Chapter 1

Leprosy: The Ancient and Stubborn Disease

Prasetyadi Mawardi

Additional information is available at the end of the chapter

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Abstract

Leprosy can be caused by an infection of *Mycobacterium leprae* commonly acquired through contact with an infected person. Clinical presentation depends on the patient's immune status at the time of infection and during the course of disease. Leprosy is associated with disability and marginalization. The Global Leprosy Strategy 2016–2020 released in April 2016 underscored its goal of "accelerating towards a leprosy free-world." Today's leprosy differs from the leprosy of the past, but yet there are still many things that are not immediately known, so it is still a broad socioeconomic challenge for scientists to solve. Leprosy has low pathogenicity, only a small proportion of infected people develop signs of the disease. If leprosy is not diagnosed and treated in the early stages, further progress of the disease is determined by the strength of the patient's immune response. Various clinical signs can be known during the early phase of leprosy, defined as indeterminate phase, so that it is difficult to diagnose the disease. Multidrug therapy (MDT) was recommended as the standard treatment. The morbidity report of leprosy will be important in epidemiology because it is based on real events and not based on estimate.

Keywords: leprosy, multidrug therapy, *Mycobacterium leprae*

1. Introduction

Leprosy or Hansen disease is caused by an infection of *Mycobacterium leprae*, an acid-fast, rod-shaped bacillus, usually acquired through contact with an infected person. However, not every person exposed to an infected contact will develop leprosy [1]. *M. leprae* multiplies slowly, and the incubation period of the disease, on average, is 5 years. In some cases, symptoms may occur within 1 year but can also take as long as 20 years to occur. Clinical presentation depends on the patients' immune status at the time of infection and during the course of disease. Leprosy is associated with disability and marginalization [2].

Fourteen countries reported more than 1000 new cases, of which three countries—India, Brazil, and Indonesia—account for more than 80% of all the cases in the world [2]. The World Health Organization (WHO) reported that there were approximately 213,899 newly diagnosed patients in 2014 (a detection rate of 3.0/100,000 population), with 94% of LPs located in only 13 countries, one of which was Indonesia [3]. Indonesia's Ministry of Health reported 16,131 newly diagnosed cases of leprosy in 2014. On the other hand, the Department of Health found 498 cases of pauci-bacillary leprosy and 3337 cases of multi-bacillary leprosy [2]; the highest number of which were found in the Jember district. ***The Global Leprosy Strategy*** 2016–2020 released in April 2016 underscored its goal of "accelerating towards a leprosy-free world" and its commitment to an approach based on the principles of initiating action, ensuring accountability, and promoting inclusion [4]. The Global Leprosy 2016–2020 aims to detect early leprosy and prompt treatment to prevent disability and reduce transmission of infection in the community. The proportion of G2D cases (2 degree disability) among newly diagnosed patients and G2D levels in a population indicates the efficiency of early leprosy detection. They also showed indirectly the level of awareness of early signs of leprosy, access to leprosy services, and the skills of health care staff in diagnosing leprosy. This strategy is designed to achieve the long-term goal of a "leprosy free world," which refers to situations where societies are free of morbidity, disability, and social consequences due to leprosy [3]. Since 1980 era, Leprosy remains a problem in public health in Indonesia. The program implemented in Indonesia reduced the prevalence to 17,539 cases in 2000. The prevalence was 86% decreased in a 15-year period. It has been noted that a significant increase in leprosy control is due to the large-scale promotion of leprosy prevention and multidrug therapy (MDT) in more than 5600 primary health centers in Indonesia [5].

2. Epidemiology

Leprosy was first described in 600 BC and was recognized in the ancient civilization of China, Egypt, and India. The global prevalence of leprosy has decreased with the widespread use of effective therapy. More than 5 million cases were documented in 1985 and fewer than 300,000 cases 20 years later. Leprosy is spread by person to person contact. Although the most important route is unclear, it is believed that *M. leprae* is spread either through the inhalation of infectious aerosols or through skin contact with respiratory secretions and wound exudates. Numerous *M. leprae* are found in the nasal secretions of patients with lepromatous leprosy. *M. leprae* cannot grow in cell free cultures. Thus laboratory confirmation of leprosy requires histopathologic finding consistent with the clinical disease and either skin test reactivity to lepromin in tuberculoid leprosy or observation of acid fast bacteria in the lesion of patients with lepromatous leprosy [6].

The post millennium development goals have begun in 2015. Achieving the Millennium Development Goals (MDGs) as targets for global development needs to be evaluated. New ongoing and sustainable targets are important for the elimination of neglected tropical diseases (NTD) in Indonesia. This review illustrates the NTD situation in Indonesia and highlights issues under NTD transmission. A multidisciplinary approach is a promising strategy to help marginalized people [7].

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Over the past 20 years, more than 16 million leprosy patients have been treated. The prevalence rate of the disease has declined by 99%: from 21.1 cases per 10,000 people in 1983 to 0.2 cases per 10,000 people by 2015. According to official reports received from 138 countries from all WHO regions, the global prevalence of leprosy by the end of 2015 was 176,176 cases (0.18 cases per 10,000 people). The number of new cases reported globally over the last 3 years is as follows: 2015: 211,973 (0.21 new cases per 10,000 people), 2014: 213,899 new cases, and 2013: 215,656 new cases (**Figures 1–4**; **Table 1**) [8].

As can be seen from the above table, only three countries reported more than 10,000 cases in 2015: **India, Brazil, and Indonesia**. With 127,326 new cases, India accounted for 60% of the global new cases; Brazil reported 26.395 new cases, representing 13% of the global new cases; and Indonesia reported 17,202 new cases, 8% of the global case load. In 2016, WHO has launched "Global Leprosy Strategy 2016–2020: Accelerate towards a leprosy-free world"-aimed at reviving leprosy control efforts and to avoid disability, especially among children affected by disease in endemic countries. This strategy emphasizes the need for ongoing expertise and increases the number of skilled leprosy staff, increases the participation of affected people in leprosy services, and reduces visible abnormalities—also called G2D defects—as well as the stigma associated with the disease. The targets of the new global strategy to be met by 2020 are [8]:

1. Without a disability among new pediatric patients.
2. The level of class-2 disability is less than 1 case per 1 million people.
3. Zero countries with laws that allow discrimination on the basis of leprosy.

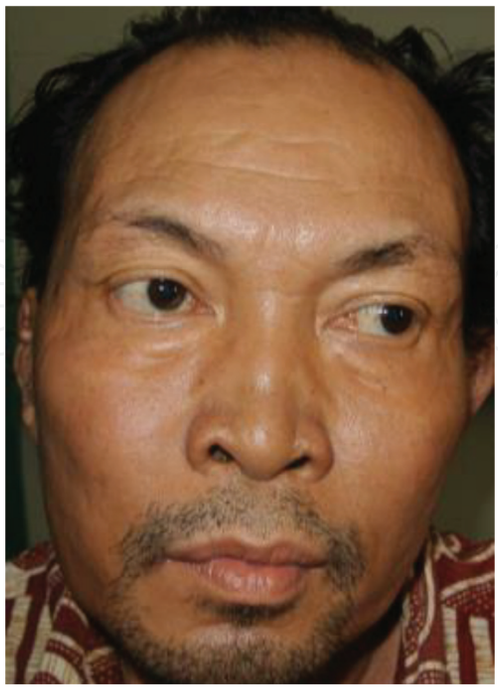

Figure 1. Madarosis on facial region in Lucio phenomenon's patient.

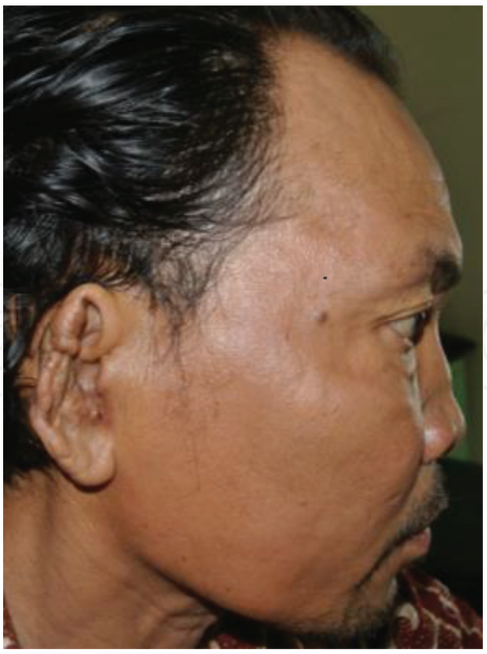

Figure 2. Infiltrate and atrophic on auricularis dextra region in Lucio phenomenon's patient.

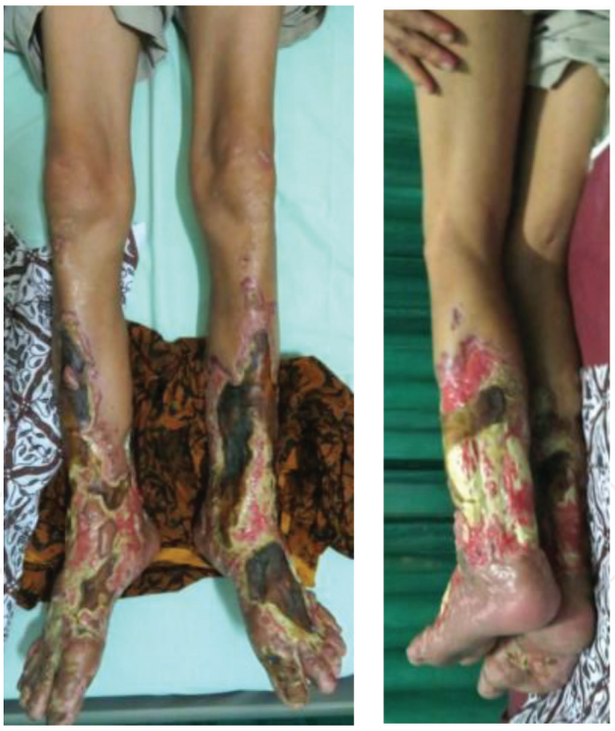

Figure 3. Ulcer on lower extremities in Lucio phenomenon's patient.

In some areas in Indonesia, leprosy is still prevalent even though the infectious disease is no longer a mystery and can be prevented and treated by adopting a clean and healthy lifestyle. Cases of leprosy continue to surface in some areas, and people who were afflicted with the disease but have been cured continue to face the stigma and discrimination. Health workers

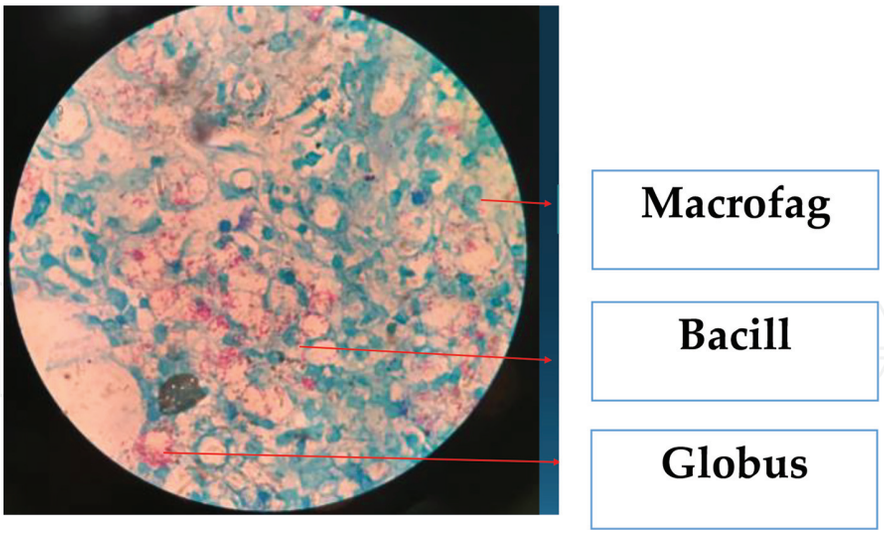

Figure 4. Histopathological examination with Wade Faraco staining in Lucio phenomenon's patient showed multiple bacilli commonly in lepromatous leprosy.

Country	Number of new cases detected					
	2010	**2011**	**2012**	**2013**	**2014**	**2015**
Bangladesh	3848	3970	3688	3141	3622	3976
Brazil	34,894	33,955	33,303	31,044	31,064	26,395
Democratic Republic of the Congo	5049	3949	3607	3744	3272	4237
Ethiopia	4430	NR	3776	4374	3758	3970
India	126,800	127,295	134,752	126,913	125,785	127,326
Indonesia	17,012	20,023	18,994	16,856	17,025	17,202
Madagascar	1520	1577	1474	1569	1617	1487
Myanmar	2936	3082	3013	2950	2877	2571
Nepal	3118	3184	3492	3225	3046	2751
Nigeria	3913	3623	3805	3385	2983	2892
Philippines	2041	1818	2150	1729	1655	1617
Sri Lanka	2027	2178	2191	1990	2157	1977
Mozambique	1207	1097	758	NR	NR	1335
United Republic of Tanzania	2349	2288	2528	2005	1947	2256
Total (%)	**211,144 (92)**	**208,039 (92)**	**217,531 (93)**	**202,925 (94)**	**200,808 (94)**	**199,992 (95)**
Global total	**228,474**	**226,626**	**232,857**	**215,656**	**213,899**	**210,758**

Table 1. New case detection trends in countries that reported >1000 new cases in the past 5 years.

encounter difficulties in reaching out to people living with leprosy to offer treatment. Although Indonesia has managed to reach a stage close to eliminating leprosy, the country has not been able to completely eradicate the disease. In some areas, such as Banten, West

Kalimantan, South Kalimantan, and East Java, leprosy remains prevalent. Tangerang District Health apparatuses in Banten province recently conducted a leprosy census and found that as many as 397 patients with leprosy were in need of serious attention. Leprosy remains a largely neglected disease, especially in the rural areas of the country, where little is known about it, and many suffer from the stigma and lack of knowledge surrounding the disease. East Java provincial Health Office Chief Dr. Harsono remarked in Surabaya that the local government would continue to take steps to reduce the number of leprosy patients and hoped that the figure will come down to less than one patient per 10,000 population. Leprosy has been around since the beginning of time, often surrounded by terrifying, negative stigma, and tales of leprosy patients being shunned as outcasts [9]. The 5-year strategy was launched previously: Strategy "The last impetus for eliminating leprosy as a public health problem" (2000–2005) aimed at eliminating leprosy as a public health problem at the country level. This is data-making and the general public, communications, and campaigns. All countries with a population of one million or more have achieved leprosy eradication as a public health problem at the national level [10].

Two successive strategies—the "Global strategy to further reduce leprosy burden and maintain leprosy control activities" (Period of planning stage: 2006–2010) and "Improved global strategy to further reduce the burden of disease due to leprosy" (Period of planning stage: 2011–2015)—maintaining an emphasis on reducing disease burden by focusing on sustainability through integration. They have moved from the target of "elimination" in terms of the prevalence of disease to the target, which emphasizes the decline in the number of new cases with G2D to promote early detection and reduction of transmission [11].

Leprosy has been linked to stigma throughout history [10]. Stigma manifestations, including self-stigma, social exclusion, and discrimination, although now more subtle with less exile, remain a reality for many affected people [12]. To help leprosy services become more responsive to problems surrounding leprosy-related stigma and reduce its impact, it is necessary to understand the stigma from the perspective of affected people and their family members. Also the views of key people in society, such as neighbors, teachers, religious leaders, and health workers, should be considered. The "human face of leprosy" edited by Gokhale and Sohoni in 1999 has emphasized the need for such stories [13].

3. Risk factor

Factors to consider are pathogenesis of germs, mode of transmission, environmental conditions, and genetic variants associated with susceptibility, immune change, and the possibility of reservoirs outside humans. Today's leprosy differs with environmental conditions, genetic variants associated with susceptibility, immune change, and the possibility of reservoirs outside humans. Today's leprosy differs from the leprosy of the past, but yet there are still many things that are not immediately known, so it is still a broad socioeconomic and challenge for scientists to solve. Research by Bakker et al. found that the risk factors of leprosy in Indonesia

are genetic, household size, and gender. People living in households with more than seven members had a risk of 3.1 [9, 10, 12].

4. Pathogenesis of leprosy

Leprosy onset is insidious. It is about the nerves, skin, and eyes. It can also attack the mucosa (mouth, nose, and pharynx), testes, kidneys, smooth/smooth muscle, reticulo-endothelial system, and vascular endothelium. Germs enter the body usually through the respiratory system. It has low pathogenicity, and only a small percentage of infected people show signs of the disease. Although infected, most of the population do not develop the disease. Upon entering the body, the bacilli will migrate to the neural network and enter Schwann cells. Bacteria can also be found in macrophages, muscle cells, and endothelial cells of the blood vessels. After entering Schwann/macrophage cells, the fate of the bacteria depends on the resistance of the infected individual to the infecting organism. Bacilli began to proliferate slowly (about 12–14 days for one bacteria split into two) inside the cell, released from the crushed cell and into the unaffected cells. Until this stage, people remain free from signs and symptoms of leprosy. When bacilli proliferate, the bacterial load increases in the body, and the infection is recognized by the immunological system. Lymphocytes and histiocytes (macrophages) invade infected tissue. At this stage, clinical manifestations may appear as nerve involvement with impaired sensation or skin patches. If not diagnosed and treated in the early stages, further progression of the disease is determined by the strength of the patient's immune response [14].

In people with strong cell-mediated immunity (CMI), granuloma formation occurs in skin nerves, and cutaneous nerve is enlarged and damaged. Often only a few infiltrated nerves are inflamed, but the inflammation inside the epineurium causes compression and destruction of the unmyelinated sensory and autonomous fibers. Myelinated motor fibers are affected last to produce motor damage. Severe inflammation can cause necrosis in the nerve. Clinical manifestations of sensory loss occur when nearly 30% of sensory fibers are destroyed. A good CMI manages to limit disease to nerve Schwann cells that result in pure leprosy. *M. leprae* can escape from nerves to adjacent skin all the time and causes classic skin lesions. Areas of the skin with relatively higher temperatures such as axilla, groin, perineum, and hairy scalp are usually spared. But in people with immature cell-cell immunity, the bacilli that enter Schwann cells multiply uncontrollably and destroy the nerves. Also, the bacilli released by infected and destroyed cells are swallowed by histiocytes. Histiocytes with bacilli in it become wandering macrophages. Bacilli multiply in this macrophage and run into other tissues through blood, lymph, or tissue fluid [14].

The modulation of lipid metabolism and reprogramming of mature Schwann cells have been suggested as a mechanism used by *M. leprae* to spread disease. New markers associated with local disease, dissemination, or occurrence leprosy reaction events include human interferon, CD163, microRNA-21, NOD2, galectin-3, and toll-like receptors. The role of keratinocytes other than macrophages is interesting to understand in the pathogenesis of leprosy. Adaptive

immune reports focus on the role of regulatory T cells and cytokines secreted by T helper cells in leprosy. Finally, a newly identified species named *M. lepromatosis* has been detected in patients with severe leprosy and erythema nodosum leprosum [8].

5. Clinical appearances

Based on two types of extreme immune responses, two polar forms (tuberculoid at one end and lepromatous in the other) of the clinical presentation of the disease occur. The disease may present with a clinical picture representing severity, anywhere in the continuous/variable spectrum between these two polar forms (see Appendix No. IV for Ridley's general overview and Jopling Hardness classification on leprosy, in the form of a continuous spectrum and Appendix III for differential diagnosis leprosy). People with a "good" CMI response develop a milder and localized form of disease (tuberculoid) with fewer bacterial loads, whereas people with weak or absent CMI develop a widespread spread of disease (lepromatous) with a high bacterial load.

The transmission of leprosy exactly is still understood. The human being is the main reservoir of leprosy infection, although by history, transmission through African green monkeys and Armadillos has been reported [15]. Other dissemination routes were suspected, but their role in the transmission of leprosy was not clearly defined [16]. *M. leprae* has a tropism for the skin and Schwann cells of the peripheral nerves. The primary sign appears as sensory neuritis, but in untreated patients seeking medical treatment at a late phase with severe motor impairment. Plantar ulcers, lytic bone lesions and ulnar nerve paralysis or lagophthalmos are frequent complications in leprosy patients [16].

Leprosy diagnosis remain based clinical findings and easy make for health workers to treat patients. Various clinical signs can be known during the early phase of leprosy, defined as indeterminate phase, so that it is difficult to diagnose the disease.

6. Immunology

M. leprae is an acid-alcohol-fast, Gram-positive obligate intracellular bacillus that shows tropism for cell and endothelial system and peripheral nervous system (Schwann cell). The leprosy bacillus has a predilection for macrophages, collecting intracellular globus. The bacteria never cultured in vitro but have been grown in the foot pads of 9-banded armadillos. Predisposed to infect cold areas of the body surface such as the skin, nasal mucosa, and peripheral nerves, the best temperature for *M. leprae* grows is 27 and 30°C. The efficacy of this pathogen within a narrow ecological niche is primarily explained by the properties conferred by two structural elements: the capsule and the cell wall [17]. The capsule is composed of two lipids, phthiocerol dimycoserosate and a phenolic glycolipid-1, which is the main target of humoral immune response, like immunoglobulin M-mediated [18]. Another important component of the cell wall is lipoarabinomannan, which is an antigen for the macrophage.

M. leprae has a predilection for Schwann cells, for specific binding to the G domain of the laminin alpha-2 chain, which is expressed specifically in the basal lamina of peripheral nerves [19]. Development of the disease depends on the immune status of patients. The role of genetics, associated with a susceptibility locus at chromosome 10p13, near the mannose receptor on the surface macrophages, is important in the phagocytosis. The other role of major histocompatibility complex (class II HLA) genes at chromosome 6 has been implicated in the clinical type of patient leprosy. The lepromatous form affects the skin and peripheral nerve, causing well-defined infiltrated plaques that are annular or ovoid form. Immunohistochemical findings in skin biopsies show mainly interleukins 4 and 10. The immune response to *M. leprae* is variable and gives rise to spontaneously changing clinical manifestations that may present as type 1 or 2 leprosy reactions [17].

The steps in the transmission of the disease are not entirely clear. However, it is acceptable that the mycobacterium reservoir is exclusively human, and it is most often transmitted through the spread of basil aerosol. In many cases, the infection appears to occur during childhood, with an incubation period ranging from 6 months to several years. Rarely, very long incubation periods of up to 40 years have been reported, although infection rates in adults with close contact with infected individuals (e.g. spouse) are as low as 5% even in long-term investigations [20].

Leprosy usually begins as an indeterminate form that can heal spontaneously, remain unchanged for long periods, or progress to a more severe form. About 95% of contact with the bacillus will result in spontaneous resolution without the development of clinical symptoms. This initial indefinite form can produce patches or macules of the skin, which is not clear with little hypopigmentation. In parallel, such patches may coincide with hypoesthesia of the corresponding skin nerve. If the disease develops, tuberculoid leprosy can develop as long as the host immune response is preserved enough. At this stage, rapid skin sensation loss due to severe neurological damage can occur, as well as local paralysis, loss of sweat and sebaceous glands, and hair loss. The skin shows macular lesions with significant hypopigmentation; peripheral nerves are infiltrated and may present as thick subcutaneous bundles. Secondary symptoms include bruised skin under hypoesthesia due to local external damage and superinfection with poor healing ulcers [21].

The lepromatous stage occurs in individuals with poor immune reactions. Clinically, this is the most severe form and can lead to mutilation. Skin lesions may appear as macules, papules, or plaques with hypopigmentation. The most affected areas are the ears, the central face, the fingers, and toes, but the distal extremities, such as the extensor surfaces of the thighs and forearms, can also be affected. Severe skin infiltrations in the peri-nasal and periorbital areas lead to "facies leonine" or lion face, associated with loss of eyelashes and lateral eyebrows ("facies leprosy"). Often, blindness can occur when the eye is exposed. Osseous resorption of the nostrils and destruction of the bridge of the nose result in severe facial mutilation. The *Mycobacterium leprae* affected throat can cause a distinctive hoarseness. In fact, all other body areas can also be affected, leading to varying clinical features. The fourth stage, called the borderline stage, also exists, which is somewhat intermediate between tuberculoid and lepromatous stages in clinical symptoms. Considering the various clinical symptoms, especially the early stages and stages of minor illness, leprosy can easily be confused with various other diseases. This is often important for historical

reconciliation, since evidence previously interpreted as supporting the diagnosis of "leprosy" should be carefully considered. In contrast, typical skeletal mutilation in the form of severe leprosy leaves a distinctive footprint of disease that may be identified in historic relics with high levels of certainty [21].

More advanced leprosy presentations have been reported and classified as tuberculoid leprosy and lepromatous leprosy. Many other clinical presentations, known as intermediate or borderline leprosy, have been identified and classified among the two types. The Ridley and Jopling System (RJ) defines five clinical presentations of leprosy: polar tuberculoid leprosy (TT), borderline tuberculoid leprosy (BT), borderline-borderline leprosy (BB), borderline lepromatous leprosy (BL), and polar lepromatous leprosy (LL) [22].

But according WHO classification, leprosy is divided into two major groups: pauci-bacillary subtype and multi-bacillary subtype. The WHO system is based on the quantity of skin lesions and the number of bacilli on skin smear. Skin smears are made by squeezing a fold of skin and making a shallow slit in the skin with a scalpel [23]. The two main categories of the WHO classification system are: (1) pauci-bacillary (PB) leprosy: ≤5 skin lesion with no bacilli on skin smear and (2) multi-bacillary (MB) leprosy: ≥6 skin lesion and may have bacilli on skin smears.

The Ridley-Jopling classification system is based on the histopathology of skin lesions and essentially represents a spectrum of disease. The spectrum of leprosy classification is not static. For example, in some cases, untreated TT can progress into LL, given a long enough time and the proper immunologic environment. There are the two classification systems that are mutually exclusive. Indeterminate and tuberculoid leprosy (TT) are commonly referred to as PB leprosy, while BB and LL are commonly referred to as MB leprosy [23, 24]. This was confirmed by the WHO Expert Committee on Leprosy at the seventh meeting in 1997, which defined a case of leprosy as follows: A case of leprosy is someone who has one or more of the following features and who still needs to complete a complete treatment: skin lesions hypopigmentation or redness with a definite loss of sensation, peripheral nerve involvement, as shown by neural thickening accompanied by loss of sensation, as well as positive skin-smears for acid-fast bacilli [24].

The following recommendations are based on the evidence just described:

a. Approximately 70% of leprosy patients can be diagnosed using a single mark of anesthetic skin patch, and this leprosy sign should be taught as widely as possible.

b. 30% of all patients, including many MB patients, do not show with this sign, and health care workers should be taught to suspect and refer other possible cases.

c. The referral of a suspect who has no anesthetic symptoms is given to a person with a higher experience who has been taught peripheral nerves should be straightforward. Palpation of only two nerves (ulnar and common peroneal) may allow diagnosis of as many as 90% of patients with neural enlargement.

d. Classification should be based on the number of skin lesions: PB < 5 patches; MB > 5 patches.

e. Skin smear on new case samples can provide quality control. Research into laboratory tests (e.g., serological or skin tests) that may be useful in the field in identifying *M. leprae* infection, diagnosing active disease, and classifying leprosy cases should be continued [25].

Leprosy patients have been traditionally classified based on the number and type of skin lesions into various clinical groups. However, according to current WHO guidelines, only the number of skin lesions determines the length of therapy patients received for leprosy. Various studies have reported and highlighted the differences between clinical and skin classification and nerve biopsy findings of leprosy patients [26]. The WHO classification (1988) for leprosy control program has differences with the 1998 WHO classification. The patients are categorized into PB and MB leprosy depending upon whether the slit skin smears demonstrate any bacilli or not. Earlier, the cases with a bacterial index of 2 or less had been categorized as PB, but later on, for feasibility and operational difficulties, all the patients with demonstrable bacilli in slit skin smear without any reference to bacterial index were to be categorized as MB, whereas 1998 WHO Classification for leprosy control program was based on the total number of leprosy lesions in the patient. This is a corollary to the fact that PB patients have good immunity and present with only limited number of lesions. Furthermore, the single lesions leprosy was also segregated on the ground that this can be treated with the limited amount of chemotherapy. On the practical side, the WHO expert committee's conclusions about new classification based on the number of lesions are translated as [27]:

1. Pauci-bacillary single lesion leprosy (SLPB)

2. Pauci-bacillary leprosy (2–5 skin lesions)

3. Multi-bacillary leprosy six or more skin lesions and also all smear positive cases

7. Pauci-bacillary

Pauci-bacillary leprosy is found in people with good CMI. The disease remains localized to produce single or little skin lesions with or without peripheral nerve involvement. The skin lesion may be macular (flat) or papule (slightly raised) and plaque. People with strong immune responses are capable of destroying large amounts of normal organisms and skin normally most of them exhibit negative skin examinations.

8. Multi-bacillary

Multi-bacillary leprosy is found in people with poor CMI. Bacilli multiply and spread more widely resulting in a common disease: usually accompanied by widespread lesions in the skin, nerves, and at lower levels in other organs such as the eyes, respiratory mucosa, testes, and reticuloendothelial system in men and usually the central nervous system and the upper reproductive system in women. The skin lesions may be multiple (borderline) or uncountable (lepromatous). Lepromatous lesions may be symmetrical and unclear bilateral macules or

diffuse infiltration, which may develop into plaque and nodule formation. In addition, there may be nasal bleeding and edema on both legs. If the patient does not receive treatment, the pauci-bacillary form of leprosy can be downgraded to the multi-bacillary form (from tuberculoid to lepromatous) through the borderline spectrum.

9. Leprosy reactions

A major problem in the management of leprosy patients is the occurrence of the leprosy reactions, which are consequences of the dynamic nature of the immune response to leprosy bacteria *(M. leprae)* that may occur before, during, or following the completion of multidrug therapy (MDT). Reactions in leprosy constitute the main complications of the disease, which can lead to serious consequences like nerve damage and deformities. Leprosy reaction is immunologically mediated episodes of acute or subacute inflammation, which interrupts the relatively uneventful usual chronic course of diseases affecting the skin, nerves, mucous membrane, and/or other sites. Reaction may occur in any type of leprosy expect the indeterminate type. Unless promptly and adequately treated, it can result in deformity and disability. Three types of reactions recognized are classified as: (1) type 1 reaction (T1R), (2) type 2 reaction (T2R) or erythema nodosum leprosum (ENL), and (3) the Lucio phenomenon [28]. Type 1 LR (T1R) and type 2 LR (T2R) are the main causes of nerve damage and permanent disability. The LR immune-pathogenesis is currently an important research focus, as it can provide relevant targets and goals for early detection and control of this episode [29].

9.1. Type 1 reaction

Type 1 reaction is associated with sudden alteration of cell-mediated immunity associated with a shift in the patient's position in the leprosy spectrum that is usually observed in borderline spectrum of the disease except very rare reports in lepromatous leprosy. If there is increase in the immunity, the shift is from borderline spectrum toward the tuberculoid pole and is called **upgrading** or **reversal reaction**. On the other hand, if there is sudden shift toward the lepromatous pole with reduction of immunity, it is called as downgrading reaction. These acute inflammatory events may accentuate the chronic course of the disease in the total clinical spectrum of the disease, usually in Borderline leprosy (BT, BB, and BL) and rare in LL. Clinical symptoms may present with complain of burning, stinging sensations in the skin lesions. They may have aches and pains in the extremities and loss of strength and/or sensory perception. Sign manifestations increased inflammation become erythematous swollen and may be tender looking like erysipelas, edema of extremities or face frequently accompanied by nerve involvement, rapid swelling with severe pain/tenderness (neuritis), and sometimes loss of nerve function [28].

9.2. Type 2 reaction

Type 2 reaction is an immune complex syndrome (antigen–antibody reaction involvement complement). It is an example of type III hypersensitivity reaction by Coombs and Gell classification.

T2R occurs mostly in lepromatous (LL) and sometimes in borderline lepromatous leprosy (LL), which occurs mostly during the course of antileprosy treatment. A few cases present for the first time with features of reactions before leprosy is diagnosed and treatment started. In one third of the cases, pain and swelling in the joints precede or are a component of other constitutional symptoms. In cutaneous onset, there may be appearance of skin lesions in the form of maculopapular, popular, nodular, or plaque type lesions before appearance of constitutional signs and symptoms. Fever, joint pain and constitutional sign and symptom, and skin lesion appear together. T2R without ENL is possible that the manifestations of the reactions may not be confined to the skin, and the patients may develop neuritis or systemic involvement or both, depending upon the target organs where immune complexes deposition occurs [28].

10. Lucio phenomenon

Lucio phenomenon is a special type of reactions observed in uniformly diffuse shinny infiltrative nonnodular form of LL, which is chiefly encountered in Mexicans. Its unique feature is that it is seen only in untreated cases. The etio-pathogenesis is less well understood. *M. leprae* are found unusually in large numbers in the endothelial cells of superficial blood vessels, and this finding may be responsible for the serious vascular complications seen during the reactive phase. There is marked vasculitis and thrombosis of the superficial and deep vessel, resulting in hemorrhage and infarctions of the skin. Clinical manifestations begin with slightly indurated red-bluish plaques on the skin with an erythematous halo, sometimes larger inflamed bullous lesions, which burst leaving a deep ulcer with jagged edges. The lesion takes about 3 weeks to develop an ulcer from the initial lesion, and it heals slowly and secondary cellulitis may complicate. Patients remain afebrile [28].

11. Management by community approach

Findings on the meaning of leprosy show confusion about the concept of leprosy and the lack of knowledge about the disease, its causes, and the mode of transmission. In addition, the views and perceptions of leprosy that have been internalized or newly acquired cause fear. The perception that leprosy is a highly contagious disease that can be transmitted by touching the same objects that have been touched by lepers is very worrying. Therefore, increasing knowledge about leprosy in affected people, community members, and health workers remains an important goal for leprosy services, and although that is not the only answer to stigma, it is an important prerequisite. Some challenges arise in relation to seeking care, recognizing the symptoms, making the right diagnosis, and sharing the diagnosis with the patient and the treatment. What is visible is the strength and influence of leprosy workers and therefore the destructive impact of their stigmatization behavior on the people they care for. White calls this the "iatrogenic stigma" or stigma produced by meeting patients with health care workers [30]. Multidrug therapy (MDT) was recommended as the standard treatment. The recommended treatment duration for MB is 12 months; otherwise, the duration for PB is

6 months. In 1997, WHO recommended treating patients with SLPB with single-dose regimen contain of 600 mg rifampicin, 400 mg of ofloxacin, and 100 mg of minocycline [16].

Corticosteroids should be given to patients experiencing leprosy reactions due to their ability as anti-inflammatory and immunomodulatory. Duration of treatment >12 weeks is recommended only if the patient is supervised by a specialist. Treatment duration is different for leprosy type 1 and type 2 reactions [31]. The morbidity report becomes very important in epidemiology because it is based on real events and not based on estimates or estimates. In addition, morbidity recording and reporting can be determined from changes in the incidence and prevalence of the disease until the results can be used for the planning and management of health problems. Full support from the Government is needed to carry out continuous activities in preventing the spread of leprosy [10].

12. Conclusion

Leprosy is still a public health problem in Indonesia. Although from year to year its prevalence decreased, new cases were still found in various populations and communities that did not belong to the risk group. Hard work is required to achieve the 2020 goal. Active case discovery is absolutely necessary for all layers of health workers, both in primary, secondary, and tertiary care. Government support both cross-program and cross-sectoral will help to reduce morbidity of leprosy. Public health centers are required to be more pro-active in sensitizing problems within their communities.

Author details

Prasetyadi Mawardi

Address all correspondence to: prasetyadimawardi@yahoo.com

Department of Dermatology and Venereology, Faculty of Medicine, Sebelas Maret University, Moewardi General Hospital, Surakarta, Indonesia

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