Analysis of interleukin 7 and platelet-derived growth factor-BB mRNA expression as potential markers in erythema nodosum leprosum

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Abstract

Erythema nodosum leprosum (ENL) is an immunological complication of leprosy characterized by acute inflammation of the skin, nerves, and other organs. Identifying laboratory parameters is important for early diagnosis of leprosy reactions. Various cytokine biomarkers have been examined and only a few studies have reported on angiogenesis in leprosy. This study aims to understand the pathomechanism of ENL by examining IL-7 and platelet-derived growth factor (PDGF)-BB mRNA expression that can be the development and consideration of new effective therapies to prevent reactions, recurrences, and defects in leprosy. The study used a cross-sectional analytic design. Sampling was done by peripheral blood from the patient and measuring mRNA expression with specific primers RT-PCR. The expression of mRNA IL-7 and PDGF-BB was significantly different between multibasilar patients without reaction and with ENL reaction, where there was an increased expression in ENL patients. This could be used as the development of potential biomarkers in ENL and development of new therapeutic intervention pathways in ENL.

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Introduction

Leprosy is a chronic infectious disease caused by Mycobacterium leprae attacks the skin, nerves, and other organs. The main problem in managing leprosy patients is the development of leprosy reactions which is an immunologically mediated episode of acute inflammation which, if not diagnosed and treated promptly, can lead to irreversible nerve damage function and permanent disability.[1,2]

There are two types of leprosy reactions; type 1 reaction (T1R) or reversal reaction (RR) associated with T helper (Th) 1 type immunity. T1R mainly occurs in borderline type leprosy (BT, BB, BL), and type 2 reactions (T2R) or erythema nodosum leprosum (ENL) associated with Th2-type immune responses. T2R mainly occurs in lepromatous (BL, LL) types of leprosy.[3,4]

ENL is an immunological complication mediated by neutrophilic immune complexes and vasculitis. This reaction is also associated with increased levels of proinflammatory cytokines, release of inflammatory cytokines, and followed by neutrophilic infiltration contributes to the development of a variety of characteristic clinical findings varying depending on the organs involved.[5,6]

Clinical manifestations and pathology that occur in leprosy depend on the patient's immune response to *M. Leprae*.[7] Identification of cytokine profile associated with the reaction may be helpful in early diagnosis and monitoring of therapy efficacy.[8] Several studies have been conducted to identify plasma factors for biomarkers associated with type 1 and type 2 leprosy reactions. The C-X-C motif chemokine ligand (CXCL) 10 and interleukin

(IL)-6 were proven as potential plasma markers for RRs, while IL-7, platelet-derived growth factor (PDGF)-BB, and IL-6 as markers for ENL reactions.[9]

IL-7 is a potent immunoregulatory cytokine produced by immune cells and tissue cells at sites of inflammation characteristic of several chronic inflammatory diseases and there is a correlation between IL-7 and parameters of disease. IL-7 is a regulator in B-cell development and proliferation and is critical for the survival of naïve and memory T cells.[10]

IL-7 primarily activates T cells and causes T cell-dependent activation of B cells, macrophages, and dendritic cells. Activation by IL-7 leads to the spread of autoimmunity and thereby via alternative cytokine-driven pathways contributes to enhanced autoimmunity and immunopathology. IL-7 also contributes to lymphoid neogenesis in patients with rheumatoid arthritis. In addition, IL-7 exacerbated tissue damage in several experimental models and induced catabolic factors in several humans in vitro assays. Together these data suggest that IL-7 plays an important role in T-cell-driven autoimmunity in several chronic inflammatory autoimmune diseases. This unique IL-7-driven inflammatory pathway may occur, at least in patient subpopulations or at certain stages of the disease, largely independent of TNF-induced immunopathology. Thus, this pathway may play a role not only in patients with arthropathy such as RA, as reported in this study, but also in other chronic inflammatory diseases. It has been reported that high levels of circulating IL-7 are detectable in LL patients with an ENL reaction compared to LL patients which support the role of B cell and T cell-mediated mechanisms in this reaction.[10,11]

PDGF is a dimeric protein released from activated platelets and is mitogenic to most progenitor mesenchymal cells like fibroblasts and smooth muscle cells. PDGF is involved in several physiological and pathological processes involved in the formation of new blood vessels, including wound repair, embryogenesis, atherosclerosis, and tumor growth.[12]

Endothelial cell proliferation and migration result in the formation of new blood vessels from pre-existing vessels, a process known as angiogenesis, which has also been studied in leprosy. In normal tissues, there is a balance between endogenous stimulators and inhibitors of angiogenesis. In the last two decades, researchers have been identifying and characterizing endogenous pro- and anti-angiogenic molecules. Growth factors shown to have significant proangiogenic effects are vascular endothelial growth factor (VEGF) and PDGF. In the ENL reaction, it is shown that there is a significant difference between ENL patients and controls in the increase in VEGF and PDGF-BB, this is an interesting finding because ENL is often associated with vasculitis. These findings require further research so that they can provide new clues in pathogenesis and markers in leprosy reactions.[9,13]

Objectives

So far, there has been no research on the pathomechanism of ENL through the IL-7 cytokine inflammatory pathway and the angiogenesis pathway through PDGF-BB by examining the functional abilities of the protein. Therefore our study aims to understand the pathomechanism of ENL by examining IL-7 and PDGF-BB mRNA expression that become the development and consideration of new effective therapies to prevent reactions, recurrences, and defects in leprosy.

Materials and Methods

This research was a cross-sectional analysis study. The samples were collected in the dermatovenereology center in Makassar and General Hospital of Haulussy Ambon. The mRNA expression was evaluated in the Laboratory of Molecular Biology and Immunology, Hasanuddin University. Eligible patients were men and women aged 16-40 years. Patients with pregnancy, tuberculosis and a history of steroids in the last two weeks were excluded. Totals of 30 multibacillary leprosy patients consisting of 15 non-reactions and 15 with ENL reactions. Patients were diagnosed based on the World Health Organization guidelines for leprosy, ENL reaction diagnosed by the finding of a sudden eruption of tender nodules, plaque, or ulceration.

The peripheral blood mononuclear cells were conducted and isolated. The DNA was extracted and quantitative real-time polymerase chain reaction (PCR) for IL-7 and PDGF-BB mRNA expression was performed using a real-time (RT) PCR Gene human IL-7 and PDGF-BB specific primer. Housekeeping Gene β-actin was quantified and used as internal controls for RT-PCR

Descriptive analyses were performed for all variables and reported as median (minimum-maximum) for non-parametric data and mean (standard deviation) for parametric data. The Mann-Whitney test was used to analyze the differences in IL-7 and PDGF-BB mRNA expression between samples with or without ENL reaction.

Results

This research was conducted at the dermatovenereology center in Makassar and General Hospital of Haulussy Ambon., with a total sample of 30 people with multibacillary type leprosy, consisting of 15 people without ENL reactions and 15 people with ENL reactions. Peripheral blood samples were taken from the patient, then extracted for being measured by RT PCR to detect mRNA expression.

Analysis of interleukin-7 mRNA expression

Analysis of IL-7 mRNA expression between multibacillary leprosy patients without reaction and with ENL reaction using the Mann-Whitney test.

Table 1 shows that the average value of IL-7 mRNA expression in the multibacillary leprosy group without reaction was 9.66 with a standard deviation of 0.43, while the average value of IL-7 mRNA expression in the multibacillary leprosy group with ENL reaction was 12.39 with a standard deviation 1.19. The median IL-7 mRNA expression value in multibacillary leprosy patients without reaction was 9.45, while the median IL-7 mRNA expression value in multibacillary leprosy patients with reactions was 12.34, while patients with ENL reaction showed increased expression. Based on the results of the analysis of the Mann-Whitney test, the value of $P<0.001$ shows a significant difference in IL-7 mRNA expression between multibacillary leprosy patients with or without ENL reaction.

Analysis of platelet-derived growth factor-BB mRNA expressions

Analysis of PDGF-BB mRNA expression between multibacillary leprosy patients without reaction and with ENL reaction using the Mann-Whitney test.

Table 2 shows the average PDGF-BB mRNA expression in the

multibacillary leprosy group without reaction was 6.83 with a standard deviation of 0.84, while the average PDGF-BB mRNA expression in the multibacillary leprosy group with ENL reaction was 9.13 with a standard deviation of 0.95. The median PDGF-BB mRNA expression in multibacillary leprosy patients without ENL was 6.82, the median PDGF-BB mRNA expression value in multibacillary leprosy patients with reactions was 9.15 mean while the patients with ENL reactions showed increased expression. Based on the analysis of the Mann-Whitney test, the value of P<0.001 shows a significant difference in PDGF-BB mRNA expression between multibacillary leprosy patients without reaction and with ENL reaction.

Discussion

ENL is an immunological complication of leprosy characterized by acute inflammation of the skin, nerves, and other organs. ENL occurs mainly during or after treatment, but there are also cases where it is an early manifestation before the diagnosis of leprosy. Episodes of ENL may regress or persist for years depending on the inflammatory response of each patient.[14]

The number of patients included in this study was 30 multibacillary leprosy patients with more males of 63.3% than females 36.7%. The youngest patient is 18 years old while the oldest patient is 40 years old. Leprosy can occur at all ages, mostly between 10-20 years and 30-60 years with more male sufferers than women (2-3 times greater). In endemic areas such as India, it is reported that the distribution of incidence is in the two highest age groups, 10-14 years and 35-44 years. Age and gender are not risk factors for ENL, as has been corroborated in various studies. Pregnancy and lactation are precipitating factors for ENL, with a higher incidence in pregnant and lactating women. Minimal evidence implicates psychological stress, puberty, co-infection, vaccination, HIV, malaria, and tuberculosis as precipitating factors but is inconclusive.[15,16]

ENL is an important public health problem in leprosy countries with significant physical, economic, and social impacts on patients and health systems. All available therapeutic management has an effect on their use: corticosteroids cause serious side effects and risk of dependence; pentoxifylline and clofazimine take time to control the reaction and thalidomide can cause a risk of peripheral neuropathy and teratogenicity.[14]

ENL reaction has been described as a deposit of immune complexes associated with cell mediated immunity involvement. The important role of the immune system in leprosy and leprosy reactions affects clinical manifestations.[17] Cytokines play roles in the protection and immunopathology of leprosy and are considered components of the leprosy reaction. Changes in cytokine activity have been reported in ENL, wherein increased levels of cytokines and other immunologic factors are associated with episodes of ENL.[8] Several studies have been conducted to measure cytokine levels associated with leprosy reactions. Barnes *et al*. reported an increase in Tumor necrosis factor (TNF) α levels in ENL patients which indicated that TNF-α could mediate immunopathological effects in leprosy reactions. Other studies have contradictive results wherein low TNF-α levels in ENL patients.[18] Belgaumkar *et al.* reported increased levels of IL-6 in patients with ENL, and another study by Stefani *et al*. reported increased levels of IL-6 and CXCL 10 in patients with RRs and is promising as a potential biomarker in RRs.[9,19]

In this study, there was a significant difference in IL-7 mRNA expression in patients with ENL compared to controls, wherein the ENL there was an increase in IL-7 mRNA expression. This study is in line with previous studies where Stefani *et al*. reported an increase in circulating IL-7 levels in ENL patients and is promising as a potential biomarker in ENL.[9]

IL-7 contributes to host cell defense by regulating the development of T lymphocytes, B lymphocytes, natural killer cells, and cytotoxic T cells. In addition, IL-7 has an important role in T-cell homeostasis and proliferation. By activating several intracellular signaling pathways, IL-7 promotes cell survival and proliferation of naïve and memory T cells.[20,21]

IL-7 is produced by cells such as liver cells, stromal cells in the bone marrow, and thymus and other epithelial cells, including keratinocytes and enterocytes. IL-7 receptor (IL-7R) is a heterodimeric complex consisting of an α-chain (CD127) and an α-chain of common cytokine receptors, which are associated with receptors for IL-2, IL-4, IL-7, IL-9, IL-15, and IL- 21, in a variety of cells. Thus, IL-7 has multiple biological activities and influences various cell types by binding to its receptors.[22]

Table 1. Analysis of interleukin-7 mRNA expression in multibacillary leprosy patients with and without erythema nodosum leprosum reaction.

IL-7	Without ENL	ENL	p
Mean ± SD	9.66+0.43	12.39±1.19	<0.001
Med	9.45	12.34	
Min-max	9.19-10.56	10.66±14.73	

IL-7, interleukin-7; ENL, erythema nodosum leprosum; SD, standard deviation.

Table 2. Analysis of platelet-derived growth factor-BB mRNA expression in multibacillary leprosy patients with and without erythema nodosum leprosum reaction.

PDGF BB	Without ENL	ENL	p
Mean ± SD	6.83±0.84	9.13±0.95	<0.001
Med	6.82	9.15	
Min-max	6.17-7.54	7.72–10.53	

PDGF, platelet-derived growth factor; ENL, erythema nodosum leprosum; SD, standard deviation.

Recent studies have shown that IL-7 is overexpressed in several autoimmune diseases. It primarily acts on T cells inducing T helper cells (Th)1- and Th17-related cytokine secretion, dendritic cell activation, chemokines, adhesion/molecular cost-stimulation and macrophage activation.[10,23]

Increased concentrations of IL-7 have also been reported in autoimmune diseases such as RA. IL-7 and IL-7R expression in RA is related to disease activity score and TNF transcription. The correlation with measures of disease activity suggests that IL-7 may substantially contribute to the perpetuation of Th1- and TNF-α-mediated proinflammatory responses in patients with RA. TNF-α production can result from direct stimulation of T cells or macrophages. In addition, since IL-7 can increase the expression level of costimulatory molecules (*e.g.*, CD69), it might mediate T-cell-dependent regulation of TNF-α by macrophages.[24]

The function and regulation of IL-7 have been studied with some general conclusions can be drawn from the review. First, most types of immune cells are tightly regulated by IL-7. Second, although there is a common effect, the final effect of IL-7 regulation differs by cell type. Finally, the expression of IL-7 positively regulates the expression of pro-inflammatory cells and cytokines, indicating that the application of IL-7 is a promising therapeutic strategy for many diseases.[25]

IL-7 is a cytokine that has a growth-promoting effect on B cell progenitors. B cells are considered precursors for antibody-secreting plasma cells. This cell type can also act as an antigen-presenting cell. B cells are involved in the initiation and regulation of cell responses. The involvement of B cells in the mechanisms of autoimmune disorders, such as RA and systemic lupus erythematosus is currently being revisited. The same is true of the role of B-cells in ENL pathogenesi.[26] B cells are not thought to be significantly involved in the pathogenesis of ENL. However, in ENL, an increase in immunoglobulin G-secreting B cells was found. The increase in IL-7 mRNA expression in the ENL reaction supports the role of B cells and T-cells mediates in the mechanism of this reaction.[27]

ENL is a humoral immune response characterized by the occurrence of immune complex phenomena due to reactions between *Mycobacterium leprae* antigens and antibodies and complement. To implicate immune complexes in causing ENL, deposition of immune complexes in tissues, presence of bacterial antigens in immune complexes, and interaction of immune complexes with complement cells and phagocytic cells are required.[6]

The vascular status of the skin is considered an important pathogenic factor in leprosy, and the study of dermal vascular changes in leprosy is an interesting subject. The underlying immunopathology of ENL involves antigen-antibody-mediated vasculitis. In chronic inflammatory processes, there is a relationship between angiogenesis and the cells involved in the inflammatory infiltrate.[28]

There have been many studies on angiogenesis in neoplasia, and the importance of angiogenesis has been recognized in inflammatory and infectious processes. Currently, new angiogenesis inhibitors that can normalize or block angiogenesis are being developed for the treatment of inflammatory diseases and neoplasia.[29]

Several studies have been conducted to identify cytokine biomarkers in leprosy reactions but only a few studies have been conducted for angiogenesis in leprosy. Several studies have correlated the neovascularization observed in leprosy with increased bacterial indices and disease progression. However, the occurrence of neovascularization in reaction episodes or regressive leprosy lesions has not been reported.[13] Therefore, a more detailed study of angiogenesis in leprosy is important to understand the pathophysiological mechanisms and to identify new therapeutic targets that may aid in the treatment of this disease.

Growth factors that have been shown to have significant proangiogenic effects are VEGF and PDGF-BB. In this study, there was a significant difference in PDGF-BB mRNA expression in patients with ENL compared to controls, whereas in ENL patients there was an increase in PDGF-BB mRNA expression. This study is in line with previous studies where Stefani *et al*. reported an increase in circulating PDGF-BB levels in ENL patients and is promising as a potential biomarker in ENL.[9]

The significant difference in PDGF-BB mRNA expression in ENL patients proves the involvement of angiogenesis in the pathomechanism of the leprosy reaction. In ENL, the angiogenesis that occurs is a response to the release of pro-inflammatory cytokines and chemokines secreted during the inflammatory process which are strong activators of endothelial cells to induce the formation and proliferation of new vessels as well as vasodilation, recruitment, and adhesion of inflammatory cells to endothelial cells. In addition, immune complex deposits can also trigger T-cell activation which will further trigger proinflammatory cytokines that cause excessive immune complex deposits and vasculitis.[28]

PDGFs and their receptors (PDGFRs) have served as prototypes for growth factors. The role of PDGF signaling has been described in early blood vessel formation and hematopoiesis. PDGF signaling is involved in a variety of diseases commonly observed in epithelial cancer, where it triggers stromal recruitment and may be involved in the epithelial-mesenchymal transition, thereby influencing tumor growth, angiogenesis, invasion, and metastasis.[11]

PDGF is involved in three groups of diseases: tumors, vascular disease, and fibrosis. A common feature that emerges in most fibrotic diseases is the release of PDGF by inflammatory cells, such as activated macrophages. These same cells also produce inflammatory cytokines that upregulate PDGFR in cells.[11]

In leprosy, inflammation of the nerves can extend across the nerve compartments, causing severe loss of myelinated large and small fibers along with disrupted non-myelinated fibers, resulting in denervated Schwann cells. This pathogenic process progresses to nerve damage and fibrosis. Fibrosis of the peripheral nerves is the final stage of leprosy neuropathy and the cause of the resulting permanent impairment of nerve function.[13] Increased expression of PDGF-BB in ENL patients can also indicate the process of nerve denervation and fibrosis that can occur. Preventive action to avoid this pathological condition is very important for the quality of life of leprosy patients. Further research on angiogenesis in leprosy and leprosy reactions is necessary to enhance our understanding of the pathomechanism and identify new therapeutic targets for leprosy. Angiogenesis inhibitor drugs can be considered for the treatment of leprosy, leprosy reactions, and for preventing the development and severity of leprosy reactions. El-Khalawany *et al*. reported a decrease in angiogenesis markers in leprosy patients after treatment with antibiotics that have antiangiogenic effects. The synergistic antiangiogenic effect of minocycline and rifampicin shows promise and effectiveness in leprosy treatment.[30] We hope that our research will contribute to the development of new intervention pathways and therapeutic targets that are effective in treating leprosy reactions and preventing permanent disability. Further research on the widespread use of antiangiogenic administration in leprosy and leprosy reactions, particularly in endemic areas, is highly desirable.

Conclusions

ENL is an acute complication of immunologically mediated leprosy. The pathogenesis of ENL involves the interaction of various factors with different inflammatory pathways. The humoral immune system, T-cell mediation, proinflammatory cytokines, immune complex deposits, and vasculitis have been implicated in the pathogenesis of ENL and are interconnected. In our study, we investigated the pathogenesis of ENL by examining the proinflammatory cytokine IL-7 and the processes of vasculitis and angiogenesis through the examination of PDGF-BB.

To our knowledge, there is only one study that has examined this inflammatory pathway by assessing blood circulation levels. In our study, we assessed the functional activity of the proteins by examining the expression of IL-7 and PDGF-BB mRNA. The results of the study revealed a significant difference in IL-7 mRNA expression and PDGF-BB mRNA expression between multibacillary leprosy patients without reactions and with ENL reactions. Patients with ENL reactions exhibited higher mRNA expression levels.

These findings are expected to provide further insights into the pathomechanism of ENL and could be used to develop targeted therapeutic interventions in managing ENL reactions. The aim is to prevent reactions, recurrences, and irreversible complications, thereby improving the quality of life and the social and economic well-being of individuals affected by leprosy.

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