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This study was carried out to compare between diagnosis of leprosy for research clinically using Ridley Jopling criteria with laboratory examination. Eighty five patients who visits outpatient clinic in Dr.A.Rivai Leprosy Hospital in Sei Kundur Mariana Palembang diagnosed clinically using Ridley Jopling criteria and histopathologically from their skin biopsies based on the illustrated manual "Leprosy in the light skin" by D.L. Leiker and E. Nunzi, published by AIFO (Italy). Correlation between diagnosis based on skin biopsies and clinical diagnosis using Ridley Jopling classification was studied. There was agreement in 50 % of cases. The correlation was highest in IL (100%) followed by BL (77.7%), BT (62.5 %), TT (58 of .3.6%), LL (53.8%), and BB (7.69 %). The other interesting observation was that only 2 of BB cases diagnosed clinically but histopathologically found 13 cases. That mean the ability or precesision of clinical diagnosis to identify of early leprosy is 15.4 % only.

Keyword :

leprosy, Ridley-Jopling classification, histopathology

Daftar Pustaka :

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CORRELATION OF HISTOPATHOLOGICAL SKIN BIOPSIES WITH CLINICAL DIAGNOSIS IN LEPROSY

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ABSTRAK

Penelitian ini dilakukan untuk membandingkan antara diagnosis kusta untuk penelitian klinis dengan menggunakan kriteria Ridley Jopling dengan pemeriksaan laboratorium. Delapan puluh lima pasien yang mengunjungi klinik rawat jalan di Rumah Sakit Kusta Dr.A.Rivai di Sei Kundur Mariana Palembang didiagnosa secara klinis dengan menggunakan kriteria Ridley dan histopatologi Jopling dari biopsi kulit mereka didasarkan pada "Kusta di kulit terang" manual digambarkan oleh DL Leiker dan E. Nunzi, diterbitkan oleh AIFO (Italia). Korelasi antara diagnosis berdasarkan biopsi kulit dan diagnosis klinis menggunakan klasifikasi Ridley Jopling dipelajari. Ada kesepakatan pada 50% kasus. Korelasi tertinggi di IL (100%) diikuti oleh BL (77,7%), BT (62,5%), TT (58 dari .3.6%), LL (53,8%), dan BB (7.69%). Pengamatan menarik lainnya adalah bahwa hanya 2 dari kasus BB didiagnosa secara klinis tapi histopatologi ditemukan 13 kasus. Itu berarti kemampuan atau precesision diagnosis klinis untuk mengidentifikasi dini kusta 15,4% saja.

ABSTRACT

This study was carried out to compare between diagnosis of leprosy for research clinically using Ridley Jopling criteria with laboratory examination. Eighty five patients who visits outpatient clinic in Dr.A.Rivai Leprosy Hospital in Sei Kundur Mariana Palembang diagnosed clinically using Ridley Jopling criteria and histopathologically from their skin biopsies based on the illustrated manual "Leprosy in the light skin" by D.L. Leiker and E. Nunzi, published by AIFO (Italy). Correlation between diagnosis based on skin biopsies and clinical diagnosis using Ridley Jopling classification was studied. There was agreement in 50 % of cases. The correlation was highest in IL (100%) followed by BL (77.7%), BT (62.5 %), TT (58 of .3.6%), LL (53.8%), and BB (7.69 %). The other interesting observation was that only 2 of BB cases diagnosed clinically but histopathologically found 13 cases. That mean the ability or precesision of clinical diagnosis to identify of early leprosy is 15.4 % only.

Keywords: *leprosy, Ridley-Jopling classification, histopathology*

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INTRODUCTION

Leprosy is best understood as two conjoined diseases. The first is a chronic mycobacterial infection that elicits an extraordinary range of cellular immune responses in humans. The second is a peripheral neuropathy that is initiated by the infection and its accompanying immunologic events, but whose course and sequelae often extend many years beyond the cure of the infection and may have severely debilitating physical, social, and psychological consequences. Both aspects must be considered by clinicians, researchers, and policymakers who deal with persons affected by this disease. Leprosy is caused by Mycobacterium leprae presses itself in different clinico-pathological forms, depending on the immune status of the host (Scollard et al. 2006).

Leprosy presents a wide range of clinical and histopathological manifestations. This great diversity puzzled and frustrated clinicians and investigators until it was appreciated that this diversity was based on the ability of the host to develop a cellular immune response to M. leprae. A practical classification scheme based on the same principles was proposed by Ridley and Jopling, enabling a degree of global uniformity in clinical practice that gave renewed impetus to research on this disease. In the same decade, the discovery by immunologists of functionally and phenotypically distinct T- and B-lymphocyte subsets and their respective roles in cell-mediated and antibody-mediated immune responses revolutionized immunology. Scientists rapidly developed an entirely new set of tools and simultaneously discovered leprosy as a challenging human disease that appeared to be an ideal model with which to examine theories and methods related to

cellular immunity in humans. The convergence of these and other factors prompted an extraordinary burst of research on leprosy during the last three decades of the 20th century (Scollard et al. 2006, Bhatia et al. 1993).

The five-part Ridley-Jopling classification identifies, at one extreme, patients with a high degree of cell-mediated immunity and delayed hypersensitivity, presenting with a single, well-demarcated lesion with central hypopigmentation and hypoesthesia. Biopsies of these reveal well-developed granulomatous inflammation and rare acid-fast bacilli demonstrable in the tissues; this is termed the polar tuberculoid (TT) (Fig.1).

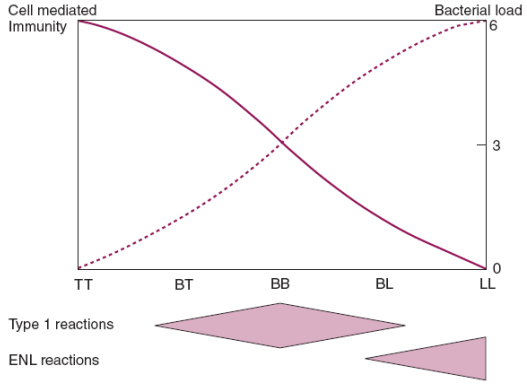

Fig. 1 The Ridley–Jopling classification and the relationship with host immunity.

© "The Ridley-Jopling Spectrum" (p. 577), from chapter 7.11.24 "Leprosy" by Diana Lockwood from "Oxford Textbook of Medicine 4th Edition" edited by Warrell, Cox, Firth, Benz (2003).

Fig 1. The Ridley-Jopling classification and the relationship with host immunity

At the other extreme, patients have no apparent resistance to M. leprae. These patients present with numerous, poorly demarcated, raised or nodular lesions on all parts of the body, biopsies of which reveal sheets of foamy macrophages in the dermis containing very large numbers of bacilli and microcolonies called globi. This nonresistant, highly infected form of the disease is termed polar lepromatous (LL). The majority of patients, however, fall into a broad borderline category between these two polar forms; this is subdivided into borderline lepromatous (BL), mid-borderline (BB), and borderline tuberculoid (BT). The study of pathological changes in leprosy lesions has contributed a great deal to understanding of the disease and clinico-pathological correlative studies have provided further insights into the disease, its varied manifestations and complications. Pathological examination helps to confirm a presumptive clinical diagnosis and also helps for exact typing (Chacko 1994, Lucus & Ridley 1989). The study was undertaken to correlate different types of leprosy histopathologically.

MATERIALS AND METHODS

A total of 85 leprosy skin biopsies from patient who visited outpatient clinic in Dr.A.Rivai Abdullah Leprosy Hospital Sei Kundur Mariana Palembang were studied over a period of two years from 2006 to 2008 included. All patient having standard clinical examination as known as Ridley Jopling criteria and small small surgery as named as biopsies and the material were sent to the Department of Pathology, Dr.Moh.Hoesin Hospital Palembang. Cases were selected regardless of their age, sex, socioeconomic status and occupation. All patients had sign informed concern before biopsies were taken. Biopsies were fixed in 10% formalin and processed. Five micron sections were stained with haematoxylin and eosin; modified Fite and studied.

RESULTS

From 85 leprosy skin biopsies only 56 cases can be diagnosed .There were 33 (65.05%) males and 23 (34.95%) females between 14 and 53 years of age. The majority of patients were in the age group of 40-49 years (25%) and the youngest affected was children with 14 years old. The distribution of cases in the leprosy spectrum based on clinical and histopathological criteria are as shown in table 1.

Table 1. Clinical and Histopathological Type of Leprosy

Type of leprosy	Clinical Number	%	Histopatho -logical Number	%
LL	9	16.07	13	23.2
BL	14	26.78	9	16.07
BB	2	3.57	13	23.21
BT	18	30.35	8	14.28
TT	9	16.07	12	21.42
IL	4	7.14	1	1.78
Total	56	100	56	100

* BT-Boderline tuberculoid leprosy
* BB-Borderline bordeline leprosy
* BL- Borderline lepromatous leprost
* LL-Lepromatous leprosy
* IL- Indeterminate leprosy

Although almost similar distribution of cases was seen in clinical and histopathological classification, number of BB cases were more by histopathological classification than by clinical classification. The correlation between clinical and histopathological classification was as shown in Table 2.

Table 2. Correlation Between Clinical and Histopathological Classification

Histopathological diagnosis	Clinical Diagnosis						% of agreement
	TT	BT	BB	BL	LL	IL	
LL (13)	1	1	--	4	7	--	53.8
BL (9)	--	1	--	7	--	1	77.7
BB (13)	--	7	1	3	1	1	7.69
BT (8)	1	5	1	--	--	1	62.5
TT (12)	7	4	--	--	1	--	58.3
IL (1)	--	--	--	--	--	1	100
Total (56)	9	18	2	14	9	4	

Overall coincidence of diagnosis of classification was seen in 28 cases (50%). The correlation between the two modes of classification was maximum at lepromatous pole than at tuberculoid pole, with the correlation being least in IL. The coincidence of classification by two modes, histopathological and clinical examination as percentage for each mode of examination was as shown in Table 3.

While correlating the histopathological diagnosis with clinical diagnosis, maximum correlation (100%) was noted in IL followed by BL (77.70%) ,BT(62.5%), TT(58.3%), LL(53.8%) and it was very poor in BB (7.69%). On the other hand, clinical diagnosis coincided with the histopathological diagnosis more often for TT (77.78.3%) and LL (77.78) type than for other types.

Table 3. Coincidence of type diagnosis of leprosy by two modes of examination expressed as percentage for each mode examination

Classification	Coincidences of diagnosis	
	Correlated /Histo %	Correlated /Clinic %
LL	53.8	77.78
BL	77.7	50
BB	7.69	50
BT	62.5	27.78
TT	58.3	77.78
IL	100	25

Table 4. Comparative study of clinico-pathological correlation by different workers (Leiker & Nunzi 2004, Bhatia et al. 1993, Jerath & Desai 1982)

Type of Leprosy	Jerath and Desai, 1982	Bhatia, et al. 1983	Nakadarni and Rage, 1999	Moorthy et al. Correlated 1999	Present study 2008
TT	74.5	50.00	97.2	46.15	58.3
BT	64.7	77.00	95.0	66.66	62.5
BB	53.8	25.00	89.0	50.00	7.69
BL	28.5	43.00	87.0	70.00	77.7
LL	61.5	91.00	98.2	80.00	53.8
IL	88.8	35.00	19.0	20.00	100

DISCUSSION

In this study clinical finding and histopathological finding were compared. Two agreement were disccused in this paper. The first one was clinical agreement meaning interobserver agreement between clinical finding compare with histopathological finding and the second one was histopathological agreement meaning the interobserver agreement between histopathological finding compare with clinical finding.

In the histopathological criteria for the diagnosis of leprosy, the presence of cellular infiltration of nerve branches is often associated with thickening of nerve branches and destruction of nerve fibres and the presence of intracellular acid-fast bacilli, in particular within nerve branches. However, in many cases of leprosy, acid-fast bacilli are not found. The distribution of cellular infiltrate around nerve branches and neurovascular bundles, hair follicles, sebaceous glands and sweat glands is sufficient to suspect leprosy but is not diagnostic. The finding of a few lymphocytes in a nerve branch, together with some proliferation of Schwann cells and a single intra-neural acid-fast bacillus is diagnostic of leprosy (Moorthy et al. 2001).

In indeterminate leprosy (IL), acid-fast bacilli are usually absent or few. The finding of higher number of bacilli indicates a development towards a lepromatous form of leprosy. The finding of epithelioid cells indicates a development towards a tuberculoid form of leprosy. The nerve shows slight proliferation of Schwann cells, a few perineural and intraneural lymphocytes and a single leprosy bacillus (Figure 2, arrow) (Leiker & Nunzi 2004),

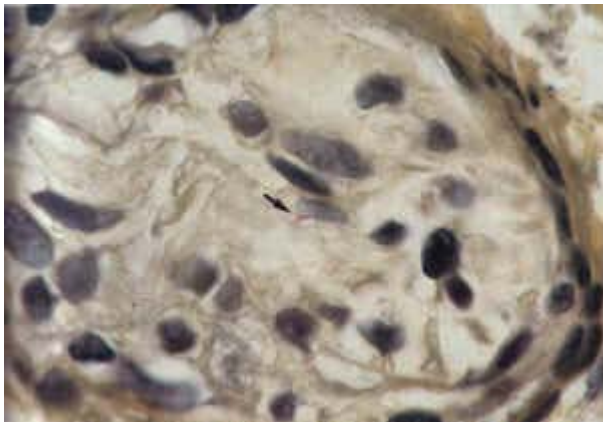

Figure 2. Indeterminate leprosy (IL)

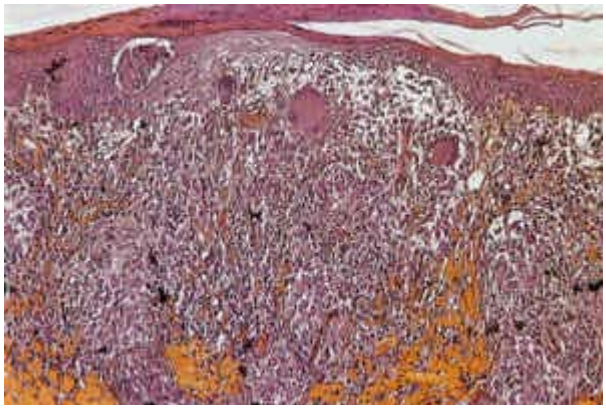

Figure 3. Tuberculoid leprosy (TT)

In tuberculoid leprosy (TT), the infiltrate consists of islands of epithelioid cells surrounded by a dense mass of lymphocytes. The infiltrates are located mainly in the superficial corium, pressing against the epidermis, with absence of an infiltrate free subepidermal zone and with flattening of the rete pegs. Langhans giant cells are often present. There is similar type of infiltrate as in Figure 2, but without any parakeratosis. Bacilli are absent (Figure 3) (Leiker & Nunzi 2004),

In borderline tuberculoid leprosy (BT), the epithelioid-tuberculoid infiltrate is separated from the epidermis by a free zone. The epithelioid cells show vacuolization and degeneration. A single Langhans giant cell is present. Bacilli were not found (Figure 4) (Leiker & Nunzi 2004),

In borderline lepromatous leprosy (BL), the infiltrates are round or band shaped containing slightly vacuolated macrophages and varying numbers of lymphocytes. The subepidermal zone is free from infiltrate. Large number of bacilli are present but globi are usually absent or few in numbers and small. Even with large number of bacilli in the nerve branches, there is relatively little destruction of nerve fibres, except in a very late stage (Figure 6) (Leiker & Nunzi 2004),

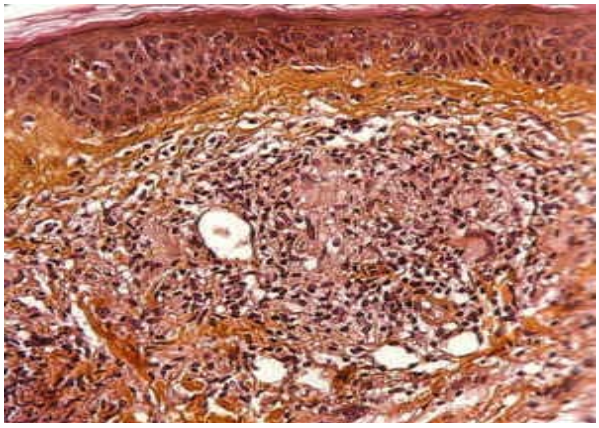

Figure. 4. Borderline Tuberculoid leprosy (BT)

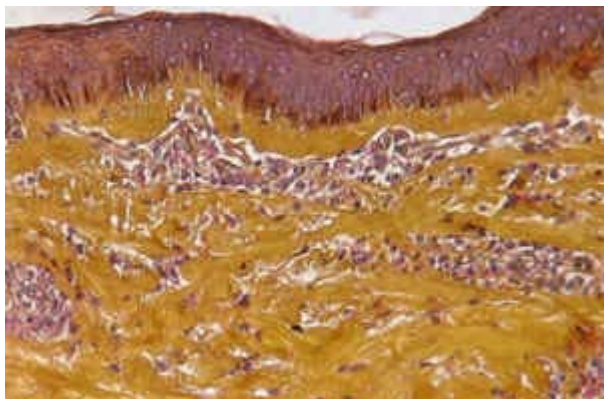

Figure. 5. Borderline leprosy (BB)

In borderline leprosy (BB), the infiltrates, separated from the epidermis by a free zone, consist of undifferentiated histiocytes and scattered lymphocytes. Fairly large number of bacilli are found, suggesting a development towards borderline lepromatous leprosy (Figure 5) (Leiker & Nunzi 2004),

A higher magnification of borderline lepromatous leprosy (BL), a showing undifferentiated histiocytes with scattered lymphocytes and bunches of bacilli, without globi (Figure 7) (Leiker & Nunzi 2004),

In lepromatous leprosy (LL), the infiltrates consist of vacuolated macrophages, containing abundant bacilli. Globi are present. In more advanced stages, giant vacuoles and very large globi are seen. Lymphocytes are few or absent. Foreign body giant cells may be present occasionally in advanced cases. The subepidermal zone is free from infiltrate. The nerve

sheaths are laminated (onion peel appearance). As compared with large number of bacilli in nerve branches, there is relatively little cellular infiltrate and relatively little destruction of nerve fibres, at least in early stages (Figure 8) (Leiker & Nunzi 2004),

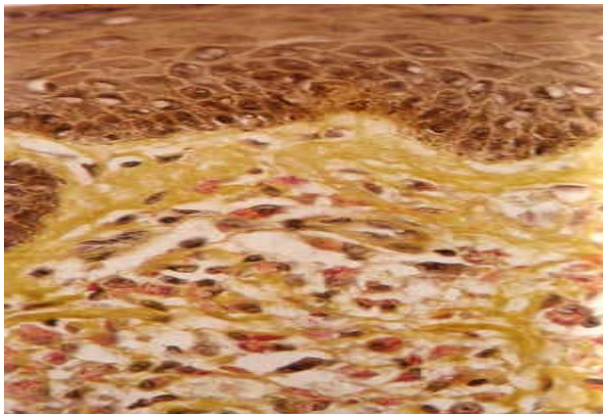

Figure. 6. Borderline lepromatous leprosy (BL)

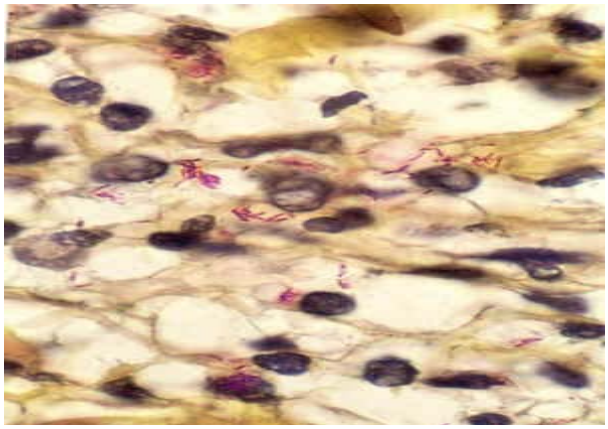

Figure 7. Borderline lepromatous leprosy (BL), magnification of the object in Figure 6

Fig. 8. Lepromatous leprosy (LL)

In present study, Ridley-Jopling classification was used to classify leprosy both clinically and histopathologically. Out of 56 cases, the diagnosis of 28 cases correlated clinically and histopathologically (50 %). The Ridley-Jopling classification is based on clinical, histopathological and immunological features, which is widely accepted by histopathologists and leprologists. The discordance between clinical and histopathological diagnosis was noticed because the clinical diagnosis was made on the lines of Ridley Jopling classification, even when a histopathologial examination had not been done (Bhatia et al. 1993). Comparative study of clinicopathological correlation by different workers in percentage can be seen in Table 4.

The correlation from table 4 almost similar at lepromatous pole (LL and BL) and the tuberculoid pole (TT and BT) like the study conducted by Nakadarni and Rage in 1999. The correlation almost similar in IL like the study conducted by Jerath and Desai in 1982. The correlation was also least in BB type leprosy similar to tht result of study conducted by Bhatia et al. (1983). There is no independent gold standard for diagnosis of leprosy. Taking any of the clinical signs, clinical types, histopathological parameters or histopathological types as a gold standard is not ideal. The variation in different studies may be due to different criteria used to select the cases and difference in number of cases of each type. Various factors also influence the histopathological diagnosis such as differences in sample size, choosing the biopsy site, age of the lesion, immunological and treatment status of the patient at the time of biopsy (Bhatia et al. 1993, Nadkarni & Rege 1982).

IL is an early and transitory stage of leprosy found in persons, whose immunological status is yet to be determined and it may progress to one of the other determinate forms of the disease. The IL type appears to be problematic due to the non-specific histology of their lesion. The diagnosis of IL also depends on many factors such as nature and depth of the biopsy, the quality of sections and number of sections examined, both H& E stained and acid-fast stained (Bhatia et al. 1993, Jopling & McDougall 1996, Harboe 1994).

CONCLUSION

Clinical diagnosis of early leprosy lesions offer difficulties even to experienced dermatologists and leprologists. A definitive diagnosis may be possible by histopathological examination. The other important point to be considered is inter-observer variation, both clinically and histopathologically. As there can be some degree of overlap between different types of leprosy, both clinically and histopathologically, correlation of

clinical and histopathological features along with bacteriological index appears to be more useful for accurate typing of leprosy than considering any one of the single parameters alone.

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