Original Article

Evaluation of Factors Associated with Retinal Hemorrhage in Patients with Acute Leukemia

Akut Lösemili Hastalarda Retina Kanaması ile İlişkili Faktörlerin Değerlendirilmesi

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ABSTRACT

Purpose: We aimed to investigate the association of retinal hemorrhage and blood parameters in patients with acute leukemia

Material-Methods: We have retrospectively investigated sixty-one acute leukemia patients with and without retinal hemorrhages and analyzed associated factors. Patients underwent a detailed ocular examination. The hematological and coagulation parameters were based on data when the retinal hemorrhages were noticed in the fundus.

Results: The study group consisted of 30 patients with acute myelocytic leukemia (AML) and acute lymphocytic leukemia (ALL) who had retinal hemorrhages and the control group consisted of 31 patients with acute leukemia without retinal hemorrhages. Approximately ½ of the patients had low vision due to retinal hemorrhage, while the other half were detected by meticulous eye examination. AML diagnosis was statistically more frequent in patients with retinal hemorrhage (p=0.02). Active disease was statistically more common in the patients with retinal hemorrhage (p=0.03). In the retinal hemorrhage group, patients had significantly lower hemoglobin, hematocrit, and platelet levels than those without hemorrhages (p=0.001, p=0.001 and p=0.001 respectively). There was no statistically significant difference in leukocytes values between two groups (p=0.634).

Conclusion: In present study we found correlation between the hematological parameters and retinal hemorrhages. In patients with active AML and profound thrombocytopenia, a visual examination should be prioritized since ocular problems may go unnoticed since many patients are asymptomatic.

Key Words: Leukemia, retina, retinal hemorrhage, leucocyte, thrombocytopenia

ÖZET

Amaç: Akut lösemili hastalarda retina kanaması ile kan parametreleri arasındaki ilişkiyi araştırmayı amaçladık

Gereç ve Yöntem: Retina kanaması olan ve olmayan 61 akut lösemi hastasını geriye dönük olarak araştırdık ve ilişkili faktörleri analiz ettik. Hastalara detaylı göz muayenesi yapıldı. Hematolojik ve pıhtılaşma parametreleri, fundusta retina kanamalarının fark edildiği andaki verilere dayanıyordu.

Bulgular: Çalışma grubunu retina kanaması olan akut miyelositik lösemili (AML) ve akut lenfositik lösemili (ALL) 30 hasta, kontrol grubunu ise retina kanaması olmayan 31 akut lösemi hastası oluşturdu. Hastaların yaklaşık ½'sinde retina kanamasına bağlı az görme mevcutken, diğer yarısı titiz bir göz muayenesi ile tespit edildi. AML tanısı retina kanaması olan hastalarda istatistiksel olarak daha sıktı (p=0,02). Retina kanaması olan hastalarda aktif hastalık istatistiksel olarak daha yaygındı (p=0.03). Retinal kanama grubunda, hastaların hemoglobin, hematokrit ve trombosit düzeyleri kanaması olmayanlara göre anlamlı derecede daha düşüktü (sırasıyla p=0,001, p=0,001 ve p=0,001). İki grup arasında lökosit değerlerinde istatistiksel olarak anlamlı fark yoktu (p=0,634).

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Sonuç: Bu çalışmada hematolojik parametreler ile retinal kanamalar arasında korelasyon bulduk. Aktif AML ve derin trombositopenisi olan hastaların göz problemlerinin çoğu asemptomatik olduğundan bunların gözden kaçmaması için göz muayenesine öncelik verilmelidir.

Anahtar Kelimeler: Lösemi, retina, retinal kanama, lökosit, trombositopeni

Introduction

Leukemic retinopathy was first described by Liebreich in 1861 [1]. Since that time, ophthalmic manifestations of leukemia have been observed commonly by ophthalmologists, and the prevalence of ocular involvement in patients with leukemia reported in the literature ranges from 9 to 90% [2-5]. Leukemic retinopathy typically refers to the intraretinal hemorrhages, white-centered hemorrhages, and cotton-wool spots seen in patients with leukemia. The term 'leukemic retinopathy' is used to describe the retinal manifestations of anemia, thrombocytopenia and hyperviscosity, rather than leukemic infiltration by neoplastic cells. Controversy exists concerning the relationship between fundus findings in leukemic retinopathy and hematologic parameters such as platelet count, hematocrit level, and leukocyte count. Several studies implicate anemia, thrombocytopenia, or leukocytosis in the pathogenesis of leukemic retinopathy, but other reports show no association between fundus findings and blood profiles [7-18]. This retrospective study was conducted to evaluate the relationship between retinal hemorrhage and hematological parameters in patients with acute leukemia.

Patients and Methods

Between the years 2018 October-2022 February the medical records of the acute leukemic patients collected retrospectively and analyzed in tertiary hospital ophthalmology clinic of Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital, University of Health Sciences, Ankara, Turkey.

Collected data included as age, gender, clinical features, acute leukemia type and disease activation, ophthalmology examinations and laboratory parameters. The eye examination consisted of measurement of visual acuity, a slit-lamp examination for ambulatory patients or a penlight examination for patients under protective isolation, and direct and indirect ophthalmoscopy after dilation of fundus. Fundus camera was used for color photodocumentation for ambulatory patients. Patients with intraretinal hemorrhages, white-centered hemorrhages, and cotton-wool spots-like retinal hemorrhages were scored as absent or present based upon the clinical examination findings. Blood parameters included white blood cell counts, hemoglobin levels, hematocrit, platelet counts, prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen, creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and C-reactive protein (CRP) levels. These values were based on data obtained when the retinal hemorrhages were noticed in the fundus. Active disease was defined as the presence of more than 5% blasts in the bone marrow.

Exclusion criteria: Patients with direct infiltration of neoplastic cells presenting as leukemic infiltrates and white centered retinal hemorrhages. Patients with retinal hemorrhages due to another diseases such as aged macular degeneration or diabetic retinopathy.

Ethical consideration: The Ethics Commitee of Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital (Ankara,

Table 1: Comparison of demographic and clinical characteristics of the groups

	Retinal Hemorrhage Group	Control group	P value
Age(mean±SD)	40±14.6	32±14.6	0.2
Male/Female	19/11	20/11	0.9
AML/ALL	23/7	16/15	0.02*
Active disease	11 (36.7%)	4 (13%)	0.03*
Visual acuity (logMar)	1.3	0.035	0.001*

SD: Standard deviation, AML: acute myelocytic leukemia, ALL: acute lymphocytic leukemia
* p<0.05, statistically significant.

Turkey) approved the protocol, dated December 2021, number 11/1. All subjects provided written informed consent. Data of the patients were treated according to the Declaration of Helsinki Guidelines.

Statistical Analysis

Statistical analyses were performed using with SPSS software (Version 26.0. Armonk, NY: IBM Corp). The numerical data were expressed as mean±standard deviation and categorical data displayed as ration (percentage). Normality assumption were tested with Shapiro wilk test and histograms. Independent T test and chi-square tests were utilized to compare groups. A p value of <0,05 was considered statistically as significant in all analyses.

Results

A total of 61 patients with acute leukemia were included in the study. Study group consisted of 30 patients who had retinal hemorrhage; 23 had myelocytic leukemia (AML) and seven had lymphocytic leukemia (ALL). Nineteen (63.3%) were male and 11 (36.6%) were female; ages ranged from 19 years to 70 years (mean ± SD, 40±14.6). In the control group 16 patients had AML and 15 patients had ALL. Of the 31-control group, 20 (64.51%) were male, and 11 (35.4%) were female. The mean age was 32±14.6 years (range, 19-65 years).

In the study group retinal hemorrhage was seen bilateral in 22 (73.3%) of 30 patients. While 16 of the patients complained of decreased vision due to retinal hemorrhage, hemorrhage was detected during eye examination in the remainder. The mean visual acuity of the patients with retinal hemorrhage was 1.3 (min/max 1.5/0) according to the logMar visual chart. The mean visual acuity of the patients without retinal hemorrhage was 0.035 (min/max 0.2/0) according to the logMar visual chart (p<0.001).

AML diagnosis was statistically higher in patients with retinal hemorrhage (p=0.02). Active disease was statistically more frequent in the patients with retinal hemorrhage (p=0.03) (Table 1).

When the groups were analyzed for laboratory parameters, the patients with AML and ALL with retinal hemorrhages had significantly lower hemoglobin, hematocrit and platelet levels than those without hemorrhages (p=0.001, p=0.001 and p=0.001 respectively) (Table 2). There was no statistically significant difference in leukocytes values between two groups (p=0.63).

Patients with retinal hemorrhages had significantly higher PT levels than those without hemorrhages (p=0.001). On the other hand, no difference was found in APTT and

Table 2: Blood parameters in AML and ALL patients with and without retinal hemorrhages

	Study group Mean ± SD	Control group Mean ± SD	P value
Complete blood count			
Hemoglobin(g/dL)	8.5±1.8	9.83±2.3	0.001
Hematocrit (%)	25.45± 5.8	29.85±7	0.001
Leukocyte (× 10^3 per µL)	3.915±3.9	4.405±2.2	0.63
Platelet (× 10^3 per µL)	46.50±39	174.50±136	0.001
Coagulation			
PT (s)	12.05± 2.2	11.1±0.9	0.001
aPTT (s)	25.4±5.21	25±3.5	0.15
Fibrinogen (g/L)	404±29.9	360.2±27.2	0.28
Biochemistry values			
Creatinine (mg/dL)	0.67±0.35	0.59±0.22	0.21
BUN (mg/mL)	13.15±8.12	11.11±3.99	0.25
AST (U/L)	18.6±21.33	21.4±13.52	0.19
ALT (U/L)	25.2±27.82	23.95±32.013	0.31
CRP (mg/dL)	16.6±68.9	5.0±14	0.001

PT: prothrombin time, aPTT: partial thromboplastin time, BUN: blood urea nitrogen, AST: aspartate aminotransferase, ALT: alanine aminotransferase, CRP: C-reactive protein, SD: Standard deviation

fibrinogen levels (p=0.15 and p=0.28, respectively). CRP was the only biochemical parameter which was found to be statistically higher in the retinal hemorrhage group (Table 2).

Discussion

This retrospective study of retinopathy in acute leukemia analyzed the relationship between the retinal hemorrhages and hematologic parameters. 76% of patients with retinal hemorrhage had AML, suggesting that AML patients were more prone to retinal hemorrhage. Approximately ½ of the patients had low vision due to retinal hemorrhage, while the other half were noticed in the ophthalmologic evaluation. Retinal hemorrhage was seen bilateral in 22 (73.3%) of 30 patients. Active disease was found statistically more frequent in the patients with retinal hemorrhage. In this study, the patients with either acute leukemia or acute lymphocytic leukemia who had retinal hemorrhages had significantly lower hemoglobin, hematocrit and mean platelet count than did patients without such hemorrhages.

Many recent clinical studies of patients with acute leukemia have discussed the relationship of retinal hemorrhages, hematocrit, and platelet count. Guyer and coworkers, in a prospective study of retinopathy in leukemia, also found a lower hematocrit in patients with ALL and retinal hemorrhages than those without [19]. Cullerlo observed that the patients with low platelet counts and extreme anemia were more likely to have retinal hemorrhages [10]. Rubenstein et al also found that thrombocytopenia alone was not associated with an increased incidence of retinal hemorrhage [12]. They found that patients with both anemia and thrombocytopenia frequently had retinal hemorrhages. Similar to these studies, our results showed a strong association between the presence of intraretinal hemorrhages and both thrombocytopenia and anemia in patients with acute leukemia.

In contrast to our findings, Abu El-Asrar et al reported that platelet counts did not differ in patients with and without retinal hemorrhages [20]. Another study done by Leonardy and

associates also noted the similar platelet counts like Abu El-Asrar et al [21]. Robb and colleagues, on the other hand, stated that there was no correlation between the presence of retinal hemorrhages and the hematologic parameters in patients with acute leukemias [11].

The correlation between the retinal findings and the leucocyte count has been the subject of much debate. Parallel to some studies, we did not observe any significant difference in leukocyte levels in patients having or those not having retinal hemorrhage [19-21]. On the other hand, Karesh et al. (1989) found that their patients with retinopathy had a non-significantly lower mean white blood cell [22]. In contrast, Jackson and associates found that high leukocyte levels were associated with retinopathy in patients with leukemia but stated that anemia and thrombocytopenia were not associated with retinal hemorrhage [23].

The limitation of the study was that the number of ALL was less than AML. The strength was that all eye examinations were performed by the same clinician at the same center.

In conclusion, our findings suggest that anemia and thrombocytopenia are an important factor in retinal hemorrhages in acute leukemia and leukocyte count is not associated with the retinal hemorrhages. Considering that retinal hemorrhage is detected incidentally during eye examination in half of the patients, it is important to evaluate the patients with active disease, anemia and thrombocytopenia for retinal hemorrhage.

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