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ORIGINAL ARTICLE

Evaluation of patients admitted to the hematology outpatient clinic for spontaneous ecchymosis: Does it suggest bleeding diathesis?

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Abstract

Background: Spontaneous ecchymosis is a common reason for referral to the hematology outpatient clinic. It is important to determine the underlying bleeding is benign or a symptom of diathesis.

Methods: The sample of this retrospective study consisted of 119 patients with normal platelet counts who presented to the adult hematology outpatient clinic with spontaneous ecchymosis between September 2021 and August 2022. The site of the ecchymosis, patients' familial and bleeding histories, and the drugs they have been using were queried. Hemogram and coagulation parameters and peripheral smear findings of the patients were recorded, and their ISTH-SSC (International Society on Thrombosis and Haemostasis Scientific and Standardization Committee) Bleeding Assessment Tool scores were calculated.

Results: The median age of the patients, of whom 113 (95%) were female and 6 (5%) were male, was 30 (18-85) years. The ecchymosis was in the extremities and the trunk in 110 (92.4%) and 9 (7.6%) patients, respectively. There was no significant difference between the patients with and without bleeding history in terms of the site of spontaneous ecchymosis, the hemogram parameters and peripheral smear findings. Similarly, the patients with and without factor deficiency have not differed significantly in terms of hemogram parameters and peripheral smear findings. Patients with any factor deficiency had significantly higher ISTH-SSC Bleeding Assessment Tool scores compared to the patients without factor deficiency.

Conclusions: The findings of the study revealed that the site of ecchymosis and hemogram and coagulation parameters cannot be used as markers in the general sense, except for the ISTH-SSC Bleeding Assessment Tool scores, which predicted factor deficiency. Another finding of the study worth mentioning is the fact that the number of patients with ecchymosis on the trunk among the patients presenting with the complaint of ecchymosis was significantly lower than that of patients with ecchymosis on the extremities.

Keywords: Ecchymosis, Factor Deficiency, Platelet.

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INTRODUCTION

Ecchymosis is a subcutaneous hemorrhage that concerns the skin and subcutaneous structure, platelet count and function, and coagulation cascade (1). The incidence of spontaneous ecchymosis in healthy individuals reported in the literature varies between 12% and 55% and it is reportedly more common among women (2-5). Bruising can easily occur in cases of physical trauma, vitamin C deficiency, conditions involving blood vessels and surrounding tissue such as connective tissue disorders, medication-related conditions, infectious diseases or platelet abnormalities such as von Willebrand disease, coagulation factor deficiencies, and coagulation defects that may develop due to conditions such as vitamin K deficiency or liver disease. Given that spontaneous ecchymosis is a common complaint, it is important to determine which cases will require further examinations.

In this context, answers were sought to the questions of the location of ecchymosis is related to the bleeding history?", "does the presence of ecchymosis suggest factor deficiency?", "is there a difference in hemogram parameters and peripheral smear findings between those with and without bleeding history?", and "are the hemogram parameters different between those with and without factor deficiency?" based on the data obtained from the patients that applied to the hematology outpatient clinic with spontaneous ecchymosis.

MATERIAL AND METHODS

The sample of this retrospective study consisted of 119 patients with normal platelet counts who presented to the adult hematology outpatient clinic with spontaneous ecchymosis between September 2021 and August 2022. The site of the ecchymosis, patients' familial and bleeding histories, and the drugs they have been using were queried. Hemogram and coagulation parameters and peripheral smear findings of the patients were recorded. Patients' spontaneous gingival bleeding, spontaneous nose bleeding, prolonged bleeding after incision, prolonged bleeding after tooth extraction, and prolonged bleeding after surgery histories were queried. In addition, in the case of female patients, prolonged postpartum bleeding history and menstrual bleeding intensity (changing pads more than once every 2 hours, no tapering in the intensity of menstrual bleeding even after 3 days, presence of clots in the menstrual blood, feeling the need to use large pads due to the high intensity of menstrual bleeding, etc.) were also investigated. Each parameter in question was scored separately. Patients' ISTH-SSC (International Society on Thrombosis and Haemostasis Scientific and Standardization Committee) Bleeding Assessment Tool scores were calculated and recorded. Factor results were evaluated according to the laboratory reference range (Factor V: 62-140%, factor VII: 70-181%, factor VIII: 56-91%, factor IX: 78-184%, factor X: 81-157%, factor XII: 58-166%, factor XIII:60-192%, von Willebrand ristocetin cofactor: 51-215 December, von Willebrand factor antigen: 52-214)

Statistical Analysis:

Statistical analyses were carried out using SPSS 26.0 (Statistical Product and Service Solutions for Windows, Version 26.0, IBM Corp., Armonk, NY, U.S., 2019) software package. The normal distribution characteristics of the variables investigated within the scope of the study were analyzed by visual (histograms, probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's tests). Comparisons featuring categorical variables were made using Pearson's chi-squared test. Comparisons featuring continuous numerical variables were made using student's t-test (for two independent samples). The probability (p) statistics of ≤ 0.05 were deemed to indicate statistical significance. The study protocol was approved by the Ethics Committee of Karatay University Faculty of Medicine (Approval No. 2022/026, Approval Date: 21.09.2022).

RESULTS

General Characteristics of the Patients

The study sample included 119 patients who presented with spontaneous ecchymosis to the adult hematology outpatient clinic where this study was conducted. The median age of the patients, of whom 113 (95%) were female and 6 (5%) were male, was 30 (min. 18, max. 85) years. The ecchymosis was in the extremities and the trunk in 110 (92.4%) and 9 (7.6%) patients, respectively. The general characteristics of the patients with spontaneous ecchymosis are shown in Table 1.

Table 1. General characteristics of the patients presented with spontaneous ecchymosis

Number of patients (n)	119
Gender (Female/Male)	113 (95%)/6 (5%)
Age (median, years)	30 (8-85)
ISTH-SSC Bleeding Assessment Tool score	1 (1-8)
Site of ecchymosis (extremities/trunk)	110 (92.4%)/9 (7.6%)
Bleeding history (yes/no)	43 (36.1%)/76 (63.9%)
Menstrual bleeding intensity complaint (yes/no)	25 (22.1%)/88 (77.9%)
Gingival bleeding (yes/no)	10 (8.4%)/109 (91.6%)
Nose bleeding (yes/no)	8 (6.7%)/111 (93.3%)
Prolonged bleeding after incision (yes/no)	6 (5%)/113 (95%)
Prolonged bleeding after surgery (yes/no)	5 (4.2%)/114 (95.8%)
Prolonged postpartum bleeding (yes/no)	4 (3.5%)/109 (96.5%)
Prolonged bleeding after tooth extraction (yes/no)	9 (7.6%)/110 (92.4%)
Familial history (yes/no)	4 (3.4%)/115 (96.4%)
Medication history (yes/no)	28 (23.5%)/91 (76.5%)

Abbreviations: ISTH-SSC, International Society on Thrombosis and Haemostasis Scientific and Standardization Committee

Evaluation of Patients According to Bleeding History

Comparison of the patients with and without bleeding history in terms of spontaneous ecchymosis site revealed that ecchymosis was located in the extremity in 41 (95.3%) and 69 (90.8%) patients with and without bleeding history, respectively. Accordingly, there was no significant difference between the two groups in spontaneous ecchymosis sites (p: 0.36).

Comparison of the patients with and without bleeding history in terms of hemogram parameters revealed no significant difference between the two groups in any hemogram parameter, i.e., hemoglobin (p=0.85), leukocyte (p=0.73), and platelet (p=0.50) levels, mean platelet volume (MPV) value (p=0.81), MPV/PLT (platelet count) ratio (p=0.45), procalcitonin (PCT) (p=0.94) level, and platelet distribution width (PDW) value (p=0.94).

Comparison of the patients with and without bleeding history in terms of presence of factor deficiency revealed no significant difference between the two groups (p=0.29). There was no significant difference between the two groups in coagulation parameters and factor levels, i.e., prothrombin time (PT) (p=0.63), international normalized ratio (INR) (p=0.64), activated partial thromboplastin clotting time (aPTT) (p=0.81), fibrinogen (p=0.83), d-dimer (p=0.15), von Willebrand factor (p=0.52), factor VIII (p=0.61) and factor 7 (p=0.89) levels.

Additionally, peripheral smears of patients with and without bleeding history were evaluated according to whether the platelets were large or small or whether they formed aggregates or not. Accordingly, there was no significant difference between the two groups in terms of peripheral smear characteristics (p=0.53) (Table 2).

Table 2. Comparison of general characteristics and laboratory findings of patients with and without bleeding history

Parameters	Patients with Bleeding History	Patients without Bleeding History	*p* value
Number of patients (n)	43 (36.1%)	76 (63.9%)	
Gender (Female/Male)	42/1 (97.7%/2.3%)	71/5 (93.4%/6.6%)	0.30
Age (median, years)	29 (18-70)	30 (18-85)	0.52
ISTH-SSC Bleeding Assessment Tool score	2 (1-8)	1 (1-1)	<0.001
WBC ($10^3/\mu L$)	6.4 (0-19.5)	5.8 (0-14.8)	0.73
Hemoglobin (g/dl)	12.8 (4.9-15.8)	13.1 (3.2-17.5)	0.85
Platelet ($10^3/\mu L$)	236 (5-742)	234 (12-379)	0.50
MPV (fL)	11.1 (8.8-410)	10.7 (8.5-428)	0.81
MPV/PLT	0.04 (0-11.7)	0.04(0.02-12.6)	0.45
PCT (ng/mL)	0.28 (0.07-13.7)	0.29 (0.08-28)	0.94
PDW	11.8 (9.6-49)	12.5(8.5-16.7)	0.94
INR	1.0 (0.93-4.8)	1.0 (0.92-10.8)	0.64
aPTT (sec.)	26 (19-36)	26.0 (20-57)	0.81
Fibrinogen (mg/dL)	2.98 (0.83-479)	2.94 (1.96-548)	0.83
D-dimer (ng/mL)	0.25 (0.19-0.76)	0.25 (0.1-3.6)	0.15
Factor deficiency Yes/No (%)	14/29 (32.6%/67.4%)	18/58 (23.7%/76.3%)	0.29
Factor VIII	66.0 (31.8-108)	48.5 (27.9-97.2)	0.61
von Willebrand Factor	100 (75-201)	121 (31.2-256.8)	0.52
Factor XIII	134 (134-149)	102 (73-145)	0.02
PT (sec.)	17.10	16.4	0.36
Factor IX	72.05	123	0.01
Factor V	74 (62-85)	63 (63-63)	0.69
Factor X	71 (68-73)	89 (89-89)	0.15
Factor XII	102 (96-108)	106 (106-106)	0.75
Factor VII	96 (61-132)	86 (86-86)	0.89

Abbreviations: ISTH-SSC: International Society on Thrombosis and Haemostasis Scientific and Standardization Committee, WBC: White Blood Cell Count, MPV: mean platelet volume, MPV/PLT: mean platelet volume/platelet count ratio, PCT: procalcitonin, PDW: platelet distribution width, PT: prothrombin time, INR: international normalized ratio, aPTT: activated partial thromboplastin clotting time

Evaluation of Patients According to Factor Deficiency

No factor deficiency was detected in 87 (73%) of the patients who applied to the hematology outpatient clinic with spontaneous ecchymosis. The remaining 32 (27%) patients had a factor deficiency. Factor deficiency defined based on laboratory reference range. Factor levels were re-studied in patients with factor deficiencies. For von Willebrand disease, von Willebrand antigen, von Willebrand ristocetin cofactor and factor VII levels were requested. Of these patients, 8 (7%) had von Willebrand deficiency (type 1), 11 (9%) had factor VII deficiency, 12 (10%) had factor VIII deficiency and 1 (1%) had both factor VIII and von Willebrand deficiencies. The distribution of patients by factor deficiency is shown in Figure 1. Factor deficiency was detected in 29 (26.4%) patients who had ecchymosis in extremities and 2 (22.2%) patients who had ecchymosis in the trunk. Accordingly, there was no significant relationship between the site of ecchymosis and factor deficiency (p=0.78).

Comparison of the patients with and without factor deficiency in terms of hemogram parameters revealed no significant difference between the two groups in any hemogram parameter, i.e., hemoglobin (p=0.57), leukocyte (p:0.80), and platelet (p=0.66) levels, MPV value (p=0.48), MPV/PLT ratio (p=0.49), PCT (p=0.21) level, and PDW value (p=0.81).

In addition, there was no significant difference between the patients with and without factor deficiency in terms of peripheral smear characteristics (p=0.17).

Evaluation of Patients According to ISTH-SSC Bleeding Assessment Tool Scores

Distribution of the ISTH-SSC Bleeding Assessment Tool scores by factor deficiency is shown in Table 3. Of the 6 male patients, five (83.3%) had a bleeding score of 1, and one (16.7%) had a bleeding score of 3. Of the 113 female patients, two (1.6%) had a bleeding score of 6, one (0.8%) had a bleeding score of 8, and the remaining 110 (97.6%) had a bleeding score of three and below. There was a significant correlation between the patients with and without factor deficiency and the ISTH-SSC Bleeding Assessment Tool scores (p=0.004). Accordingly, patients with any factor deficiency had significantly higher ISTH-SSC Bleeding Assessment Tool scores than patients without factor deficiency.

Table 3. Distribution of the ISTH-SSC Bleeding Assessment Tool scores by factor deficiency

ISTH-SSC Bleeding Assessment Tool Scores *p*: 0.004	Patients without Factor Deficiency	Patients with any Factor Deficiency
Score 1	59 (67.8%)	18 (56.3%)
Score 2	26 (29.9%)	6 (18.8%)
Score 3	1 (1.1%)	5 (15.6%)
Score 4	0	0
Score 5	0	1 (3.1%)
Score 6	1 (1.1%)	1 (3.1%)
Score 7	0	0
Score 8	0	1 (3.1%)

Abbreviations: ISTH-SSC, International Society on Thrombosis and Hemostasis Scientific and Standardization Committee

DISCUSSION

As in other studies in the literature, 95% of the patients presenting with spontaneous ecchymosis included in this study were female (2). The ecchymosis was in the extremities in 92.4% of the patients. The fact that the ecchymosis was in the extremities could be attributed to the presence of physical traumas (6). Then again, patients without a history of trauma were included in this study. 23.5% of the patients had a history of antiaggregant, non-steroidal anti-inflammatory and selective serotonin reuptake inhibitors group drug use. These medications are known to be effective on primary hemostasis (7). Therefore, it is critical to query the medications patients have used and have been using. In addition, given that the diets with low protein content and vitamin C and K deficiencies may also predispose to ecchymosis, patients' dietary habits should also be queried. Patients' alcohol intake was queried in this study, yet a detailed inquiry about nutrition was not made, which can be considered one of its limitations. It is important to query the presence of hemorrhagic diathesis in the family (8). 3.4% of the patients included in the study had a familial history of hemorrhagic diathesis. However, they did not have detailed information about their familial history. 75% of these patients had factor 7 deficiency, a finding which suggests that patients with a familial history of hemorrhagic diathesis should be further analyzed, even if no abnormality is detected in the initial laboratory tests.

The site of ecchymosis may be important in terms of bleeding diathesis, but there are no studies on ecchymosis unrelated to trauma in adult patients. The analysis of patients in terms of ecchymosis site revealed that 92.4% and 7.6% of the patients had ecchymosis in the extremities and in the trunk, respectively. Factor deficiency was detected in 26.9% of the patients. There was no significant relationship between the presence of factor deficiency and the ecchymosis site. Further large-scale studies are needed to shed more light on this subject.

Patients' spontaneous gingival bleeding, spontaneous nose bleeding, prolonged bleeding after incision, prolonged bleeding after tooth extraction, and prolonged bleeding after surgery histories were queried. In addition, in the case of female patients, prolonged postpartum bleeding history and menstrual bleeding intensity were also investigated. Analysis of the patients with and without bleeding history in terms of whether they had

factor deficiency did not reveal any significant difference between the two groups.

Querying the menstrual cycle of female patients can provide key information in terms of bleeding diathesis. Studies conducted on this subject demonstrated that changing pads more than once every 2 hours, no tapering in the intensity of menstrual bleeding even after 3 days, presence of clots in the menstrual blood, and the need to use large pads due to high intensity of menstrual bleeding were associated with excessive menstrual bleeding (9,10). The actual prevalence of hemophilia carriage is unknown. The diagnosis of women with mild factor deficiency and female hemophilia carriers may be overlooked (11). In this study, 22.1% of the patients described excessive menstrual bleeding. A factor deficiency was detected in 32% of these patients. Of these patients, 75% had factor VIII deficiency and 25% had factor 7 deficiency.

The ISTH-SSC Bleeding Assessment Tool is used to detect abnormal bleeding and determine the severity of bleeding (8). Each type of bleeding is scored according to its severity, whether it requires medical intervention, and the method used in its treatment. ISTH-SSC Bleeding Assessment Tool scoring has been shown to be effective in determining bleeding severity and screening for hereditary bleeding disorders (12-18). In parallel, in this study, patients with a factor deficiency had a significantly higher ISTH-SSC Bleeding Evaluation Tool score compared to the patients without a factor deficiency.

The findings of the study revealed that the site of ecchymosis and hemogram and coagulation parameters cannot be used as markers in the general sense, except for the ISTH-SSC Bleeding Assessment Tool scores, which predicted factor deficiency. Another finding of the study worth mentioning is the fact that number of the patients with ecchymosis on the trunk among the patients presenting with the complaint of ecchymosis was significantly lower than that of patients with ecchymosis on the extremities.

Declarations

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

The study protocol was approved by the Ethics Committee of Karatay University Faculty of Medicine (Approval No. 2022/026, Approval Date: 21.09.2022).

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