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SHORT COMMUNICATION **PERIOPERATIVE MEDICINE**

The impact of reproductive hormone changes on the immune response of patients with leukemia

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ABSTRACT

Background & Objective: Leukemias have been associated with various immune and endocrine changes. Several studies have established a correlation between an imbalance in pituitary hormones and sex steroids and the initiation of illness in either one or both genders. The hormone changes can affect normal physiological homogeneity of the human body, thus effecting health as well as the course of unrelated diseases. We aimed to investigate the influence of alterations in reproductive hormones on the immune response of individuals diagnosed with leukemia.

Material and Methods: In this case-control study, a total of 130 subjects, out of which 80 patients were known cases with hematological cancer, were enrolled at the Medical City Department/Hematology Center in Baghdad, Iraq, from February-October 2022. Out of 80 patients diagnosed with leukemia, 45 patients had acute myeloid leukemia (AML), and 35 patients had acute lymphoblastic leukemia (ALL). The study involved 50 healthy controls. Estradiol (E2), triiodothyronine (T3), follicle-stimulating hormone (FSH), and progesterone levels were measured using both ELISA and the immunofluorescence assay method in all participants. C-reactive protein (CRP), ferritin, and neutrophil-to-lymphocyte ratio (NLR) was also determined.

Results: The findings of the study demonstrated a significant elevation in the levels of CRP, ferritin ($P < 0.001$), and NLR ($P = 0.01$) in the individual's group when compared to the control group. Serum progesterone was increased in patients diagnosed with AML and ALL in comparison to the control group ($P = 0.01$). FSH was elevated ($P = 0.02$) in AML and decreased in ALL. This difference was found to be statistically significant. The levels of T3 and E2 were found to be significantly reduced in both AML and ALL patients when compared to the control group ($P = 0.1$ and 0.02 respectively).

Abbreviations: ACTH - Adrenocorticotropic Hormone; ALL - Acute Lymphoblastic Leukemia; AML - Acute Myeloid Leukemia; E2 – Estradiol; LH - Luteinizing Hormone NLR - Neutrophil-To-Lymphocyte Ratio

Conclusions: The findings of the study offer empirical support for the impact of hormones on the immune response in leukemia pathogenesis.

Key words: Leukemia; Reproductive Hormones; Immune Response

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1. INTRODUCTION

Blood cancer, also known as hematologic cancer, is a malignancy originating from blood-forming tissues, including the bone marrow and immune system cells. Blood cancer encompasses various types of malignancies, including leukemia, lymphoma, and multiple myeloma. In leukemia, the bone marrow generates atypical white blood cells, referred to as leukemia cells.[1] The stem cells located in the anterior pituitary are responsible for differentiating into distinct cell types that secrete various hormones, such as adrenocorticotropic hormone (ACTH), growth hormone (GH), prolactin, thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH).

The tropic hormones exert control over various physiological processes such as immunity, growth, reproduction, and metabolism.[2] Despite the higher incidence and mortality rates of leukemia in males compared to females, this hematological malignancy is not currently classified as hormone-regulated. Diverse levels of hormonal exposure are associated with varying effects on treatment-free survival in both males and females. Studies have examined the quantitative concentrations of progesterone, adrenal precursors, androgens, estrogens, catechol estrogens, luteinizing hormone (LH), and follicle-stimulating hormone (FSH). The treatment-free survival median for males was comparatively shorter in duration when compared to that of females.

The steroid sex hormones exert an influence on leukemias and lymphomas that are determined by sexual characteristics. Males may exhibit increased vulnerability to developing ALL due to diminished levels of estrogen compared to females.[3] The occurrence of tumor growth and metastases in humans has been associated with a range of endocrine systems, including those that govern reproductive functions. Extensive documentation exists regarding the correlation between prenatal exposure to exogenous hormones and an increased susceptibility to cancer in offspring. A limited number of studies have demonstrated a heightened occurrence of fetal leukemia in women using hormonal contraceptives. Sex steroids belong to one of the two families of nuclear receptors.

A growing body of empirical evidence indicates a potential association between autoimmune thyroid disease and acute leukemia. Thyroid hormones play a crucial role in regulating hematopoiesis and utilize receptors that bear resemblance to those found in differentiation factors such as retinoids. Consequently, this association holds potential significance for further investigations into the mechanisms underlying growth control in leukemia.[4] The occurrence of low T3 syndrome is common among patients who are admitted to critical care units due to severe illnesses, including pneumonia, Hodgkin's disease, and chronic lymphocytic leukemia.[5] Certain subtypes of human leukemia cells exhibit an augmented proliferation in the presence of growth hormone (GH), and previous studies have demonstrated the prevalence of growth hormone receptor (GHR) on the cellular surface of the majority of these cells.

We examined the impact of reproductive hormone changes on immune response of patients with leukemia.

2. METHODOLOGY

This case-control study was conducted on participants with hematological cancer (specifically acute and chronic leukemia) who were treated at the Medical City Department/Hematology Center in Baghdad, Iraq, from February-October 2022. Participants' were diagnosed by senior medical professionals through the analysis of fundamental clinical features, patient histories, and biochemical testing.

A total of 130 people in two groups were included in the study. Control group consisting of 50 individuals who were deemed healthy and, 80 patients diagnosed with leukemia, including 45 patients diagnosed with AML (Group AML) and 35 with ALL in the Group ALL. Patients with reactions, renal disorders and liver disease were excluded.

Blood samples were taken from all subjects to measure FSH, T3, E2, Progesterone, NLR, CRP, Ferritin, WBC count, neutrophil count, and lymphocyte count. Personal and medical history of each subject was obtained, including age, sex, diseases suffered and duration of illness. All research participants provided informed consent before blood collection.

A total of six milliliters of anticoagulated K3-EDTA blood were collected from each research group's subjects. This blood was then divided into one milliliter portions for the purpose of conducting a complete blood count. Plasma was isolated from the rest of the blood through centrifugation at a speed of 1006 Xg for 10 min at a temperature of 4°C. The separated plasma was subsequently stored at a temperature of negative 20 degrees Celsius (-20 ˚C) for the purpose of assessing E2 levels using the Enzyme-Linked Immunosorbent Assay (ELISA) technique. Additionally, T3, FSH, and progesterone levels were determined using the immunofluorescence assay method as per the instructions provided by the manufacturer. Furthermore, the concentration of C-reactive protein (CRP) was also determined.

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2.1. Ethical considerations

The study was approved by the Ethical Committee of the Medical City Department /Baghdad Teaching Hospital and the College of Science /University of Al-Qadisiya. All research participants provided informed consent before blood collection. In addition, all methods and protocols were performed under the standard guideline and regulations.

2.2. Statistical analysis

The mean and standard deviation (SD) are statistical measures employed to characterize data. The Andersen-Darling test was employed to assess the normality of the data, with a significance level of $P \leq 0.05$. The distinction between control and experimental subjects was assessed using Student's t-test. The researchers employed a one-way analysis of variance (ANOVA) to examine whether there were any statistically significant differences between the control group and the group of patients. Tukey's post hoc analysis was employed in the ANOVA to evaluate the statistical significance. The statistical significance of the results was established $P \leq 0.05$ in all cases.

3. RESULTS

A total of 130 subjects were included in the study, consisting of 80 patients diagnosed with leukemia, 45 patients in Group AML (19 females and 26 males), with a mean age of 32.32 ± 2.69 y, and 35 patients in Group ALL (16 females and 19 males), with a mean age of 35.794 ± 0.63 y.

Further, 50 subjects were enrolled as the control group (28 female and 22 male), with an average age of 41.8 ± 1.5 y.

The clinical and biochemical variables of patients diagnosed with leukemia were compared to those of a Control Group, as presented in Table I. The serum levels of CRP exhibited a statistically significant increase ($P < 0.001$) in patients in Group AML and Group ALL when compared to the Control Group, as indicated in Table I. The results indicate a statistically significant increase in ferritin levels in both leukemia groups (Groups AML and ALL) when compared to the Control Group ($P < 0.001$, Table I). Additionally, a significant difference in ferritin levels was observed between the two leukemia groups.

There was a notable rise observed in white blood cell (WBC) counts in both leukemia groups when compared to the control group ($P = 0.04$). A notable reduction in neutrophil counts was observed among patients of Group AML in comparison to the Control Group ($P = 0.03$) while insignificant alterations were noted in Group ALL, as depicted in Table 2. The findings indicated that there were no statistically significant alterations in lymphocyte counts ($P = 0.32$). Additionally, the findings suggest that the neutrophil-to-lymphocyte ratio (NLR) is significantly elevated in all groups of patients when compared to the control group ($P = 0.01$).

The levels of progesterone, FSH, and T3 were quantified using the immunofluorescence assay method in both leukemia groups and control groups. There was a significant increase in progesterone levels observed in both Groups AML and ALL patients when compared to the Control Group ($P = 0.01$) (Table I). There was a notable rise in FSH levels among patients in Group AML in comparison to the control group. Conversely, patients in Group ALL exhibited a decrease in FSH levels. This difference was statistically significant ($P = 0.02$). The findings demonstrated a statistically significant

Table 1: Comparison of the biochemical parameters in study groups

Parameters	Group AML (n = 45)	Group ALL (n = 35)	Control Group (n = 50)	P-value
CRP (mg/l)	216.05 ± 31.6 [b]	133.78 ± 4.45 [a]	4.13 ± 1.79 [a]	< 0.001
Ferritin (ng/ml)	327.86 ± 26.82 [b]	269.03 ± 8.33 [c]	84 ± 34.055 [a]	< 0.001
WBC	11.58 ± 3.99 [b]	27.25 ± 2.06 [c]	7.57 ± 0.16 [a]	0.04
Neutrophil count	37.43 ± 4.68 [b]	41.16 ± 6.78 [a]	56.75 ± 13.22 [a]	0.03
Lymphocyte count	28.08 ± 4.21 [a]	24.19 ± 1.51[a]	30.89 ± 1.04 [a]	0.32
NLR	3.16 ± 0.66 [b]	6.26 ± 0.51[c]	1.90 ± 0.06 [a]	0.01
Progesterone (ng/ml)	6.625 ± 2.281[b]	6.90 ± 2.16 [b]	2.96 ± 1.58 [a]	0.01
FSH (mlU/ml)	9.26 ± 3.73 [b]	2.86 ± 1.50 [c]	6.21 ± 1.79 [a]	0.02
T3 (ng/ml)	0.58 ± 0.18 [b]	0.52 ± 0.133 [b]	1.29 ± 0.38 [a]	0.01
E2 (pg/ml)	251.72 ± 10.06 [b]	245.99 ± 8.82 [b]	445.22 ± 39.93 [a]	0.02

Data presented as Mean ± SD. A one-way ANOVA. CRP: C-reactive protein, WBC: white blood cells, NLR: neutrophil-to-lymphocyte ratio, FSH: Follicle-stimulating hormone, T3: Triiodothyronine, E2: Estradiol.

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reduction in T3 levels among all patients in Groups AML and ALL in comparison to the control group. Significant differences were observed in leukemia patients compared to the control group, as indicated by the statistical analysis ((P = 0.01) (Table I). The levels of E2 were found to be significantly lower in patients of both Groups AML and ALL, when compared to the control group (P = 0.02).

4. DISCUSSION

The results of this investigation demonstrate a statistically significant increase in the levels of CRP and serum ferritin levels in the serum of individuals in Groups AML and ALL in comparison to the Control Group ($P \leq 0.05$). However, there was a substantial disparity in ferritin levels among the different groups of patients. This finding aligns with the conclusions drawn by Mosab and Fang Wang et al. in their respective studies,[6] which found the hypogonadism secondary to antineoplastic treatment (characterized by elevated levels of LH and FSH owing to the lack of negative feedback from the gonads).

There was a notable rise in WBCs counts observed in both groups of patients with leukemia in comparison to the control group ($P \leq 0.05$).

In the current findings a significant increase was demonstrated in progesterone levels in Groups AML and ALL when compared to the control group ($P \leq 0.05$). The patients exhibited a more pronounced effect in comparison to the control group.

Patients in Group AML exhibited a notable elevation in FSH levels, whereas patients in Group ALL demonstrated a decrease in FSH levels when compared to the control group ($P \leq 0.05$). This finding agrees with the findings of a study conducted by Huina et al.,[7] which found the hypogonadism secondary to antineoplastic treatment (characterized by elevated levels of LH and FSH owing to the lack of negative feedback from the gonads).

The findings demonstrated a statistically significant reduction in T3 levels among all patients with AML and ALL when compared to the control group. Moreover, the changes observed in T3 levels were found to be highly significant in leukemia patients compared to the control group.

The findings of the study indicated a statistically significant decrease in serum E2 levels among patients of Groups AML and ALL compared to the control group ($P \leq 0.05$). However, no significant alterations in E2 levels were observed within the patient groups themselves.

The primary characteristic of leukemia is the unregulated accumulation of white blood cells, which may include malignant cells. While it is true that males have a higher likelihood of being diagnosed with and succumbing to leukemia compared to females, it is important to note that this particular form of blood cancer is not currently classified as hormone-regulated.

CRP is a type of acute-phase protein that is synthesized in the liver as a result of cytokine stimulation, specifically interleukin-6 (IL-6) signaling. CRP plays a crucial role in modulating the inflammatory response through its ability to enhance the functionality of phagocytes and initiate the activation of the complement system. The study conducted by researchers revealed that individuals diagnosed with various types of cancer, including hematologic malignancies, exhibited lower rates of survival when their levels of CRP were elevated.[8] A highly sensitive CRP in AML, when compared with a control group, is in agreement with this study.[9] The elevation of CRP levels in patients can be attributed to various factors, such as the body's reaction to tumor necrosis, localized tissue damage, or concurrent inflammation. Proteins such as CRP are involved in the systemic inflammatory response associated with cancer. CRP serves as an indicator of inflammation and nutritional status, and has shown potential as a prognostic factor for predicting the survival of leukemia patients and other types of cancer.[10]

Ferritin is a protein synthesized through mammalian metabolic processes, primarily serving as a means to store iron within tissues. Additionally, it is classified as an acute phase protein. Elevated blood ferritin levels may indicate the presence of an underlying medical condition, such as specific types of cancer, which can lead to excessive iron accumulation within the body.[11] Overt and subclinical inflammation may induce higher baseline levels in all patients. Furthermore, it is possible that this marker could serve as a prompt for conducting a diagnostic workup to identify any underlying pathological inflammation. Additionally, it may indicate the potential advantages of utilizing augmented or targeted immune interventions. It has been observed that individuals diagnosed with cancer exhibit elevated levels of blood ferritin, a phenomenon that has been linked to an increased production of this protein by macrophages. The role of hepcidin in promoting iron uptake by macrophages during inflammatory processes has been documented.[12] Another study indicates elevated serum ferritin levels due to elevated transferrin receptors on malignant clones of leukemic cells. Additionally, high cell destruction rates reveal ferritin carriage and raise serum levels, which are also consistent with the study results by Albert and Schmidt.[13]

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Based on previous studies conducted by Sameh and Rudresha et al.,[14,15] WBCs are highly effective combatants against infections. Typically, they undergo controlled growth and division in accordance with the body's requirements. However, individuals diagnosed with leukemia experience a condition where the bone marrow overproduces an excessive number of abnormal WBCs that exhibit impaired functionality. The phenotypes of these cells are influenced by the leukemia microenvironment, resulting in the polarization of neutrophils into cells that combat leukemia.[16]

Progesterone is an essential hormone that plays a crucial role in maintaining overall health by modulating the immune response in various disorders, including autoimmune, infectious, and malignant conditions. This modulation occurs through its influence on both the innate and adaptive immune systems.[17] Research studies have demonstrated a notable enhancement in immune system functionality as a result of the administration of the hormone progesterone. This proposed mechanism suggests that the suppression of infection with microorganisms and the subsequent adaptive inflammatory response may be achieved through the administration of progesterone at significantly elevated levels. This has the potential to be a unique focus not only in the field of cancer therapeutics but also in the management of inflammatory and autoimmune diseases.[18,19] In contrast, the utilization of oral medications containing a combination of estrogen and progestin has been associated with an increased risk of leukemia. Chemotherapy has the potential to disrupt hormonal equilibrium, albeit without a direct correlation to the presence of leukemia. Generally, hormone levels remain unaffected until the disease has advanced to the glands responsible for hormone production or unless the treatment for leukemia directly affects these glands.[20,21] Another research by Mohammad et al. showed that cancer could impair fertility directly by affecting reproductive organs and indirectly by inhibiting reproductive function or delaying reproduction due to cancer treatment.[22]

The primary role of FSH is to regulate the reproductive system. Certain therapies for leukemia have the potential to indirectly affect FSH levels. This can occur through the detrimental effects on the ovaries or testicles, which subsequently influence the production of hormones by these organs.[7]

Patients with ALL who have low serum T3 levels demonstrate a negative clinical status and prognosis.[23] Thyroid hormones (T3 and T4) are crucially involved in the processes of metabolism, growth, and development. Although there is no direct causal link between leukemia and low levels of T3, various factors related to leukemia and its treatment have been found to potentially impact thyroid hormone levels, resulting in a decrease in T3 level. The exact mechanisms underlying the phenomenon of low T3 have not yet been completely understood. The involvement of multiple cytokines, particularly in patients with hematological malignancies who are critically ill, and the subsequent upregulation of various cytokines, hinder the synthesis of thyroid hormones, indicating a systemic inflammatory response in cancer patients with elevated levels of CRP.[23] There were notable and statistically significant differences observed in leukemia patients when compared to the control group.[24] According to research done by Salvatore & colleagues,[25] a correlation between decreased levels of T3 serum and an increased absolute neutrophil count, indicating that alterations in IL-6, IP-10, and MCAF are the main factors influencing T3 serum levels, particularly in patients with coexisting hematological malignancies. A potential indicator for prognostic evaluation in future clinical applications of leukemia could be the presence of low levels of T3.[26]

The statement of current study is in accordance with the findings of Samir & colleagues,[27] who Serum E2 levels were quantified in patients with acute leukemia, and the potential diagnostic value of these levels was extrapolated in a clinical context. Furthermore, it is worth noting that estrogen deficiency is associated with significant alterations in bone marrow hematopoiesis, leading to the inhibition of stem cell differentiation into myeloid and lymphoid lineages. E2 is subject to the influence of various variables, including age, the menstrual cycle, pregnancy, and specific medical conditions. The relationship between blood levels of E2 and leukemia lacks conclusive evidence. Some chemotherapy medications have the potential to induce testicular or ovarian failure in both males and females, leading to potential alterations in the levels of E2.

5. Conclusions

The main findings of the current study indicate that patients with leukemia exhibited elevated levels of CRP, ferritin, and NLR. These increases can be attributed to the augmentation of pro-inflammatory reactions and a deficiency in the regulation of anti-inflammatory responses. The presence of irregular hormone levels, specifically heightened progesterone and FSH, alongside diminished T3 and E2 levels, may have an impact on the immune response of individuals with leukemia. This observation has the potential to provide novel insights into the development of strategic therapeutic approaches for leukemia.

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7. Conflict of Interest

The authors declare no conflict of interest exist.

8. Author contribution

All authors took part in the conduct of the study, search of data, compilation of the data and preparation and editing of the manuscript.

All authors of read the manuscript and approve it for publication.

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