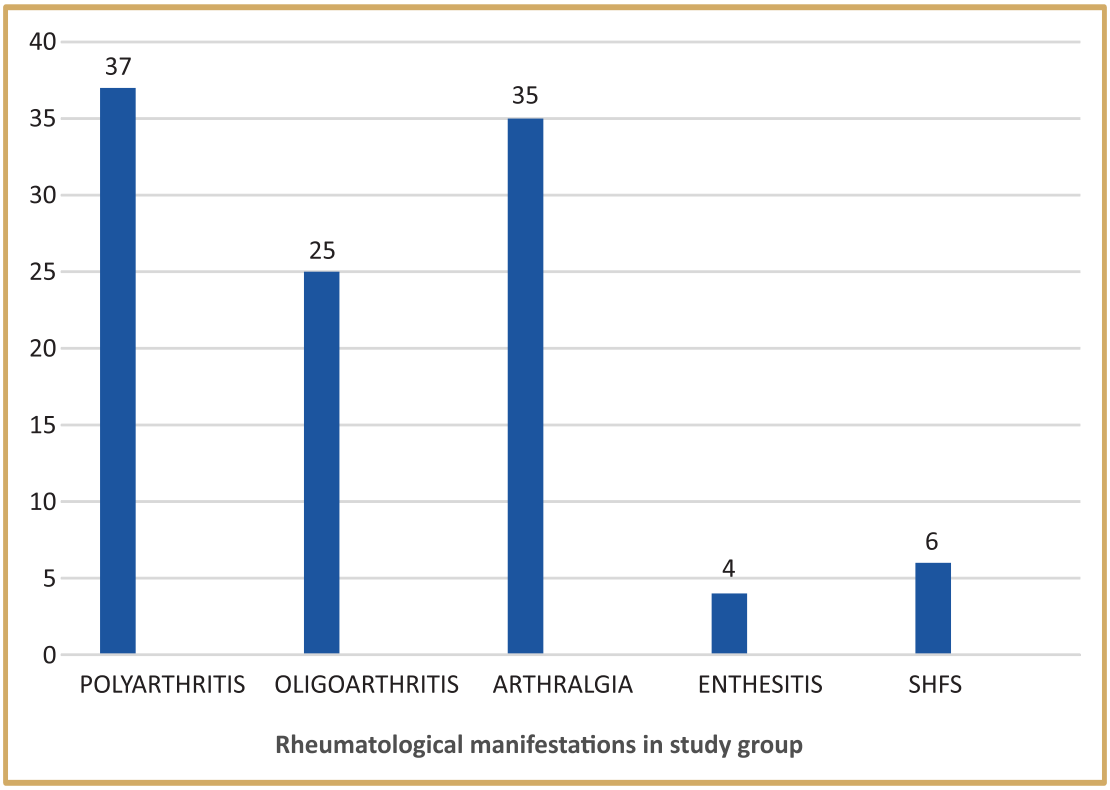

Fig. 3 : Rheumatological manifestations in the study group.
(SHFS = Swollen Hand Feet Syndrome)

Table 2 : Acute phase reactants in leprosy patients with and without rheumatic manifestations.

Serological Markers	With Rheumatic Manifestations (Total Number – 121)	Without Rheumatic Manifestations (Total Number – 69)
Elevated- Reactive Protein	44	24
Positive Rheumatoid Factor	18	14
Elevated Erythrocyte Sedimentation Rate	56	27
Positive Antinuclear Antibody	3	4

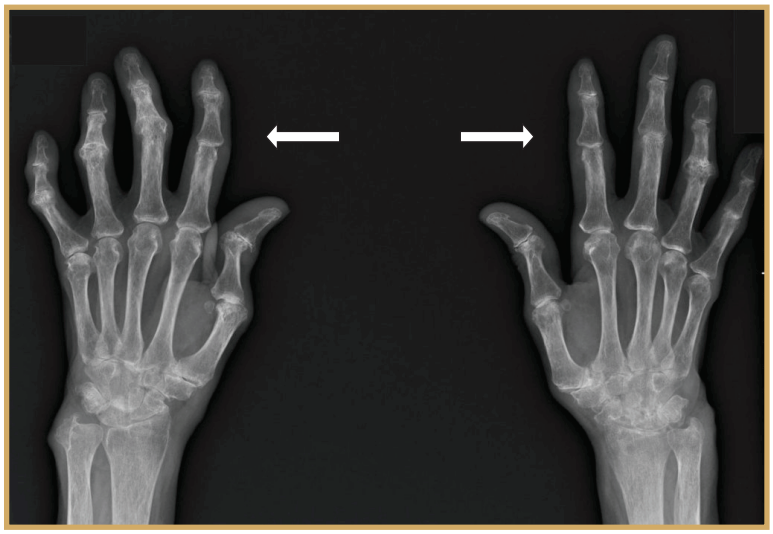

Fig. 4 : X-ray image shows juxta articular osteopenia in small joints of the hands.

arthritis while 14 were without arthritis. ESR was raised in 83 patients (83%) while positive ANA was seen in 7 patients (7%) (Tables 1 and 2)

X-ray of the affected joints in arthritis included soft tissue swellings and juxta-articular osteopenia, erosions and joint space narrowing (Fig. 4).

Discussion

As per the eighth meeting of the WHO (2012), a case of leprosy is defined as an individual who has not completed the course of treatment and has one or more of the three cardinal signs: 1. Hypopigmented or erythematous skin lesion(s) with definite loss/impairment of sensation, 2. Involvement of the peripheral nerves, as demonstrated by definite thickening with sensory impairment, 3. Skin smear positive for acid-fast bacilli (AFB). Any one of these signs has been regarded as sufficient for the diagnosis of leprosy in majority of the cases (WHO 2012). While hypoanesthetic/anesthetic, hypopigmented anhidrotic skin lesions are the classical dermatological manifestations of leprosy, patients presenting with predominant rheumatological features in the absence of classic dermatological manifestations are difficult to diagnose. Rheumatological manifestations may be part lepra reactions of leprosy (Ramu & Ramnujam 1964), these may involve skin, articular and soft tissues (Prasad et al 2013). The joint involvement in leprosy with an incidence of up to about 75% has been recorded in some of the leprosy clinics (Alcocer et al 1979, Mandal et al 2008, Vengadakrishnan et al 2004). In the present study, arthritis was observed in 62% of the patients which was observed to be symmetrical polyarthritis in 37% cases while asymmetric oligoarthritis in rest of the cases. Atkin et al. in their study reported arthritis in 50% of their patients. They also described the chronic symmetric polyarthritis identical to Rheumatoid Arthritis (Atkin et al 1987). There has been no formal classification of arthritis in leprosy. However, three types of joint involvement have been noted: (1) A chronic insidious onset arthritis, (2) an acute arthritis seen during type 2 lepra reactions, and (3) neuropathic or Charcot's

arthropathy. The reactionary episodes probably contribute maximum towards occurrence of arthritis (Periera et al 2009). The insidious arthritis occurs without any reactionary episode and tends to involve multiple peripheral joints, especially the small joints of hands and feet in a symmetrical manner. The other joints including knees and elbows can be involved (Cossermelli-Messina et al 1998). Histopathologically the synovium shows nonspecific granuloma, epithelioid cells and sometimes *M. leprae.* About 1–5 % of leprosy patients are reported to develop arthritis of the small joints of the hands and feet akin to that seen in rheumatoid arthritis (Malaviya et al 1985, Schneider et al 1985). The polyarticular symmetrical small joint pattern of involvement in leprosy can easily be confused with that of rheumatoid arthritis (Mandal et al 2008). The juxta-articular erosions seen in rheumatoid arthritis at times can be seen in leprosy radiologically (Chauhan et al 2010).

In our study, rheumatoid factor was positive in 32 cases (32%) of which 18 had arthritis while 14 were without arthritis. Immunological markers like rheumatoid factor and antinuclear antibodies (ANA) are commonly positive in lepromatous leprosy which further complicate the diagnosis. Detection of the anticyclic citrullinated peptide (anti-CCP) antibodies in the blood is helpful in being specific for rheumatoid arthritis (Riberio et al 2008). Leprosy arthritis coexisting with RA was reported in 21% patients by Salvi & Chopra (2013), while RA developing after resolution of leprosy arthritis was seen in 10% patients in the study by Wakhlu et al (2018).

Type II reaction, also called ENL, is an immune complex disease and is seen in the BL and LL types. It presents as painful red nodules which may ulcerate, along with fever, malaise, and joint and neuritic pains and eye and other organ involvement including lymphadenopathy and orchitis. Arthritis is a well-known classical association of lepra reactions, especially Type II, with the incidence being more than 57% (Vengadakrishnan et al 2004). In one-third of the cases, patients with type 2 reactions may have a rheumatic onset and present with pain and swelling in the joints that precede the dermatological manifestations. There are case reports of type 2 reactions with manifestations mimicking systemic lupus erythematosus (SLE), polyarteritis nodosa, and Behcet's syndrome (Danda & Cherian 2001). Charcot's joints, also known as neuropathic arthropathy, develops insidiously without any obvious symptoms and is related to impaired sensations of joints and the surrounding tissues. It 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. Despite the availability of effective anti-leprosy treatment, leprosy continues to be one of the major aetiological causes of neuropathic joints in the developing world. Earlier, close to 10% of leprosy patients had Charcot's arthropathy as a result of long-standing peripheral neuropathy (Messner 1979), however, exact incidence remains to be elucidated specially in the context of current clinical profile of leprosy. Reviewing previous literature, it was reported that musculoskeletal symptoms were the initial manifestation of leprosy (Pereira et al 2009, Vengadakrishnan et al 2004). Rheumatological manifestations can occur separately or in conglomeration of various reactions. Enthesitis, elicited by tenderness on palpation of attachment sites of tendons to bone, ligament or joint capsule has been reported in relation to leprosy (Atkin et al 1990, Carpintero-Benitez et al 1996). Patients of leprosy have a number of autoantibodies which may cause diagnostic difficulties. These include CRP, RF, ANA, anti-neutrophil cytoplasmic antibodies (ANCA), and even anti- phospholipid antibodies, double stranded deoxyribonucleic acid (ds-DNA), and anti-CCP (Garcia 1993, Miller & Werner

1988). Serological markers like rheumatoid factor, ANA, ESR, and CRP has been reported in association with various forms of leprosy while the incidence of anti-CCP is reported to be lower (Chopra 2014).

The possible mechanism of rheumatological manifestations in leprosy are due to inflammatory involvement of musculoskeletal system due to different degree of reactions, trophic changes followed by infections, restricted movement leading to muscle disuse atrophy, muscle infiltration by lepra bacilli leading to weakness, dactylitis due to reactions, Mycobacterium (*M. leprae*) specific osteomyelitis. It has been hypothesized that slow growing mycobacteria may induce chronic arthritis by various immunological mechanisms. In genetically susceptible individuals, infection with *M. leprae* activates T lymphocytes which leads to production of various lymphokines. These lymphokines further activate B cells to produce agalactosyl immunoglobulins, which perpetuate chronic inflammation and synovitis (Rook & Stanford 1992). The role of mycobacterial heat shock protein, especially the 65kD heat shock protein is being researched in the pathogenesis of RA as it is an important target for arthritogenic T cells (Cossermelli-Messina & Cossermelli 1997).

While the present study provides valuable data pertaining to clinical presentation of rheumatological manifestations and relevant biomarkers in various types of leprosy cases, it would be important to study the usefulness of different types of management protocols using anti-leprosy regimens and currently available drugs.

Conclusions

This study shows that rheumatic manifestations continue to be a common occurrence in leprosy in cases being treated at tertiary care centre settings. Early recognition of leprosy in these patients especially when reporting to rheumatology/ doctors other than leprologists/ dermatologists, will lead to start of early treatment which will further reduce the deformities and complications in leprosy.

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