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The Interaction Between Female Hormonal Imbalances and Acute Myeloid Leukemia :Review

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Abstract

Acute myeloid leukemia (AML) is a heterogeneous myeloid disorder resulting from the abnormal proliferation of immature myeloid cells, leading to bone marrow failure. Leukemias are among the most common hematologic malignancies. The development of AML has been linked to several factors, including inherited genetic changes, previous illnesses, environmental and occupational factors, exposure to infectious agents, and some previous treatments. However, none of these factors apply to all cases. Scientific evidence suggests a relationship between hormonal imbalances, particularly pituitary hormones and steroids, and the onset of the disease. These hormonal imbalances can disrupt the body's physiological balance, which in turn affects overall health and the course of other diseases, even if they are not directly related to leukemia. This review aims to highlight research on the relationship between various hormonal axes and AML, and how this understanding may contribute to the development of new targeted therapeutic strategies.

Keywords: acute myeloid leukemia (AML), progesterone, Estradiol, follicle-stimulating hormone (FSH) and luteinizing hormone (LH).

Introduction

Cancer is the second leading cause of death worldwide after cardiovascular disease. Despite significant advances in early detection and treatment methods, which have contributed to improving survival rates for a large number of patients[1]. Leukemia remains a global health challenge due to its increasing impact on morbidity and mortality. Leukemia ranks eleventh in prevalence and tenth in mortality among cancers. It arises from somatic mutations in hematopoietic stem cells or multipotent progenitor cells, leading to their transformation into abnormal neoplasms capable of self-dividing and differentiating into various types of blood cells [2].

These cancerous cells are characterized by irregular and random growth, often accompanied by an excessive increase in one type of white blood cell, which disrupts the balance of blood cell

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production and negatively affects bone marrow function. A blood smear is the primary means of diagnosing the disease by detecting this abnormal increase in white blood cells. Leukemia is classified into two main types based on its pattern of progression: acute leukemia, in which immature cells grow rapidly and are unable to perform their functions, and chronic leukemia, in which cells grow at a slower rate and may retain some of their functions [3]. Acute myeloid leukemia (AML) is the most common type of acute leukemia in adults as shown in Fig.1 , accounting for approximately 80% of acute leukemia cases. Its incidence is estimated at approximately 5 cases per 100,000 people annually, and approximately 20,830 new cases were recorded in 2015, resulting in more than 10,000 deaths. The incidence of AML increases significantly with age, from approximately 1.3 cases per 100,000 people under the age of 65 to more than 12.2 cases per 100,000 in those over this age. Despite therapeutic advances that have improved outcomes in younger patients, the prognosis for older patients remains poor. Studies indicate that up to 26% of patients over the age of 65 may die within the first year of diagnosis, despite receiving currently available treatment[4].

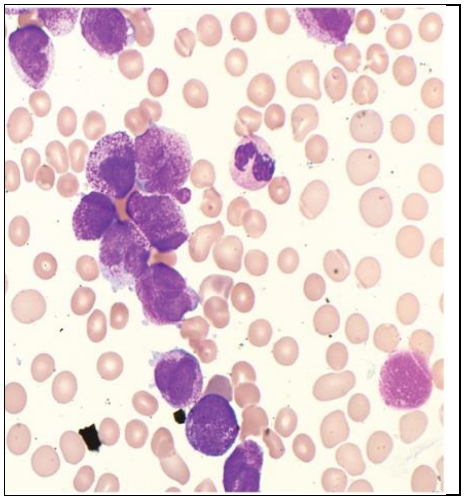

Figure (1). AML Bone Marrow Haematopathology

Sign and Symptoms

The clinical symptoms of acute myeloid leukemia (AML) are similar to those of many other less serious diseases, which can lead to delayed diagnosis. This is due to the decreased production of healthy blood cells in the bone marrow due to abnormal proliferation of blasts. A general feeling of malaise and decreased activity level are common early symptoms .Affected individuals often experience shortness of breath during normal daily activities, which is associated with anemia resulting from a deficiency in red blood cells. Other clinical signs include: bleeding symptoms resulting from a severe drop in platelet count, such as spontaneous bruising, pinpoint red spots on the skin (purpura), prolonged bleeding after minor cuts, swollen gums, and sometimes a mild fever. Patients may experience recurrent infections, especially in areas such as the mouth or around the anus, along with loss of appetite and weight loss. Bone or joint pain, and in some cases, an enlarged spleen or liver may also occur. Bleeding disorders are a common complication. They may begin with minor bleeding, such

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as nosebleeds or blood in the urine, but they can progress to serious bleeding within the brain or lungs, which can be fatal. Infection is one of the most serious complications, which increases in severity during chemotherapy due to a decrease in white blood cell counts, particularly neutrophils. This makes the patient susceptible to severe infections, which can be the leading cause of death. In rare cases, a tumor may develop resulting from the accumulation of blast cells outside the bone marrow, known as solid myeloma or myelosarcoma. This tumor may be preceded by a silent phase in which no clear signs of disease appear in the blood or marrow. It is treated therapeutically, similar to AML, using systemic chemotherapy, and may later require a bone marrow transplant[5,6,7,8].

Classification of Acute Myeloid Leukemia

AML is classified according to several international classification systems that aim to improve diagnostic accuracy and relate disease subtypes to treatment responses and clinical outcomes. Among the most important of these classifications are: WHO Classification and French-American-British (FAB) Classification listed in Table (1), The WHO Classification is based on a combination of morphological, immunological, and molecular genetic criteria, in addition to clinical factors . This classification is currently the standard in clinical practice, providing greater accuracy in differentiating between different types of AML, especially with the advancement of genetic and cytogenetic analysis techniques. The French-American-British (FAB) classification is considered a classic classification are listed in Table (2), and relies primarily on the morphological characteristics of blast cells in the bone marrow, in addition to some cytochemical tests. AML is divided into nine main subtypes (from M0 to M7) based on the degree of differentiation of the blasts and the histological line to which they belong [9,10]

Table (1): WHO classification for Acute Myeloid Leukemias

Types	Genetic Abnormalities
	AML with t(8:21)(q22;q22); RUNX1-RUNX1T1
	AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);
	CBFB-MYH11
	APL with PML-RARA
	AML with t(9;11)(p21.3;q23.3); MLLT3-KMT2A
	ML with t(6;9)(p23;q34.1); DEK-NUP214
	AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2,
	MECOM

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AML with recurrent genetic abnormalities	AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); RBM15-MKL1
	AML with BCR-ABL1 (provisional entity)
	AML with mutated NPM1
	AML with biallelic mutations of CEBPA
	AML with mutated RUNX1 (provisional entity)
	AML with minimal differentiation
	AML without maturation
	AML with maturation
	Acute myelomonocytic leukemia
	Acute monoblastic/monocytic leukemia
	Acute erythroid leukemia
	Pure erythroid leukemia
	Acute megakaryoblastic leukemia
	Acute basophilic leukemia
	Acute panmyelosis with myelofibrosis
Myeloid sarcoma	
Myeloid proliferations related to Down syndrome	Transient abnormal myelopoiesis
	ML associated with Down syndrome

Table (2): FAB Classification of Acute Myeloid Leukemias

M0	**AML with no Romanowsky or Cytochemical Evidence of Differentiation**
M1	Myeloblastic leukemia with little maturation
M2	Myeloblastic leukemia with maturation
M3	Acute promyelocytic leukemia (APL)
M3h	APL, Hypergranular variant
M3v	APL, Microgranular variant
M4	Acute myelomonocytic leukemia (AMML)

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M4eo	AMML with dysplastic marrow eosinophils
M5	Acute monoblastic leukemia (AMoL)
M5a	AMoL poorly differentiated
M5b	AMoL, differentiated
M6	Acute erythrocytic leukemia
M6a	AML with erythroid dysplasia
M6b	Erythroleukemia
M7	Acute megakaryoblastic leukemia (AMkL)

Acute Myeloid Leukemia Diagnosis

The diagnosis of Acute Myeloid Leukemia (AML) involves a multi-step approach. Initially, the morphology of blood or bone marrow cells is assessed under a microscope to detect the presence of blast cells and determine their lineage. This is followed by immunophenotyping, which helps confirm the diagnosis, distinguish AML from other types of leukemia, and identify its specific subtype. Finally, cytogenetic and molecular analyses are conducted to examine chromosomal abnormalities and detect gene mutations, which are crucial for prognosis and treatment planning[11].

Risk factors of acute myeloid leukemia (leukemogenesis)

It is resulting from recurrent genetic alterations in hematopoietic stem cells accumulated with age that contributed to the development of AML. These genetic variations include different factors such as exposure to high-dose radiation, exposure to high-dose benzene smoking Some chemotherapeutic drugs, such as alkylating agents, are used to cause DNA damage within cancer cells. These drugs work in several different ways, but their primary effect is to cause oxidative damage within DNA molecules[12,13] Obesity has been found to be an endogenous risk factor that increases the risk of AML.This may be related to the increased blood insulin levels (hyperinsulinemia), insulin resistance, elevated leptin levels, decreased adiponectin levels, and shortened telomeres observed in these patients [14,15].Also other risk factors may affect and increase the chance of AML development like blood disorders including polycythemia vera, and thrombocytopenia, and some congenital syndromes such as Down syndrome, Fanconi anemia, appear to raise the risk of AML[16].

Treatment of AML

Treatment for AML relies on a combination of specialized approaches, with chemotherapy being the first and most widely used treatment. It is divided into two phases: the induction phase, which aims to destroy cancer cells and achieve remission, often requiring hospitalization, followed by the consolidation phase, which aims to eliminate remaining cells and prevent recurrence Targeted therapy has emerged as an effective option, targeting specific genetic mutations such as FLT3 or IDH1/2 using targeted drugs that improve treatment outcomes when combined with chemotherapy In high-risk or relapsed cases, stem cell (bone marrow) transplantation is used, where the patient's marrow is destroyed and replaced with healthy cells from a donor, providing the opportunity for

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long-term treatment Immunotherapy is a promising field still under investigation and is sometimes used in recurrent or resistant AML to help the immune system attack cancer cells Radiation therapy has a limited role and is used only in special cases, such as preparing the body for a marrow transplant or if the cancer has spread to the central nervous system Finally, surgical intervention is not used in AML due to the disseminated nature of the disease[17,18]. The steps involved in treating AML[19] are shown in Fig. 2.

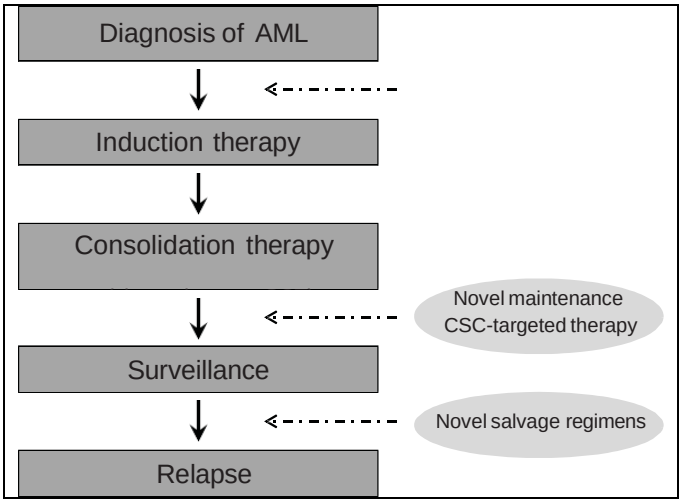

Figure (2). Treatment paradigm of AML

Effect of hormones in AML

Tropic hormones play a crucial role in regulating key physiological functions, including immune response, growth, reproduction, and metabolism. Although leukemia occurs more frequently and leads to higher mortality rates in males than in females, it is not currently classified as a hormone-driven disease. However, differences in hormone levels have been linked to variations in treatment-free survival outcomes across both sexes [20,21]

Effect of FSH and LH in AML

The Gonadotropin-stimulating hormones, particularly follicle-stimulating hormone (FSH) and luteinizing hormone (LH), are essential elements in regulating reproductive system function. They play a pivotal role in the development and maturation of ovarian follicles in females and in stimulating the production of sex hormones in both sexes. In addition to their physiological functions, growing evidence suggests that FSH is involved in the development and progression of some tumors associated with the reproductive system, including ovarian tumors, endometrial cancer, testicular tumors, and prostate cancer. Correlational studies have shown a relationship between elevated levels of FSH or its metabolites in the blood and an increased risk of developing these tumors, suggesting a potential role for FSH in promoting a stimulating environment for tumor cell growth [22,23] .Furthermore, FSH levels

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may be indirectly affected by targeted treatments for non-reproductive diseases, such as some leukemia treatment protocols, which may damage the gonads (ovaries or testes), leading to dysfunctional reproductive hormone secretion and, consequently, hormonal disturbances including changes in FSH levels. This highlights the importance of monitoring the hypothalamic-pituitary-gonadal axis during and after chemotherapy, and the need to understand the interactions between hormonal factors and tumorigenesis for early diagnosis and therapeutic intervention[24,25]. Some research has shown that FSH is linked to the progression of some cancers, including its direct effect on acute leukemia cells, where it stimulates their proliferation and spread via receptors on their surface. LH is also present at variable levels in some cancers and has effects related to the regulation of sex hormones, which may play a role in the biology of cancer cells[26] .Studies have shown that the expression of FSH and LH receptors in leukemia cells makes these hormones influential factors in disease progression, supporting the hypothesis that endocrine pathways may be exploited as new therapeutic targets. Furthermore, reviews have shown that high FSH levels may be associated with poor outcomes in some cancers, indicating their importance as a biomarker[27].Furthermore, research focusing on the effects of chemotherapy and radiation on FSH and LH levels has shown that these hormones reflect the health of the reproductive system and can influence the severity of the treatment's effects on body cells, including leukemia. [28,29]

Effect of progesterone in AML

Progesterone is a key biological hormone that plays a crucial role in maintaining immune homeostasis and modulating immune responses across various disease states, including autoimmune disorders, bacterial infections, and malignancies such as cancer. Its immunomodulatory effects are exerted on both the innate and adaptive arms of the immune system[30]. Numerous studies have demonstrated that administering high concentrations of progesterone can enhance immune function. This enhancement is believed to occur via mechanisms that suppress bacterial proliferation while simultaneously regulating the inflammatory cascade. Such findings position progesterone as a promising agent in the therapeutic landscape of cancer and inflammatory or autoimmune conditions[31]. Interestingly, although progesterone shows immunoregulatory and anti-inflammatory potential, some evidence suggests that the use of oral hormone therapies containing both estrogen and synthetic progestins may be associated with an increased risk of hematologic malignancies such as leukemia. It is well-documented that chemotherapy can disrupt hormonal balance, either directly through cytotoxic effects on endocrine organs or indirectly through disease progression involving these glands. However, in the early stages of malignancy, significant hormonal changes are typically not observed unless the endocrine glands are specifically affected[32]. Moreover, progesterone has been shown to exert antiproliferative effects in certain tumor types[33]. Within the tumor microenvironment, progesterone may influence immune cell populations by promoting the differentiation of dendritic cells and modulating cytokine secretion patterns toward a more homeostatic and less pro-inflammatory profile[34].These properties highlight its dual role: it acts as a potential therapeutic modifier and also as a biomarker of endocrine disorders in cancer patients... Clinically, in women diagnosed with acute myeloid leukemia (AML), chemotherapy-induced ovarian suppression frequently leads to a marked decline in progesterone levels, contributing to menstrual irregularities, infertility, and premature menopause,It is also noteworthy that in certain disease conditions, endogenous progesterone levels

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may rise as part of the body's physiological response, although this is highly context-dependent and varies based on the stage and nature of the disease[35].

Effect of Estradiol in AML

of hematopoietic stem cells into myeloid and lymphoid lineages. Importantly, estradiol levels are subject to a range of physiological influences, including age, menstrual status, pregnancy, and the presence of systemic illness. While some studies suggest a link between reduced circulating estradiol and leukemia pathophysiology, definitive causal relationships remain elusive. Moreover, certain chemotherapeutic agents are known to induce gonadal toxicity, leading to ovarian or testicular failure, which can further suppress estradiol production in both male and female patients[40].Female patients with AML frequently experience a marked reduction in estradiol levels following chemotherapy. This decline contributes not only to infertility and early-onset menopause but also to diminished bone mineral density, Estradiol (E2), a potent form of estrogen, plays a critical role in regulating numerous physiological processes, including cellular proliferation, differentiation, and immune modulation. In the context of acute myeloid leukemia (AML), fluctuations in estradiol levels are believed to influence disease progression and the behavior of dysfunctional or leukemic white blood cells[36]. Emerging evidence suggests a correlation between decreased E2 levels and alterations in estrogen receptor expression within the bone marrow, reinforcing the potential utility of estradiol as a biomarker for diagnosis and disease monitoring in AML patients[37].Although a number of clinical trials and therapeutic advancements have been explored in AML treatment, none have been specifically directed at modulating estradiol levels. Instead, most current approaches focus on broader anti-leukemic strategies, including novel drug regimens and combination therapies[38,39] .To date, there are no approved clinical or investigational treatments that target estradiol modulation directly in AML patients. The current study under discussion quantified serum estradiol (E2) levels in patients with acute leukemia and evaluated their potential diagnostic significance in a clinical context. It is particularly noteworthy that estradiol deficiency has been associated with profound disruptions in bone marrow hematopoiesis, notably impairing the differentiation thereby increasing the risk of osteoporosis. Consequently, hormone level monitoring, particularly of estradiol, is essential for both in long-term survivorship care and understanding the broader endocrine implications of AML and its treatments [41] .

Conclusions

Sometimes, along with targeted therapy, chemotherapy is the primary treatment for most cases of acute myeloid leukemia (AML), and may be followed by a stem cell transplant. Some studies have shown hormonal changes in AML patients, characterized by elevated FSH, LH, and progesterone levels, and significantly decreased estradiol levels. These changes are attributed to the effects of the disease itself or aggressive treatments such as chemotherapy and stem cell transplantation, which may affect the hypothalamic-pituitary-gonadal axis Despite advances in treatment, long-term survival outcomes remain poor for many adult patients with AML. Hormonal monitoring is recommended as part of a comprehensive evaluation, especially in patients undergoing intensive therapy, due to its

impact on general and reproductive health. Incorporating this aspect into clinical trials and standardizing its assessment methods will improve the quality of care and support future recommendations based on strong evidence.

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Author's Declaration

The study protocol was approved by the Medical Ethics Committee of Oncology Teaching Hospital, Medical City for Cancer Management in Baghdad, Iraq ethical review committee (No. 4809/3/2/ dated 2023/12/17.). All members gave composed informed assent after checking on the review depiction. at [Al-Nahrain University/College ofCollege of Science, Department of Chemistry]. This approval underscores our commitment to ethical research practices and the well-being of our participants.

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