Correlation Between Risk Factors, Coinfection, and Recurrence of Erythema Nodosum Leprosum (ENL) in Patients with Multibacillary Leprosy

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KEYWORDS

Leprosy, Recurrent ENL, Coinfection, Tropical Disease

ABSTRACT:

Objective: The objective of this study was to determine the correlation between the incidence of co-infection and recurrence of Erythema Nodosum Leprosum (ENL).

Methods: A retrospective cross-sectional study was conducted using secondary medical record data from MB leprosy patients with and without ENL recurrence at Dr. Soetomo Academic General Hospital, Surabaya (2020–2024). A non-probability sampling technique was used.

Results: Total 95 patients met the inclusion and exclusion criteria. Male 74 patients (77.9%) more than female. The dominant age is <40 years as many as 60 patients (63.2%). Nutritional status was obtained most in the normal category 79 patients (83.2%). Results based on leprosy type the most number was type LL 37 patients (38.9%). The bacterial index was obtained the most with a number of <3 as many as 55 patients (57.9%), and the morphological index 0 in 50 patients (52.6%). The results of the onset of ENL were mostly obtained during MDT treatment, 53 patients (55.8%). Patients with co-infection without recurrence of ENL were 20 patients (43.5%), and patients with co-infection and recurrence of ENL were 26 patients (56.5%). The p value = 0.126, this shows that the incidence of co-infection with and without recurrence ENL is not significantly different, but the results of viral co-infection on ENL recurrence were significant showed p value = 0.030 and r = 0.218.

Conclusion: Viral co-infection related recurrent of ENL.

1. Introduction

Leprosy is a long-term infection caused by *Mycobacterium leprae*. This disease manifests in various forms of skin lesions and nerve damage, with symptoms ranging from mild skin discoloration to severe deformities and disabilities [1]. Patients with MB leprosy often develop severe immunologic complications in the form of Erythema Nodosum Leprosum (ENL) especially in Lepromatous Leprosy (LL) and Borderline Leprosy (BL) [2]. The ENL reaction occurs due to the formation of immune

complexes containing antigens derived from *Mycobacterium leprae*, this complex triggers a series of events leading to vasculitis phenomena, resulting in the development of soft and erythematous skin nodules and other systemic manifestations [3]. The count of new MB leprosy cases in 2016 and 2017 declined in comparison to 2015; however, the prevalence of patients experiencing ENL continues to increase almost every year (2015: 32%, 2016: 32%, 2017: 36%) [4]. The quantity of recent Hansen's disease cases discovered diminishes each year, yet the count of individuals facing ENL persists in rising, which may exert an adverse effect on the standard of life of sufferers, increased mortality, and a negative impact on the economic status of sufferers [5], [6]. Risk factors that can play a role in the occurrence of ENL such as gender, age, type of leprosy, *bacterial index* (BI), *morphological index* (MI), nutritional status and co-infection [7]. A *cross-sectional* study by Motta et al., on the relationship between co-infection and the occurrence of ENL, showed that co-infection was significantly associated with ENL ($p < 0.0001$) and the most common co-infection found was chronic oral infection (40/88; 45.5%) followed by urinary tract infection, sinus disorders, hepatitis B and C [8]. The results of the analysis also showed that MB leprosy patients with co-infection had a 42.963 times higher risk of experiencing ENL compared to MB leprosy patients without co-infection significantly. The incidence of ENL continues to increase with chronic and recurrent reactions [4].

Recurrent in ENL occurs 28 days or more after stopping ENL treatment. This condition appears influenced by several interrelated aspects. Risk factors suspected of triggering ENL recurrent are classified as inherent and external elements. Intrinsic factors consist of a history of previous ENL, type of leprosy, immune status and genetics. Extrinsic factors consist of stress, the presence of other infections, and hormonal changes. Currently, good research in Indonesia regarding the relationship between the incidence of co-infection and ENL recurrent in leprosy patients is still lacking, as well as data at Dr. Soetomo Surabaya hospital, so it does not provide clear information regarding whether there is a relationship between co-infection and ENL recurrence in MB leprosy patients.

2. Methods

This study was analytical observational research employing a retrospective cross-sectional design, conducted at the Dermatovenereology Outpatient Clinic of Dr. Soetomo Academic General Hospital in Surabaya. The research targeted MB-type leprosy patients who experienced ENL reactions. The sample comprised all individuals who satisfied the designated inclusion criteria. The inclusion criteria encompassed all patients documented in medical records with a confirmed diagnosis of MB leprosy along with ENL reactions, "both recurrent and non-recurrent, as well as those with co-infections," within the "Leprosy Division" of the "Dermatovenereology Outpatient Clinic" at Dr. Soetomo Hospital, Surabaya, from 2020 to 2024. Meanwhile, the exclusion criteria pertained to medical records that lacked confirmation of a co-infection diagnosis. Sampling followed a consecutive sampling method, utilizing secondary data extracted from the medical records. Patient data were obtained from both physical and electronic medical records of individuals diagnosed with multibacillary leprosy and ENL reactions in the "Leprosy Division" of the "Outpatient Clinic of Dermatology and Venereology" at Dr. Soetomo Hospital, Surabaya. All gathered data and study findings were documented in a data collection sheet for further analysis is categorized according to the objectives and types of data, after which the suitable statistical method is chosen. Univariate analysis is employed to outline the characteristics of the basic data in terms of frequency distribution, which is presented in the form of

graphs and tables. Bivariate analysis uses the Chi-Square test and Fisher exact test. The decision of the hypothesis test results can be applied, significant if $p \leq 0.05$.

3. Results

A total of 95 patients fulfilled both the inclusion and exclusion criteria. Where it was found that male was 74 patients (77.9%) more than females. The dominant age was <40 years as many as 60 patients (63.2%). Nutritional status in this study was indicated by BMI measurements, obtained the most in the normal category 79 patients (83.2%). The results based on leprosy type were shown with the largest number being type LL 37 patients (38.9%) then type BL as many as 35 patients (36.8%). The bacterial index was obtained the most with a number of <3 as many as 55 patients (57.9%), and the morphological index 0 was obtained in 50 patients (52.6%). The results of the most ENL onset were obtained during MDT treatment, namely 53 patients (55.8%) (Table 1).

Patients with co-infection without ENL recurrence were 20 patients (43.5%), and patients with co-infection and ENL recurrence were 26 patients (56.5%). The p-value = 0.126, this indicates that the incidence of co-infection of MB patients with ENL with and without recurrence is not significantly different, so proceed to divide by co-infection type as well as viral, bacterial, parasitic and fungal (Table 2). "The results of the analysis of the correlation between the incidence of viral co-infection and ENL recurrence showed significant with a p-value = 0.030 (p <0.05) (Table 3). The results of the analysis of the relationship between the incidence of bacterial co-infection and ENL recurrence showed a p-value = 0.568, this indicates that there is no correlation (Table 4). The results of the analysis of the incidence of parasitic co-infection and ENL recurrence showed a p-value = 0.1000 (Table 5). The analysis of the correlation between fungal co-infection and ENL recurrence showed a p-value 0.437 (Table 6).

Table 1

General description		n	%
Gender			
	Man	74	77.9%
	Woman	21	22.1%
Age			
	<40 years	60	63.2%
	≥40 years	35	36.8%
BMI			
	Underweight	15	15.8%
	Normal	79	83.2%
	Overweight	1	1.1%
Types of leprosy			
	BB	23	24.2%
	BL	35	36.8%
	LL	37	38.9%
Bacterial index			
	<3	55	57.9%
	≥3	40	42.1%

Morphological index			
	0	50	52.6%
	<5	30	31.6%
	≥5	15	15.8%
Onset of ENL			
	Before MDT	18	18.9%
	During MDT	53	55.8%
	After RFT	24	25.3%

Table 2

			No recurrent	Recurrent	Total	p-value
	No co-infection	n	29	20	49	
ENL		%	59.2%	40.8%	100%	0.185
	Co-infection	n	20	26	46	
		%	43.5%	56.5%	100%	

Table 3

			No recurrent	Recurrent	Total	p-value
	Other than viruses	n	43	32	75	
Viral co-infection		%	57.3%	42.7%	100%	0.030
	Virus	n	6	14	20	r = 0.218
		%	30%	70%	100%	

Table 4

			No recurrent	Recurrent	Total	p-value
	Other than bacteria	n	43	38	81	
Bacterial co-infection		%	53.1%	46.9%	100%	0.568
	Bacteria	n	6	8	14	
		%	42.9%	57.1%	100%	

Table 5

			No recurrent	Recurrent	Total	p-value
	Other than parasites	n	46	44	90	
Parasitic co-infection		%	51.1%	48.9%	100%	1,000
	Parasite	n	3	2	5	
		%	60%	40%	100%	

Table 6

			No recurrent	Recurrent	Total	p-value
	Other than Fungal	n	44	44	88	
Fungal co-infection		%	50%	50%	100%	0.437

Fungal	n	5	2	7
	%	71.4%	28.6%	100%

4. Discussion

The results of this study showed that patients with viral co-infection were obtained in total 20 patients. The relationship between the incidence of viral co-infection and ENL recurrence showed significant results with a value of $p = 0.030$ ($p < 0.05$) and the result of $r = 0.218$, this means that it has a weak relationship. Viral co-infection associated with ENL recurrence occurred in 14 patients (70%). The results of the identification of viral co-infection associated with recurrence in this study consisted of COVID-19 infection, varicella, hepatitis B, and influenza. In the remainder, there were no recurrences of ENL were influenza and herpes zoster

SARS-CoV-2 infection causes a cytokine storm, a condition in which large amounts of pro-inflammatory cytokines such as IL-6 and TNF-α are released. SARS-CoV-2 is known to increase neutrophil infiltration into tissues. Neutrophils play an important role in the pathogenesis of ENL, as skin lesions in ENL often show significant neutrophil infiltration. This high neutrophil activity contributes to inflammation and the formation of immune complexes in tissues [9].

Varicella-zoster virus infection has been shown to exacerbate ENL, potentially triggering a severe reaction in affected patients. Simultaneous infection with two different pathogens places additional stress on the immune system. This overload can sometimes tip the balance toward the exaggerated inflammatory response characteristic of ENL [10].

Studies on IL-7 and platelet-derived growth factor BB (PDGF-BB) mRNA expression have shown differential expression in ENL patients compared to those without such reactions, suggesting a possible role for biomarkers in predicting ENL recurrent. This background of hepatitis co-infection may further disrupt the normal cytokine balance, increasing the likelihood of ENL recurrent [11]. Influenza infection activates a robust immune response involving multiple cell types such as macrophages, lymphocytes, and dendritic cells. This response can sometimes inadvertently activate latent antigens associated with *M. leprae* or enhance pre-existing inflammatory processes, potentially triggering an ENL episode in susceptible individuals [12]. Influenza infection, however, creates an imbalance in cytokine production. Pro-inflammatory cytokines such as TNF-alpha play a key role in fighting pathogens but can also drive autoimmune-like reactions seen in ENL. If these pro-inflammatory signals intersect with residual *M. leprae* -specific immunity, they can trigger an ENL [11], [13]. Patients with viral co-infection increase the risk of ENL recurrence, and if not treated appropriately, it will worsen the patient's condition and reduce the patient's quality of life.

The results of the correlation between bacterial co-infection and ENL recurrence with a p value = 0.568. Of the 14 patients, only 8 patients were associated with ENL recurrence. Bacterial co-infections associated with ENL recurrence consisted of typhoid fever, bacterial vaginosis, syphilis, urinary tract infection, and acute suppurative otitis media. This study also identified bacterial co-infections that were not associated with ENL recurrence including chronic periodontitis, chronic gingivitis, and tuberculosis. These co-infections were identified in chronic ENL.

The results of the analysis of the relationship between parasite co-infection and ENL recurrence in this study showed insignificant results with a p-value of 0.1000. There was a total of 5 patients with parasite co-infection, and only 2 patients had ENL recurrence with parasite co-infection in the form of crusted scabies, the remaining 3 patients did not have ENL recurrence with parasite co-infection in the form of scabies, cutaneous larva migrans, and pediculosis capitis.

The results of the analysis of fungal co-infection showed a p-value = 0.437. Patients with fungal co-infection accompanied by ENL recurrence were only found in 2 patients with co-infection in the form of vulvovaginal candidiasis and tinea corporis et cruris. Patients with fungal co-infection and no ENL recurrence were 5 patients, there were onychomycosis, and tinea pedis. Onychomycosis is a fungal infection of the nail plate which is generally caused by dermatophytes such as *Trichophyton rubrum* and *Trichophyton mentagrophytes*. This infection is usually limited to the nail area and rarely causes a systemic inflammatory response, as well as tinea pedis, does not have a significant impact on triggering ENL recurrence, because it does not interact directly with the *M. leprae antigen* [14].

There are several limitations in this study. Not all ENL patients with recurrence accompanied by co-infection were examined further by experts such as dentists, internists, and pulmonologists, so there was no written follow-up regarding the diagnosis and treatment of co-infection and making patient data included as excluded.

5. Conclusion

There is an association between viral infection and ENL recurrence with a weak association strength. There is no relationship between bacterial, parasitic, and fungal co-infections on ENL recurrence. Another research design is needed to examine the relationship between co-infection risk factors and ENL recurrence.

References

[1] D. A. R. Dewi, C. B. P. Djatmiko, I. Rachmawati, N. Arkania, N. M. Wiliantari, and F. Nadhira, "Immunopathogenesis of Type 1 and Type 2 Leprosy Reaction: An Update Review," *Cureus*, vol. 15, no. 11, 2023.

[2] R. M. Bhat and T. P. Vaidya, "What is new in the pathogenesis and management of erythema nodosum leprosum," *Indian Dermatol. Online J.*, vol. 11, no. 4, pp. 482–492, 2020.

[3] E. Negera *et al.*, "New insight into the pathogenesis of erythema nodosum leprosum: the role of activated memory T-cells," *Front. Immunol.*, vol. 8, p. 1149, 2017.

[4] C. Fransisca *et al.*, "A retrospective study: epidemiology, onset, and duration of erythema nodosum leprosum in Surabaya, Indonesia," *Berk. Ilmu Kesehat. Kulit dan Kelamin*, vol. 33, no. 1, pp. 8–12, 2021.

[5] S. L. Walker, E. Lebas, S. N. Doni, D. N. J. Lockwood, and S. M. Lambert, "The mortality associated with erythema nodosum leprosum in Ethiopia: a retrospective hospital-based study," *PLoS Negl. Trop. Dis.*, vol. 8, no. 3, p. e2690, 2014.

[6] D. J. Chandler, K. S. Hansen, B. Mahato, J. Darlong, A. John, and D. N. J. Lockwood, "Household costs of leprosy reactions (ENL) in rural India," *PLoS Negl. Trop. Dis.*, vol. 9, no. 1, p. e0003431, 2015.

[7] H. K. Kar and A. Chauhan, "Leprosy reactions: pathogenesis and clinical features," in *Indian Assosiation of Leprologist Textbook of Leprosy*, New Delhi: Jaypee Brothers Medical Publishers Ltd, 2017.

[8] A. C. F. Motta, K. J. Pereira, D. C. Tarquínio, M. B. Vieira, K. Miyake, and N. T. Foss, "Leprosy reactions: coinfections as a possible risk factor," *Clinics*, vol. 67, pp. 1145–1148, 2012.

[9] D. E. Antunes, I. M. B. Goulart, and L. R. Goulart, "Will cases of leprosy reaction increase with COVID-19 infection?," *PLoS Negl. Trop. Dis.*, vol. 14, no. 7, p. e0008460, 2020.

[10] C. Kennedy and B. Naafs, "Borderline lepromatous leprosy, Erythema Nodosum Leprosum and a generalized varicella zoster virus infection: a deadly combination.," *J. Eur. Acad. Dermatology Venereol.*, vol. 31, no. 9, 2017.

[11] F. K. Bandjar *et al.*, "Analysis of interleukin 7 and platelet-derived growth factor-BB mRNA expression as potential markers in erythema nodosum leprosum," *Dermatology Reports*, vol. 16, no. 1, p. 9773, 2023.

[12] M. K. Sandre, S. M. Poenaru, and A. K. Boggild, "Erythema nodosum leprosum triggered by antecedent influenza vaccine and respiratory tract infection: a case report," *J. Cutan. Med. Surg.*, vol. 23, no. 1, pp. 114–116, 2019.

[13] L. S. Nascimento *et al.*, "Toxoplasma gondii infection and high levels of IgE are associated to erythema nodosum leprosy (ENL)," *PLoS One*, vol. 19, no. 6, p. e0300704, 2024.

[14] L. A. R. Fróes Jr, T. S. Toma, M. Jachiet, L. Rousset, R. E. Poderoso, and M. A. B. Trindade, "Bacterial, fungal and parasitic co-infections in leprosy: A scoping review," *PLoS Negl. Trop. Dis.*, vol. 17, no. 5, p. e0011334, 2023.