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Clinical and pathological features of different types of leprosy

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Abstract. – OBJECTIVE: This study aimed to investigate the clinical and pathological features of leprosy bacillus-related neuropathy in different clinical stages.

PATIENTS AND METHODS: Four patients confirmed to have leprosy between 2012 and 2020 were chosen as the primary study subjects. The patients' clinical data were retrospectively analyzed to investigate the clinical and pathological features of the different clinical types of leprosy.

RESULTS: Each patient had a different degree of deformity. For instance, in Case 1, upon dermatological examination, the eyebrows were not falling off, and the face was slightly invaded. The great auricular nerve was thickened, and there were plaques on the back of the right hand with ill-defined edges but no itching. No atrophy in the thenar or hypothenar was observed, though pain and a warm sensation were noted. The swelling of the right leg was accompanied by sensory abnormalities. Moreover, the bilateral ulnar nerves were swollen, and demyelination changes were observed upon nerve biopsy. A small number of granulomas were noted in the nerve interstitium, and the acid-fast staining was positive. Additionally, in Case 2, on dermatological examination, scars were observed on the front of the tibia, and large, reddish, symmetrically distributed patches were seen on the back. Satellite foci were visible as well. Contracture was observed in the little finger, and the ulnar nerve was damaged. Skin and nerve biopsy revealed leprosy bacillus via acid-fast staining.

CONCLUSIONS: Early detection and treatment are important methods of preventing and reducing damage to peripheral nerve function in patients with leprosy.

Key Words:
Leprosy, Clinical characteristics, Pathological characteristics, Leprosy bacillus, Neuropathy.

Introduction

Leprosy is an ancient disease with a 5,000-year history. It is a chronic infectious granulomatous illness caused by leprosy bacillus, which mainly invades the skin and peripheral nerves. Early detection, diagnosis, and treatment can prevent damage and physical disability. After the worldwide implementation of treatment interventions with rifampicin, dapsone, and clofazimine (multi-drug therapy [MDT]) began in 1950, the disease's annual worldwide incidence decreased from about one million per year at the beginning of the twentieth century to about 200,000 per year in the twenty-first century. The number of cases has since remained relatively stable. When China began introducing MDT in 1983, the annual incidence of the disease in the country decreased from around 1,000 cases that year to 695 cases in 2019, down from around 100,000 per year in the 1950s[1]. Patients from all parts of the country have since gathered in the non-leprosy epidemic area of Beijing, at Neurology of Beijing Tiantan Hospital of Capital Medical University, and Beijing Institute of Tropical Medicine of Beijing Friendship Hospital of Capital Medical University[2-5]. In this study, the four patients diagnosed with leprosy from 2012 to 2020 were nonlocal patients with peripheral neuropathy as their initial symptom. Herein, their cases are reported and analyzed.

Patients and Methods

Studied Patients

The subjects of the present study were patients confirmed to have leprosy in our hospital

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from 2012 to 2020. The patients' clinical data were collected, and the clinical and pathological characteristics of their leprosy bacillus-related neuropathy were analyzed in different clinical stages. This study was conducted in accordance with the Declaration of Helsinki of the World Medical Association and was approved by the Ethics Committee of Beijing Tiantan Hospital of Capital Medical University. All patients signed an informed consent form.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) the patients had leprosy confirmed by slit-skin smear and skin pathological diagnosis according to the Redly-Joplin pathotype classification; (2) the patients were older than 18 years; and (3) the patients signed an informed consent form.

Main Observation Indexes

This study mainly observed and analyzed the general epidemiological data of the patients, including their sex, age, place of birth, course of disease, past medical history, clinical symptoms, auxiliary examination results, neurological function test results, pathological results, and clinical prognosis.

Statistical Analysis

The data processing was conducted with the SPSS 20.0 statistical software (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Armonk, NY, USA). The measurement data were expressed as the mean ± standard deviation (x ± s). The enumeration data were expressed as a percentage (%). A W-test was adopted as the normality test, and an F-test was adopted as the homogeneity test of variance. A *t*-test was used to compare the groups, and a non-parametric test was used to compare the groups with a normal noncompliance distribution. A chi-square test was applied to the enumeration data. A p-value <0.05 was considered statistically significant.

Results

Case 1

This patient was a 40-year-old man born in Bijie, Guizhou. He was admitted to the hospital due to "hypohidrosis of [the] limbs for one year and [a] half, numbness, and pain of [the] limbs for one year" in May 2012. The patient suffered a traumatic rupture of the spleen 18 years prior that improved following surgical treatment. A diagnosis of cervical spondylosis was made in another hospital over the course of one month. The patient denied having a history of hypertension and diabetes. He had an eight-year drinking history of 250 ml per day but had abstained from alcohol for six months prior to visiting the hospital. Pachylosis had been discovered in the right forearm 18 months prior. No numbness and pain were noted in the right hand, except the thenar. One year before, the right medial forearm had gradually become numb, though no sweating was reported. The numbness had developed from the last three fingers to all fingers in the space of one month. Simultaneously, it was found that the lateral skin of the right lower extremity was numb, with no sweating. The right limbs had poor cold and heat sensation, and pain occurred when the skin was gently touched. Moreover, a feeling of numbness with pain and hypohidrosis had been noted in the medial side of the left forearm, the posterior part of the left leg, and the back of the left foot 10 months prior. The pain was characterized by a persistent needle-like sensation and showed no evident improvement after treatment. The patient's condition continued to progress. One month prior, a lumbar puncture had been performed in our hospital, but the results showed no obvious abnormalities. However, electromyography indicated peripheral neurogenic injury. The bilateral limbs were asymmetrically numb during hospitalization, more significantly on the right side. Hypohidrosis was discovered in the left knee joint and underneath the elbow joint. Anhidrosis was found in the right knee joint and underneath the elbow joint. However, during the course of the disease there was no limb weakness or muscle atrophy, and urination and defecation were normal. Neurological examination showed the muscle volume and tension to be normal, and the limb muscle strength was Grade 5. The tendon reflexes of all four limbs were slightly active, and the plantar reflex was neutral. Moreover, there were no pathological signs. The bilateral finger-to-nose tests, alternating movement tests, and heel-knee-tibia tests were stable. The gait was normal, and the Romberg test results were negative. The neck was soft, and the meningeal stimulation test results were negative. The pinprick sensation was decreased in the polyneural distribution area. The tuning fork vibration sense was lessened from around 7 cm above the medial wrist of the left forearm to the wrist (left ulnar nerve); from 15 cm above the posterior ankle of the left leg to the ankle (left tibial nerve); from 7 cm below the me-

dial elbow of the right forearm to the wrist (right ulnar nerve); from below the right lateral elbow joint to the wrist (right radial nerve); from 20 cm above the lateral knee of the right lower extremity to the sole (right superficial peroneal nerve); from the medial knee joint to the sole (femoral nerve); below the left elbow and left ankle; below the right elbow; and in the right ankle, though it was significant on the right side (multiple nerves).

The dermatological examination found that the patient's eyebrows were not falling off and that his face was slightly invaded. The great auricular nerve was thickened. There were plaques on the back of the right hand with ill-defined edges, though no itching was noted. Similarly, there were patches on the back of the right hand with unclear boundaries and no itching. No atrophy was seen in the thenar or hypothenar, though pain and a sensation of warmth were noted. The swelling of the right leg was accompanied by sensory abnormalities. The bilateral ulnar nerves were swollen as well.

The laboratory tests yielded the following. Blood TORCH: The EB virus VCA-IgG, cytomegalovirus antibody IgG, and herpes simplex virus type I results were positive, while the remaining test results were negative. CSF TORCH: The cytomegalovirus antibody IgG and herpes simplex virus type I results were positive, and the remaining test results were negative. The blood and cerebrospinal fluid GM1 antibodies and paraneoplastic lesions were generally normal, as were the three major smears. A cerebrospinal fluid culture showed no bacterial growth. The CSF protein electrophoresis was negative. The serum and cerebrospinal fluid myelin basic protein showed a normal toxin screening, and no other toxicants were detected in the serum or urine. The levels of mercury, arsenic, chromium, cadmium, thallium, and lead were within the normal range. Subprotein screening did not detect M components by serum protein electrophoresis or immunofixation electrophoresis. The urine light chain quantification was within the reference range. The acylcarnitine report indicated that the measured amino acid and acylcarnitine levels were normal. The urinary organic acid spectrum report showed that the spectrum was basically normal and did not indicate diseases within the monitoring range. Moreover, the antinuclear antibody, extractable nuclear antigen series, and anti-neutrophil cytoplasmic antibodies were normal. The nerve biopsy staining showed demyelinating changes in the nerves. A small number of granulomas were seen in the interstitial nerve, and the acid-fast staining was positive (Figure 1).

Case 2

This patient was a 50-year-old man born in Hanzhong, Shanxi. He was admitted to the hospital in August 2009 due to "numbness of [the] limbs for more than 13 years, pain of both upper limbs for five months, and weakness of both hands for more than one month." Hypesthesia had gradually started to appear in both forearms and the bilateral knee joints 13 years prior. It showed unconscious when burned or traumatized, which was accompanied by anhidrosis and dryness at the site of hypoesthesia. A burning pain in the fingertips of the left hand had gradually begun to occur five months prior and had expanded upward within 4-5 days, eventually involving the left limb, left shoulder, left neck, and left occipital region. The pain was persistent and reportedly difficult to endure. Both hands had exhibited grip weakness for one month, which manifested as difficulty in picking up a glass, writing, and holding chopsticks, and was particularly significant in the left hand. Around two weeks prior, numbness and a burning pain had appeared in both hips and in the dorsal thigh. Multiple independent blisters had covered the limbs since the fall of 1993. New blisters were colorless and clear before becoming purplish red and yellow and, finally, scabbing over, leaving scars that resembled burn scars.

The neurological examination identified incomplete paralysis/paresis in the right superior rectus and inferior oblique. Interosseous muscle atrophy was discovered in both hands. The split-and-merge finger strength was Grade 4. Light touch and pinprick sensations were reduced below the elbow and knee joints, and the tuning fork vibration sense and joint position awareness were lessened below the right elbow, left shoulder, and both knees. The bilateral finger-to-nose tests, alternating movement tests, and heel-knee-tibia tests exhibited clumsiness. The neck demonstrated absent resistance. However, the Brudzinski's and Kernig's sign tests were negative.

The dermatological examination noted scars on the front of the tibia. A wide range of reddish, symmetrically distributed patches were observed on the back. Satellite foci were visible as well. Small finger contracture and ulnar nerve damage were observed.

The results of the laboratory tests were as follows: cerebrospinal fluid routine: clear; pressure: 135 mmH_2O; cell count: 62/μl; WBC: 8/μl.

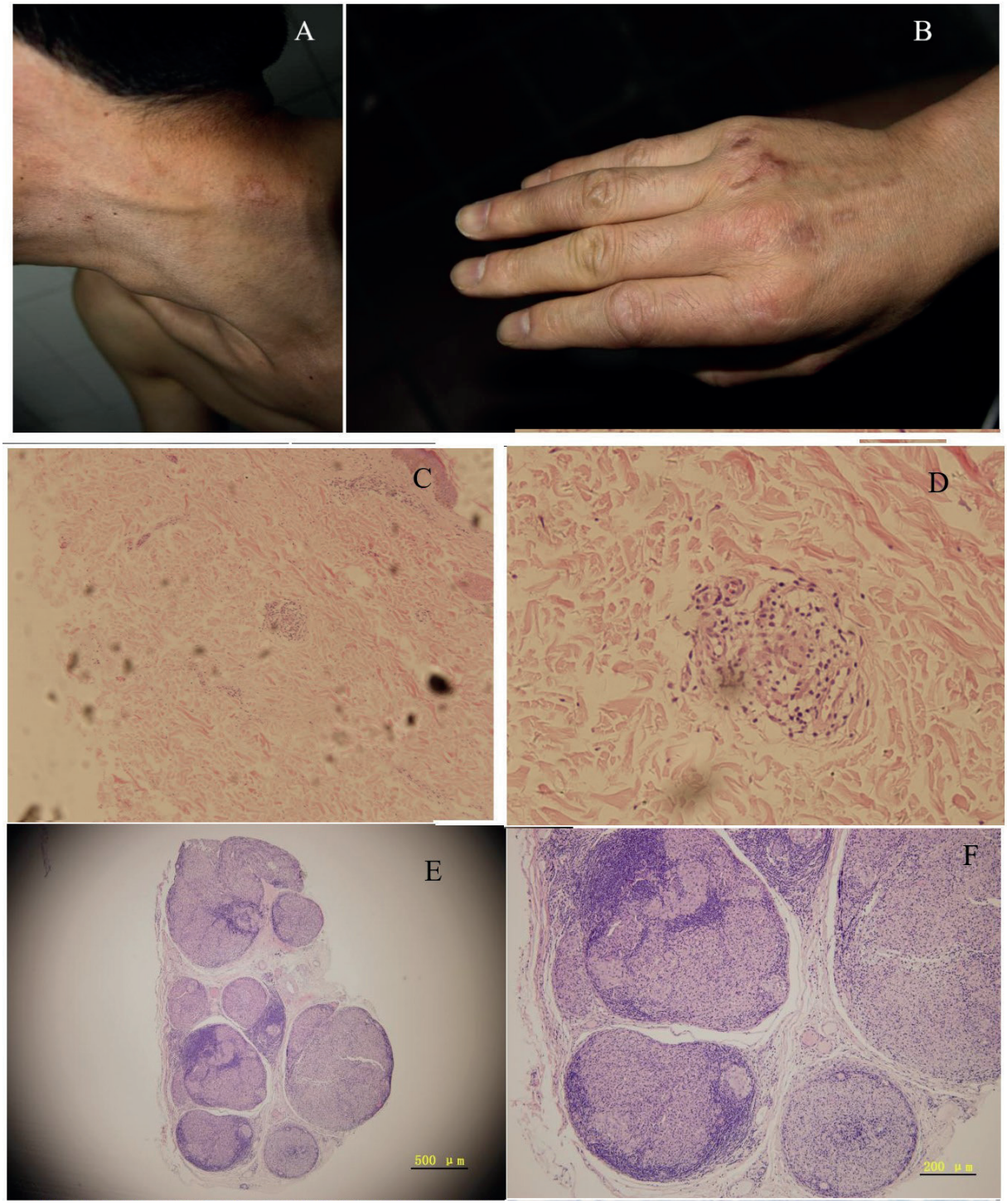

Figure 1. Clinical and pathological features of the skin and nerves in Case 1. **A,** Thickened great auricular nerve. **B,** Erythema in the right back. **C,** The epidermis was thin, and the non-invasive zone was not apparent. A granuloma (x40) was noted in the dermis. **D,** Lymphocytes and epithelioid cells (X400) were noted in granulomas around the appendages. **E,** Demyelinating changes were observed in the nerve, and a large number of granulomas (X40) was observed in the nerve sheath. **F-G,** A large number of lymphocyte and epithelioid cell infiltration (X400) was observed in the granuloma.

Figure continued

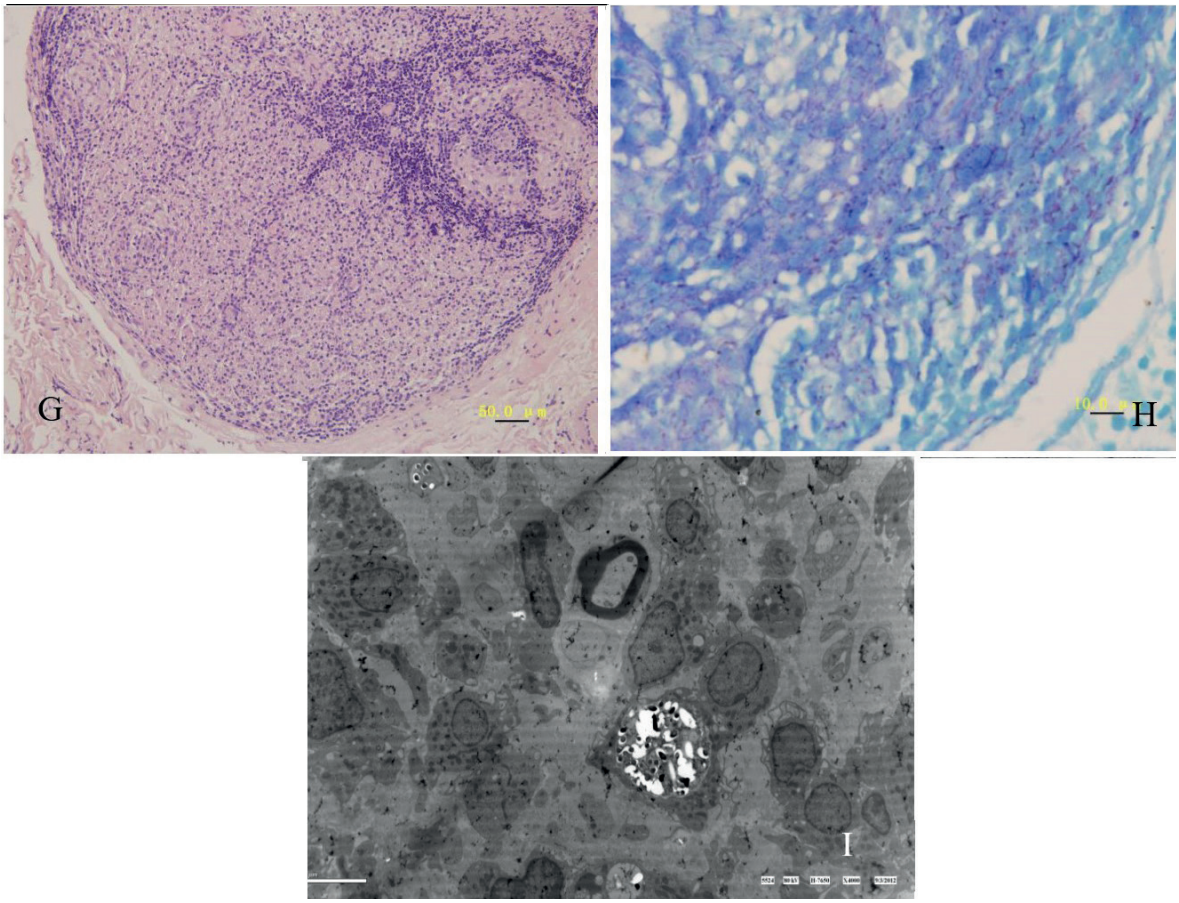

Figure 1. ***(Continued).*** **F-G,** A large number of lymphocyte and epithelioid cell infiltration (X400) was observed in the granuloma. **H,** Acid-fast staining (+++). **I-A** large number of lipid droplets were noted in the electron microscopy images, and bacteria were noted around the lipid droplets.

CSF biochemistry: protein 55 mg/dl; sugars and chlorides: normal. The synthetic rate of the CSF protein was normal within 24 h, and the CSF oligoclonal bands were negative. The results of the CSF anti-acid, ink, and gram staining were negative. The skin and nerve biopsies revealed leprosy bacillus under acid staining (Figure 2).

Case 3

This patient was a 50-year-old man born in Aba, Sichuan. He was treated in 2008 following progressive bilateral small finger contracture for four years. The patient fell from a horse four years prior and suffered a hand injury. Following this, the right little finger and forearm underwent progressive contracture. Physical examination showed that the patient's eyebrows were not falling off, and no plaques, erythema, or papules were observed on his skin. The right-hand evidenced claw-hand finger contracture and burns. The right hand had thenar and hypothenar atrophy, but pain and a sensation of warmth were no longer present. The neuropathological examination found demyelinating changes. Acid-fast bacteria were noted under acid-fast staining (Figure 3).

Case 4

This patient was a 56-year-old man born in Zhuzhou, Hunan. He had suffered from left lower limb disability for 20 years with no evident cause, as well as systemic plaques for four months. The symptoms had become progressively aggravated. For 10 years, both feet had been insensitive to cold and heat. Within the last four months, the patient's entire body had undergone geographic changes, with the left lower limb gradually becoming so thin that he was unable to lift his foot. Howev-

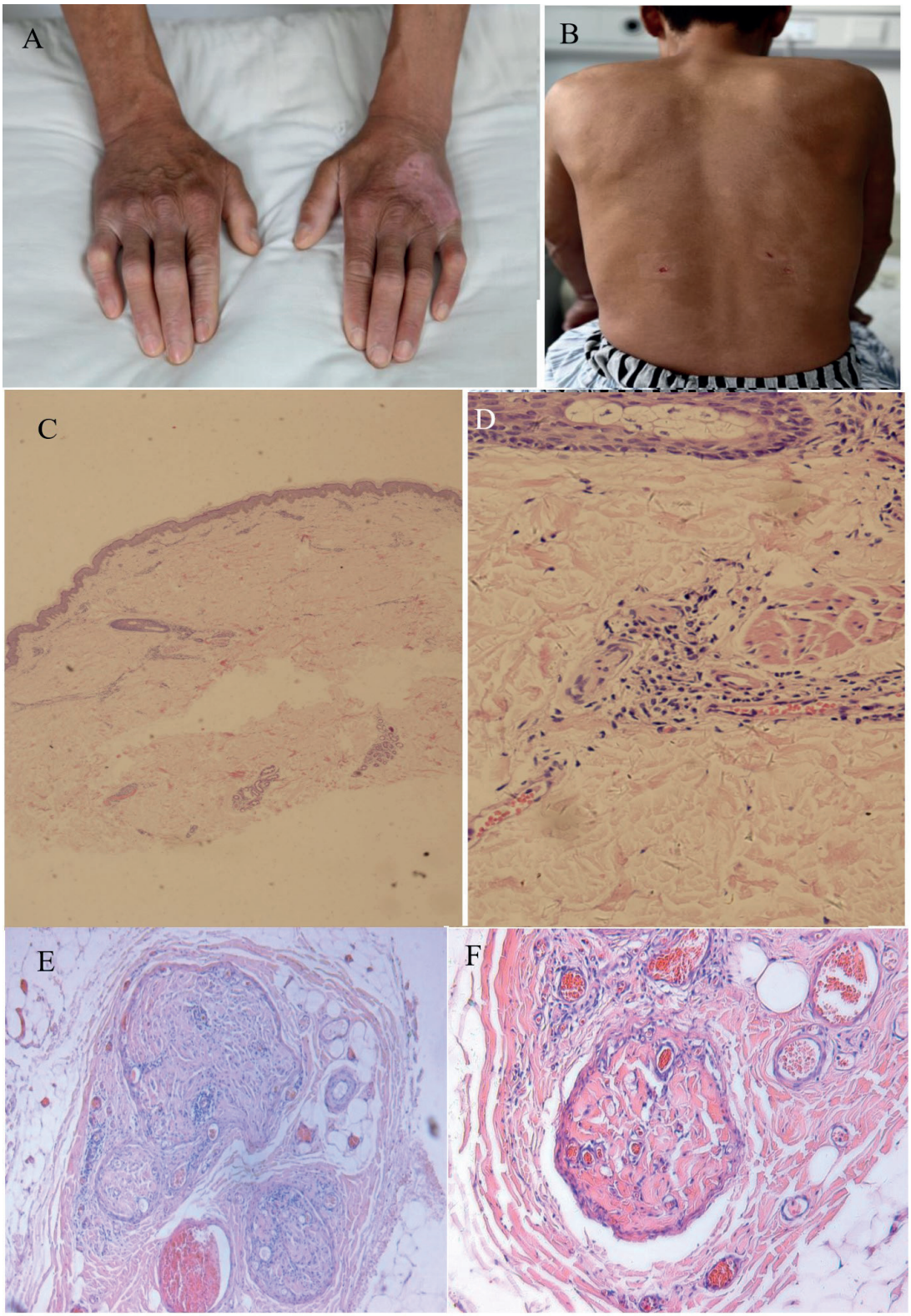

Figure 2. Clinical and pathological features of the skin and nerves in Case 2. **A,** Small finger contracture and erythema on the back of the left hand. **B,** Erythema on the back. **C,** The epidermis was thin, and the non-invasive zone was not apparent. A small granuloma (x40) was noted in the dermis. **D,** Lymphocytes and epithelioid cells (x400) were noted in granulomas around the appendages. **E,** Granulomatous infiltration (x100) was observed in the nerve sheath. **F,** Demyelinating changes (x400).

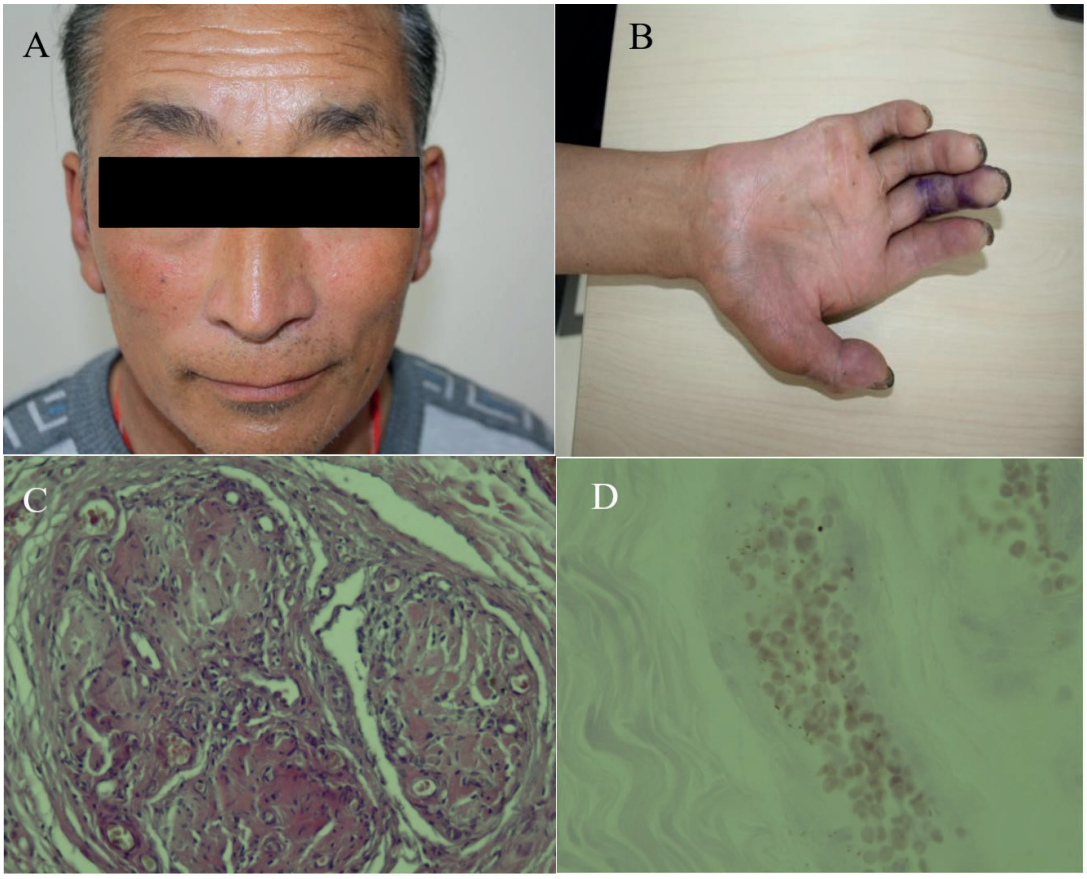

Figure 3. Clinical and pathological features of the skin and nerves in Case 3. **A,** The eyebrows were not falling off. **B,** Left finger contracture and thenar and hypothenar atrophy. **C,** Visible demyelinating changes (X400). **D,** Visible acid-fast bacteria (x 400)

er, he improved after taking vitamins orally. He was diagnosed with peripheral neuritis in Xuanwu Hospital, and oral administration of ginkgo leaves was prescribed. A blood transfusion was given, and the embolism was unimpeded. Nonetheless, the patient did not improve after being given vasodilators and came in for a consultation. The physical examination showed that the outer one-third of both eyebrows had fallen off and that the face was infiltrated without facial paralysis. A large number of geomorphic plaques were seen on the back, with visible satellite foci. Large ulceration, incrustation, atrophy, and perpendicular foot were seen on the left hip. Atrophy was noted in the pathological epidermis of the skin. The subepidermal non-infiltrating zone was not obvious. A large number of granulomas were seen under the superficial dermis and dermis, and epithelioid cells were observed inside the granulomas. Peripheral lymphocytic infiltration was noted. The acid-fast staining was negative (−) (Figure 4).

Discussion

Leprosy is a chronic granulomatous infectious disease caused by *Mycobacterium leprae* that mainly involves the skin and peripheral nerves[3]. Patients with multi-bacterial leprosy are known to be a source of infection, leading to the disease's spread via bacterial droplets and damaged skin[6,7]. Leprosy is one of the earliest-known infections in human beings. *Mycobacterium leprae* were discovered by Hanson, a Norwegian scientist, in 1883; thus, leprosy is also known as Hanson's disease[8]. Since the worldwide introduction of MDT in the 1960s, there have been around 200,000 newly developed cases globally every year[9]. The disease continues to spread in several high-incidence countries (e.g., India, Brazil, Southeast Asia)[10]. China began introducing MDT in 1983; since then, the annual number of cases has stabilized at around 1,500-2,000[1]. The 673 new cases in 2019 mainly occurred in Yunnan, Guizhou, Si-

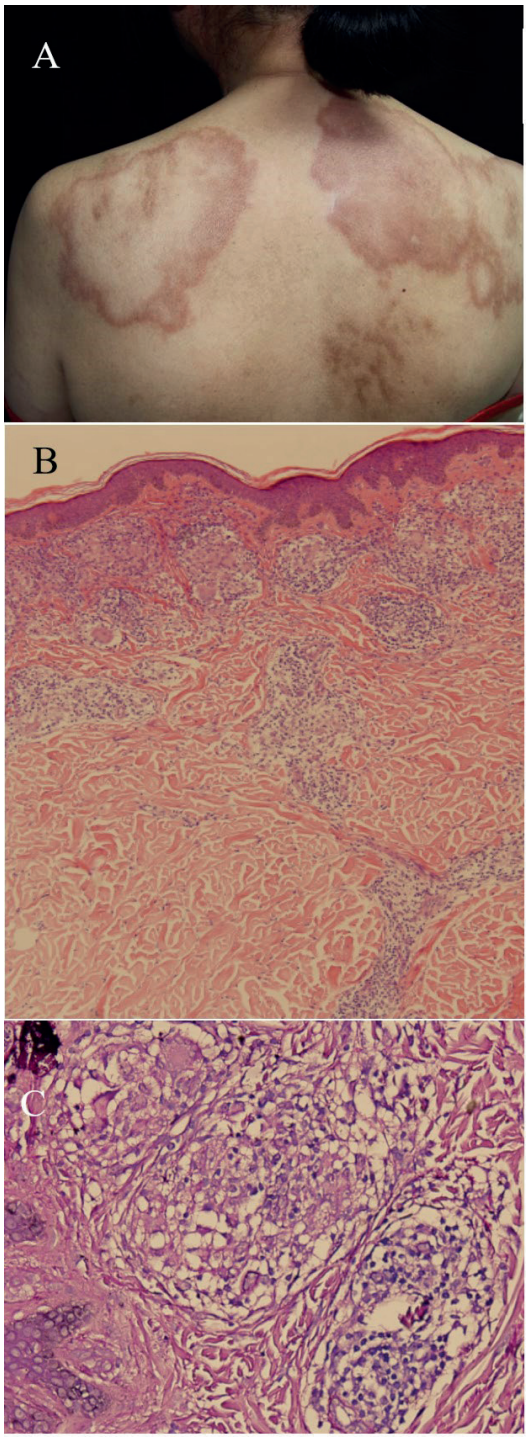

Figure 4. Clinical and pathological features of the skin and nerves in Case 4. A, Large, symmetrical patterned plaques were noted on the back. The skin in the center was normal and symmetrical, with satellite foci on the edge. The skin lesions were accompanied by numbness and were not sensitive to cold or heat.B, No atrophy was noted in the epidermis. The subepidermal non-infiltrating zone was not evident. A large number of granulomas (x40) were seen under the superficial dermis and dermis. C, Epithelioid cells and lymphocytes (x400) were noted in the granulomas. The acid-fast staining was negative

chuan, Guangdong, and Hunan. The four patients in the present study came from Sichuan, Guizhou, Southern Shaanxi, and Hunan, consistent with the country's high-prevalence areas. Leprosy has a broad clinical spectrum and can be divided into five types: tuberculous leprosy, borderline tuberculoid leprosy, intermediate borderline leprosy, borderline lepromatous leprosy, and lepra lepromatosa[11,12]. As *Mycobacterium leprae* infect the peripheral neurotropic Schwann cells, neurotropism and nerve fiber damage occur[3,13].

Herein, Case 1 had experienced skin involvement of the right forearm for 18 months prior to seeing a doctor. The main symptoms included left and right asymmetrical progressive limb sensory disorders. A detailed nervous system physical examination and neuro-electrophysiological auxiliary examination revealed ulnar nerve and common peroneal nerve involvement (lateral skin numbness of the right lower extremity with no sweating, numbness of the posterior left leg and back of the left foot with pricking and persistent pain and hypohidrosis). Acid-fast staining of the affected skin biopsied showed acid-fast bacilli[14]. However, the electron microscope examination of the nerve biopsy had the highest diagnostic value: *Mycobacterium leprae* were seen in the Schwann cells and showed foamy degeneration. The nerve components were destroyed, and the nerves were thickened. Based on these observations, the patient was diagnosed with borderline tuberculoid leprosy with Grade I disability.

Case 2 experienced skin lesions for the first time 16 years prior. Distal hypesthesia of all four limbs had gradually decreased 13 years prior. Physical examination of the nervous system suggested ulnar involvement. Acid-fast bacilli were found through acid-fast staining of the skin biopsied. The patient was diagnosed with borderline lepromatous leprosy with Grade II disability[15].

Case 3 had a history of trauma with right ulnar nerve injury that had become progressively aggravated. No evident plaques or skin lesions were found on the body. Demyelinating changes were observed via a nerve biopsy. AF was positive (+). The patient was diagnosed with pure nerve leprosy (PNL) with Grade II disability.

Case 4 had a contact history outside the home. The left leg had progressively atrophied, and the patient was unable to lift his foot. Geographic lesions were seen on the back and limbs. The pathological results revealed granulomas in the superficial dermis and dermis appendages, within which epithelioid cells were observed. The skin nerves

were thickened, and the acid-fast staining was negative. The patient was diagnosed with intermediate borderline leprosy with Grade II disability.

Beijing has a low prevalence of leprosy[16]. Herein, the four subjects were nonlocal patients with initial symptoms of peripheral nerve disability and skin lesions and primary manifestation of peripheral nerve involvement. They were not taken seriously the first time they were examined[17], although nerve damage is the most serious consequence of leprosy. The longer the diagnosis is delayed, the higher the rate of physical deformity, which can result in social discrimination of patients with leprosy[18]. Thus, early detection and treatment are important methods for preventing and reducing leprosy nerve damage. Leprosy should be used as a differential diagnosis for patients from endemic areas with skin damage associated with peripheral neuropathy, even in low-prevalence areas. If a patient has limb sensory impairment, disability, and facial paralysis, checks for skin damage in covered areas should be performed[2,16].

Mycobacterium leprae have long-term survival and slow reproduction in peripheral neurotropic Schwann cells *in vivo*. They cause a chronic granulomatous inflammatory response and destroy myelin and axonal structures. The main neuropathology of leprosy is demyelinating changes. In clinical settings, the primary manifestation is peripheral nerve damage. The ulnar nerve is most commonly affected, followed by the great auricular nerve, the common peroneal nerve, and the median nerve. The disease is characterized by discharge-like tenderness or spontaneous pain, loss of sensory and motor function, muscular atrophy, and joint deformity, and the inflammatory reactions lead to the enlargement of the involved nerves. Physiological examination of this disease shows a slowed conduction velocity, prolonged incubation period, and decreased or even absent amplitude after secondary axonal damage. The cell membranes of leprosy bacteria contain a large number of lipids and metabolize *in vivo* to ingest the body's lipids. As a result, a large number of lipid droplets form around the leprosy bacillus under pathological examination and electron microscopy, which is a major feature of the disease's pathology[19,20].

The two stable polar forms in the spectrum of leprosy dermatosis are tuberculous leprosy and lepra lepromatosa. Cell immunity is strong in tuberculous leprosy, with less than three skin lesions and almost invisible *Mycobacterium leprae*. Immunity is weak in lepra lepromatosa, with multiple symmetrical skin lesions containing a large number of *Mycobacterium leprae*. The variety of infections noted between these types form the borderline disease spectrum. In this study, Case 3 was diagnosed with PNL, which is a type of tuberculosis leprosy, while Case 1 was diagnosed with borderline tuberculosis leprosy. Here, the lesions appeared as a number of large light-red patches with defined edges and satellite foci. The nerves of these patients were involved in an early and obvious capacity. The neuropathy was asymmetrical. Case 2 was diagnosed with borderline lepra lepromatosa. Here, the skin lesions were symmetrical and numerous, with macules, papules, plaques, and nodules. In this patient, nerve involvement appeared late, and the neuropathy was symmetrical. Both borderline tuberculosis leprosy and borderline lepra lepromatosa can lead to thickened nerves and/or nerve pain. The peripheral areas of the limbs gradually develop sensory loss and paralysis due to nerve damage. Here, the four patients suffered from different degrees of deformity after being admitted to our hospital.

This study has the following shortcomings: first, it was not randomized or controlled. Therefore, there is a certain risk of bias. Second, it was a single-center clinical trial, and the sample size was small. In the future, a multi-center clinical study with a larger sample size should be conducted.

Conclusions

Even in areas with a low prevalence of the disease, early detection and treatment are important methods for preventing and reducing damage to peripheral nerve function in patients with leprosy.

Conflict of Interest

All of the authors had no personal, financial, commercial, or academic conflicts of interest separately.

Ethical statement

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of our hospital. All participants had signed the informed consent.

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