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Original Research Article

Types of anemia in hematological malignancy

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ABSTRACT

Background: Anemia is a condition where a person's hemoglobin or red blood cells (RBC) levels are inadequate. This disease affects about one-third of the population of the world. Anemia has been linked to higher morbidity and mortality rates in patients with hematological malignancies. This study aimed to investigate the causes and types of anemia in a group of patients with hematological malignancies at Hiwa Cancer Center, Sulaymaniyah, Iraq.
Methods: A total of 41 patients diagnosed with hematological malignancy were recruited. Relevant patient information was gathered. Their records, including demographic data, complete blood count (CBC) findings at presentation, blood films, and bone marrow slides, were reviewed and recorded. Furthermore, erythrocyte sedimentation rate, reticulocytes count, Coombs test, iron status, prothrombin time (PT), and activated partial thromboplastin time (APTT) were evaluated.
Results: Data of this study showed that the most prevalent hematological malignancy in 41 patients was chronic lymphocytic leukemia (24.4%) and the less prevalent form was multiple myeloma (5%). Furthermore, in our study, results showed that the most frequent type of anemia was normocytic (76%) and the least frequent form was macrocytic anemia (7%).
Conclusions: The current study proved that normocytic anemia is the most common type of anemia among patients with hematological malignancies.

Keywords: Anemia, Thalassemia, Sickle cell anemia

INTRODUCTION

Definition of anemia

Anemia is a prevalent condition characterized by insufficient hemoglobin or red blood cell levels, affecting approximately one-third of the global population.[1] It is associated with increased morbidity and mortality, particularly in vulnerable groups such as children and women of childbearing age. In patients with hematological malignancies, anemia further complicates the disease course, contributing to fatigue, reduced quality of life, and poorer clinical outcomes. The etiology of anemia in these patients is multifactorial, involving factors such as bone marrow infiltration, chronic inflammation, nutritional deficiencies, and treatment-related side effects. Despite its clinical significance, the specific patterns and prevalence of anemia types in hematological malignancies remain understudied in certain populations.

Anemia is a physiological disorder where a person's hemoglobin or red blood cells (RBC) levels are inadequate or fall below normal levels. This disease affects about one-third of the population of the world. Anemia has been linked to higher morbidity and mortality rates in children and women, poor birth outcomes, lower productivity in adults, and children's cognitive and behavioral development.[1] School-going children and women of childbearing age are among the most seriously impacted groups.

RBC count, mean corpuscular volume, blood reticulocyte count, blood film analysis, and Hb electrophoresis are

procedures and methodologies used to diagnose anemia. Moreover, a hematocrit or low Hb concentration is commonly used to diagnose it. Hemoglobin concentration is the most frequent hematological diagnostic technique and the indication used to characterize anemia in the population and clinical practice. Tiredness, fatigue, breathing problems, bounding pulses or arrhythmias, and conjunctival and palmar pallor are the most common clinical indications of anemia induced by Hb's crucial role in oxygen transfer to the tissues.[1]

Types of anemia

Anemia of chronic disorders

Anemia of chronic disease (ACD) or anemia of chronic inflammation is the most prevalent cause of anemia among patients. It is the second most prevalent reason for anemia, following IDA. It might be hard to determine the incidence rate of this illness since it is commonly mistaken with IDA and is typically a diagnosis of exclusion. With the increasing age, the ACD also increases and affects 77% of the elderly who have no identifiable cause of anemia, indicating a complicated etiology.[2]

Iron deficiency anemia

Iron-deficiency anemia (IDA) is the most common cause of microcytic hypochromic anemia or is dietary iron insufficiency. It is known as a crucial health complication globally. Other factors that might cause iron deficiency and anemia include bleeding, gastrointestinal malabsorption, and *Helicobacter pylori* infection.[3] A common kind of nutritional imbalance and deficiency is IDA. For example, it is responsible for around half of all anemia cases worldwide. Individuals with type 2 diabetes show a much higher frequency of IDA, particularly those with nephropathy.[4]

IDA is indicated by reduced iron levels and low hemoglobin levels. Moreover, pregnant females must be evaluated on a routine basis, and children under one year should be tested. If an individual does not react to the treatment, iron supplementation is required, followed by further tests. A gastrointestinal endoscopy must be performed on women who have been confirmed with iron deficiency anemia.[5]

Megaloblastic anemia

It is identified by the existence of large red blood cell precursors known as megaloblasts in the bone marrow. It is composed of a heterogeneous group of (Ma). Such kind of anemia happens due to the compromised production of DNA, and it will stop the division of the nucleus. On the other hand, protein synthesis and RNA-dependent cytoplasmic maturation do not affect to that extent. The cytoplasm of erythroblasts and nucleus mature at different rates due to this reason.[6]

Pernicious anemia

The most frequent and common cause of cobalamin deficiency (CD) anemia is pernicious anemia (PA). Medical and clinical visibility of CD results from PA. It is a long process that might result in reversible hematological and neurological problems. As a result, timely screening and detection of PA and appropriate cobalamin treatment are necessary. The occurrence of parietal cell antibodies, intrinsic factor (IF) autoimmune gastritis, and poor cobalamin absorption in the terminal ileum are all symptoms of PA. IF antibodies in the gastric mucosa and serum identify two kinds of IF antibodies. The 1st antibody type binds to cobalamin binding sites, while the type II antibody attaches to ileal mucosa receptors and prevents IF binding.[7] Pernicious anemia is often caused by a "conditioned" vitamin B12 shortage caused by a lack of intrinsic stomach factors. This causes macrocytic anemia and a specific megaloblastic form of erythropoiesis.[8]

Hemolytic anemia

Anemia described by the early death or destruction of red blood cells is called hemolytic anemia (HA). It may be chronic or fatal. HA must be included in the appropriate differential diagnosis for any normocytic or macrocytic anemia. Reticulocytosis, high amounts of lactate dehydrogenase, elevated unconjugated bilirubin, and reduced haptoglobin levels all suggest hemolysis. The direct antiglobulin test helps to distinguish immunological from nonimmune sources. A peripheral blood smear should be conducted to determine aberrant red blood cell morphologies when hemolysis is evident. Thrombotic microangiopathies, direct trauma, infections, systemic illnesses, and oxidative assaults are extrinsic non-immune causes. Drugs may induce hemolytic anemia in a variety of ways. Hemolytic anemia should be considered if anemia or severe hyperbilirubinemia develops quickly in the newborn period.[9]

Hemoglobinopathies

One of the world's most common hereditary disorders includes hemoglobinopathies. It consists of all genetic hemoglobin disorders. The most common kinds of thalassemia are α- and β-thalassemia; the primary structural hemoglobin variations are HbS, E, and C. Each category contains numerous varieties and mixed forms. Clinical symptoms are from mild hypochromic anemia to moderate hematological illness to severe. A red blood cell (RBC) count with erythrocyte indices and a hemoglobin test are used to diagnose it regularly.[10]

Thalassemias

It is a heterogeneous genetic disorder that happens because of the reduced formation of alpha and beta chains of hemoglobin (Hb). The oxygen-carrying part of the red blood cells is hemoglobin. There are two proteins present

in hemoglobin, known as alpha and beta. The oxygen-carrying capacity of red blood cells will be affected if the body cannot produce either of these two proteins correctly. This will lead to anemia initiated in early childhood and may last throughout life. (Thal) is a genetic condition, which means that it is transmitted or carried by at least one of the parents.[11]

Sickle cell anemia

Sickle cell is a multisystem illness due to a single gene mutation. It affects all organs of the body. This subtype of normal adult hemoglobin (HbA), which may be inherited from the mother and father (parents) (homozygosity for the HbS gene) or one parent, coupled with some other hemoglobin variation, including hemoglobin C (HbC), or with β-thalassemia, describes the participation of aberrant erythrocytes impacted by HbS. (compound heterozygosity). The deoxygenation and polymerization of HbS cause the breakdown of erythrocytes and the loss of cations and water.[12]

Aplastic anemia

The problem of the marrow producing blood is referred to as "aplastic." Although the bone marrow looks "empty," it may still be susceptible to hematopoiesis. Bone marrow failure can happen without diminished cellularity in myelodysplastic syndromes and paroxysmal nocturnal hemoglobinuria (PNH).[13]

Fanconi anemia

Fanconi anemia (FA) is an X-linked recessive and autosomal condition. Its symptoms include solid tumors, loss of bone marrow, developmental anomalies, and acute myelogenous leukemia. In the past few years, FA patient treatment has improved substantially, leading to a high rate of children surviving to adulthood. Even though the proteins in the FA pathways still have to be given a definite biological purpose, these advances have been made. Finding the FA pathway's biological roles may help improve FA medication options and reduce the chance of death from the disease.[14]

Anemia in Hodgkin and non-Hodgkin lymphoma

In about 40% of Hodgkin's lymphoma (HL) patients, the symptoms of anemia can be found. It can be commonly seen in later stages and is frequently linked with B symptoms, including weight loss, night sweats, and fever. Anemia is relatively mild and normochromic and normocytic, and the Hb values range between 10 and 12 g/dl.[15] The results of many past types of research show the occurrence of anemia in people having non-Hodgkin lymphoma. Approximately 37.1% of the patients suffer from HB levels that indicate anemia.[16]

Anemia in multiple myeloma

Because many factors play a role in the progression of anemia in people with multiple myeloma, the primary cause is a deficiency in red cell synthesis by the bone marrow. Due to chemotherapy, the marrow replacement with myeloma cells and cumulative marrow suppression are two causes of poor erythropoiesis. Therefore, the primary cause of decreased erythropoiesis is faulty erythropoietin formation or a poor erythroid marrow reaction to erythropoietin.

According to Beguin et al, the serum erythropoietin levels were low in about 25% of myeloma patients. Such figure jumped to 50% of individuals with stage III illness and 60% of patients with renal impairment. Erythropoietin is a survival protein that inhibits proerythroblasts from undergoing apoptosis or programmed cell death and is the principal growth factor for erythroid precursors. Consequently, low erythropoietin values lead to lower red cell synthesis and shorter red cell survival. Depending on these results, the use of (rHuEpo) which stand for recombinant human erythropoietin in treating anemia caused by myeloma might be beneficial.[17]

Anemia in chronic myeloid leukemia

At the time of diagnosis, many people with chronic-phase chronic myeloid leukemia (CML-CP) exhibit anemia. However, the prognosis is unclear. There was no notable variation between the moderate and non-moderate anemia groups in terms of molecular responses or survival. Furthermore, this discovery prompted questions concerning the cause of CML-related anemia. Two factors might explain the mechanism. First, high granulocyte production in the bone marrow (BM) microenvironment, and secondly, Park et al observed that the amount of hematopoietic stem cells in CML was more significant than in the control group (normal marrow). Changes in the BM microenvironment might cause patients of CML to have faulty hematopoiesis.[18]

Anemia in chronic lymphocytic leukemia

Anemia indicates a variety of disorders and not a disease itself. The latest assessment is required for each episode of anemia to establish whether it is a relapse of the initial condition—in our patient's case, autoimmune hemolysis. Whether a patient has or does not have CLL, it's crucial to remember that gastrointestinal angiodysplasia, diverticulosis, and myelodysplasia are prevalent causes of anemia in older individuals. Moreover, several problems and relationships are more common in CLL patients, including the following: Spleen enlargement autoimmune hemolytic anemia (as shown in our patient's first episode) is a condition in which the immune system attacks the blood. Due to significant disease involvement, the marrow is suppressed. Drug or chemotherapy-induced marrow suppression, thrombocytopenia, coagulopathy, or gastrointestinal blood loss caused by pharmacological side

effects (glucocorticoids or ibrutinib), aplasia of pure red blood cells.[19]

Anemia in acute myeloid leukemia

Acute myeloid leukemia (AML) is a genetically, epigenetically, and medically diverse illness defined by the aggregation and proliferation of immature myeloid cells in the bone marrow (BM). AML has long been thought to be an immune-responsive disease, and it remains the most prevalent reason for people to have allogeneic hematopoietic stem cell transplantation (alloHSCT). Moreover, a small link between graft-versus-host disease and AML relapse reduction as well as alloHSCT's inability to avoid relapse in the majority of people who experience transplantation with active disease, highlight alloreactive T cells' limited efficacy and the requirement of more powerful and particular AML targeting.[20]

Anemia in acute lymphocytic leukemia

ALL is a type of hematologic disease in which immature lymphoid cells arise in the bone marrow, peripheral blood, and other organs. It affects about 4000 people in the United States each year and accounts for 75 to 80% of acute leukemias in youngsters, resulting in juvenile leukemia; nevertheless, ALL only accounts for around 20% of all adult leukemias. Since ALL is a biologically diverse disease, morphologic, biologic, immunologic, cytogenetic, and molecular genetic attributes of leukemia lymphoblasts are essential to ascertain the identification, which indicates other possible causes of bone marrow failure and define ALL subtypes. Such difference emphasizes the point that leukemia may attack at any point throughout the lymphoid development process.[21] This study aimed to investigate the frequency and types of anemia in patients with hematological malignancies at Hiwa Cancer Center, Sulaymaniyah, Iraq. By analyzing demographic, clinical, and laboratory data, we sought to identify the most common forms of anemia and their associations with specific malignancies, providing insights to guide diagnostic and therapeutic strategies for improved patient management.

METHODS

This retrospective study was conducted following approval by the research center ethical committee of Hiwa Cancer Center in Sulaimania, Iraq, from January 2021 to December 2021. The study included 41 patients diagnosed with hematological malignancies at Hiwa Hospital during this period. Patients were selected for inclusion based on having a confirmed diagnosis of hematological malignancy through standard diagnostic methods including bone marrow examination and peripheral blood analysis, along with available complete blood count results demonstrating anemia (hemoglobin <12 g/dl for women or <13 g/dl for men).

Exclusion criteria were applied to patients with incomplete medical records lacking essential diagnostic or follow-up data, those with anemia attributable to non-malignant causes such as nutritional deficiencies or chronic renal failure, and patients who had received blood transfusions within the previous four weeks which could potentially alter hematological parameters.

Comprehensive patient data were collected from medical records, including demographic information, complete blood count results at presentation, peripheral blood film findings, and bone marrow examination reports. Additional laboratory parameters evaluated included erythrocyte sedimentation rate, reticulocyte count, direct Coombs test results, iron status, serum vitamin B12 and folate levels, C-reactive protein, lactate dehydrogenase, serum total bilirubin, prothrombin time, and activated partial thromboplastin time. Bone marrow procedures were performed by experienced nurses in the minor procedures department, with aspirate slides prepared using Leishman stain and core biopsies processed in the histopathology department. Peripheral blood films were similarly prepared and stained with Leishman stain following standard protocols.

Laboratory analyses were conducted using standardized equipment and methods: complete blood counts were performed using Swelab™ Lumi automated hematological analyzers (Boule Diagnostics AB, Sweden), erythrocyte sedimentation rate was measured with a JOKOH analyzer (Japan), reticulocyte counts were determined manually using methylene blue staining, and biochemical parameters including iron studies, vitamin B12/folate, C-reactive protein (CRP), lactate dehydrogenase (LDH), and bilirubin were analyzed using Cobas c311/Cobas e411 analyzers (Roche, Germany). Coagulation studies (PT and APTT) were performed using a STA Compact Max analyzer (Diagnostica Stago, France) following manufacturer protocols.

Statistical analysis was performed using statistical package for the social sciences (SPSS) version 26, with continuous variables expressed as mean±standard deviation and categorical variables presented as frequency distributions and percentages. This comprehensive approach ensured systematic evaluation of anemia characteristics in the studied hematological malignancy population while maintaining rigorous methodological standards.

RESULTS

A total of 41 patients were diagnosed with types of anemia that were stated in this study. 24 of them were males (59%) while 17 (41%) of them were females. The study was conducted based on the mean age. The mean was 54 with a standard deviation of ±17 and the range was from (4 to 80) years old (Figure 1).

As illustrated in Figure 2 the types of hematological malignancy are as follows: 10 (24.4%) of the patients were

diagnosed with AML, 6 (14%) with ALL, 10 (24.4%) with CLL, 3 with CML (7%), 2 (5%) with multiple myeloma, HL and NHL were found in 5 patients each (12.1%).

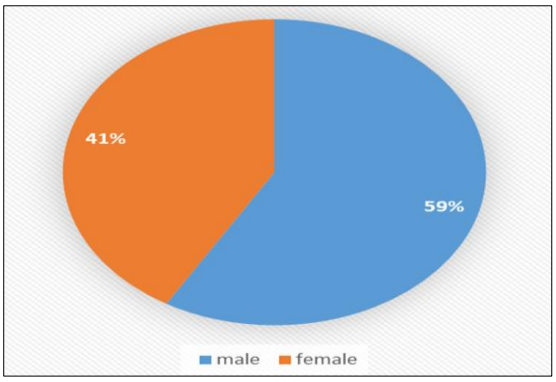

Figure 1: The percentage of males and females among 41 patients.

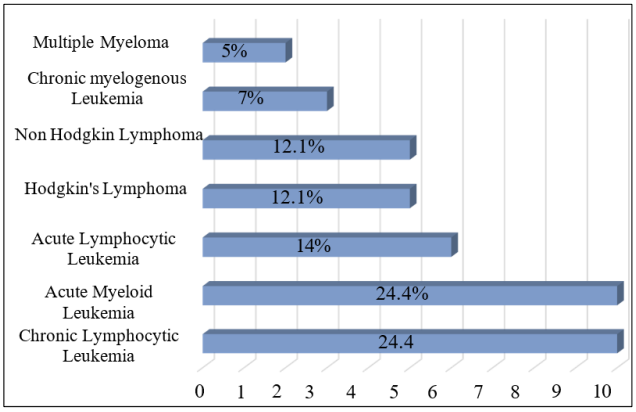

Figure 2: The types of hematological malignancy among 41 patients.

Moreover, the morphology of the WBC is shown in Figure 3. Around 11 (27%) patients showed blast cells, 10 (24%) patients showed mature looking lymphocytes, 6 (15%) of them had reactive lymphoid cells, 11 (27%), of them, showed no immature cells, and three of them (7%) had left shift in the myeloid lineage.

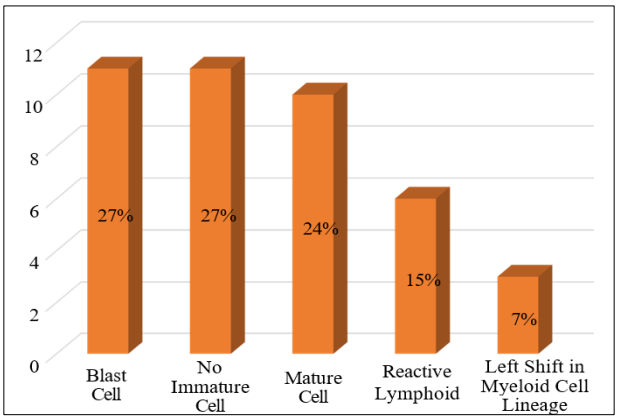

Figure 3: WBC morphology among 41 patients.

Furthermore, Figure 4 shows the types of anemia among the 41 studied patients. Normocytic anemia was found in 31 (76%), patients, microcytic anemia in 7 (17%), and macrocytic anemia in three patients only (17%).

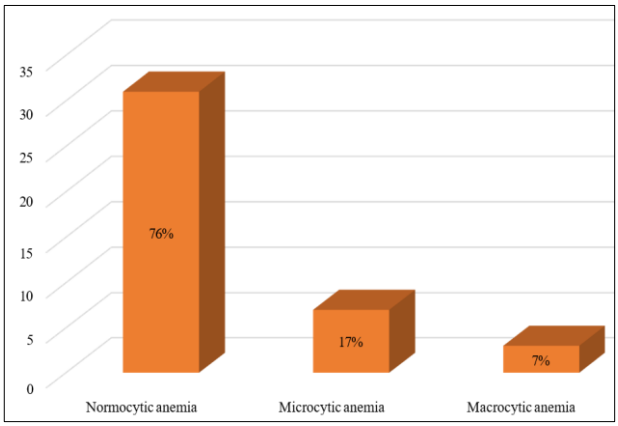

Figure 4: The types of anemia among 41 patients.

Figure 5 represents the bone marrow findings. 10 of them are normal (24%), 16 of them are suppressed (39%) and 15 of them are hypercellular (37%).

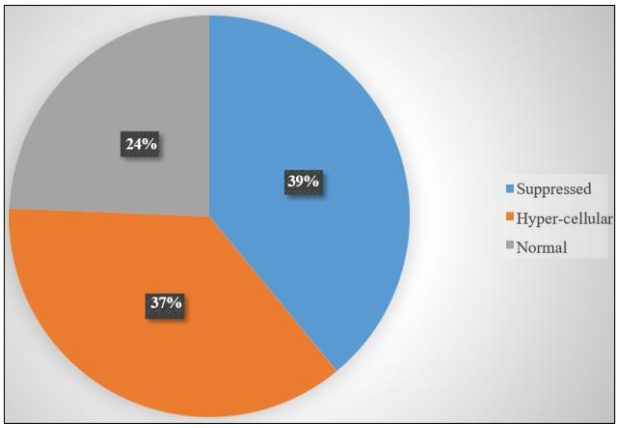

Figure 5: Bone marrow findings among 41 patients.

Also, hematological work up in the studied group was conducted. The hemoglobin levels ranged between 5-13 g/dl with a mean of 9.6 g/dl and a standard deviation of ±5 SD. Also, another parameter is WBC ranged 2.3-264×10^9/l, mean of 9.6×10^9/l with a standard deviation of ±20. Platelet ranged 6-600×10^9/l, mean 137.3 and the standard deviation is ±110. Moreover, another parameter is ESR ranged 7-105 mm/l. Their mean is 50 mm/l and the standard deviation is ±30. Reticulocyte counts in30 patients are normal and in11 patients are increased. Positive Coombs test patients are 5 and negative ones are 36. The mean PT of the patients was 14s and the mean PTT was 37s. The last parameter is iron status 7 of the patients had low iron and 34 with normal iron.

The frequencies of the types of anemia in the different hematological malignancies that we observed among our

patients are shown in Table 2. As mentioned before the most common type of anemia was normocytic anemia followed by microcytic then macrocytic anemia.

Table 1: The hematological work up in the studied group.

Variables	Values (mean±SD), range
Hb (g/dl)	9.6±5, 5-13
WBC×10⁹/l	20±80, 2.3-264
Platelet×10⁹/l	137.3±110, 6-600
ESR mm/l	50±30, 7-105
Reticulocyte count	Normal: 30, increased: 11
Coombs test	Positive: 5, negative: 36
PT (mean (second))	14 (13-33)
PTT (mean (second))	37 (27-46)
Iron status	Low: 7, normal: 34

Table 2: The frequency of different types of anemia among different hematological malignancies in the studies cohort.

Hematological malignancy	Types of anemia, N (%)
AML (n=10)	Normocytic: 8 (80), microcytic: 2 (20)
ALL (n=6)	Normocytic: 5 (83), microcytic: 1 (17)
CLL (n=10)	Normocytic: 8 (80)^a, microcytic: 2 (20)
CML (n=3)	Normocytic: 3 (100)
MM (n=2)	Normocytic: 2 (100)
HL (n=5)	Macrocytic: 3 (60)^b, microcytic: 2 (40)
NHL (n=5)	Normocytic: 5 (100%)^c

^a 5/8 CLL patients had positive Coombs test, ^b 3/5 HL patients had high reticulocyte count, ^c 3/5 NHL patients had high reticulocyte count, a: five out of the eight CLL patients with normocytic anemia had positive coombs test and high reticulocyte count, b: three out of the five HL patients with macrocytic anemia had high reticulocyte count, and c: three out of the five NHL patients with normocytic anemia had high reticulocyte count

DISCUSSION

Anemia is a disorder where a person's hemoglobin or RBC levels are inadequate or fall below normal values. This study was comprised of 41 anemic patients diagnosed with different hematological malignancies. Among our patients 59% were males and 41% were females. Results of this study showed that the most prevalent hematological malignancy in our cohort was chronic lymphocytic leukemia (24.4%) and the less prevalent one was multiple myeloma (5%), which is inconsistent with earlier studies which estimated that multiple myeloma accounts for 1% of all cancer diagnoses.[9] NHL is most common in individuals over 20 years of age, with incidence increasing with age.[22]

In our study, all patients with NHL had normocytic anemia, consistent with other studies.[22] HL is rare and usually presents in young adults. Sixty percent of our patients had macrocytic anemia and 40% had microcytic anemia.[23] ALL is a malignancy of lymphoblasts (B or T) with uncontrolled proliferation of immature lymphocytes, eventually causing bone marrow failure. In the current study, most ALL patients had normocytic anemia.[24] ALL is the most common childhood malignancy, occurring five times more frequently than AML.[25] AML is characterized by clonal expansion of immature blast cells in the bone marrow, resulting in bone marrow failure. The incidence of AML is 4.2 per 100,000 populations annually. Our AML patients exhibited normocytic anemia, consistent with earlier reports. CLL is marked by the accumulation of small, mature-appearing lymphocytes in the bone marrow, blood, and lymphoid tissues. The incidence of CLL varies geographically, with twice the risk in men compared to women.[26] CLL patients in our study had normocytic anemia with a positive Coombs test and high reticulocyte count, indicative of autoimmune hemolytic anemia.[26]

This finding is consistent with many previous reports. The kind of anemia known as normocytic normochromic anemia occurs when RBCs are the same size (normocytic) and have a normal central pallor (normochromic). Microcytic anemia is characterized by the presence of small, frequently hypochromic red blood cells in a peripheral blood smear and a low MCV. Macrocytic anemia is characterized by macrocytosis (MCV more than 100 fl) in the presence of anemia.[27] In our study, results showed that the most prevalent kind of anemia in 41 patients is normocytic anemia with 76% and the less prevalent form is macrocytic anemia with 7%.

In our study, it was found that 39% of bone marrow cells were suppressed. Similarly, 37% of patients had hypercellular bone marrow and 24% of patients had normal bone marrow cells. These bone marrow findings are in agreement with other reports concerning the different effects of hematological malignancies on bone marrow cellularity.

This study has several limitations that should be acknowledged. Firstly, the sample size was relatively small (n=41), which may limit the generalizability of the findings to broader populations.[28] Secondly, the study was conducted at a single center (Hiwa Cancer Center in Sulaymaniyah, Iraq), and regional variations in disease presentation or management might not be captured.[7] Additionally, the retrospective design limited control over data quality and completeness, especially in relation to nutritional status, detailed treatment history, and longitudinal follow-up, which could influence the types and severity of anemia observed.[29] Finally, the exclusion of patients who had recently received transfusions might have led to underestimation of certain anemia patterns, such as those related to acute treatment effects.[30] Future multicenter studies with larger, more diverse cohorts and

prospective data collection are needed to validate and expand upon these findings.[31-33]

CONCLUSION

Anemia is a common consequence of patients with hematological malignancies and it can be caused by a variety of factors such as tumor cell infiltration into the bone marrow, hemolysis, inadequate diet, and immune system problems as a result of the disease or cytotoxic therapy. Anemia causes fatigue, exhaustion, dizziness, headache, dyspnea, and low energy, all of which harm a patient's quality of life. Because anemia is so common in patients with hematologic malignancies, it must be treated as part of the overall illness management plan to improve quality of life.

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