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Mini-Review Article

Role of Lymphocytes and Atyphical Lymphocytes in Dengue Hemorrhagic Fever: A Literature Review

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ABSTRACT

Dengue hemorrhagic fever (DHF) is still a major problem in the world. It diagnosis is based on clinical and supporting examinations including leukocytes and platelets examinations, as well as antigen and antibody tests for dengue virus. Prompt and early diagnosis will reduce the risk of disease severity. Examination of lymphocytes and atypical lymphocytes are done to strengthen the diagnosis of dengue hemorrhagic fever patients. Lymphocytes in dengue hemorrhagic fever have their own characteristics and roles in relation to the body's immune system. Lymphoctes and atypical lymphocyes are increased in DHF patients. In this review, the characteristics and role of lymphocytes and atypical lymphocytes are described in dengue hemorrhagic fever.

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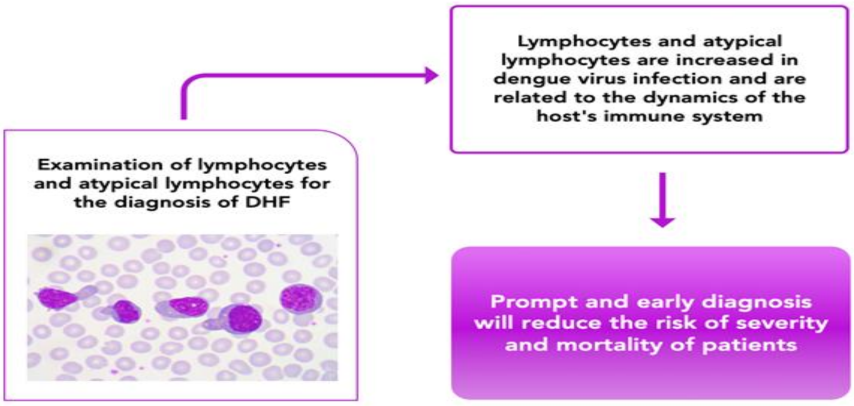
G R A P H I C A L A B S T R A C T



Introduction

Dengue hemorrhagic fever (DHF) can be a life-threatening disease if it develops into dengue shock syndrome (DSS). The DHF signs include high and sudden fever, thrombocytopenia, leukopenia, lymphocytosis, and increased hematocrit which can cause bleeding complications, severe shock with undetected blood pressure, and pulse which can result in the death [1]. Diagnosis of DHF is based on the World Health Organization (WHO) criteria which are classified into four degrees based on the disease severity. In cases of DHF, thrombocytopenia and leukopenia were found. Neutropenia, eosinopenia, basopenia, monocytopenia, lymphocytosis, and atypical lymphocytes were found changes in color, contour, and texture on a 60x magnification microscope [2].

Lymphocytes in dengue infection

Lymphocytes are white blood cells found in the immune system and mainly play a role in adaptive immunity. Lymphocytes are generally divided into B lymphocytes (B cells), T lymphocytes (T cells), and natural killer cells (NK cells). Lymphocytosis is occurred due to infection dengue [3-5].

In DHF, there is an increase in viral replication in monocytes or macrophages through Fcy receptors by heterotypic antibodies that fail to neutralize the virus through the Fc portion of Ig-G which forms a viral antibody complex.

Increase in dengue virus infection was first reported in 1977 where IgG antibodies depended on the Ig-G subclass, this phenomenon was observed using polyclonal and monoclonal dengue virus antibodies [6]. Circulating dengue virus binds to specific IgG and forms immune complexes. These immune complexes are found in 48-72% of DHF patients. The role of dengue virus-specific T lymphocytes in the infection healing is not known. It is suspected that dengue virus-specific CD4+ and CD8+ T lymphocytes are able to lyse cells infected with dengue virus by eliminating these monocyte cells. Therefore, controlling infection, virus-specific T lymphocyte activation depends on the viral epitope, especially NS3, E, and NS1 which occupy CD4+ and CD8+16. The dengue virus antibody complex causes cross-reactive activation of CD4+ and CD8+ cytotoxic lymphocytes releasing cytokines and lysing infected monocytes mediated by these lymphocytes [7]. There are several theories about lymphoctes in DHF.

First is the mediator theory, the mediator theory is based on several things, namely virus-infected macrophages secrete mediators or cytokines, the function of cytokines is as mediators in natural immunity caused by stimulation of infectious substances, as regulators regulate lymphocyte activation, proliferation, and differentiation, as a non-specific activator of inflammatory cells and as a stimulator of growth and differentiation of mature leukocytes.

The critical period in DHF is short, and then followed by a fast healing period without sequelae, experts have compared it to septic shock [8].

This theory was developed together with the role of endotoxin and lymphocyte cells. Endotoxin will activate the cytokine cascade especially TNF-ά and interleukin-1. In DHF shock, there is 75% endotoxemia, while in those who are not shocked, there is 50%. Tumor Necrosis Factor Alpha increases from the start of the disease course and will decrease after the infection subsides, interleukin-6 increases in DHF with shock [2].

In general, an incoming viral infection will elicit a response from T lymphocytes, and then virus-specific serotype peptides will be carried by MHC class I and presented on the viral surface. The viral epitopes are recognized by CD4+ and CD8+ T lymphocytes which then activate T lymphocytes by releasing lymphokines at higher levels. Activated monocytes release factors as a result of interaction with cytotoxic lymphocytes. This cycle produces high levels of lymphokines such as IL-2, monokines such as TNF and chemical mediators such as C3a and C5a in a short time [9].

The next theory is the theory of apoptosis, namely the physiological process of cell death which is a reaction to various stimulants. This process can be divided into two stages, namely damage to the cell nucleus, and then changes in cell shape and cell membrane permeability. As a result of this apoptosis, fragmentation of the cell's DNA will occur, cytoplasmic vacuolization, blebbing and binding of plasma membrane granulations into subcellular DNA containing apoptotic bodies [10].

Cytotoxic T lymphocytes signal protease proteins that induce target cell apoptosis. As a result of DEN virus infection, activated T lymphocytes show high levels of T expression and are highly susceptible to apoptosis. In severe cases of DHF, there is liver damage, Councilman bodies are present. It is possible that this is an apoptotic process in liver cells. Theories that focus on cellular processes override those of immunopathology. According to the experts in this field, viral replication events in macrophages are also opposed when viral apoptosis occurs and scattered cells are eaten by macrophages or phagocytosed [11-13].

Furthermore, the endotoxin theory indicates that as a result of shock in DHF, ischemia will occur in the tissues and in the intestine, at that time translocation of bacteria occurs so that both the bacteria and their metabolic products, including endotoxins in the intestinal flora, can enter the circulation as a result of endotoxins, can exacerbate the current shock [14-17].

Intestinal bacterial endotoxin plays a role in the severity of clinical symptoms of DHF, because endotoxin activates the cytokine cascade, especially TNF (Tumor Necrotizing Factor) and interleukin-1 (IL-1). In DHF shock, there is 75% endotoxin and in DHF without shock, there is 60%. In severe gastrointestinal bleeding, endotoxin levels were found to be higher than those with mild gastrointestinal bleeding. Intestinal bacterial endotoxins can enter the blood circulation due to the translocation of intestinal bacteria into the blood circulation due to damage to the intestinal lumen [16, 18].

Atypical lymphocytes

Increase of atypical lymphocytes is an increase in blue plasma lymphocytes, namely reactive lymphocytes as an immune response indicating the presence of a virus and can be observed in peripheral blood smears [19-21]. Dengue virus infection causes activation of the immune system, impaired immune response such as inversion of the CD4/CD8 ratio not only interferes with the immune system's ability to clear the virus, but also causes excess production of cytokines that influence T lymphocytes to differentiate into atypical lymphocytes [22, 23].

The number of blue plasma lymphocytes is calculated per 100 leukocytes. Blue plasma lymphocytes are lymphocytes with dark blue cytoplasm and are larger in size [22]. Wide cytoplasm is with fine to very pronounced vacuolization and clear perinuclear areas. The nucleus is located at one edge of the cell, oval, or kidney-shaped [25]. Nuclear chromatin is coarse and sometimes nucleoli are present in the nucleus. In the cytoplasm, there are no azurophilic granules, the area adjacent to the erythrocytes is not indented and does not turn blue. If a person's blue plasma lymphocyte value reaches ≥ 4%, it can be ascertained that the person is infected with the dengue virus. The average number of blue plasma lymphocytes in patients with dengue fever (DF) and dengue hemorrhagic fever (DHF) peaked on the sixth day of illness [25, 26]. Patients with dengue shock syndrome (DSS) have the highest number of blue plasma lymphocytes at the time of shock. The number of blue plasma lymphocytes for each clinical type has a significant difference and higher according to the severity of clinical spectrum. The more severe the immune response that occurs, the more severe the clinical spectrum experienced [2, 22].

Conclusion

DHF is still a health problem and can lead to severity. Lymphocytes and atypical lymphocytes are increased in dengue virus infection and are related to the dynamics of the host's immune system. However, the DHF diagnosis considers clinical and other supporting aspects to reduce the risk of severity and mortality of patients.

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