

Leprosy in The Department of Dermatology, Chang Gung Memorial Hospital at Kaohsiung from 1988 to 2004: A Clinical and Histopathologic Study of 13 Cases

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Background: Leprosy has long been in Taiwan, but it has never been eradicated. Incidental cases are easily overlooked nowadays because most younger dermatologists are unfamiliar with this disease.

Methods: We review and analyze 13 cases diagnosed as leprosy at the Department of Dermatology, Chang Gung Memorial Hospital at Kaohsiung from 1988 to 2004, all of which were histopathologically proven.

Results: The ages of the 13 recruited patients ranged from 31 to 73 (mean, 58.6) years, without a gender preference (male: female, 7:6). Two male patients were under 40 years old; one was a foreign worker from Thailand and the other was a local person in Penghu working as the chief officer on a fishing boat. The most-common clinical subtype was lepromatous leprosy (5/13), followed by borderline lepromatous leprosy, borderline tuberculoid leprosy, and tuberculoid leprosy (each 2/13), and then borderline leprosy and indeterminate leprosy (each 1/13). The initial clinical impression before the histopathological diagnosis included granuloma annulare, generalized eczema, lymphoma, syphilis, papular urticaria, cutaneous tuberculous infection, Sweet's syndrome, erythema annulare centrifugum, and hematoma. Most of these patients only received irregular treatment after the diagnosis was made and were soon lost to follow-up.

Conclusions: With increasing numbers of foreign workers and immigrants living in Taiwan in recent years, leprosy seems to have become a challenging diagnosis for younger dermatologists. Dermatologists should keep this ancient disease in mind and not overlook it. Because of the necessity of prolonged medication, complete treatment and long-term follow-up of leprosy cases will remain a major problem in public health.

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Key words: lepromatous leprosy, borderline leprosy, tuberculoid leprosy, indeterminate leprosy, *Mycobacterium leprae*.

Leprosy or Hansen's disease, is a chronic infectious disease, usually causing a granulomatous reaction in the skin and accompanied by neurologic defects. As an ancient disease probably described in

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sacred writings from India in the 6th century B.C., there were still 719,300 newly registered cases claimed by the World Health Organization (WHO) in 2000.^(1,2) Leprosy is still a great threat to public health in endemic countries such as Nepal, Madagascar, Myanmar, Indonesia, and is the worst threat in India and Brazil, where approximately 83% of all the leprosy cases live.⁽³⁾

In Taiwan during the Japanese colonial period, the main organization that treated and detained leprosy patients was Taipei Mackay Hospital, with more than 500 recorded patients in 1928. In the postwar era, Lo-Sheng Sanatorium Hospital became the largest organization for taking care of leprosy patients with more than 900 patients in 1945.⁽⁴⁾ Over the past 2 decades, however, leprosy has rarely been diagnosed clinically in Taiwan, with only 105 cases newly diagnosed from 1991 to 2003.⁽⁵⁾

The diverse clinical manifestations of leprosy can be reduced to 2 kinds of changes, a granulomatous spectrum and the reactional states. The most-detailed description of the granulomatous spectrum of leprosy came from Ridley and associates, integrating both clinical and histologic changes and dividing leprosy into polar tuberculoid (TT), borderline tuberculoid (BT), borderline (BB), borderline lepromatous (BL), and lepromatous leprosy (LL), based on the high to low resistance of the host.^(6,7) Ridley's classification is, however, not useful in treatment decisions or performance in routine dermatological practice. The classification into multibacillary and paucibacillary cases as suggested by the WHO seems to provide more-useful guidelines for treatment decisions.⁽⁸⁾

In the present study, we reviewed and analyzed 13 cases of leprosy diagnosed within the period of 1988-2004 in the Department of Dermatology, Chang Gung Memorial Hospital at Kaohsiung.

METHODS

The medical records and histopathology results, including special stains, of the 13 leprosy cases were collected and thoroughly reviewed. Those with only a clinical diagnosis without histopathological workup were excluded. The clinical information included gender, occupation, residence, age at the time of diagnosis, skin manifestations, initial clinical diagnosis, and treatment course. The various sub-

types of leprosy are defined and diagnosed based on Ridley's classification, as follows: (1) patients presenting clinically with generalized, numerous, symmetrical skin lesions and histopathologically with numerous foamy macrophages aggregated in a xanthoma-like appearance containing numerous bacilli with Wade-Fite staining were classified as LL; (2) patients presenting clinically with less-numerous, asymmetrical, but still generalized skin lesions and histopathologically with foamy macrophages mixed with small amounts of lympho-plasma cells and numerous bacilli with Wade-Fite staining were classified as BL; (3) patients presenting clinically with several localized skin lesions and histopathologically epithelioid cells without distinct granulomas, scanty foamy macrophages, and few bacilli with Wade-Fite staining were classified as BB; (4) patients presenting clinically with as few as 3-10 skin lesions and histopathological granuloma formation with peripheral lymphocytic infiltration following the neurovascular bundles and skin appendages as well as scanty bacilli with Wade-Fite staining were classified as BT; (5) patients presenting clinically with fewer than 3 lesions and histopathologically compact granuloma formation with dense lymphocytic infiltration surrounding the neurovascular bundles and skin appendages without bacilli found with Wade-Fite staining were classified as TT; and (6) patients who could not fit into any of the other just-described categories such as with more than 3 lesions found clinically but no bacillus found with Wade-Fite staining were classified as indeterminate leprosy (IL).^(9,10)

On the other hand, according to the WHO classification, patients who were experiencing no reactions and had fewer than 5 skin lesions should be classified as having paucibacillary disease, while those with more than 5 skin lesions were considered as having multibacillary disease.⁽⁸⁾ In general, paucibacillary disease can be represented by IL, TT, and BT, while multibacillary disease may include BB, BL, and LL.

RESULTS

In the 13 patients examined, there were 7 males and 6 females, whose ages ranged from 31 to 73 years with a mean of 58.6 years (Table 1). Lepromatous leprosy (LL) was diagnosed in 5 patients, mostly with generalized, numerous, sym-

Table 1. Clinical Summary of Leprosy Patients in Chang Gung Memorial Hospital at Kaohsiung from 1988 to 2004

Patient no.	Age (years)	Gender	Occupation	Residence	Year of diagnosis	Clinical impression	Ridley-Jopling classification	WHO classification	Fitzpatrick's classification	Treatment and course
1*	54 69	F	Vender	Kaohsiung City	1988 2003	Sweet's syndrome Hematoma; malignancy	LL LL	MB MB	MB MB	lost to follow-up dapsons + rifampicin
2	73	M	Veteran	Pingtung City	1992	Leprosy	BT	PB	PB	irregular treatment
3	50	F	Untraceable	Kaohsiung City	1992	Leprosy	BT	PB	PB	irregular treatment
4	56	F	Veteran's spouse	Kaohsiung, Gangshan	1994	Leprosy; lymphoma	BL	MB	MB	lost to follow-up
5	61	M	Veteran	Kaohsiung City	1995	Granuloma annulare	LL	MB	MB	dapsone + rifampicin
6	51	F	Untraceable	Kaohsiung City	1995	Mycosis fungoides; leprosy	LL	MB	MB	dapsone + rifampicin
7	62	F	Farmer	Pingtung, Nanjhou	1995	Papular urticaria; cutaneous tuberculosis	BB	MB	MB	lost to follow-up
8	43	F	Farmer	Pingtung, Wandan	1996	Leprosy; granuloma annulare	TT	PB	PB	rifampicin
9	73	M	Veteran	Kaohsiung, Gangshan	1997	Leprosy	TT	PB	PB	dapsone + rifampicin
10	31	M	Foreign worker	Thailand	1999	Leprosy	BL	MB	MB	lost to follow-up
11	55	M	Merchant	Kaohsiung, Meinung	2002	Erythema annulare centrifugum	IL	MB	PB	dapsone + rifampicin
12	64	M	Retired worker	Kaohsiung, Renwu	2004	Syphilis	LL	MB	MB	lost to follow-up
13	35	M	Shipman	Penghu, Magong	2004	Leprosy; lymphoma	LL	MB	MB	lost to follow-up

Abbreviations: TT: polar tuberculoid; BT: borderline tuberculoid; BB: borderline; BL: borderline lepromatous; LL: lepromatous leprosy; IL: indeterminate leprosy; MB: multibacillary; PB: paucibacillary.

* Diagnosed in 1988 and lost follow-up. Recurrent in 2003.

metrical, erythematous papulomacules, while indurated dermal nodules or annular plaques were found in 2 cases. In histopathology, cases of LL showed numerous foamy macrophages with extensive cellular infiltrates almost invariably separated from the flattened epidermis by a narrow grenz zone. With Wade-Fite staining, bacillus clusters were easily observed (Figs. 1, 2). Two cases with borderline lepromatous leprosy (BL) also showed multiple erythematous papules with annular plaque formation which was less symmetrical and numerous than that in LL (Fig. 3). Of special interest was 1 woman (case 1) who was initially diagnosed as having LL in 1988, and had since suffered from erythematous papuloplaques on the trunk and limbs, poor healing digital ulcers with onychomadesis (Fig. 1), and persistent conjunctivitis (rabbit eye). In 2003, due to nasal obstruction and frequent epistaxis, she received a nasaoendoscopic examination, and the surgical specimen showed pathology of granulomatous inflammation with numerous bacillus clusters with Wade-Fite staining. This is a very typical LL case with systemic manifestations and nasal involvement. Two patients with borderline tuberculoid leprosy (BT) presented a few brownish to erythematous plaques with granuloma formation. Scanty acid-fast bacilli were found. Tuberculoid leprosy (TT) was seen in 2 patients, one exhibiting a single infiltrated plaque and the other

exhibiting 2 annular plaques. Both of these patients had sensory loss. No acid-fast bacilli were identifiable, and a lot of epithelioid macrophages forming granulomas with Langhans' giant cells were noted (Fig. 4). One woman diagnosed as having borderline leprosy (BB) presented with several small macules

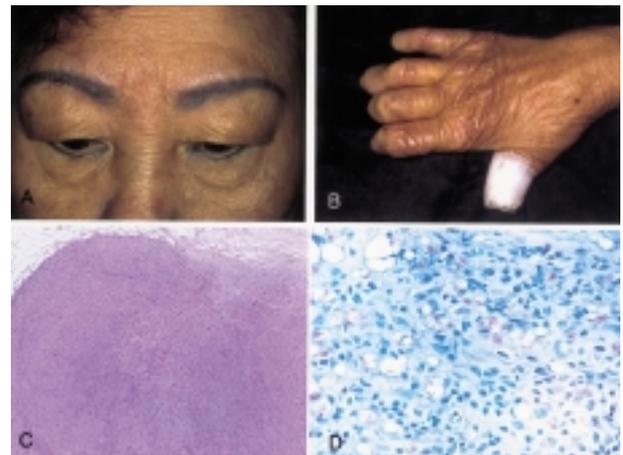


Fig. 1 A 69-year-old LL female with recurrence. (A) Loss of eyebrows and eyelashes with conjunctivitis (rabbit eye); (B) poor healing of digital ulcers with onychomadesis; (C) histopathology showing a well-circumscribed subcutaneous nodule composed of foamy histiocytes (hematoxylin-eosin, x 20); (D) abundant bacillary clusters observed with Wade-Fite staining (Wade-Fite, x 400).

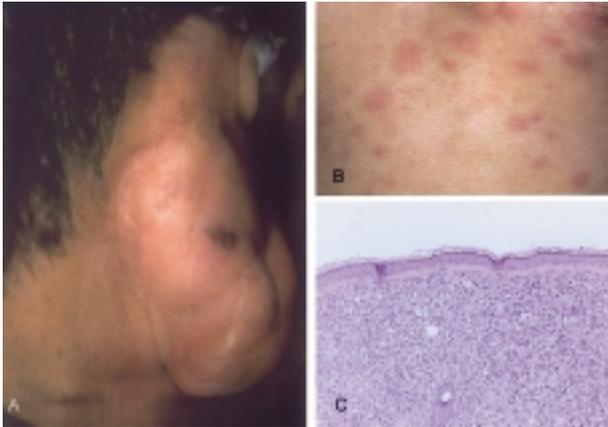


Fig. 2 A 35-year-old LL male. (A) A large elastic nodule over the retroauricular area; (B) multiple erythematous macules with a symmetrical distribution; (C) histopathology of the retroauricular nodule showing numerous foamy macrophages separated from the flattened epidermis by a narrow grenz zone (hematoxylin-eosin, x 40).

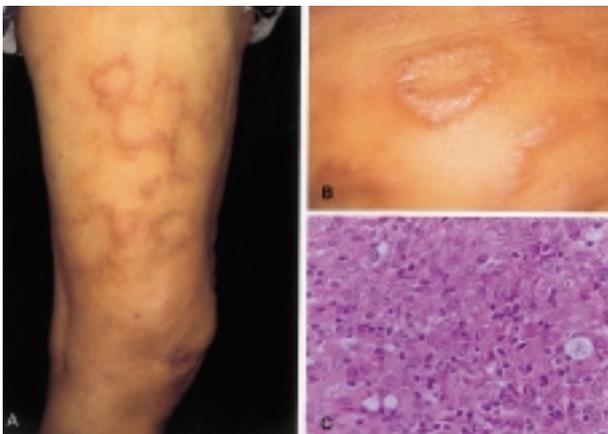


Fig. 3 A 56-year-old BL female. (A) Multiple large, annular plaques with an asymmetrical distribution; (B) close-up view of annular lesions showing elevated erythematous borders; (C) histopathology showing mixed infiltration of lymphocytes and foamy macrophages (hematoxylin-eosin, x 400).

on the bilateral forearms without foamy macrophages nor granuloma formation in histopathology but showing perineural lympho-plasma cell infiltration. One man with indeterminate leprosy (IL) showed multiple annular plaques on the face and trunk with microscopically very dense lympho-plasma cell infiltration around the nerves.

According to the WHO classification, there

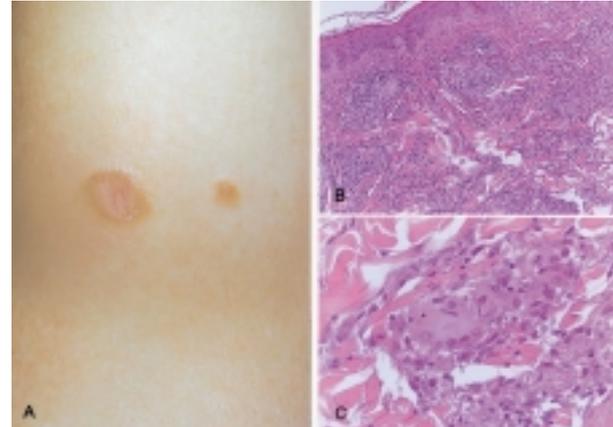


Fig. 4 A 43-year-old TT female. (A) Two annular plaques over her forearm; (B) histopathology showing multiple epithelioid macrophages forming granulomas (hematoxylin-eosin, x 100); (C) Langhans' giant cell formation (hematoxylin-eosin, x 400).

were 9 multibacillus and 4 paucibacillus patients.

Treatment of these patients was based on their immune status and the WHO classification; for paucibacillus patients (BT or TT), treatment was initiated with 600 mg rifampicin monthly with or without 100 mg dapsone daily, while most of the multibacilli patients were soon referred to Lo-Sheng Sanatorium Hospital and Kaohsiung Christian Hospital to acquire clofazimine. In retrospective telephone interviews, most of those patients had received only irregular treatment and were eventually lost to follow-up. The background and clinical profiles of our cases are summarized in Table 1.

DISCUSSION

Leprosy, primarily a disease of developing countries, is endemic to all continents, especially India, Brazil, Myanmar, Madagascar, Mozambique, and Nepal, which accounted for 88% of new cases in 2001, with prevalences exceeding 5 per 10,000 population in these countries.⁽¹⁾ In 2003, 514,718 new cases were reported, among them 405,147 were from Southeast Asia (WHO, 2004). In 2004, there were 458,428 new cases reported globally. In Taiwan, newly registered cases have dramatically decreased in recent years. Totally 4365 cases were registered in 1981, gradually declining to 1118 cases in 2005. The latest prevalence data in 2005 was estimated to be at

0.49 per 10,000.^(11,12) Only 110 cases were newly diagnosed from 1991 to 2004 and the case-detection rate ranged from 0.01 to 0.06 per 100,000 in the past decade.^(5,12) The epidemiology of leprosy infection in 2004 for neighboring countries that have close trading and socioeconomic relationship with Taiwan is summarized in Table 2, and stated as follows (registered cases; prevalence rate per 10,000): China (3261; 0.03), the Philippines (3334; 0.42), Vietnam (1203; 0.15), Thailand (1775; 0.3), and Indonesia (18,083; 0.8). Australia and Japan reported no cases in 2004.⁽¹³⁾

In our series of 13 enrolled cases, most were middle-aged to elderly people, with only 2 men diagnosed before 40 years of age (cases 10 and 13). No gender difference was found. Case 10 was a 31-year-old foreign laborer from Thailand, and case 13 was a 35-year-old chief officer working on fishing boat out of Penghu. In total, 4 veterans or their spouses living in the veterans dormitory district were identified in the present study, with the latest case diagnosed and recruited in 1997. The mean age of these 4 patients was older than the mean of the entire group (65.6 vs. 58.8 years). In a review of vocational categories of the 356 enrolled leprosy patients living in Lo-Sheng Sanatorium Hospital, 38.76% (138/356) were veterans.⁽¹⁴⁾ Other studies have also shown that around half of all newly diagnosed cases in Taiwan are foreign labors or foreign spouses.⁽⁴⁾ Since the incubation time and latency period of leprosy can be as long as several decades, the exact time point of infection and contagious route of leprosy in these patients remain difficult to determine. Of major concern is the possibility of recent infection though contact with foreign

workers and spouses originally from China and endemic Southeast Asian countries as well as those people working and traveling in China.

Since 1966, the classification of leprosy by Ridley and Jopling into 5 subtypes (TT, BT, BB, BL, and LL) based on the immunologic response of the host to *M. leprae* has been widely adopted.⁽¹⁵⁾ According to this classification, the most-common clinical subtype in our study was LL (5/13), followed by BL, BT, and TT (each 2/13), and then BB and indeterminate leprosy (IL) (each 1/13). However, differentiation between leprosy subtypes is sometimes difficult or impossible. In the US, the Public Health Service recommends that the classification of leprosy be based on clinical evaluation, skin smears from several sites, and skin biopsies. However, skin smears present only a 10%~50% positive rate and are rarely performed in regular dermatological practice. In 1998, the WHO Expert Committee on Leprosy suggested the use of the number of the clinical lesions for classification: patients not experiencing reactions and having fewer than 5 skin lesions are to be classified as having paucibacillary disease, while those with more than 5 skin lesions are to be classified as having multibacillary disease.^(3,8) According to this definition, 4 cases were classified as paucibacillary and 9 cases were multibacillary in our series. Some authors prefer to define multibacillary as any bacillus detectable in tissue sections or smears and paucibacillary as no detectable bacillus.⁽⁶⁾ According to this scheme, we had 5 paucibacillary cases and 8 multibacillary cases. Among newly detected cases in 2004 globally, the ratio between paucibacillary and multibacillary cases varied, with

Table 2. 2004 Leprosy Situation in Neighboring Countries of Taiwan

Country/Territory	Population	Registered prevalence	Prevalence rate*	Newly detected cases	Case detection rate†
China	1,303,473,000	3261	0.03	1404	0.11
Philippines	80,089,000	3334	0.42	2397	2.99
Vietnam	81,286,000	1203	0.15	949	1.17
Thailand	61,930,000	1775	0.3	705	1.1
Indonesia	214,889,000	18,083	0.8	14,641	6.8
Australia	19,729,000	0	0	4	0.02
Japan 2001	127,335,000	0	0	10	0.01
Taiwan	22,708,280	1118‡	0.49	5	0.02

* Number of cases per 10,000 population.
 † Number of cases per 100,000 population.
 ‡ Latest data for May 2005.

approximately 39% in India and 79% in the Western Pacific area (including China and Taiwan) being multibacillary.⁽¹³⁾ Case 11 in our study highlighted the inadequacy of the different classification systems for leprosy; he had multiple skin lesions with sensory loss and dense lympho-plasma infiltration around the neurovascular bundles, but with no bacilli found with Wade-Fite staining. In Ridley's classification, this is an indeterminate case, while in the WHO's classification, he is classified as multibacillary due to the presence of more than 5 skin lesions, but in Fitzpatrick's classification, it is paucibacillary due to undetected bacilli with Wade-Fite staining. In spite of the imperfections of the different classification systems, the integration and combined use of these systems may help determine the host immunity to *M. leprae*, treatment options, and disease outcomes.

Leprosy, like syphilis, is a great imitator and can mimic many other skin diseases, which is truly reflected in our small series; 7 of the 13 studied cases were initially clinically misdiagnosed as Sweet's syndrome, granuloma annulare, papular urticaria, cutaneous tuberculosis, erythema annulare centrifugum, and syphilis. The diverse manifestations of different subtypes of leprosy may pose diagnostic challenges, especially for multibacillary disease (BB, BL, and LL), which may vary from annular plaques, pin-sized to small macules, and eczematous papules to subcutaneous nodules.

Multidrug treatment (MDT) with rifampicin, dapsone, and clofazimine as recommended by the WHO in 1982 remains the mainstay for leprosy treatment.^(3,16) With implementation of MDT, the global prevalence was reduced from 12 per 10,000 in 1985 to slightly below 1 per 10,000 in 2002.⁽³⁾ For paucibacillary disease (TT or BT), the WHO recommends a combination of unsupervised 100 mg dapsone daily and supervised 600 mg rifampin monthly with 6 cycles in 9 months. For multibacillary disease (BB, BL, and LL), the WHO recommends unsupervised 100 mg dapsone daily, supervised 600 mg rifampin monthly, unsupervised 50 mg clofazimine daily, and supervised 300 mg monthly with 24 cycles in 36 months or 12 cycles in 18 months.⁽³⁾ In 1997, the WHO Expert Committee suggested that it might be possible to reduce the duration of MDT for multibacillary disease from 2 to 1 year and also recommended treatment of a single paucibacillary lesion with 1 dose of ROM (600 mg rifampin, 400 mg

ofloxacin, and 100 mg minocycline). Long-term follow-up with this regimen, however, is lacking.^(3,17) Other therapeutic agents, including rifabutin, ofloxacin, sparfloxacin, levofloxacin, minocycline, and clarithromycin, are usually reserved for drug-resistant cases.^(3,16,18,19)

In some recent extensive reviews of treatment and control programs, it was found that leprosy, far from being eliminated as a public health problem, still causes considerable long-term morbidity in both developing and developed countries. The experience in Yemen highlights how a poor healthcare infrastructure and communication systems, difficult terrain, inadequate resources, and political instability continue to constrain the treatment of leprosy. With improvements in those factors, the prevalence of leprosy declined from 1.9 per 10,000 population in 1989 to 0.5 per 10,000 population in 1996.⁽²⁰⁾ In our experience, the main reasons for irregular and incomplete treatment of most patients in Taiwan may include (1) the lack of awareness by patients of the obstinacy of the disease and therefore poor compliance with the treatment guidelines, (2) the limited dispensation of dapsone and clofazimine in Taiwan, and (3) inadequate surveillance and follow-up of registered cases in the current disease control system.

In conclusion, leprosy is uncommon in Taiwan but has never been eradicated. Based on our results, special attention should be paid to (1) older veterans originally from China and living in veterans dormitory districts and (2) younger people who have close contact with foreign workers or new immigrants from Southeast Asian countries. Strict measures should be taken to implement the comprehensive registration, complete treatment, and long-term follow-up of diagnosed cases. Leprosy still remains a diagnostic challenge for dermatologists in Taiwan. Younger dermatologists should keep this ancient disease in mind and never overlook it.

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高雄長庚紀念醫院皮膚科 1988 至 2004 年間 13 例癩瘋病 之臨床與組織病理研究

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- 背景：** 癩瘋，這個古老的疾病在台灣卻未曾消失。由於年輕一輩的醫師對這個疾病逐漸陌生的緣故，偶發的病例常常被忽略。
- 方法：** 我們回顧並分析高雄長庚紀念醫院 1988-2004 年間 13 位經病理切片診斷證實為癩瘋病的案例。
- 結果：** 在這 13 名經臨床與病理確定診斷為癩瘋的病例中，患者的年齡分佈從 31 至 73 歲（平均 58.6 歲），並沒有性別的差別（男：女=7：6）。有兩位男性患者年齡在 40 歲以前；其中一位是泰籍的外籍勞工，另一位則是在地的澎湖人，在漁船上擔任大副。此外，有四人來自眷村（4/13）。臨床亞型最常見的為癩瘋型癩瘋（5/13），其次依序為中間癩瘋型癩瘋、中間類結核型癩瘋與結核型癩瘋（均為 2/13），以及中間型癩瘋與未定型癩瘋（均為 1/13）。最初的臨床診斷包含了環狀肉芽瘤、全身濕疹、淋巴癌、梅毒、丘疹狀蕁麻疹、表皮結核菌感染、舒威特氏症候群、遠心性環狀紅斑、以及血腫。大部分的病人在確診後僅接受不規則的治療並很快地失去追蹤。
- 結論：** 近年來，台灣有越來越多的外籍勞工與移民，癩瘋似乎將成為診斷上的挑戰，年輕一輩皮膚科醫師依舊必須謹記在心以免忽略了癩瘋的診斷。由於癩瘋的治療漫長，完整的治療與長期追蹤是公共衛生學上即將面對的課題。
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關鍵字： 癩瘋型癩瘋，中間型癩瘋，類結核型癩瘋，未定型癩瘋，癩瘋分枝桿菌。

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