L-1α and IL-8 levels in leukopenic leukemic Patients With Bacteremia

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ABSTRACT:

BACKGROUND:

Interleukin-1α and Interleukin-8 are an inflammatory cytokines. They are a heterogeneous group of humeral mediators of the inflammatory response. In leukemic patient's leukopenia developed as a result of cytotoxic chemotherapy and/ or disease itself. Therefore, those patients were suffering from low number of leukocytes in addition to defects in the function of these cells. Normally leukocytes are the main source of cytokines production.

METHODS:

IL-1α and IL-8 were studied in (84) adult patients, males and females and more than 15 years old. The leukemic patients were suffering from leukopenia and bacteremia. The study including (20) healthy. Interleukin-1α and interleukin-8 concentrations were measured by using a commercially available enzyme-linked immunosorbent assay (ELISA).

RESULTS:

Statistical analysis shows significant increase in the levels of IL-1α and IL-8 between leukopenic leukemic patients with bacteremia and healthy control group.

CONCLUSION:

Leukopenic leukemia patients strikingly show distinct increases in plasma IL-1α and IL-8 levels during bacteremia.

KEYWORDS: Bacteremia, Leukemia.

INTRODUCTION:

Leukemias are a heterogeneous group of neoplasms arising from the malignant transformation of haemopoietic cells. Leukemia cells proliferate primarily in the bone marrow and lymphoid tissues where they interfere with the normal haemopoiesis and immunity; then emigrate into peripheral blood and infiltrate other tissue.Leukemias are classified according to the cell types primarily involved (lymphoid or myeloid) and as acute or chronic based upon the natural history of the disease [1-3].The specific drug which is used for treatment of leukemia generally aggressive. Their major antitumor effects are on actively dividing cells, so normal tissues with a high rate of cells proliferation are also affected by these agents [4, 5]. Decreased immunity is on the top of these effects caused by these drugs [6]. Leukopenia may occur as a result to this treatment. Leukopenia is defined as circulating leukocytes count is less than $4x10^9$ cell/litter [7].

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Leukocytes are normally the main producers of inflammatory cytokines [8, 9].Cytokines are produced by lymphocytes, monocytes, macrophages, and, for some cytokines, also fibroblast, neutrophils, endothelial cells, or mast cells [10]. The major functional activities of cytokines are concerned with the regulation of the development and behavior of the immune effector cells. Interleukin-1α is rapidly synthesized by mononuclear cells, primarily monocytic phagocytes that have been stimulated by microbial products or inflammation. The molecular weight of the mature forms is 17,500 [11, 12]. Among cytokines, only IL-1 and tumor necrosis factor (TNF) can induce IL-8 gene expression at the transcriptional level [13]. IL-8 is produced by many different cell types such as monocytes, macrophages, endothelial cells, fibroblasts and neutrophils. Interleukin-8 may play major roles in the in flammatory process by recruiting neutrophils and T-cells into inflammatory sites. Another important function of IL-8 is its ability to activate neutrophils following their attachment to vascular endothelium. IL-8 is one of the chemokines which are 8-to-10 kd proteins with 20 to 70 percent homology in amino acid sequences [14].

Because of the fact that the patients included in our study have disturbances in their innate immune system this immunological study was conducted to detect the role of IL-1α and IL-8 in the circulation of those patients during bacteremia.

MATERIALS AND METHODS:

A total of 28 adult patients (more than 15 years of age). Those leukemic patients suffering from leukopenia and bacteremia (16 males, 14 females). They were admitted to Baghdad teaching hospital. Those patients with (Acute myeloid leukemia =19, Chronic lymphoid leukemia =5, Acute lymphoid leukemia =2, Chronic myeloid leukemia=2). They were bacteremic patients. 20 apparently health adult individuals. Males and females.

Two milliliter of blood was taken from each patients and healthy controls. The blood was injected into a plane tube with no anticoagulant, left to clot at room temperature then centrifuged. Serum was collected in two separated tubes and stored at (-40°c) until used for investigation (Estimation of serum IL-1α and IL-8 levels) (18). The IL-1α and IL-8 concentrations were measured by using a commercially available enzyme-linked immunosorbent assay (ELISA).

The principle of the test was carried out according to the assay procedure given by manufacturing company Immunotech. Sample results are calculated by interpolation from a standard curve that is performed on the same assay as that of the sample. Data have been analyzed statically using SPSS program version 10. Analysis of quantitative data was done using ANOVA. Acceptable level of significant was considered to be below 0.05.

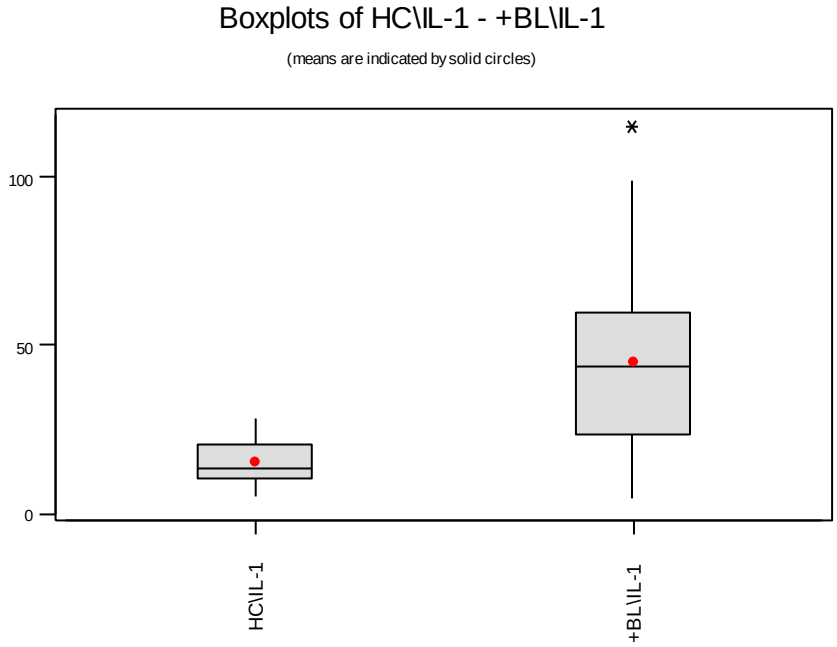
RESULTS:

Figure (1) shows the distribution of ELISA reading of IL-1α of the healthy control group and leukopenic leukemia patients with bacteremia.

The mean reading of healthy control group was 15049 pg/ml a SD of ±6.89, while the mean reading of leukopenic leukemia patients was (45.04 pg/ml a SD of ±26.66).

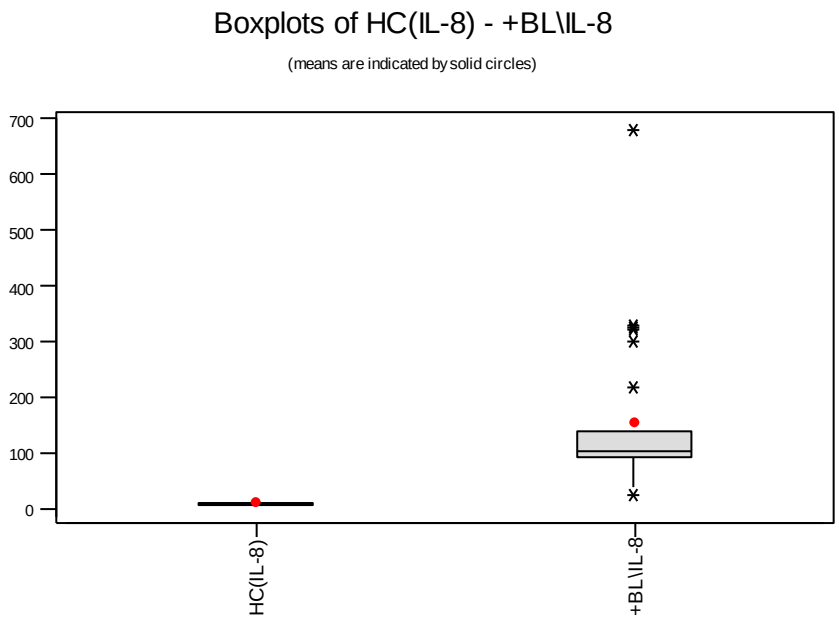
Figure (2) show the distribution of the ELISA reading of IL-8 of the healthy control and leukopenic patients with bacteremia.

The mean reading of healthy control group was (9.9 pg/ ml SD of ± 2.7). While the mean reading of the leukopenic patients with bacteremia was (152 pg/ml SD of ± 133.5).



HC\IL-1: IL-1α level in healthy control group
+BL\IL-1: IL-1α level in leukopenic leukemia patients with positive blood culture

Figure 1: The distribution of the ELISA reading of IL-1α of the healthy control, leukopenic patients with positive blood culture



HC (IL-8): IL-8 level in healthy control group
+BL\IL-8: IL-8 level in level in leukopenic patients with positive blood culture

Figure 2: The distribution of the ELISA reading of IL-8 of the healthy control, leukopenic patients with positive blood culture

DISCUSSION:

Statistical analysis shows increase in serum IL-1α in the plasma of leukopenic patients during bacteremia figure (1). There is significant difference between healthy control group and leukopenic leukemia patients with bacteremia (P=0.002). This is an expected result since it is well known that Gram negative bacteria and their endotoxins (lipopolysaccharide), as well as the cell wall components of Gram positive bacteria (peptidoglycans, teichoic acid) can activate the inflammatory cascades. Those molecules bind to membrane-bound and soluble receptors (CD14, mannose binding protein, toll-like receptors/ TLRs) inducing excessive production and release of pro-inflammatory mediators which include IL-1 and others [17]. this cytokine is mainly secreted by leukocytes, especially monocytes. However, bone marrow toxicity as the result of chemotherapy and the disease itself lead to reduced number of leukocytes in leukemic patients; this factor may be lead us to cytokine concentrations were unrelated to leukocyte counts. We conclude cytokine release in leukopenic leukemia patients during bacteremia dose not depend on circulating leukocyte [18]. This increase may be indicating source other than leukocytes for cytokines production in leukopenic leukemia patients during leukopenia [19]. Statistical analysis shows increase in the level of IL-8. There was significant difference between healthy control group and leukopenic patients with bacteremia.

This results was explained by that the high levels of IL-8 in leukopenic patients with bacteremia is a part of an effectors phase characterized by the production of IL-1 and tumor necrosis factor alpha (TNF-α) and then the production of IL-6 and IL-8 as result of blood stream invasion by Gram negative as well as Gram positive bacteria [20, 21]. This finding is in agreement with the finding by Schonbohn et al. (1995) during a study of plasma levels of IL-8 in patients undergoing chemotherapy for acute myelogenous leukemia. This result also confirms results of an analysis of serum IL-8 concentration in neutropenic cancer patients with Gram negative bacteremia. This result may be due to that endothelial cells instead of leukocytes become the most important producers of IL-8 during bacteremia in patients with chemotherapy induced leukopenia. The TLRs on endothelial cells act as pattern recognition receptors that induce the production of IL-8 upon binding of bacterial cell wall components [19]. Endothelial cells become important producers of IL-8 during the inflammatory response against bacteria through TLR-2 and TLR-4 signaling. Recently, the involvement of Toll-like receptors (TLRs) as pattern recognition receptors in the innate immune response was demonstrated. The TLRs are characterized by an extracellular domain contain leucine-rich repeats and intracellular domain sharing a high degree of similarity with the IL-1 receptor [22].

CONCLUSION:

The exact mechanism of the inflammatory response in leukemic patients with disturbed innate immunity is not completely clear. Leukopenic leukemia patients strikingly show distinct increases in plasma IL-1α and levels during bacteremia, suggesting that there may be source other than leukocytes for IL-1α and IL-8. because of cytokines seems to be promising diagnostic parameter, further studies about the role of IL-1α and IL-8 levels in an inflammatory response in leukopenic leukemia patients with bacteremia may be recommended.

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