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Original Article HEMATOLOGY

Morphologic evaluation of megakaryocytes in immune thrombocytopenia patients older than 80 years

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ABSTRACT

OBJECTIVE: In immune thrombocytopenia (ITP), which is a common acquired bleeding disorder, cytotoxic T-cell-mediated cellular immune response against both circulating platelets and bone marrow megakaryocytes are the most important mechanisms in the pathogenesis.

METHODS: In our study, we evaluated the features of 33 patients with ITP, over 80 years of age.

RESULTS: The median age of the patients was 90, 15 patients were female (45.4%). The mean platelet count of the patients was 39×10^9/L and the mean mean platelet volume was 10,33fL. Twelve patients had a target thrombocyte count greater than 30×10^9/L, while 20 patients had a target platelet count of 75×10^9/L or greater with an absolute indication of antiaggregation. In the environmental spread, 18 dysplasia findings were observed.

CONCLUSION: Morphologic observations suggesting dysplasia including micromegakaryocytes and a non-dysplastic but dysmegakaryopoietic finding, multiple segmented nuclei may be related to the degree of thrombocytopenia and response to treatment. Likewise, nondysplastic features including immature forms, emperipolesis, bare nucleus, hypolobulation, and hypersegmented nucleus were related to the degree of thrombocytopenia.

Keywords: Dysmegakaryopoiesis; dysplasia; immune thrombocytopenia; megakaryocyte.

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As a common acquired bleeding disorder, the pathogenesis of immune thrombocytopenia (ITP) is not completely understood. Reduced life of platelets due to antibody-mediated platelet destruction, cytotoxic T-cell-mediated cellular immune response toward both circulating platelets, and altered megakaryopoiesis in the bone marrow are the most common and studied mechanisms. Although not valid for every patient, a triggering cause like infections leading to immune activation may be possible [1, 2].

The annual incidence of ITP has been reported as 1–5/100.000 adults and the tendency towards chronicity makes the prevalence outpace the incidence. The age distribution of adult patients with ITP shows a moderate decline right after childhood and increases with a peak after 60 years. In epidemiological studies, the incidence of ITP was observed to increase after 70 years with a predominance of males though the overall gender tendency is toward females [3, 4]. In a regional study from Turkiye, the mean annual incidence was 2.92/100.000 though the incidence in age groups was not reported [5].

Age-related variations in platelets were thoroughly studied but there are only two very brief reports regarding the course and variations in ITP in the very old patient group (>80 years) [6–8]. Megakaryocyte dysplasia is defined by the World Health Organization (WHO)

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2017 classification of myeloid neoplasms as micromegakaryocytes, megakaryocytes with non-lobated nuclei, and multiple separated nuclei with the last as the least specific for myelodysplasia [9]. Based on these suggestions of morphology, we aimed to evaluate the bone marrow examinations of patients with ITP who are older than 80 years in respect of dysplasia and assess the morphologic observations with clinical findings and outcomes.

MATERIALS AND METHODS

Study Cohort

In this retrospective analysis, our cohort included 33 patients with ITP who are over 80 years of age. Within these patients, bone marrow biopsy specimens were available in 16 patients. All patients who underwent bone marrow biopsy had consent forms at the time of admission. Inclusion criteria included a diagnosis of ITP according to the criteria mentioned below, being aged 80 and older, no obvious dysplasia in myeloid and erythroid lines more than 10% based on WHO 2016 criteria and myelodysplastic syndrome (MDS) defining cytogenetic abnormalities [8]. Medications that the patients received due to comorbidities including hypertension, coronary artery disease, or diabetes were recorded from their medical files due to the possible development of drug-mediated thrombocytopenia.

Within each bone marrow sample, 200 megakaryocytes were evaluated by two reviewers who are blind to the patient or the results.

The study was conducted in accordance with the Declaration of Helsinki, Ethical Principles for Medical Research. This study was approved by the Trakya University Faculty of Medicine Ethical Committee (11/04, May 09, 2022).

Definitions

Definition of ITP

In this special population of patients, diagnosis of ITP was established by excluding certain confounding factors including drug-induced ITP by questioning the use of heparin, quinine (including beverages), sulfonamides, acetaminophen, ibuprofen, naproxen, ampicillin, glycoprotein IIb/IIIa inhibitors, herbal tea consumption, viral infections, chronic liver disease, and the most important differential diagnosis, myelodysplasia. With the exclusion of other causes of thrombocytopenia, we enrolled patients with platelet counts <100.000/mL who are >80 years of age.

Highlight key points

- In advanced age, dysmegakaryopoiesis may be one of the leading causes of ITP.
- In patients over 80 years of age with a pre-diagnosis of ITP, bone marrow biopsy should be evaluated in terms of differential diagnosis, as well as careful examina.
- Changes in megakaryopoiesis can guide both differential diagnosis and progression.

Definition of myelodysplasia

All patients were initially evaluated with their complete blood counts and peripheral smear. Signs of dysplasia for three lineages were investigated. For erythrocytes, the presence of ovalomacrocytes, elliptocytes, acanthocytes, stomatocytes, teardrops, nucleated erythrocytes, basophillic stippling, and Howell–Jolly bodies; for myeloid cells, the presence of pseudo-pledger huet anomaly, auer rods, hypogranulation, nuclear sticks, hypersegmentation and for platelets, hypogranulation or agranulation were investigated. As aging itself is a cause of dysplasia to a certain degree, bone marrow biopsy was performed in patients with morphological concerns. Bone marrow aspiration-biopsy and chromosomal evaluation were used to confirm or support the diagnosis. The presence of certain chromosomal abnormalities suggesting MDS including del (7q), del (5q), del (13q), del (11q), del (12p), del (9q), idic (X) (q13), t (11;16), t (3;21), t (1;3), t (2;11), inv (3), t (6;9) were considered as MDS regardless of morphological observations and are excluded. Actual demonstrations of megakaryocytic alterations are demonstrated in Figure 1.

Indication of Treatment

The treatment of ITP in the general population is for patients who have platelet counts <30.000/mL due to the low bleeding nature of the disease. But as the patients age, they bear additional medical conditions including cardiovascular diseases like coronary heart disease, stroke, and atrial fibrillation. For such conditions, they may need antiplatelet or anticoagulant therapies. For this reason, we adopted individual treatment targets and thresholds. For patients who have coronary stents, or recent episodes of arterial thrombosis, we accepted a platelet level of 75.000/mL as the threshold for ITP treatment. Likewise, for patients who are indicated for anticoagulant treatment

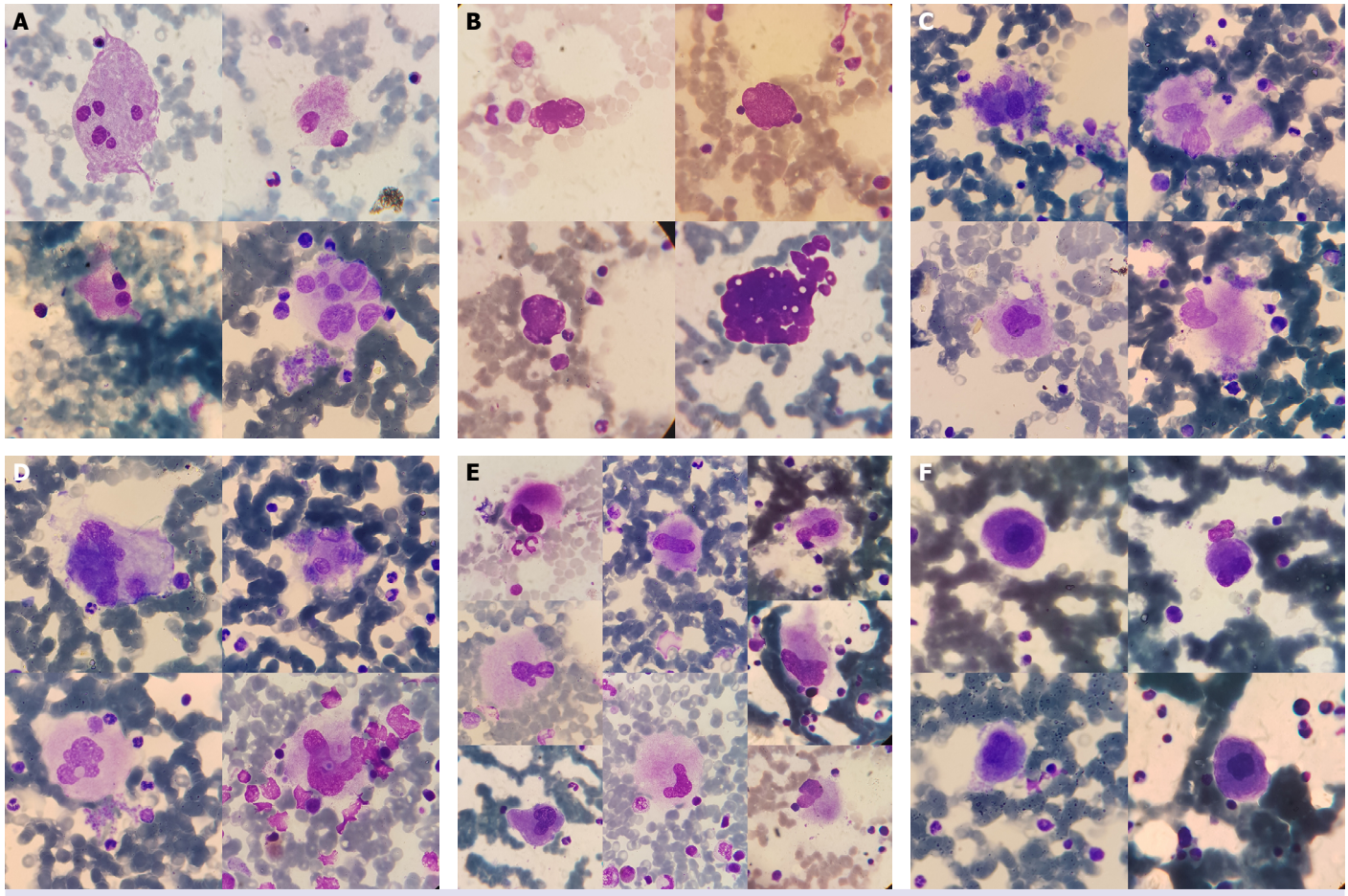

FIGURE 1. **(A)** Multiple separate nuclei. **(B)** Bare nucleus. **(C)** Budding. **(D)** Emperipolesis. **(E)** Hypolobulation. **(F)** Micromegakaryocyte.

and with a high ChadsVasc score, we accepted a minimum platelet level of 50.000/mL for the indication of ITP treatment. For patients who did not bear such risk factors, a level of 30.000/mL of platelets was accepted. As stated by the consensus group, there are definitions for ITP regarding time. All new cases are accepted as "newly diagnosed ITP", ITP 3–12 months as persistent, and >12 months chronic ITP. Treatments for ITP were classified as "watch and wait," corticosteroids (1 mg/kg methylprednisolone), intravenous immunoglobulins (IVIG), splenectomy, and elthrombopag, thrombopoietin agonist.

Definition of response to treatment

As defined by the consensus statement, complete response (CR) is defined as a platelet count of at least 100×10^9/L, response (R) is defined as doubling the initial platelet count or reaching a level between 30 and 100×10^9/L. No response is defined as platelet counts staying below 30×10^9/L despite treatment.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Version22 software (Chicago, IL). Numerical variables were expressed as median and range. Categorical variables were expressed with count and frequency. Comparison of numerical variables was performed with non-parametric tests (Mann–Whitney) and categorical variables were analyzed with Chi-square test.

RESULTS

Clinical Variables

The median age of patients was 90±4.5 years (80–93). 15 patients were female 45.5%), while 18 were male (54.5%). The mean platelet counts at presentation was 39×10^9/L (6–96) and the mean-mean platelet volume was 10.3 fL (8–14). Target platelet levels were varying due to concomitant chronic diseases and antiplatelet therapies. 13 patients had a need for a target platelet level over 30×10^9/L while 20 patients had a need of a target

platelet level over 75×10^9/L (60.0%) due to the requirement of antiplatelet treatment (acetylsalicylic acid for coronary artery disease or stroke primary and secondary prevention). None of the patients received medications which may be related to drug-induced thrombocytopenia. 18 patients showed dysplasia on their peripheral smears (54.5%). During the initial presentation, an increased LDH level more than upper normal limits was observed in 9 patients while an increased CRP level was observed in 6 patients. 19 patients received treatment including corticosteroids and IVIG in 12 patients, rituximab in 5 patients and eltrombopag in 5 patients. CR was observed in 13 patients while partial response in 5 patients and 1 patient remained refractory.

18 patients had undergone bone marrow aspiration (54.5%). The mean age in patients who had bone marrow biopsy was 85.01±3.3 years. 6 patients were female while 12 were male. 6 patients did not receive treatment for ITP, 8 patients received and responded to corticosteroids and 4 patients responded to eltrombopag as second-line treatment. The need for treatment and responses to treatments were similar in patients who had and had not bone marrow biopsies.

Cytogenetic abnormality supporting dysplasia was observed on one patient while 15 patients showed standard risk for MDS. Bone marrow cellularity was decreased in 7 patients and normal in 9 patients. 5 patients had decreased megakaryocytes in their bone marrow aspiration (31.25%), normal in 7 patients (43.75%), and increased in 6 patients (37.5%). Reticular fibers in the bone marrow were grade 0/3 in 8 patients, 1/3 in 6 patients and 2/3 in 2 patients. Clinical variables in patients with ITP as well as the subgroup of patients who have undergone bone marrow biopsy are summarized in Tables 1 and 2.

Table 1. Clinical variables of patients

	Patients, Total (n=33)
Median age (range, years)	90 (80–93)
Female/male	15/18
Median platelet count, x10^9/L (SD)	39 (21.3)
Median mean platelet volume, fL	10.3
Target platelet count	
>30x10^9/L	13
>75x10^9/L	20
Dysplasia on peripheral smear	18
Increased CRP level	6
Increased LDH level	9
Patients receiving any treatment	19
Treatment types	
Corticosteroid	12
IVIG	10
Eltrombopag	5
Rituximab	5
Response type	
Complete response	13
Partial response	5
No response	1
Reticular fibers in bone marrow	
Grade 0/3	8
Grade 1/3	6
Grade 2/3	2
Bone marrow cellularity	
Normal	8
Decreased	7
Increased	1

SD: Standard deviation; CRP: C-reactive protein; LDH: Lactate dehydrogenase; IVIG: Intravenous immunoglobulins.

Morphology

Regarding dysmegakaryopoiesis, dysplastic and nondysplastic features were separately evaluated. Nondysplastic features included immature forms, emperipolesis, budding, cytoplasmic vacuoles, bare nucleus and hypolobulation while dysplastic features included multiple segmented nucleus, micromegakaryocyte, and hypogranulation. Observation of the specified morphologic abnormality in more than 25% of all megakaryocytes was accepted as present.

Multiple segmented nucleus was observed in 8 patients (50%) (Fig. 1A), bare nucleus was observed in 8 patients (50%) (Fig. 1B), budding was observed in 8 patients (50%) (Fig. 1C), immature forms was observed in 6 patients (37.5%), emperipolesis was observed in 5 patients (31.25%) (Fig. 1D), hypolobulation was observed in 9 patients (56.25%) (Fig. 1E), hypogranulation was observed in 4 patients, and micromegakaryocytes were observed in 10 patients (62.5%) (Fig. 1F).

Comparisons

Bone marrow cellularity was not related to age, platelet levels, or response to treatment. Megakaryocytic cellularity was related to initial LDH, with hypocellularity in patients with higher LDH levels (p=0.005).

TABLE 2. Comparisons of morphologic observations with clinical variables

Morphologic characteristics	Number of patients (percent)	Relations with initial platelet counts	Relations with response to treatment	Relations with initial elevated LDH level	CRP
Non-dysplastic features					
Immature forms	6 (37.5)	**0.006**	0.22	0.72	0.62
Emperipolesis	5 (31.25)	0.42	0.51	**0.005**	**0.006**
Budding	8 (50)	0.49	0.62	0.66	0.584
Cytoplasmic vacuoles					
Bare nucleus	8 (50)	**0.007**	0.41	0.28	0.65
Hypolobulation	9 (56.25)	**0.006**	0.23	0.44	0.42
Dysplastic features					
Multiple segmented nucleus	8 (50)	**0.007**	**0.006** (poor response)	0.28	0.55
Micromegakaryocyte	10 (62.5)	**0.008**	**0.005** (poor response)	0.44	0.61
Hypogranulation	3 (18.8)	0.05	0.61	0.68	0.45
Cellularity of megakaryocytes					
Normal	7	0.41	0.65	**0.005**	**0.68**
Hypo	5				
Hyper	6				

LDH: Lactate dehydrogenase; CRP: C-reactive protein.

Within non-dysplastic features, the presence of immature forms, bare nucleus, and hypolobulation were observed more frequently in patients with higher initial platelet counts (p=0.006, 0.007 and 0.006, respectively) but not related with response to treatment or other laboratory values. Emperipolesis was related to higher initial LDH and CRP levels (p=0.005 and 0.006). Budding was not related to initial platelet counts, CRP or LDH levels, and response to treatment.

On the other hand, within dysplastic features, the presence of micromegakaryocytes was related to higher initial platelet counts (p=0.008), and the presence of multiple-segmented nuclei was related to worse responses to treatment (p=0.006). Hypogranulation was not related to initial platelet counts, CRP or LDH levels, and response to treatment.

Comparisons are summarized in Table 2.

DISCUSSION

In the WHO classification of myeloid neoplasms, dysplasia is accepted only if present in more than 10% of the specific lineage [9]. Recent studies on MDS have focused on the cytogenetic abnormalities which are all aimed towards decision-making on treatment and prognosis. However, morphologic abnormalities, especially in megakaryocytes are generally neglected. Morphologic evaluation is challenging and standardization solutions are suggested [10–12]. Almost all bone marrow reports with a pre-diagnosis of MDS have been passing megakaryocytes simply as "present and hypolobulated" and this is what has led us to evaluate thoroughly the samples which were performed with a concern of dysplasia in patients over 80 years old. Dysplasia and the status of megakaryopoesis in this age group should be assessed in different dimensions; first, age-related decrease in bone marrow cellularity with age-related dysmegakaryopoiesis and second, alterations in megakaryopoiesis due to ITP.

Dysplasia-Age-Related Alterations

Age-related decrease in bone marrow cellularity is highly investigated in various studies reporting a constant decline with age reaching almost below 30% after the age of 80 years [6]. In this perspective, age-related dysplasia may be observed and at least be sought in every patient presenting with cytopenia. In patients with ITP, the effect of age and bone marrow cellularity has

been investigated in two studies. In the first study, the patients were grouped as <60 years and >60 years, and no difference was observed in both groups. Although the mean age was 70, 78 years in this study, the effect of age may be underrated since none of the patients were over 80 years old [10]. In the second study, patients with ITP over 70 years of age were evaluated and decreased bone marrow cellularity was suggested to be related to poor response to eltrombopag [13]. In our study, we did not observe a relationship between bone marrow cellularity with age, laboratory values at presentation, or response to treatment. This lack of relation may be related to the limited number of patients in our study as well as the generally low number of patients with such an age as well as with an uncommon disorder.

Dysmegakaryopoiesis is a challenging observation and needs expertise and effort. International Working Group on Morphology of MDS (IWGM-MDS) has suggested clear morphologic definitions with links to dysplasia or nondysplastic alterations of megakaryocytes [12]. In this guide, hypolobulation is suggested to be observed in normal bone marrow as well as MDS with 5q deletion where thrombocytosis is expected. In our study, we observed hypolobulated megakaryocytes in 7 of the 16 bone marrow samples with a relation with higher initial platelet counts still thrombocytopenic but higher counts than patients without hypolobulation. Although in these patients, 5q deletion was not detected, this observation may be related to the pathogenetic mechanism of ITP in these patients; dysmegakaryopoiesis rather than peripheral platelet destruction.

The presence of micromegakaryocytes is accepted as sign of dysplasia in almost every MDS definition though they may also be observed in transient abnormal myelopoiesis which is observed in infants with Down syndrome and MDS-myeloproliferative disorders (MPN). In our study, megakaryocytes with the exact definition of micromegakaryocytes in the IWGM-MDS [11] have been observed in 8 (50%) of the patients and it was related to higher initial platelet counts. In these patients, though the finding is highly related to MDS, only 1 patient showed a karyotype related to MDS. This made us think that these observations of micromegakaryocytes as well as hypolobulated megakaryocytes may be related to a process which is not dysplastic but also not normal but may be age related or ITP related. In this perspective, our observation of a higher number of immature megakaryocytes in the same group of patients who have presented with thrombocytopenia but higher counts may be related to age and ITP pathogenesis since immature forms are defined in IWGM-MDS [11] but are hard to be recognized and differentiated from mature megakaryocytes and micromegakaryocytes.

Regarding the response to treatment, the presence of multinucleated or multiple segmented nuclei and micromegakaryocytes was related to poor response to any lines of treatment, which suggested an ongoing but not definite process of dysplasia, which may be explained with a definition of age-related dysmegakaryopoiesis, not definite MDS.

ITP and Increased Autoimmunity in the Very Old

Bone marrow evaluation of patients with ITP has shown that even pathologists with experience may not recognize the alterations of ITP, since megakaryocyte morphology may vary regardless of dysplasia [14]. Infiltration may be easily excluded and increases in reticuline fiber may suggest MPN but in our experience, combination of clinical data including patient history and examination should be taken into consideration while evaluating the bone marrow. In the pathogenesis of ITP, not only peripheral platelet destruction via antibody-mediated and cellular immune pathways but also suppressed megakaryocyte production and maturation are demonstrated [14, 15]. Morphological alterations of ITP megakaryocyes included extensive cytoplasmic vacuolization, hypogranularity, and smoothing of the cellular membrane with conflicting reports suggesting the inseparability of ITP megakaryocytes from normal [15]. In our study, we did not observe cytoplasmic vacuolization in any patients and hypogranularity in just 3 patients and in these 3 patients, presenting platelet counts, biochemical variables or response to treatments were undistinguishable. This may be explained by the difficulty in recognition of such alterations as well as these changes may or may not be related to age factor.

As autoimmunity is generally stated to be increased with age, the incidence of ITP increases proportionally with age [2, 15, 16]. This leaves us with unanswered questions regarding the pathogenesis of ITP which shows individuality. Antibody mediated platelet destruction, increased T cell-mediated destruction, or dysmegakaryopoiesis may be certain in each patient, with different ages and gender. In our patient group, we observed that dysplastic or just altered, megakaryopoiesis is affected in certain patients, presenting with not just

thrombocytopenia, they may present with a higher number of platelets and may not respond to treatments towards suppression of the immune activation or even a stimulation of megakaryopoiesis.

In the scarce knowledge of ITP in very old individuals, one letter to the editor briefly summarizes the clinical variables [6], one single center study reports the clinical outcomes [7] and a third study mainly focuses on the bleeding of ITP patients who are older than 67 years [8]. In these reports, the status of megakaryopoiesis and pahogenetical hypothesis were not evaluated. In our study, we tried to focus on the morphology of the bone marrow and tried to reach outcomes based on the morphological evaluation of megakaryopoiesis which may be pathogenetical in this rare condition-patient group.

Conclusion

We observed dysmegakaryopoiesis in a considerable number of our patients with a relation with a higher but still low number of platelets. These patients also responded inadequately to treatments. But still, they lacked the qualities of MDS such as cytogenetical abnormalities and overt megakaryocytic dysplasia. This may be explained by age since this specific group of patients also has a risk of decreased bone marrow cellularity and an increased risk of autoimmunity. The pathogenesis of ITP in these groups of patients may differ from patients who are much younger and even in childhood. Age-related alterations in megakaryopoiesis may cause a susceptibility to ITP as well as a poor response to conventional treatments.

However, there are various limitations which concerned us about our observations. First of all, morphologic evaluation of megakaryopoiesis is difficult, needs experience and worldwide information of accurate definitions and explanations for each alteration. Misinterpretation may always be certain, and this needs to be clarified with an increased number of megakaryocytes to be evaluated for each patient. The second limitation is the lack of specificity of the staining. Universal staining is Romanowsky and May-Grunwald, but immune staining is trending and becoming more handy; which may help us with granularity as well as the expression of surface antigens. The third and may be the most unpassable limitation is the limited number of patients in that age and disease groups. International collaboration may be useful in this limited group of patients.

Ethics Committee Approval: The Trakya University Non-Interventional Scientific Research Ethics Committee granted approval for this study (date: 09.05.2022, number: 11/04).

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