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Research Article

Etiological Investigation of Patients Visiting a Hematology Polyclinic for Anemia

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Abstract

Objectives: Per the World Health Organization, anemia is defined as a hemoglobin level below 13 g/dL in men, below 12 g/dL in nonpregnant women, and below 11 g/dL in pregnant women. Information on patients who visited to our hematology polyclinic with anemia between September 2014 and March 2015 was retrospectively reviewed, and 103 patients were included in the study.

Methods: Anemia was classified into three groups: nutritional anemia and anemia due to production inadequacy in group I; anemia due to increase in erythrocyte destruction in group II; and anemia due to bone marrow infiltrating diseases and hematological malignancies in group III. NCSS 2007 & PASS 2008 statistical software programs were used for statistical analysis. Kruskal-Wallis and Mann-Whitney U test for quantitative data and tests of Pearson chi-square and Fisher-Freeman-Halton tests for qualitative data were used for analysis.

Results: The mean ages of groups I, II and III were 47.7, 47.5, and 63.3 years, respectively. Additionally, the mean age of group III was significantly higher. HT and DM were present as additional comorbidities in 20% and 35% of anemia cases, respectively. Although the DM ratio was higher in groups I and II, it was notable that all diabetic patients in group III had a diagnosis of MM. There was a statistically significant difference between (median) PLT levels between groups I and III. The mean LDH level in group II, measured as 573.8 U/ml, was found to be higher than that in the other groups. Mean sedimentation rates were detected in groups I, II and III as 40.7 mm/h, 56.43 mm/h and 73.6 mm/h, respectively.

Conclusion: Because nutritional anemia was followed by physicians in internal medicine, nutritional anemia was seen at a lower rate in our study than in prevalence studies. For health interpretations, extensive screenings and etiological studies should be performed in anemic patients.

Keywords: Differential diagnosis of anemia, etiology of anemia, hematologic malignancies presenting with anemia

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Anemia is identified as hemoglobin (Hb) and hematocrit (Hct) levels less than 2 standard deviations below the normal mean levels according to age and gender.[1] According to the WHO data, anemia is considered when the hemoglobin level is <13.5 gr/dl in men, <12 gr/dl in premenopausal women and <13 gr/dl in postmenopausal women.[2] According to the WHO global database on anemia, anemia was detected in 24.8% of the world's total population, 41.8% of pregnant women, 30.2% of women in reproductive age, 12.7% of men and 23.9% of elderly individuals between 1993 and 2005. Iron deficiency anemia (IDA) was seen in more than 50% of anemic patients.[2]

Anemia can be a symptom of other diseases, rather than being a disease in itself. For this reason, careful evaluation of the patient's medical history is important; the duration and severity of anemia, medication history, dietary habits,

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other symptoms, and complaints of chronic illness (weight loss, fever, fatigue) should be investigated.[3] Identification of anemia type is important for diagnostic approach and differential diagnoses. The basic laboratory parameters that we use to determine anemia type are hemogram, serum iron (SI), total iron binding capacity (TIBC), transferrin saturation, vitamin B12, folate, ferritin, reticulocyte count, direct and indirect Coombs test, total and indirect bilirubin, lactate dehydrogenase (LDH) and peripheral blood smear. Other cytopenias accompanying the disease should be considered in differential diagnoses, and further investigation should be requested according to etiology.

Patients who visited the hematology outpatient clinic of the Dr. Lutfi Kirdar Kartal Training and Research Hospital between September 2014 and March 2015 for anemia were retrospectively reviewed. In our study, we aimed to determine the etiologic differences and comparative evaluation of these patients.

Methods

One patient/day was randomly selected from patients aged ≥18 years who were referred to our hematology department for anemia between September 2014 and March 2015. A total of 103 patients were evaluated retrospectively according to the WHO anemia criteria. The patient's age and gender, comorbid diseases, sedimentation rate (ESR), Hb, MCV, RDW, WBC, PLT levels, iron parameters, vitamin B12 and folic acid levels, creatinine level, bone marrow biopsy and diagnosis were recorded. According to the data, 3 groups were formed:

Group I: Nutritional anemias: anemia of iron deficiency (IDA), anemia of folic acid and vitamin B12 deficiency, anemia due to lack of erythrocyte production, i.e., aplastic anemia (AA), and anemia of chronic disease (ACD).

Group II: Anemias due to an increase in erythrocyte destruction (acquired hemolytic anemia and hemoglobinopathies).

Group III: Bone marrow infiltrating diseases and hematologic malignant diseases (leukemia, lymphoma, myelodysplastic syndrome (MDS), multiple myeloma (MM), myelofibrosis (MF).

Statistical Analysis

For statistical analysis, the NCSS (Number Cruncher Statistical System) 2007 & PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA) program was used. Descriptive statistical methods (median, standard deviation, median, frequency, odds, minimum, and maximum) were used when evaluating study data. The Kruskal-Wallis test was used to compare the three groups with no normal distribution, and the Mann-Whitney U test was used to determine the group causing the difference. The Pearson chi-square test, Fisher's test and Freeman-Halton test were used for comparison of qualitative data. Significance was evaluated at $p<0.01$ and $p<0.05$ values.

Results

The study was performed with 103 cases consisting of 33 males (32%) and 70 females (68%) at the hematology department of Dr. Lutfi Kirdar Kartal Training and Research Hospital. The patients' ages ranged from 18 to 84 years, with a median age of 53.67±18.55 years. The median age of the male patients was 52 (18-84) years, and the median age of the female patients was 61.09 (18-81) years.

The median levels of hematologic parameters in our study were as follows: Hb: 9.23 gr/dl (3.4-11.9); MCV: 81.85 fL (52.2-121); platelet count: 238.39/mm^3 (3-1162); RDW: 17.74 (12.7-29); iron: 62.02 µg/L (50-289); ferritin: 148.73 ng/ml (1.2-2000); LDH: 318.64 U/ml (100-3359); and sedimentation: 54.55 mmHg (4-138). The diagnostic distributions of the cases in Group I were IDA at 63.15% (n=36), ACD at 15.7% (n=9), vitamin B12 deficiency at 14.03% (n=8) and AA at 7.01% (n=4). No anemia due to folic acid deficiency was found. Group II included 50% (n=4) hemoglobinopathies and 50% (n=4) acquired hemolytic anemia. Group III included MDS (n=16), MM (n=11), leukemia (n=8) and lymphoma (n=3) diagnostic subgroups. The diagnostic distribution of patients in groups I and III are shown in Figures 1 and 2.

The median ages of groups I, II and III were 47.70 years (18-81), 47.5 years (18-74) and 64.3 years (26-48), respectively. When stratified according to disease, the median age was 40.7 years (18-72) in IDA, 71.3 years (54-80) in ACD, 54.25 years (33-79) in AA, 46.5 years in vitamin B12 deficiency, 29.5 years (18-51) in hemoglobinopathy, 56.2 years (41-74) in acquired hemolytic anemia, 52 years (26-73) in leukemia

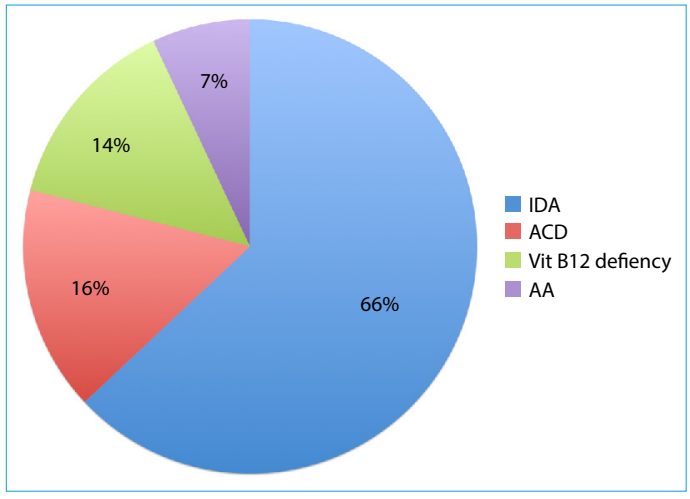

Figure 1. Diagnostic Distribution of Group-I cases.

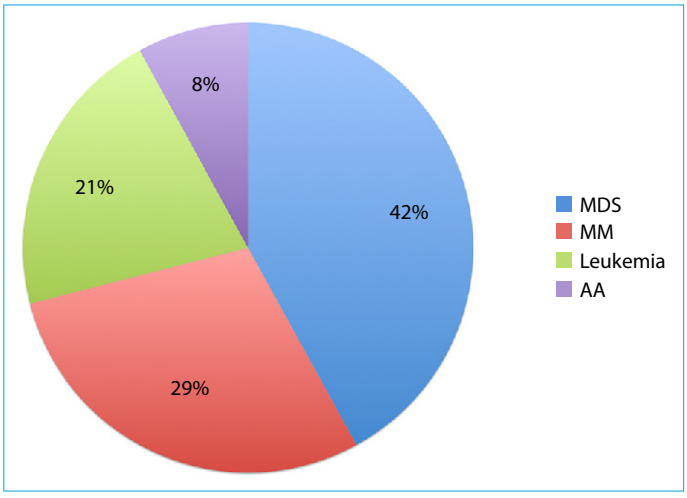

Figure 2. Diagnostic Distribution of Group-III cases.

and lymphomas, 71 years (55-84) in MDS and 66.9 years (48-68) in MM. The highest median age was seen in MDS and anemia of chronic disease (Table 1).

Group I contained 71.4% (n=40) females and 28.6% (n=17 males. Group III contained 55.6% (n=22) females and 44.4% (n=16) males. In Group II, 100% (n=8) of the patients were female.

Comorbid disease was present in 44.0% (n=44) of the cases. The comorbid disease cases included 47.7% diabetes mellitus (n=21), 56.8% hypertension (n=25), and 59.1% other diseases (chronic renal failure, peripheral arterial disease, hypothyroidism, coronary artery disease, systemic lupus erythematosus, breast cancer, leiomyosarcoma, tuberculosis, Parkinson's disease) (n=26).

The median Hb levels in Groups I, II, and III were 9.45 gr/dl, 8.14 gr/dl and 9.13 gr/dl, respectively. Hb, WBC and RDW level differences were not significantly different across groups (p>0.05).

The median MCV levels were 76.46 fL, 86.88 fL and 89.12 fL in groups I, II and III, respectively. In the IDA group, the median MCV was 68.6 fL, and two patients had both IDA and ACD. The median MCV was 96 fL, 86.1 fL and 91.1 fL in AA, ACD, and vitamin B12 deficiency, respectively. Four of the vitamin B12 deficient patients also had IDA. The median MCV was 108.1 fL in patients with only vitamin B12 deficiency. The hemoglobinopathy and acquired hemolytic anemia groups' median MCV levels were 78.3 and 100.6 fL, respectively. The median MCV levels in the MDS, MM, leukemia and lymphoma groups were 90.17 fL, 88.8 fL, 90.5 fL and 80.3 fL, respectively. There was a statistically significant difference in the MCV levels of the cases according to the groups (p=0.001; p<0.01). According to pairwise comparisons to identify the group that created the difference, the MCV levels of group 3 were significantly higher than those of group 1 (p=0.001; p<0.01). There was no statistically significant difference between the MCV levels of groups 2 and 3 (p=0.605; p>0.05) or between the MCV levels of group 1 and group 2 (p=0.109; p>0.05).

Even though there was no statistically significant difference in the Hct levels of the patients according to the groups (p=0.076; p>0.05), it was noteworthy that Hct levels in group 2 were lower than in the others.

The median platelet (PLT) counts were 277.610/mm^3 in group I, 194.750/mm^3 in group II and 187.080/mm^3 in group III. In the IDA group, both thrombocytopenia (11.4%) and thrombocytosis (2.8%) were seen. Thrombocytopenia was demonstrated in the AA, MDS, vitamin B12 deficiency, and leukemia groups at frequencies of 75%, 33.3%, 37.5%, and 50%, respectively. There was a statistically significant difference between the PLT counts according to the groups (p=0.035, p<0.05). According to pairwise comparisons made, the PLT count of group III was significantly lower than that of group I (p=0.011; p<0.05). There was no statistically significant difference in the PLT counts of groups II and III (p=0.543; p>0.05) and the PLT counts between groups 1 and 2 (p=0.320, p>0.05).

The median iron levels in groups I, II, and III were 44.60±35.14, 77.33±25.62, and 89.09±58.25, respectively.

Table 1. Evaluation of Demographic Characteristics According to Diagnoses

	Group I (n=57) Median±SD (Median)	Group II (n=8) Median±SD (Median)	Group III (n=38) Median±SD (Median)	p
Age	47.70±18.47 (49.5)	47.5±17.64 (49.5)	64.33±13.86 (66.5)	0.001[a]•
Gender, M/F, n (%)	17/40 (28.6/71.4)	0/8 (0/100)	16/22 (44.6/55.4)	0.036[b]••
Comorbidity, Absent/Present	35/22 (62.5/37.5)	5/3 (62.5/37.5)	17/21 (44.7/55.3)	0.257[c]
Existing Comorbidities				
DM	13 (61.9)	2 (66.7)	6 (30.0)	0.072[c]
HT	11 (52.4)	1 (33.3)	13 (65.0)	0.569[c]
Others	12 (57.1)	2 (66.7)	12 (60.0)	1.000[c]

[a]Kruskal Wallis testi; [b]Pearson Ki-kare testi; [c]Fisher-Freeman-Halton testi; •p<0.01; •• p<0.5; Multiple comorbidities are seen.

Rationally, the iron levels of the IDA and ACD groups were lower (33 and 43.75, respectively). There was a statistically significant difference in the iron levels of the cases according to diagnosis (p=0.001, p<0.01), and the iron levels of group 2 and group 3 were significantly higher than those of group 1 (p=0.015, p=0.001, respectively, p<0.05) (Table 2). The median TDBK of groups I, II, and III were 372.83±88.84, 355.33±85.12, and 283.56±53.85, respectively. The highest value, which was 412.6, was detected in the IDA group, as expected (Table 2).

Significant difference at an advanced level was detected statistically between the TIBC levels of the cases according to the groups (p=0.001; p<0.01). The TDBC levels of group II and group III were significantly lower than those of group I (p=0.018, p=0.001, p<0.05). The TIBC levels of group III cases were also significantly lower than those of group II (p=0.025, p<0.05).

The median transferrin saturation (TS) of group I was 12.81±11.19%, and in the IDA and ACD subgroups, TS was 7.27±5.67% and 17.86±9.8%, respectively. The median TS values in groups II and III were 23.80±11.52% and 32.48±22.20% respectively. Significant differences were detected between the levels of TS in the cases according to the groups (p=0.001, p<0.01). The TS levels of group II and group III were significantly higher than those of group 1 (p=0.001; p=0.018, p<0.05). There was no statistically significant difference in the TS levels of group II and group III (p=0.447, p>0.05).

The median ferritin levels were 58.15±121.63 ng/ml in group I, 106.40±118.14 ng/ml in group II and 301.32±389.46 ng/ml in group III. The median ferritin values according to diagnosis were 16.33±32.2 ng/ml, 104±77.82 ng/ml, 313.87±501.2 ng/ml, 309.47±321.54, and 133.4±141.98 ng/ml in IDA, ACD, MDS, AA, and MM patients, respectively. The highest median ferritin level was 576.85±314.99 ng/ml in the leukemic group. The vitamin B12, folate, total protein, albumin and creatinine levels of the cases did not show statistically significant differences (p>0.05).

The median LDH levels of groups I, II and III were 305.06±525.48 U/L, 573.88±422.74 U/L and 276.94±271.14 U/L, respectively. The highest LDH level was found in patients with vitamin B12 deficiency, with a value of 1599±1396.85 U/L. In the other disease groups, a high median LDH level was determined, with 743.2±457.77 U/L in acquired hemolytic anemia cases and 323.33±104.71 U/L in hemoglobinopathies. A highly statistically significant difference was detected between the LDH levels of the groups (p=0.001; p<0.01). This difference was related to the fact that LDH levels of group 2 and group 3 were significantly higher than that of group 1 (p=0.038, p=0.001, p<0.05). In addition, LDH levels in group 2 were significantly higher than in group 3 (p=0.003, p<0.01).

The median ESR was 40.77±29 mm/h, 56.43±41.08 mm/h, and 73.62±38.50 mm/h in groups I, II, and III, respectively. The median ESR was 27.59±22.82 mm/h in IDA cases, 66.66±30.14 mm/h in ACD cases, 73.5±34.97 mm/h in AA cases, 96.66±36.63 mm/h in lymphoma cases, 56.15±31.21 mm/h in MDS cases, 72.5±46.06 in leukemia cases and 100.5±21.94 mm/h in MM cases.

A highly statistically significant difference in the ESR levels of the cases according to group was detected (p=0.001; p<0.01). According to the pairwise comparisons made, the ESR levels of group 3 were significantly higher than those of group 1 (p=0.001; p<0.01). There was no statistically significant difference in the sedimentation levels of group 2 and group 3 (p=0.290; p>0.05). There was also no statisti-

Table 2. Evaluation of Laboratory Findings According to Diagnoses

	Group I Median±SD (Median)	Group II Median±SD (Median)	Group III Median±SD (Median)	p
Iron	44.60±35.14 (34)	77.33±25.62 (77)	89.09±58.25 (70.5)	0.001**
Total iron binding capacity (TIBC)	372.83±88.84 (375)	355.33±85.12 (332)	283.56±53.85 (285.5)	0.001**
Transferrin saturation	12.81±11.19 (8.7)	23.80±11.52 (22.9)	32.48±22.20 (25.3)	0.001**
Ferritin	58.15±121.63 (16)	106.40±118.14 (103)	301.32±389.46 (184)	0.001**
Vit B12	304.39±289.86 (247)	274.20±42.85 (252)	473.39±403.86 (300)	0.192
Folate	8.49±4.39 (7.4)	7.83±4.31 (7.8)	7.06±3.44 (5.9)	0.351
LDH	305.06±525.48 (182)	573.88±422.74 (451)	276.94±271.14 (216)	0.001**
Total Protein	7.16±0.70 (7.3)	7.02±0.46 (6.8)	7.71±1.11 (7.4)	0.100
Albumin	4.04±0.49 (4.1)	4.34±0.31 (4.5)	3.89±0.67 (4)	0.296
Sedimentation	40.77±29.60 (33.5)	56.43±41.08 (58)	73.62±38.50 (77.5)	0.001**
Creatinine	0.81±0.32 (0.7)	0.84±0.24 (0.9)	0.99±0.49 (0.9)	0.281

Kruskal Wallis Test; **p<0.01; *p<0.05.

cally significant difference in the sedimentation levels of group 1 and group 2 (p=0.356, p>0.05).

Discussion

Anemia is one of the most important health problems that needs to be diagnosed, treated and followed up. Although important clues are often obtained by examining the clinical symptoms and findings in the patient's history, all information must be evaluated together with laboratory findings to arrive at a definite diagnosis. When the etiology of anemia in the patient is being investigated, the parameters and morphology of erythrocytes, the number of reticulocytes, and the number of WBCs and PLTs should be evaluated in addition to serum Hb and Hct levels. Incomplete or incompatible examinations according to the diagnostic algorithms for differential or confirmatory diagnosis, unnecessary blood transfusions in patients, implementation of iron replacement therapy in the majority of patients without transfusion and disregarding of etiological studies are common mistakes.[4] In our center, reticulocyte levels could not be evaluated in all of our patients due to the inability to perform the reticulocyte count test effectively. The results of iron, TIBC, ferritin, folate, vitamin B12, LDH, albumin, total protein, sedimentation and routine biochemical tests were examined in all patients. Percent transferrin saturation was calculated using iron and TIBC values. A total of 103 patients were included in the study. Bone marrow biopsies were administered to 50 patients for diagnostic purposes. Studies with patients under 60 years old in Turkey frequently showed that the prevalence of anemia was higher in women than men.[5] The prevalence of anemia was found to be 30% for females and 18.2% for males in a study of 2187 patients (1407 females and 780 males) aged 18-92 years in Düzce by R. Memisogullari et al.[6] The prevalence of anemia in Turkey was reported to be 11% in a study by Cetin et al.[7] In our study, 68% of patients were female, and 32% were male. These data were compatible with the global medical literature.

The median age of the patients was 47.7 years in group I, 47.5 years in group II and 64.3 years in group III. The youngest patients were found in the IDA group (median age 40.7 years). The high median age of group III is due to the increased the frequency of hematological malignancies among those over 60 years of age. In MM patients, the median age at diagnosis is 66.[8] MDS occurs mainly in older adults, with a median age at diagnosis of ≥65 years in most series and a male predominance.[9] AML shows a rapid increase from the age of 40 years, and ALL peaks at approximately 50 years of age in adulthood.[10,11] In a study of 170 anemic elderly patients by Artz and Thirman in 2011, IDA in 25.3%, chronic inflammation anemia in 9.8%, hematologic malignancies in 7.5% and unexplained anemia in 43.7% were determined.[12]

In our study, 30 patients were over 65 years of age. It was revealed that there was MDS in 30%, MM in 26.6%, ACD in 20%, IDA in 13.3%, AA in 6.6%, and hemolytic anemia in 3.3% of these patients. Hematological malignancies were found to be significantly more frequent in our study than in general because only hematology outpatient clinic patients were evaluated. Since nutritional anemia is diagnosed and treated in internal medicine and family medicine outpatient clinics, nutritional anemia was rare in our study.

In the elderly population, particularly in those over 65 years of age, an increase in IDA frequency is observed. In the United States of America (USA), approximately 3 million people were screened in the Third National Health and Nutrition Examination Survey (NHANES III) conducted between 1988 and 1994. Iron deficiency was found to be the cause in 16.6% of anemias seen in people over 65 years old. In our study, 11.76% of the patients diagnosed with IDA were over 65 years of age; thus, IDA patients are usually diagnosed and treated in internal medicine outpatient clinics instead of hematology departments. IDA is the most common cause of anemia. According to the NHANES III data, IDA is present in 1-2% of all adults.[13] In the United States, the female/male ratio was reported as 1.3/2.1 in patients with iron deficiency.[14] This ratio was reported as 1.48:1 in the study conducted in Ankara and 2:1 in the study conducted in Van and its region.[15] In our study, this ratio was found to be 2.6:1 and higher than other literature. The reason for IDA in 63.15% of the patients in group I is due to the high number of women in this group.

In our study, aplastic anemia was equally seen in both genders. The male/female ratio was found to be 1.6:1 in the Turkish study with 73 aplastic anemia patients.[16]

In India, the M/F ratio was reported as 0.8 in a study of 482 megaloblastic anemia patients by Gupta et al.[17] In our study, the M/F ratio was 0.6 in patients with vitamin B12 deficiency. Folic acid deficiency was not demonstrated.

Female dominance in group II was consistent with the literature. In a Korean study that included 32 patients with autoimmune hemolytic anemia, 31 of these patients were female.[18] In Turkey, there are not enough studies on autoimmune hemolytic anemia in adults.

Hematologic malignancies are generally more common in males.[19] In a study by Estey et al.,[10] it was reported that AML is the most common type of acute leukemia in adults, the incidence increases with age, and the M/F ratio is 3/2 in terms of gender difference. In the literature, it is reported that as age approaches adulthood, male dominance in-

creases in ALL.[19] In studies conducted in terms of gender differences, the M/F ratios of KLL, HCL, HL, NHL and MM are 2/1, 4.2/1, 1.5/1, 2/1 and 1.5/1, respectively, and male dominance is seen in all diseases.[20–22] Male dominance is also present in chronic myeloproliferative diseases.[23–26] Similarly, MDS is common in men.[27] In our study, the number of female patients was higher in patients with hematological malignancies. We believe that the inconsistency between international data and our study data is related to the limited number of our patients.

DM and HT are the most common comorbidities in our study. Although there was no statistically significant difference between the groups, DM incidence was higher in groups I and II. It is reported in the literature that anemia is seen in approximately one quarter of diabetic patients.[28] It is estimated that the rate of anemia in diabetic patients is 3-4 times greater than in nondiabetic patients.[14] Hosseini et al.[29] found anemia in 30% of 365 patients with type 2 DM, and the morphological distribution of these anemias were 15.1% normocytic, 14.4% microcytic and 1% macrocytic. Grosmann et al.[30] found anemia in 10.8% of type 2 diabetic patients with normal renal function and 2.7% of nondiabetic patients. Our study included 21 patients with type 2 DM, 13 in group I, 2 in group II, and 6 in group III. The etiology of anemia in group I DM patients was consistent with the literature. There are not enough studies about the relationship between group II and DM. All of the patients in group III were in the MM group. It has been suggested that Type 2 DM is a risk factor for MM, but the relationship between them is not understood. Khan et al.[31] reported that DM, especially glucose loading, is a risk factor for multiple myeloma.

There was no statistically significant difference in the Hb levels of the groups. The median Hb level at the time of application in patients with IDA was 8.4 g/dl in a study in the USA.[32] The rationale for the higher median Hb values in Group I than in other studies is that AA, ACD, vitamin B12 and folate deficiency anemia were present in this heterogeneous group, and the majority of patients were directed to our clinic after the treatment was started. In ACD, the Hb value generally appears to indicate mild anemia, above 10 g/dl, but 20% of patients may have severe anemia (Hb≤8 g/dl).[20]

IDA is the most common cause of microcytic anemia. The median MCV in IDA is usually ≤78 fL. MCV was normal in all of the patients diagnosed with ACD. In a study with 102 patients, Altintas et al.[33] found that the median MCV was 64.5 fL in the IDA group, the median MCV in the ACD group was 78.6 fL, and the median MCV in the group with IDA and ACD was 71.5. In our study, the median MCV in group I was 76.4 fL. The median MCV values of IDA and ACD in this group were found to be consistent with the literature. The MCV was observed to be below 78 fL in 32 patients with IDA diagnosis. Four patients with MCV detected in the normal range were accompanied by vitamin B12 deficiency. In megaloblastic anemia, MCV is usually between 110 and 130. In our study, 4 megaloblastic anemia patients had MCV>110 fL. The other four patients had MCV values <110 fL because these cases were accompanied by IDA. Chan et al.,[34] in a study of 272 patients with vitamin B12 deficiency, reported macrocytosis in 252 patients and MCV<110 fL in only 20 patients. The difference in the ratio between this study and our study is related to the fact that we included a few vitamin B12-deficient patients.

In our study, the median MCV in group III was 89.12 fL. Despite the presence of macrocytic MDS in group III, there was no statistically significant difference in MCV values between groups II and III because other hematological malignancies were associated with normochromic anemia in general. The median MCV in group II was 86.8 fL, and this value was consistent with the literature.

There was a statistically significant difference in the PLT values of groups I and III. The higher platelet level in group I is associated with reactive thrombocytosis due to IDA. The lower PLT value of group III is caused by thrombocytopenia due to bone marrow infiltration and malignancies. The causes of reactive thrombocytosis are infections, tissue damage, cancers and inflammatory diseases, iron deficiency anemia, various drugs, splenectomy and hemolysis, etc. In our study, 4 IDA patients had thrombocytosis (11.4%), and one IDA patient had thrombocytopenia (2.8%). In current publications, the incidence of reactive thrombocytosis during IDA diagnosis is reported to be 13.3-27.9%.[37,38] Our data are compatible with the current literature.

RDW is the mathematical expression of anisocytosis. The normal range for RDW is 11.6 to 13.4. In particular, it is used for the differential diagnosis of IDA and thalassemia. In the studies, the median RDW was 16.3±1.8%, and the RDW sensitivity was 94% in iron deficiency anemia.[39,40] In a study by Bessman et al.,[41] RDW was found to be normal in chronic disease anemia. In a study by Altintas et al.,[36] the median RDW value in the IDA group was 21.1±4.6%, and the sensitivity of RDW in IDA was 95.4%. In a study by Gupta et al.,[42] RDW was found to be significantly higher in patients with megaloblastic anemia than in patients with AA, and it was reported that RDW could be used in differential diagnosis. In our study, the median RDW value in all groups was above 17, but no statistically significant difference was found between the groups. The median RDW values in the groups with IDA, ACD AA, and vitamin B12-deficiency anemia were

18.9, 14.6, 17.4 and 20.9, respectively.

Serum iron is between 50-150 µg/dl in healthy people. The total iron binding capacity is normally between 300-360 µg/dl. In IDA, the serum iron level is low, and TIBC is high. In ACD, serum iron is seen as normal or low, and TIBC is seen as low. Transferrin saturation in IDA is usually less than 20%, and sometimes transferrin saturation is in the range of 10%-20% in chronic disease anemia. However, IDA is definitely detected in patients with transferrin saturations below 10%.[3,20,43] In our study, since both IDA and ACD were present in group I, serum iron was significantly lower than in the other groups. Median transferrin saturation was 12.8% in group I, consistent with the results in the literature. The median iron level of group III was higher than that of the other groups due to frequent transfusions. The TIBC level was found to be statistically significantly higher in group I than in the other groups, in accordance with the literature.

Serum ferritin is the best noninvasive test for the evaluation of iron deposits. The normal range of serum ferritin level is 40-200 ml. Since ferritin is an acute phase reactant synthesized in the liver, serum ferritin levels increase in cases of liver disease, infection, fever, inflammatory disease and malignancy. In these cases, the high ferritin causes errors in evaluating stored iron.[3,20,43] Studies have shown that when the ferritin value is less than 12 ng/mL, IDA is definitely diagnosed, and when the ferritin value is more than 100 ng/ml, the IDA is excluded from diagnosis at large.[44] In the study by Altintas et al.,[42] the median ferritin value was 4.6 ng/ml in the IDA group, 489.6 ng/ml in the ACD group, and 61.2 ng/ml in both the IDA and ACD groups. However, in two separate studies excluding infectious and inflammatory conditions, when the cut-off value of serum ferritin was accepted as 30 mg/dl, the sensitivity and specificity of serum ferritin were reported to be 92% and 98%, respectively.[45,46] In our study, the median ferritin level in group I was 58.15 ng/ml. In this group, the median ferritin level of patients with only IDA was 17.4 ng/ml. Initiation of iron therapy before admission to the hematology outpatient clinic was the main reason for our patients' higher ferritin values. The median value of ferritin in our ACD group was 133 ng/ml, which is lower than in the literature. The median ferritin value of group III was 301.32 ng/ml and was significantly higher than the other groups due to frequent transfusions. In a study by Salvatore et al.,[47] the median ferritin level was to be 2362 ng/ml in low-risk MDS patients who underwent transfusion once a month for more than 1 year. The ferritin level was lower in group 3 than in Salvotere et al.[47] because our patient groups were not homogenous, and a limited number of MDS patients participated in our study. Ferritin levels above 2000 ng/mL were detected in only 1 MDS patient.

Serum LDH levels are elevated in hemolytic anemias due to the release to plasma following the disintegration of erythrocytes.[48] In our study, the median LDH was 573 U/ml in group II (hemolytic anemia and hemoglobinopathy group).

There was a statistically significant difference between the sedimentation levels between groups I and III. The median ESR was 73.6 mm/h in group III. In a study of patients with anemia and ESR above 50 mm/h, 27.9% of cases were included in oncologic/hematological malignancies, 19.9% were included in infections, 13.3% were included in nephrological diseases, 10.6% were included in rheumatic diseases, 9.6% were included in gastroenterological diseases, 7.3% were included in cardiovascular diseases, and 2.7% were included in endocrinological diseases. In addition, 5% of cases were not included in any group.[49] Haque et al.[50] evaluated 100 patients with ESR levels above 100 mm/h, 41% of patients had malignancy and 30% had hematology malignancy among all patients. Patients with high ESR and anemia should be evaluated for possible hematological malignancies. The highest ESR levels were revealed in the MM group at 100.5 mm/h. The myeloma group and older population contributed to the high ESR rate in group III.

Limitations in our study can be listed as a single-center, retrospective and a small group of patients.

Conclusion

The etiologic distribution of patients treated for anemia was 34.35% IDA, 15.5% MDS and 10.67% MM, 8.73% ACD, 7.76% leukemia, 7.76% vitamin B12 deficiency anemia, 3.88% aplastic anemia, 7.76% hemoglobinopathies and acquired hemolytic anemia, and 2.91% lymphoma. The gender distribution of the patients was 68% female and 22% male. When the causes of anemia in patients over 65 years were compared with other studies, hematological malignancies were found to be more common. MDS and MM were the leading causes in this group. Because IDA and CDA were less frequently directed to the hematology department, these diseases were seen at low rates. In Group III, the rate of female patients was found to be higher than in the literature. It is thought that there is a need for extensive studies to make more robust interpretations. The MM frequency was notable even though there are not enough studies showing the relationship between DM and MM. More extensive screening and etiological studies should be performed in patients admitted to the hematology department for anemia. The choice of the approach for anemic patients, i.e., treating patients or directing patients to the hematology department, is usually the duty of internal medicine and family medicine physicians. All of this is as important as the approach of the hematologist.

Disclosures

Ethics Committee Approval: The study was approved by the Local Ethics Committee.

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