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Original Article

The Role of Bone Marrow Biopsy in Mild Anemia of Older Patients

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ABSTRACT

Objective: Unexplained Anemia(UEA) cases may require Bone Marrow Aspiration(BMA) and Bone Marrow Biopsy (BMB) for diagnostic purposes.These procedures are performed interventionally and may lead to various complications.In our study, we planned to investigate the necessity of these procedures in UEA cases with mild anemia and grade 1 anemia with Hemoglobin (Hb) level between 10-12 g/dL.

Methods: Our study is retrospective and patients diagnosed with UEA who applied to the hematology outpatient clinic were included in the study. BMA and BMB results, as well as physical examination results and all laboratory findings of 40 AA patients over the age of 50 with Hb of 10-12 g/dL were examined.Peripheral smears and bone marrow storage iron of all cases were examined. Presence of bistopenia/pancytopenia, splenomegaly, dysplastic findings, and cases of anemia with a known and obvious cause were excluded from the study.

Results: When the results of the cases evaluated due to AA were examined, malignant or non-malignant hematological disease was not found. In the patient group aged 44 and over, Anemia of Chronic Disease (ACD) ranked first with 62.5%, while Iron Deficiency Anemia (IDA) ranked second with 37.5%.

Conclusion: As a result; In cases of UEA, grade 1 anemia, Hb 10-12 g/dL, detailed physical examination, detailed system interrogation, imaging methods and peripheral smear show the importance of laboratory examinations.Our study results suggest that BMA and BMB examinations are not an absolute necessity in this patient group if anamnesis, physical examination and correct tests are performed. Current guidelines emphasize the need to perform BMA and BMB in UEA cases. Hb<10 g/dL is accepted as real and significant anemia. Additionally, findings such as the presence of dysplasia and bistopenia/pancytopenia are significant findings for Myelodysplastic Syndrome(MDS) and Aplastic Anemia. Our study shows that when these findings are excluded in patients with Grade 1 anemia, a differential diagnosis of anemia can be made without BMA and BMB.

INTRODUCTION

The World Health Organization (WHO) explained that hemoglobin (Hb) levels below 13 g/dL in men and 12 g/dL in women as anemia.[1] The prevalence of anemia in the geriatric patients is 11% in men and 10.2% in women.[2] Iron deficiency anemia (IDA) is the most common cause of anemia worldwide, and the incidence of anemia of chronic disease (ACD) increases with age and human lifespan.[3] Older patients examined for anemia may have underlying causes, which may be complex and difficult to diagnose, such as solid gastrointestinal tumors, including myelodysplastic syndrome (MDS).[4]

In anemia studies, peripheral smear examinations, parameters such as laboratory examinations, and reticulocyte counts can provide insights into many etiological factors.[5] Despite these examination methods, 20–40% of anemia cases cannot be diagnosed. This is known as unexplained anemia (UEA).[1] In such cases, bone marrow examination can also be performed.[6] Bone marrow aspiration (BMA) and bone marrow biopsy (BMB) are invasive procedures that can cause complications such as long-term local pain, osteomyelitis, bleeding, nerve damage, and wound infection.[7]

An Hb level of 10–12 g/dL was defined as mild anemia.[8] In our study, we investigated whether a bone marrow biopsy should be performed in older patients with mild anemia if a diagnosis cannot be made despite examinations.

MATERIALS AND METHODS

This was a retrospective study. 40 Patients, aged >44 years,

who visited our hospital's hematology outpatient clinic between March 2016 and October 2016 were included. The Hb levels in the men and women included in the study were 10–13 g/dL, and 10–12 g/dL, respectively. The reticulocyte percentages and peripheral smears of all patients were scanned. Those with serum B12 levels below 200 pg/mL were defined as B12 deficiency anemia. The presence of at least one of the following criteria: Serum iron below 50 ug/dL, iron binding capacity above 350 µg/dL, and transferrin saturation below 20% was considered IDA. Serum folic acid levels below 3 ng/mL were considered indicative of folic acid deficiency anemia. Patient histories, physical examination results, and laboratory test results were evaluated. Patients with chronic kidney disease, chronic liver disease, chronic heart diseases, hypothyroidism, chronic infections, rheumatic diseases, or chronic inflammatory diseases that do not meet the IDA criteria (serum iron above 50 µg/dL, iron binding capacity below 350 µg/dL, transferrin saturation 20% above) were evaluated as UEA.

Although our study was retrospective, the peripheral smear examinations and reticulocyte counts of all patients were performed again by a single physician. Patients with anemia on their hemogram, leukopenia (WBC count <4000/mL), and thrombocytopenia (platelet count<150000/mL) were excluded from the study. Patients with dysplasia on peripheral smear examination or a mean corpuscular volume (MCV)>100 fL were excluded. When serum immunoglobulin levels and results of serum protein electrophoresis of the patients were examined, those with detected M proteins were not included in the study. Patients with palpable lymphadenomegaly, splenomegaly, or obvious signs of infection on physical examination were excluded. The BMB and BMA results of all patients were evaluated. To ensure standardization of the aspiration examinations, at least 500 cells were counted and evaluated by the same hematologist. According to the iron levels specified in the BMB reports of our hospital, stored iron was classified into five groups: 0, +1, +2, +3, and +4. Those with 0 and +1 stored iron levels were evaluated as having IDA. Those with stored iron levels of +2, +3, or +4 were considered to have sufficient stored iron. In the bone marrow evaluation, 10% or more atypical cells were considered dysplastic. A reticulocyte count of <1% in the peripheral blood smear was considered reticulocytopenia, and a count of >2% was considered a sufficient reticulocyte count. This count was based on reticulocyte values corrected for hematocrit levels. In addition, although not mandatory in our study, radiological images of the patients were examined, if available.

Statistical Methods

Statistical analyzes were obtained using the Number Cruncher Statistical System (NCSS) 2007 program(UT, Kaysville, USA). In addition to descriptive statistical methods (standard deviation, median, frequency, mean, ratio, maximum, and minimum), the Mann–Whitney U test was used to compare parameters that did not show a normal distribution in the comparison of quantitative data. Statistical importance was accepted at $p<0.01$ and, $p<0.05$ levels.

RESULTS

Of the 40 patients, 77.50% (n=31) were female and 22.50% (n=9) were male. The age in the cases vary between 44 and 88, with the mean age of 63.78±10.00 years.

When the ages of the cases are evaluated; 35.00% (n=14) were below 60 years old, 40% (n=16) were between 60 and 70 years old, and 25% (n=10) were above 70 years old. Of the patients, 35% (n=14) were below 60 years of age and 65% (n=26) were above 60 years of age. All of the patients, 57.50% (n=23) were below 65 years of age and 42.50% (n=17) were above 65 years of age (Table 1).

Hypertension and diabetes mellitus were present in 65 % (n=26) and 42.50% (n=17) of the patients, respectively (Table 2).

All of the patients under 65 years of age, 43.50 % (n = 10) were diagnosed with IDA and 56.50% (n=13) were diagnosed with ACD; of those aged 65 years and older, 29.40% (n=5) were diagnosed with IDA and 70.60% (n=12) with

Table 1. Breakdown of age and sex

Age (years)	
Min-Max.	44-88 (62.5)
(Median)	63.78±10.00
Avg±Sd	
<60 years	14 (35.0)
Age group (years); n (%)	
60-70 years	16 (40.0)
>70 years	10 (25.0)
Age group (years); n (%)	
<60 years	14 (35.0)
≥60 years	26 (65.0)
Age group (years); n (%)	
<65 year	23 (57.5)
≥65 year	17 (42.5)
Sex; n (%)	
Female	31 (77.5)
Male	9 (22.5)

Table 2. Hypertension, presence of diabetes mellitus and distribution of diagnoses

Hypertension; n (%)	
None	14 (35.0)
Present	26 (65.0)
Diabetes Mellitus; n (%)	
None	23 (57.5)
Present	17 (42.5)
Diagnosis; n (%)	
IDA	15 (37.5)
ACD	25 (62.5)

Table 3. Evaluation of cases based on age (Cut-off point 65)

	Age (years)		
	<65 year (n=23) n (%)	≥65 year (n=17) n (%)	p
Diagnosis			
IDA	10 (43.5)	5 (29.4)	0.364
ACD	13 (56.5)	12 (70.6)	

Pearson Chi-Square Test

Table 4. Evaluation of cases based on sex

	Sex		
	Female (n=31) n (%)	Male (n=9) n (%)	P
Diagnosis			
IDA	14 (45.2)	1 (11.1)	0.117
ACD	17 (54.8)	8 (88.9)	

Pearson Chi-Square Test.

ACD. No statistically significant differences were found between the diagnoses of the patients according to age (p=0.364; p>0.05) (Table 3).

Among female patients, 45.20 % (n = 14) were diagnosed with IDA, 54.80% (n=17) of them were diagnosed with ACD, 11.10% (n = 1) with IDA, and 88.90% (n = 8) of them were diagnosed with ACD. There is no statistically significant differences were found between the diagnoses of the cases according to sex (p=0.117; p>0.05) (Table 4).

Ferritin measurements of cases diagnosed with IDA were mean 89.07±11.34 and median 32 and the ferritin measurements of cases with a diagnosis of ACD were 149.98±15.22 and the median was 78. Ferritin levels in patients diagnosed with ACD were significantly higher than those in patients diagnosed with IDA (p=0.021; p<0.05) (Table 5).

DISCUSSION

In our study, the average age is 63.78 (Table 1). The most common anemia in people over the age of 60 is ACD.[9] The frequency of UEA also increases with age.[1] BMA or BMB may be required in cases of UEA.[10] However, these procedures are invasive and BMA and BMB associated with various complications as bleeding, local pain or drop foot. [7] Therefore, indications for these procedures must be determined accurately and precisely.

Joosten et al.[11] described the causes of anemia among older people as 34% ACD, 17% UEA, 15% IDA, 7.30% post-hemorrhagical anemia, 5.60% vitamin deficiency anemia, 5.10% various hematological malignancies. Chernetsky et al.[12] explained that the causes of anemia in older age groups as 13.20% renal failure, nutritional status in 4%, and UEA in 15 %. In our study, the most common anemias were IDA and ACD, respectively (Table 3). No gender difference was observed between diagnoses (Table 4). The common chronic diseases in our study are hypertension and diabetes mellitus (Table 2). According to the national health and nutrition examination survey III (NHANES III) data, the prevalence of anemia in the population aged 65 years and over in the United States is 10.60%. The most common causes of these are 33.6% UEA, 19.70% renal failure, 16.60% IDA, and 5.80% MDS. In the NHANES III data, patients with macrocytosis were evaluated using the BMA and BMB, and patients with anemia accompanied by leukopenia or thrombocytopenia were not excluded from the study. In this study, MDS did not have an important place among the etiological causes because of the low frequency of macrocytic anemia. According to NHANES III, 66% are of non-nutritional origin and, 34% of all anemia cases are of nutritional origin. This was a long-term observational study, and cases could not be evaluated using a peripheral smear. NHANES III shows that a correct diagnosis can be made in 65-70% of cases over the age of 65 years without bone marrow examination same us.[13]

Additionally, as another finding of our study, as expected; Ferritin levels were observed to be higher in ACD than in IDA (Table 5).

In their study of the Brazilian population, Cliquet et al.[14] showed that the frequency of anemia in people aged 60 years and older is 36.50%. The most common causes in

Table 5. Evaluation of ferritin levels based on diagnoses

	Ferritin			
	n	Min-Max. (Median)	Avg±Sd	p
Diagnosis				
IDA	15	13-352 (32)	89.07±113.42	0.021*
ACD	25	16.7-624 (78)	149.98±152.26	

Mann Whitney U Test *p<0.05.

this study are ACD, IDA, and UEA.[14] Similar to NHANES III data, this study showed that the frequency of MDS increases with age. For this reason, it has been stated that MDS contributes to the high frequency of UEA cases.[13,14]

As our study was not a prevalence study, we did not have data on the frequency of anemia. However, detailed hematological examinations were performed in all cases. No hematological or non-hematological diseases were detected in the BMA or BMB results. These results are similar to those reported in the literature. For example, the NHANES III study results, similar to those of our study, showed that the most common cause of anemia in the elderly population is ACD, and the second most common cause is ICD. In the NHANES III, the frequency of MDS is 5.80%.[13,14] However, no patient was diagnosed with MDS in this study. Leukopenia, macrocytosis, thrombocytopenia, and the presence of profound anemia were excluded from our study at the beginning of our study, and there were no exclusion criteria in NHANES III.[13] At the same time, in our study, patients with dysplasia in the peripheral blood smear were not included in the study, which reduced the possibility of MDS. However, there have been no studies on this topic in our country.

Hematology guidelines for the diagnosis of MDS emphasize the necessity of thrombocytopenia and/or leukopenia and/or dysplasia in peripheral smears in addition to anemia.[15] In our study, cases with mild anemia (Hb>10 g/dL) were included in the study. We believe that if the BMB and BMA are not performed in cases of mild anemia, the possible delay in the diagnosis of MDS and AA will not negatively impact the patient's health.

In previous studies[4,16] although the necessity of performing BMA and BMB in UEA cases is emphasized, we conclude that performing BMB and BMA examinations in cases of mild isolated anemia (Hb>10 g/dL) requires detailed physical examination, detailed system interrogation, and laboratory examinations, including peripheral smears.

Work limitation

The small number of cases in our study was an important limitation. Therefore, our results should be validated in larger patient groups.

Conclusion

BMA and BMB are invasive interventional procedures with various complications. As long as the Hb level is not <10 g/dL and there is no evidence of anemia, leukopenia, thrombocytopenia, macrocytic anemia, or dysplasia in the peripheral smear, there is a delay in the diagnosis of possible diseases such as AA and MDS, suggesting that it has no effect on overall survival as it does not delay treatment. In addition, our study suggests the importance of accurate physical examination, peripheral smear examination, detailed systemic questioning, and detailed examination of laboratory tests in elderly patients with anemia and Hb>10 g/dL.

Ethics Committee Approval

The study was approved by the Kartal Dr. Lütfi Kırdar Training and Research, Clinical Research Ethics Committee (Date: 12.08.2016, Decision No: 2016/514/89/4).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: Z.K., G.Y.; Design: Z.K., G.Y.; Supervision: Z.K., G.Y.; Fundings: Z.K., G.Y.; Materials: Z.K., G.Y.; Data collection &/or processing: Z.K., G.Y.; Analysis and/or interpretation: Z.K., G.Y.; Literature search: Z.K., G.Y.; Writing: Z.K., G.Y.; Critical review: Z.K., G.Y.

Conflict of Interest

None declared.

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İleri Yaş Hafif Anemide Kemik İliği Biyopsisinin Yeri

Amaç: Açıklanamayan anemi (AA) vakaları tanısal amaçlı olarak kemik iliği aspirasyonu (KİA) ve kemik iliği biyopsisi (KİB) işlemlerini gerektirebilmektedir. Bu işlemler girişimsel uygulanmakta olup beraberinde çeşitli komplikasyonlara yol açabilmektedir. Çalışmamızda hafif düzeyde anemisi olan, hemoglobin (Hb) düzeyi 10-12 gr/dL arası olan grade 1 anemili AA vakalarında bu işlemlerin gerekliliğinin araştırılması planlanmıştır.

Gereç ve Yöntem: Çalışmamız retrospektif olup, hematoloji polikliniğine başvuran AA tanılı hastalar çalışmaya dahil edilmiştir. Hb 10-12 g/dL, 50 yaş üstü 40 AA'lı hastanın KİA ve KİB sonuçları yanısıra fizik muayene sonuçları ve tüm laboratuvar bulguları incelenmiştir. Tüm vakaların periferik yaymaları ve kemik iliği depo demiri incelenmiştir. Bistopeni/pansitopeni varlığı, splenomegali, displastik bulgular, nedeni belli ve açık olan anemi vakaları çalışma dışı bırakılmıştır.

Bulgular: AA nedeniyle değerlendirilen vaka sonuçları incelendiğinde malign veya nonmalign hematolojik hastalığa rastlanmamıştır. 44 Yaş ve üzeri olan hasta grubunda grubunda kronik hastalık anemisi (KHA) %62.5 ile ilk sırada yer alırken, demir eksikliği anemisi (DEA) %37.5 ile ikinci sırada yer almıştır.

Sonuç: Sonuç olarak çalışmamız; AA, grade 1 anemi, Hb 10-12 g/dL olgularında ayrıntılı fizik muayene, ayrıntılı sistem sorgulaması, görüntüleme yöntemleri ve periferik yayma, laboratuvar incelemelerinin önemini göstermektedir. Anamnez, fizik muayene ve doğru tetkiklerin uygulanması halinde, bu hasta grubunda KİA ve KİB incelemesinin mutlak bir gereklilik olmadığını çalışma sonucumuz düşündürmüştür. Güncel kılavuzlar AA vakalarında KİA ve KİB yapılması gerektiğini vurgulamaktadır. Hb<10 gr/dL oluşu gerçek ve anlamlı anemi olarak kabul görmektedir. Ayrıca displazi, bistopeni/pansitopeni varlığı gibi bulgular Myelodisplastik Sendrom (MDS) ve Aplastik Anemi için anlamlı bulgulardır. Grade 1 anemi olan hastalarda bu bulgular dışlandığında KİA ve KİB olmadan anemi ayırıcı tanısı yapılabileceğini çalışmamız göstermektedir.

Anahtar Sözcükler: 1. Derece anemi; açıklanamayan anemi; ileri yaş; kemik iliği aspirasyonu; kemik iliği biyopsisi.