

Original Article

Leprosy mimicking connective tissue disease - a challenge for rheumatologists

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Abstract: Objectives: To improve clinician awareness of the symptoms and diagnosis of leprosy to prevent misdiagnosis and improper treatment. Methods: We analyzed three leprosy cases misdiagnosed as connective tissue diseases and reviewed the relevant literature. Results: The three patients were misdiagnosed as having rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis and rheumatoid arthritis overlap syndrome. Skin biopsy at our hospital confirmed the true diagnosis: leprosy. The clinical differences between leprosy and connective tissue disease are summarized. Conclusions: Leprosy can have varied and complex presentations that mimic connective tissue disease. Leprosy awareness should be increased to avoid delayed diagnosis and treatment.

Keywords: Connective tissue diseases, leprosy, delayed diagnosis

Introduction

Leprosy is a chronic infectious disease caused by the bacillus *Mycobacterium leprae*. It is globally distributed; however, it is especially prevalent in developing countries in Asia, Africa, and Central/South America, while it is quite rare in developed countries [1]. The overall prevalence of leprosy in China is low, due to the active implementation of prevention and control programs. However, over a thousand new leprosy cases are detected annually in China, and the case detection rate was 0.120/100,000 in 2009 [2]. In some areas such as Yunnan, the annual detection rate was 0.856/100,000. The number of new cases detected in 2011 in India, Brazil, and Indonesia were as high as 127,295, 33,955, and 20,033, respectively [1], indicating leprosy is still a serious threat especially in developing countries.

Leprosy mainly affects the skin and peripheral nerves, but it also spreads to the bones and visceral organs with abnormal immune markers resulting in complicated and varied clinical manifestations. Leprosy is commonly misdiagnosed as connective tissue disease, thus affecting the prognosis and causing further dis-

ease spread. It is a challenge for rheumatologists to differentiate leprosy from connective tissue disease. In this study, we retrospectively analyzed three cases of leprosy mimicking connective tissue disease. We also reviewed the relevant literature and summarized the clinical differences between the two diseases. This study aimed to improve clinician awareness of the symptoms and diagnosis of leprosy to prevent misdiagnosis and improper treatment.

Cases presentation

Three patients with leprosy misdiagnosed as connective tissue diseases were admitted to the first affiliated hospital of Shantou University Medical College between June 2012 and April 2014. Their data were analyzed retrospectively, and the relevant literature was reviewed. All patients gave informed consent prior to their inclusion in the study.

Case 1

A 22-year-old woman developed facial erythema, eye redness, and blurred vision 15 years previously. She was examined by an ophthalmologist for her eye symptoms and was diag-

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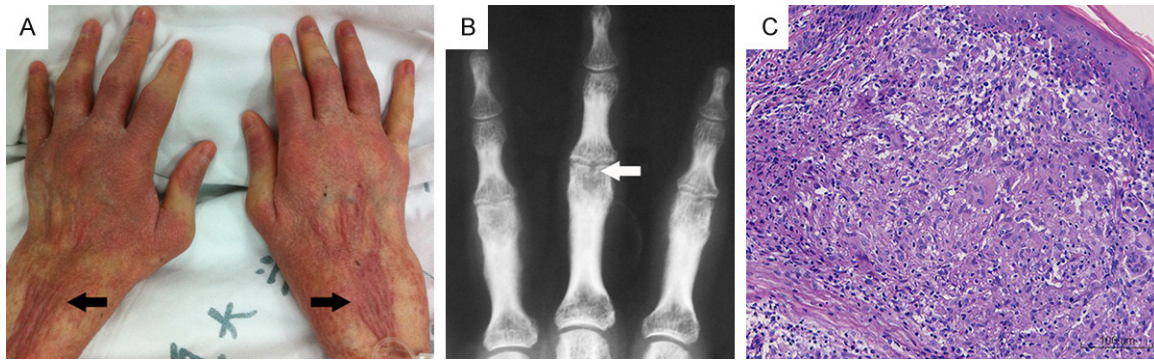


Figure 1. Clinical and pathological manifestations of Patient 1. A. Enlarged peripheral nerves (black arrows) at the extensor surface of the wrists, and swelling and tenderness of the wrists, MCP, and PIP joints. B. Radiographic examination revealed subchondral erosions on the center of the phalanges of the left hand (white arrow). C. Skin biopsy of the skin lesions on the right forearm revealed tuberculoid granuloma without caseous necrosis in the superficial dermis (HE stain).

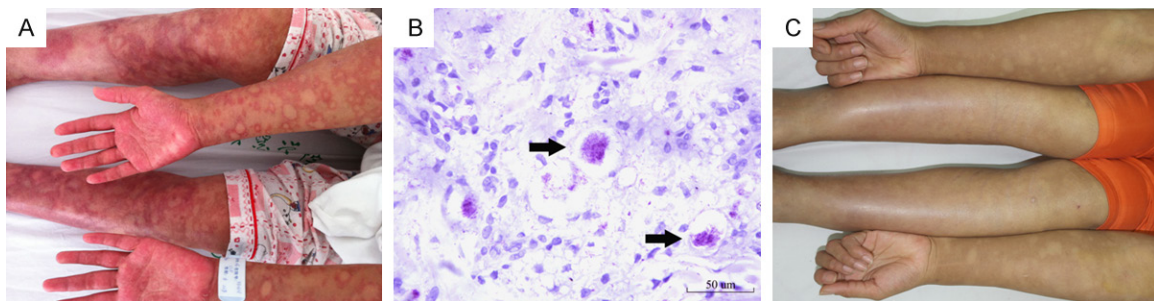


Figure 2. Clinical and pathological manifestations of Patient 2. A. Dense, nonuniform erythema on the limbs, some of which was annular. B. An acid-fast stain of the skin biopsy indicating the presence of intracellular acid-fast bacilli of *M. leprae* (black arrow). C. Erythema on the limbs was relieved and had slight pigmentation after one-year of effective treatment.

nosed with glaucoma. She received surgical treatment but lost her vision 2 years later. Symmetrical polyarthritides involving the metacarpophalangeal (MCP) joints, proximal interphalangeal (PIP) joints, wrists, elbows, knees, ankles, and metatarsophalangeal (MTP) joints began 11 years previously. Diffuse systemic erythema developed approximately 1 year previously, and the patient was diagnosed with rheumatoid arthritis (RA) and dermatitis exfoliativa at another hospital. She was treated with prednisone and methotrexate (MTX), but the outcome was poor. Her mother also had a history of arthritis.

Physical examination revealed facial flushing, diffuse erythema with brown granular papules on the trunk and upper limbs, ichthyosiform skin lesions on her lower limbs with skin hypoesthesia, enlarged peripheral nerves on the extensor surface of her wrists, and swelling and

tenderness of the wrists, MCP, and PIP joints with limited wrist movement (**Figure 1A**). Laboratory tests revealed a low white blood cell count ($3.29 \times 10^9/L$, normal value ranges $4.0-10.0 \times 10^9/L$), but the patient's immunoglobulins, complement components C3 and C4, rheumatoid factor (RF), anti-cyclic citrullinated peptide antibody (anti-CCP), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antinuclear antibody (ANA), anti-extractable nuclear antigen (anti-ENAs), anti-double stranded DNA (anti-dsDNA), and anti-cardiolipin antibody (aCL) were normal. Radiographic examination revealed subchondral erosions on the center of the PIP joint of the left hand and soft tissue swelling of the wrists, MCP, and PIP joints (**Figure 1B**), but her feet were normal. Magnetic resonance imaging of the patient's wrists revealed tenosynovitis and bony erosions at the distal ends of the ulna. Skin biopsy of lesions on the right forearm and right leg

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Figure 3. Clinical and pathological manifestations of Patient 3. A. Eye-brow loss (white arrow) and scattered dark red papules on the face. B. Thickened and hardened skin with erythema on the lower limbs. C. Acid-fast stain of the skin biopsy showing numerous acid-fast bacilli of *M. leprae* (black arrow). D. Papules on the face disappeared after therapy. E. Erythematous, edematous skin on the lower limbs was relieved after therapy.

revealed tuberculoid granuloma without caseous necrosis in the superficial dermis. The granuloma primarily contained epithelial and Langhans giant cells with a peripheral lymphocyte infiltration. Staining for acid-fast bacilli (AFB) was negative (**Figure 1C**). These findings supported the diagnosis of tuberculoid leprosy.

Case 2

A 22-year-old woman presented with an 8-year-old rash and a fever of 2 weeks' duration. She developed facial erythema 8 years previously, followed by annular erythema on her trunk and limbs with numbness and anhidrosis. She had been diagnosed as having systemic lupus erythematosus (SLE) with anti-nuclear antibody (ANA) and anti-dsDNA positive 6 years previously. She was treated with prednisone and MTX; however, the rash did not improve. Over the previous 2 weeks, the rash had become aggravated, and a fever developed. She did not have photosensitivity, alopecia, recurrent oral ulcers, Raynaud's phenomenon, or arthritis.

Upon physical examination, the patient had bilateral facial erythema, dense, nonuniform erythema on her trunk and limbs, some of which was annular (**Figure 2A**), and skin hypoesthesia on her extremities. Laboratory testing revealed a positive ANA (1:320), as well as elevated ESR (28 mm/h, normal value ranges 0-20 mm/h) and CRP (31.40 mg/L, normal value ranges 0-8 mg/L). The patient's stools, liver, and renal functions were normal, as were her complement levels and immunoglobulins. She was negative for anti-dsDNA, anti-ENAs, aCL, and antineutrophil cell cytoplasmic antibody (ANCA). A skin biopsy of the thigh revealed a foam cell infiltration surrounding the dermal appendages and nerves, and AFB staining was positive (++) indicating the presence of intracellular acid-fast bacilli (**Figure 2B**). These findings were consistent with lepromatous leprosy.

Case 3

A 41-year-old woman had suffered with a rash for 5 years and arthritis for 2 years. Five years

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ago, she developed nonpainful, nonpruritic erythema all over her body, with skin thickening and hardening on her limbs. Bilateral leg pain and ankle swelling and pain had developed 2 years previously. Bilateral skin sensory loss on the lower extremities had developed 1 year previously. Raynaud's phenomenon was observed. She tested positive for RF at another hospital, was diagnosed with systemic sclerosis (SSc) and RA overlap syndrome, and was treated with low-dose prednisone and tripterygium. However, she did not respond to treatment.

Physical examination revealed eyebrow loss; scattered dark red papules on her face (**Figure 3A**); thickened, hardened skin on her limbs; erythematous, edematous skin with hypoesthesia on her lower extremities (**Figure 3B**); and swelling and tenderness of her ankles. Laboratory testing revealed elevated CRP (12.50 mg/L), ESR (48 mm/h), RF (60 IU/mL, normal value ranges 0-20 IU/L), and gamma globulin (20.50%, normal value ranges 9.2-18.2%). Stools, urine, cardiac, liver, kidney, and thyroid functions were all normal. The patient tested negative for anti-CCP, ANA, anti-ENAs, anti-centromere antibody (ACA), anti-dsDNA, aCL, and ANCA. The arteriovenous color ultrasounds of both lower limbs were normal. Skin biopsies of the thigh revealed lepromatous leprosy. AFB staining was positive (+++) (**Figure 3C**).

After their leprosy diagnoses were confirmed, these three patients were transferred to the local leprosy center for treatment. One month later, the mother of Patient 1 was also diagnosed with leprosy and received treatment at the local leprosy center. After one-year of effective treatment, the skin lesions of Patients 2 and Patient 3 were relieved (**Figures 2C, 3D and 3E**), and bacterial detecting on acid-fast-stained smears made from skin slits were negative. Patient 1, who lived in another city, reported via telephone follow-up that the rash and arthritis were improved.

Review and discussion

The diagnosis of leprosy is often delayed in developed countries and non-endemic regions. The occurrence rate of delayed leprosy diagnosis is reported to be 66% in China and as high as 82% in Britain [3, 4]. The three cases discussed in the present manuscript were easily misdiagnosed as connective tissue disease

because of the appearance of a rash and/or arthritis and the presence of autoantibodies.

Articular involvement in leprosy is the third most frequent manifestation, after dermatological and neurological involvement. The wrists, PIP joints, MCP joints, elbows, ankles, and knees can be affected [5-13]. Radiological abnormalities in patients with arthritis due to leprosy can include soft tissue swelling surrounding the joints, osteoporosis, joint space narrowing, and complete destruction that resembles RA [6, 9, 10, 12].

Arthritis due to leprosy can be divided into four types: Charcot joint, septic arthritis, acute polyarthritis of lepra reaction (APLR), and chronic arthritis [5]. Charcot joint, also known as neuropathic arthropathy, is characterized by an insidious onset, joint dislocations, and debilitating deformities, but not bony erosion. Charcot joint usually involves the weight-bearing joints of the lower limbs, such as the knees and ankles; however, hand joints, such as the wrist might also be affected [11]. APLR is acute in onset and affects the small joints of the hands and feet, with the arthritis settling down within a few weeks [5]. Chronic arthritis manifests as symmetrical polyarthritis clinically identical to RA [5, 12]. The pathology might be related to the cross-reactive immune responses caused by leprosy bacilli infection and mediated by T cells [9, 14]. Bony erosion can be seen in the styloid process of the ulna and is only present in lepromatous leprosy [9]. Tenosynovitis accompanied by enlarged superficial nerves also suggests possible leprosy-related infection [5, 15].

Leprosy patients may also be RF and anti-CCP positive. However, the occurrence rate of RF positivity among leprosy patients is only 2.6-21% [8, 12], which is lower than that of RA patients (62.3-90%) [8, 16]. The occurrence rate of anti-CCP positivity among leprosy patients is only 2.6-3.1% [8, 17], which is lower than that of RA patients (64.4-81.2%) [8, 18]. Anti-CCP antibody appears to be unrelated to articular involvement of leprosy or RF, as reported by Ribeiro et al, who tested 76 leprosy patients with articular involvement and found none were anti-CCP positive [8].

Patient 1 in the present study had symmetrical polyarthritis accompanied by tenosynovitis,

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Table 1. Comparison of clinical features between arthritis in leprosy and rheumatoid arthritis

	Onset	Symmetrical polyarthritis	Joints involved	Bony erosion	Rash	Peripheral nerve damage	RF positive	Anti-CCP positive
Arthritis in leprosy	Insidious (Lepa reaction is acute)	Yes (except for Charcot joint)	Wrist, MCP joint, PIP joint, ankle, knee, MTP joint	Rare (styloid process of the ulna, center of PIP joint)	Common	Common, early stages	2.6-21%	Rare
RA	Slow	Yes	Wrist, MCP joint, PIP joint, ankle, knee, MTP joint, shoulder, elbow, cervical vertebra	Common (Wrist, edge of MCP and PIP joint, knee, MTP joint, elbow)	Rare	Uncommon, late stages	62.3-90%	64.4-81.2%

RA, Rheumatoid arthritis; RF, Rheumatoid factor; anti-CCP, Anti-cyclic citrullinated peptide antibody; PIP, Proximal interphalangeal; MCP, Metacarpophalangeal; MTP, Metatarsophalangeal.

Table 2. Comparison of clinical features between leprosy and systemic lupus erythematosus

	Sex	Loss of eyebrows	Alopecia	Skin hypoesthesia and anhidrosis	Enlargement of peripheral nerves	Skin pathological examination
Leprosy	Common in men	Yes (lepromatous leprosy)	Rare	Yes, early stages	Yes	Tuberculoid granuloma without caseous necrosis or acid-fast bacilli of <i>M.leprae</i> can be found
SLE	Common in women	Rare	Yes	Uncommon	Rare	Lupus band test (+)

SLE, Systemic lupus erythematosus.

and hand radiographs revealed both osteoporosis and bone erosions resembling RA. However, the presentation differed from that in RA in that RF and anti-CCP were negative, the superficial nerves were enlarged, and subchondral erosion was observed in the center of the PIP joint (**Figure 1B**). This also indicates that joint erosions can occur in tuberculoïd leprosy, in contrast with a previous report stating that joint erosion only occurs in lepromatous leprosy [9]. Comparisons between arthritis in leprosy and RA are listed in **Table 1**.

Skin lesions related to leprosy can have varied and complex manifestations including macules, papules, nodules, psoriasis-like lesions, annular erythema, and pigmentation. Autoantibodies can be detected in some cases, which may result in the condition being easily mistaken for SLE [19, 20]. It has been reported that leprosy patients can be RF positive, in addition to developing other autoantibodies, including ANA, anti-SSA, anti-SSB, anti-dsDNA, anti-ssDNA, aCL, anti-beta 2 glycoprotein 1, and ANCA [13, 19-25]. The presence of autoantibodies in leprosy sera might be associated with the release of autoantigens due to tissue injury or the molecular mimicry of the pathogens that induce cross-reactivity [21]. However, the following can help to differentiate leprosy from SLE: leprosy is more common in men, it often causes loss of eyebrows instead of alopecia, and its associated peripheral nerve damage primarily occurs during the early stages of the disease. Reportedly, 55% of leprosy patients present with some degree of peripheral nerve damage at diagnosis [26], whereas only 3.9% of SLE patients present with such lesions [27]. A skin biopsy is useful in cases for which definitive diagnosis is difficult. AFB staining might reveal the presence of acid-fast bacilli, while a positive lupus band test indicates SLE. Clinical comparisons between leprosy and SLE are listed in **Table 2**.

Leprosy was reportedly misdiagnosed as SSc in Patient 3. Both leprosy and SSc cause swollen hands and feet, thickened and hardened skin, hyperpigmentation, and Raynaud's phenomenon [28]. However, SSc might present with specific features, such as a mask-like face, restricted mouth opening, telangiectasia, and calcinosis. SSc patients also have specific autoantibodies, such as anti-Scl70 and ACA, with the distinguishing pathological hallmark

of obliterative vasculopathy of small arteries and arterioles combined with vascular and interstitial fibrosis in the target organs.

The three patients discussed in this manuscript were misdiagnosed for 5-15 years. Possible reasons for this include: 1) leprosy has complex and varied clinical manifestations, including skin lesions as well as joint and nerve involvement and abnormal immune markers; therefore, it is easily mistaken for connective tissue disease; 2) leprosy is rare in nonendemic regions and has a long incubation period; and 3) the clinicians were not flexible in applying disease classification criteria and used only limited and simplified clinical thinking. Therefore, to avoid delayed leprosy diagnosis and treatment, it is extremely important to improve clinician awareness and strengthen public education regarding leprosy.

Conclusions

Leprosy can present with varied and complicated skin lesions as well as arthritis and positive autoantibodies. A detailed disease history and comprehensive examination is required for patients with a rash or arthritis of unknown origin. Specifically, superficial nerve and skin sensory examinations should be conducted. For those positive for autoantibodies, the differential diagnosis should include diseases besides connective tissue diseases. Skin biopsy and leprosy bacilli tests are necessary for highly suspicious patients.

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Disclosure of conflict of interest

None.

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