Review

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Platelet morphology

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Abstract

Background: The examination of a peripheral blood smear is mandatory in case of unexplained thrombocytopenia or thrombocytosis. First, the number of platelets should be estimated in order to confirm the platelet count determined by the haematology analyser, and to rule out causes of spuriously low or elevated platelet counts. Second, the size and morphological features of the platelets, which may provide information on the underlying cause of the low or enhanced platelet count, have to be assessed.
Content: This review summarizes the physiological and pathological features of platelet size and morphology, circulating megakaryocytes, micromegakaryocytes and megakaryoblasts, and provides an overview of current guidelines on the reporting of platelet morphology.
Summary: In the diagnostic work-up of a patient with thrombocytopenia, the size of the platelets is of diagnostic relevance. Thrombocytopenia with small platelets is suggestive of a defect in platelet production, whereas the presence of large platelets is more likely to be associated with enhanced platelet turnover or hereditary thrombocytopenias. Morphological platelet abnormalities may affect the granulation and the shape and are frequently associated with abnormalities of platelet size. Platelet anomalies can be found in various haematologic disorders, such as myelodysplastic syndromes, myeloproliferative neoplasms, acute megakaryoblastic leukaemia or hereditary thrombocytopenias.

Keywords: blood smear; platelet morphology; platelets; thrombocytes.

Introduction

The examination of a peripheral blood (PB) smear should be requested in every case of unexplained thrombocytopenia or thrombocytosis. First, the morphological analysis should include the estimation of the number of platelets in order to confirm the platelet count determined by the haematology analyser, and to rule out causes of spuriously low platelet counts due to platelet aggregates, platelet satellitism or platelet phagocytosis [1–4]. The identification of pseudothrombocytopenia (PTP) due to anticoagulant-induced platelet aggregation is crucial, because a misinterpretation as a "true" thrombocytopenia may lead to serious diagnostic and therapeutic consequences such as bone marrow biopsy, initiation of corticosteroid therapy, platelet transfusion or even splenectomy [2]. PTP can be caused by various anticoagulants such as ethylenediamine tetra-acetic acid (EDTA), citrate, heparin, oxalate or hirudin, occurring with an incidence of 0.1–0.2% for EDTA, which is the most commonly used anticoagulant for automated blood counts [2, 5, 6]. Figure 1 shows a large platelet aggregate in a patient with EDTA-induced PTP.

Falsely elevated platelet counts may result from small circulating particles such as erythrocyte fragments, microerythrocytes, fragments of leukaemia cells, cryoglobulins or fungi [1, 7, 8]. The second diagnostic step is to assess the size and morphological features of the platelets, which may enable the analyst to get information on the underlying cause of the low or enhanced platelet count.

In this review article the physiological and pathological features of platelet size and morphology, as well as the morphological characteristics of circulating megakaryocytes, micromegakaryocytes and megakaryoblasts are summarized. Furthermore, the article provides a short overview of current guidelines concerning the reporting of the platelet morphology in clinical laboratory routine.

Characteristics of physiological platelet morphology

Platelets have a round or oval shape in EDTA-anticoagulated blood and measure 1.5–3 μm in diameter [1, 9, 10]. In

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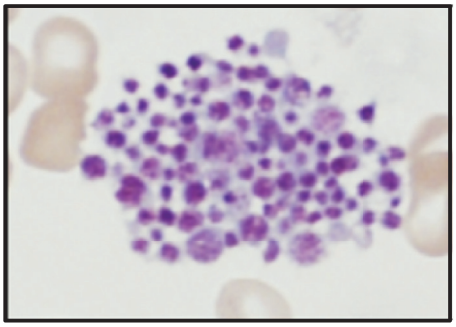

Figure 1: Platelet aggregate in EDTA-induced PTP.

blood smears made from native capillary blood, the platelets tend to aggregate and are found in star-shaped forms due to activation [1, 9]. The platelet cytoplasm contains fine azurophilic granules that may appear scattered throughout the cytoplasm or concentrated in the centre of the platelet, which has been termed granulomere. The granulomere corresponds functionally to the secretome [10]. The peripheral colourless or weakly basophilic part of the cytoplasm, that does not contain granules, is known as the hyalomere [1, 9, 10]. An example of physiological platelet morphology is presented in Figure 2A.

Assessment of the platelet size

The platelet size is of diagnostic relevance, especially when it is set in relation to the platelet count.

In PB smears, the platelet size can be easily interpreted by comparing the platelet diameter with the diameter of the red blood cells. Large platelets (3–7 µm) are called macrothrombocytes, whereas platelets reaching the size of erythrocytes or lymphocytes (larger than 7, up to 20 µm) are designated giant platelets [1, 11]. Healthy subjects usually have less than 5% of large platelets [11].

In the assessment of the platelet size, knowledge of the physiological heterogeneity of platelet diameters as well as potential preanalytical influencing factors, such as storage artefacts, is crucial for the correct interpretation. In EDTA-anticoagulated blood, the platelets may swell and degranulate during storage, leading to a large and hypogranular appearance on PB smears [1, 11]. The platelet size shows a wide heterogeneity, or platelet anisocytosis, which is more pronounced in neonates than in adults, because of the occurrence of larger-size platelets at birth [10]. In case of increased thrombopoiesis, young, larger platelets are more frequently apparent [9]. Hence, in the diagnostic work-up of a patient with thrombocytopenia, the size of the platelets is of diagnostic relevance. Thrombocytopenia with small platelets is suggestive of an

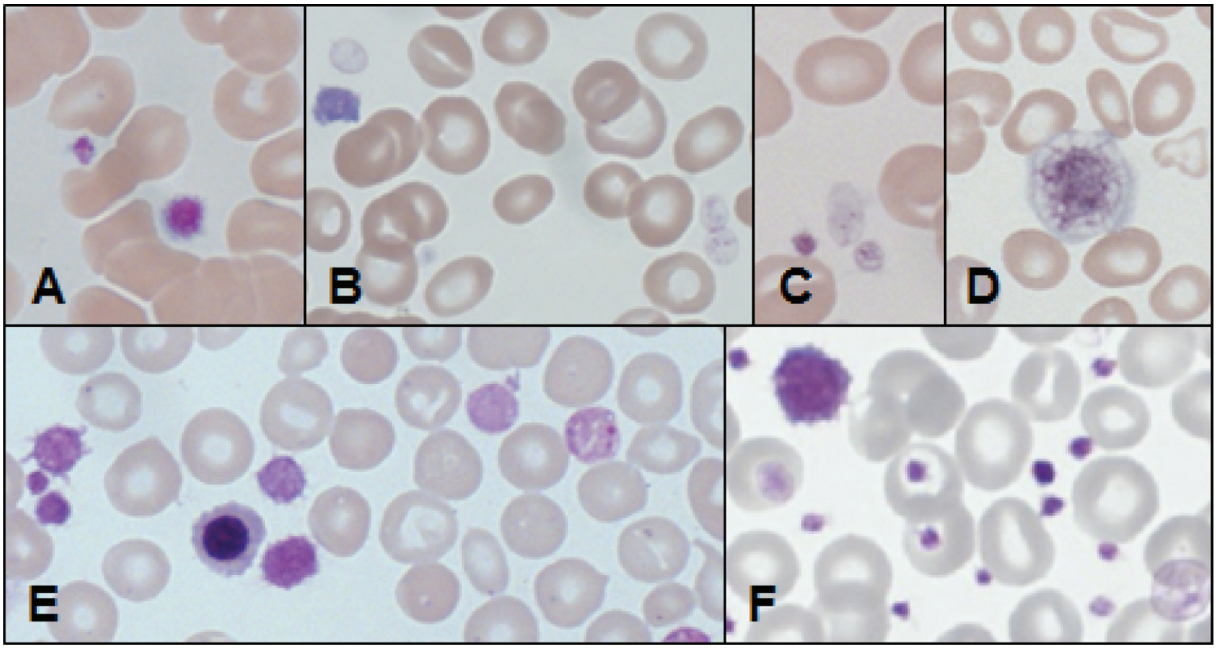

Figure 2: Physiological and pathological platelet morphology.
(A) Normal platelets; (B) and (C) agranular and hypogranular platelets in a patient with a myelodysplastic syndrome; (D) giant platelet; (E) platelet anisocytosis, large platelets and platelets with abnormal granulation in a patient with primary myelofibrosis; (F) platelet anisocytosis, a giant platelet and granulation anomalies in a patient with essential thrombocythaemia.

Table 1: Acquired causes of large platelets [1, 9, 15].

Storage artefacts
Physiological platelets in neonates
Immune thrombocytopenia
Thrombotic microangiopathies
Disseminated intravascular coagulation
Myeloproliferative neoplasms (essential thrombocythaemia, polycythaemia vera, primary myelofibrosis, chronic myeloid leukaemia)
Myelodysplastic syndromes
Myelodysplastic/myeloproliferative neoplasms
Megakaryoblastic leukaemia
Postsplenectomy states and hyposplenism
Drug-induced (cholestyramine, erucic acid)

impaired platelet production in the bone marrow, such as in cases of aplastic anaemia, chemotherapy, ionizing radiation, drug toxicity, megaloblastic anaemia or bone marrow infiltration, whereas the presence of large platelets is more likely to be associated with enhanced platelet turnover and will suggest, for example, disorders such as immune thrombocytopenia, thrombotic microangiopathies or disseminated intravascular coagulation [1, 12–14]. Furthermore, large platelets can be observed in hereditary thrombocytopenias, postsplenectomy states and hyposplenism [1]. Marked platelet anisocytosis is a typical morphologic feature of myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN), as shown in Figure 2E, F [1, 10]. Tables 1–3 yield an overview of the various

Table 2: Inherited thrombocytopenias with large/giant platelets [1, 16–19].

Disease	Gene	Inheritance	Platelet size
Bernard-Soulier syndrome	*GP1BA, GP1BB*	AR	Giant, large
	GP9	AD	
PRKACG-related thrombocytopenia	*PRKACG*	AR	Giant/large
MYH9-related disease	*MYH9*	AD	Giant/large
SLFN14-related thrombocytopenia	*SLFN14*	AD	Giant/large/normal
Grey platelet syndrome	*NBEAL2*	AR	Large
ACTN1-related thrombocytopenia	*ACTN1*	AD	Large
ITGA2B/ITGB3-related thrombocytopenia	*ITGA2B, ITGB3*	AD	Large
TUBB1-related thrombocytopenia	*TUBB1*	AD	Large
GF1B-related thrombocytopenia	*GF1B*	AD	Large
Paris-Trousseau thrombocytopenia (Jacobsen syndrome)	*FLI1*	AR	Large
TRPM7-related thrombocytopenia	*TRPM7*	AD	Large
Tropomyosin4-related thrombocytopenia	*TPM4*	AD	Large
FLNA-related thrombocytopenia	*FLNA*	XL	Large
DIAPH1-related thrombocytopenia	*DIAPH1*	AD	Large
SRC-related thrombocytopenia	*SRC*	AD	Large
GATA1-related disease	*GATA1*	XL	Large
GALE-related thrombocytopenia	*GALE*	AR	Large
GNE myopathy with congenital thrombocytopenia	*GNE*	AR	Normal/large

AD, autosomal dominant; AR, autosomal recessive; XL, X-linked.

Table 3: Causes of small platelets [1, 13–19].

Inherited diseases	Gene	Inheritance
Wiskott-Aldrich syndrome, X-linked thrombocytopenia	*WAS*	XL
CYCS-related thrombocytopenia	*CYCS*	AD
FYB-related thrombocytopenia	*FYB*	AR
Thrombocytopenia-absent radius syndrome	*RBM8A*	AR
Congenital amegakaryocytic thrombocytopenia	*MPL*	AR
Inherited thrombocytopenia	*PTPRJ*	AR
Acquired		
Impaired platelet production in the bone marrow (aplastic anaemia, chemotherapy, ionising radiation, drug toxicity, bone marrow infiltration, megaloblastic anaemia)		

AD, autosomal dominant; AR, autosomal recessive; XL, X-linked.

acquired (Table 1) and inherited (Table 2) causes of large and/or giant platelets, as well as small platelets (Table 3).

Acquired abnormalities of platelet morphology

Morphological platelet abnormalities may affect the granulation (hypogranular/agranular platelets, presence of singular large granula) and the shape (irregular to bizzare, cytoplasmatic blebs), which may both occur simultaneously in one patient and are frequently associated with abnormalities in platelet size [1, 10, 15, 20].

Abnormalities of platelet morphology can especially be found in haematopoietic neoplasms, but are also seen in non-malignant states. Haematologic neoplasms that are typically associated with platelet anomalies are MDS, acute megakaryoblastic leukaemia, myelodysplastic/myeloproliferative neoplasms, MPN and the recently defined group of myeloid neoplasms with germline predisposition and pre-existing platelet disorders [10, 19, 21].

In MDS, the varying platelet anomalies result from a defect in thrombopoiesis [19]. Platelet anisocytosis, hypogranular/agranular platelets (Figure 2B), platelets with a single large granule, hyperchromatic platelets, giant platelets (Figure 2D), and occasionally platelets with concentrated granules in the centre that may even resemble lymphocytes, can be found in MDS [10, 12, 15, 19, 20]. Sometimes strands of megakaryocyte cytoplasm, formed of numerous platelets, are observed in PB smears [20]. Other typical features of MDS, such as erythroblastaemia, poikilocytosis, pseudo-Pelger cells or circulating myeloblasts, have to be incorporated in the interpretation of the PB smear [1, 9, 19]. In cases of acute megakaryoblastic leukaemia, despite the occurrence of micromegakaryocytes (Figure 4F–H) and megakaryoblasts (Figure 4I), which are the hallmark of acute megakaryoblastic leukemia, platelet anisocytosis and agranular macroplatelets are frequently found [10].

MPN which are usually associated with a varying degree of platelet anomalies are the essential thrombocythaemia (ET), polycythaemia vera (PV) and primary myelofibrosis (PMF) [19]. In these disorders, platelet dystrophy may either result from defects in thrombopoiesis or the release of granules from hyperaggregable platelets [19]. Typical morphological signs are sometimes marked platelet anisocytosis, large or giant platelets, hypogranular/agranular platelets and “empty” appearing platelets, solely circumfered by a slim pink cytoplasmic margin (Figure 2E, F) [10, 19]. In addition to the mentioned platelet anomalies, the analyst has to look for further morphological features typically for MPN, such as basophilia, which may occur in PV, ET and PMF, as well as leukoerythroblastosis and poikilocytosis with tear drop cells in PMF [9, 19].

The revised fourth edition of the World Health Organization (WHO) classification of tumours of haematopoietic and lymphoid tissues contains the new category of myeloid neoplasms with germ line predisposition. Within this category, three disorders have been classified as myeloid neoplasms with germ line predisposition and pre-existing platelet disorders, designated myeloid neoplasms with germ line *RUNX1*, *ANKRD26* and *ETV6* mutation [21, 22]. Affected patients have variable platelet counts with usually normal platelet size and morphology and variable degrees of platelet dysfunction, leading to a mild-to-moderate bleeding tendency. Knowledge of these rare disorders is of clinical relevance, because the patients may develop malignant hematopoietic neoplasms such as MDS or acute myeloid leukaemia (AML) [21].

Several non-malignant states can show a disturbed platelet morphology as well, and thereby especially hypogranularity/agranularity, caused by in vivo or in vitro discharge of platelets following platelet activation. In vitro degranulation can result from difficult venepuncture, platelet aggregation, cardiopulmonary bypass or can be EDTA-induced [1, 23]. In

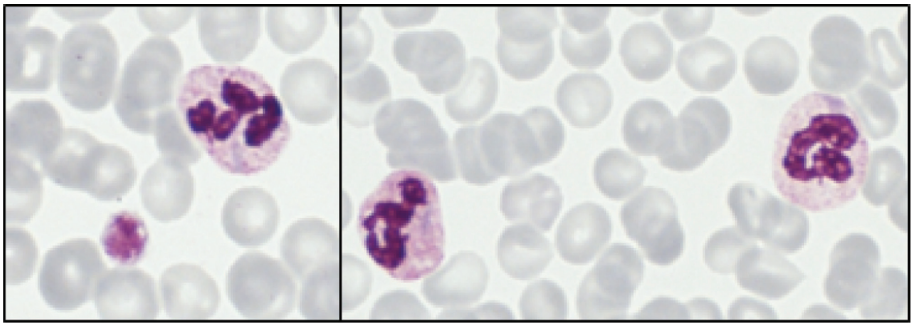

Figure 3: May-Hegglin anomaly.
A large platelet and three mature neutrophils with large cytoplasmic May-Hegglin inclusions, which resemble Döhle-bodies.

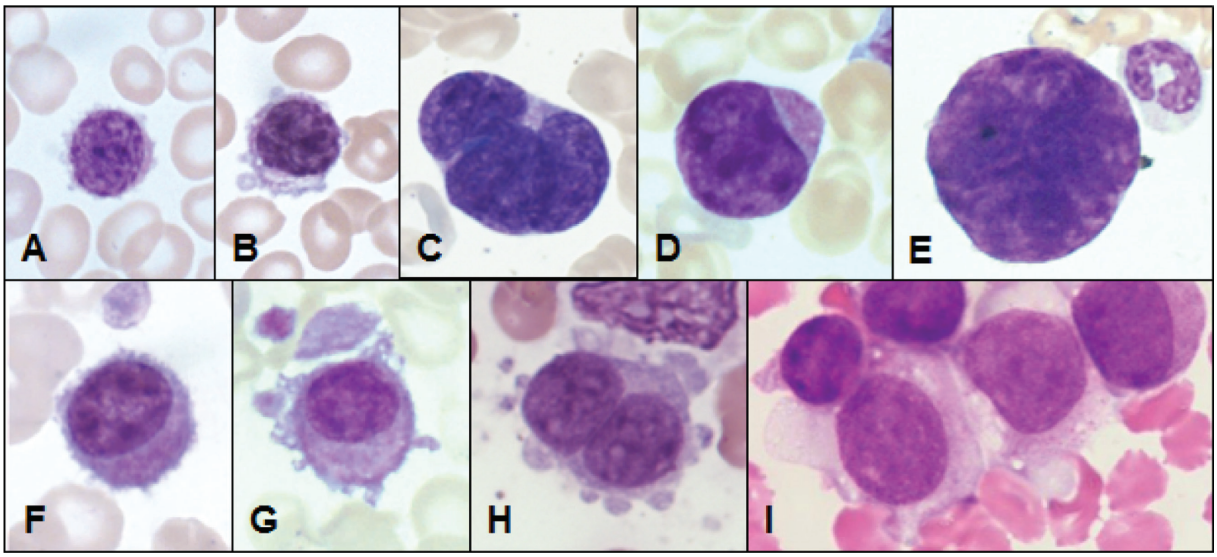

Figure 4: Circulating megakaryocytes, micromegakaryocytes and megakaryoblasts.
(A–E) Megakaryocytes; (F–H) micromegakaryocytes; (I) megakaryoblasts.

vivo degranulation leading to hypogranular/agranular platelets on a PB smear can, for example, occur in disseminated intravascular coagulation [1, 19].

Very large platelets have also been reported originating from a drug-induced influence on the lipid metabolism observed in patients under cholestyramine treatment for hypercholesterolaemia or erucic acid for adrenoleukodystrophy [10].

Anomalies of platelet morphology in inherited platelet disorders

Inherited platelet disorders are rare diseases, but are of clinical importance, as they can be easily misclassified as immune thrombocytopenia, especially when no other family members are affected or when diagnosis is made in adulthood [24, 25]. The inherited platelet disorders that are diagnosed in adults are usually non-syndromic at birth and do not or induce only mild spontaneous bleeding complications, in contrast to those diagnosed in childhood [24]. To date, more than 30 inherited disorders, derived from 50 gene defects have been identified and have been reviewed in detail elsewhere [16, 17, 24, 26]. A comprehensive list of hereditary macrothombocytopenias and microthrombocytopenias is presented in Tables 2 and 3, respectively.

The diagnostic work-up initially consists of a detailed family and bleeding anamnesis, an automated complete blood count, morphological assessment of peripheral blood smears by light- and, where appropriate, also immunofluorescence microscopy, platelet function analysis by light transmission aggregometry, flow cytometry and molecular analysis [27].

An international study on 3217 patients showed that blood smear analysis by light- and immunofluorescence microscopy alone was able to identify inherited platelet disorders in 27% of the subjects [28].

From a cytological point of view, the inherited platelet disorders can present with normal, small, large/giant and/or hypogranular/agranular platelets (Tables 2–4) [1, 16, 17, 19, 24]. As abnormalities of the platelet size and morphological appearance have been described in varying degrees in the majority of inherited platelet disorders, assessment of the platelet size is of importance in guiding the differential diagnosis of the various conditions. In that context, the determination of the platelet diameter and the percentage of large platelets by optical microscopy and by software-assisted image analysis has been proven as a valuable additional tool for discrimination between some hereditary thrombocytopenias and immune thrombocytopenia, and between some disorders within the group of hereditary thrombocytopenias by assigning the inherited diseases to groups with giant platelets, large platelets, normal or slightly increased platelet size and those with normal or slightly decreased platelet size [31].

Large/giant platelets are, for example, characteristic for *MYH9*-related disease (May-Hegglin anomaly, Epstein syndrome, Fechtner syndrome, Sebastian syndrome), Paris-Trousseau thrombocytopenia/Jacobsen syndrome, *GATA1*-related disease, thrombocytopenia associated with

Table 4: Causes of hypogranular/agranular platelets [1, 2, 16–19, 29, 30].

Inherited	Gene	Inheritance
Grey platelet syndrome	*NBEAL2*	AR
Chediak-Higashi syndrome	*LYST*	AR
Hermansky-Pudlak syndrome	*HPS*	AR
Griscelli syndrome	*MYO5A, RAB27A, MLPH*	AR
Wiskott-Aldrich syndrome	*WAS*	XL
Thrombopenia-absent radius syndrome	*RBM8A*	AR
GATA1-related disease	*GATA1*	XL
Arthrogryposis renal dysfunction and cholestasis syndrome	*VPS33B, VIPAR*	AR
Acquired		
In vitro degranulation (difficult venipuncture, platelet aggregation, EDTA-induced, cardiopulmonary bypass)		
In vivo degranulation (disseminated intravascular coagulation)		
Myelodysplastic syndromes		
Myeloproliferative neoplasms (essential thrombocythaemia, polycythemia vera, primary myelofibrosis)		

AD, autosomal dominant; AR, autosomal recessive; XL, X-linked.

sitosterolaemia, filamin A (*FLNA*)-related thrombocytopenia, Bernard-Soulier syndrome, Grey platelet syndrome, *TUBB1*-related thrombocytopenia and *ITGA2B/ITGB3*-related thrombocytopenia [1, 19, 24].

Within the inherited thrombocytopenias, the most impressive morphological changes can be seen in the *MYH9*-related diseases, which are caused by mutations of the gene encoding for the heavy chain of non-muscle myosin IIA (myosin-9), as some of these disorders show cytoplasmic inclusions in the neutrophil granulocytes) [1, 19, 24]. The inclusions originate from abnormal localisation of *MYH9* in association with ribosomes, and show variations in the number and size of those inclusions, dependent of the genotype [24]. In the May-Hegglin anomaly, the neutrophils show large, faint, light blue, spindle-shaped or irregular cytoplasmic inclusions located at the cell periphery, that are also called "Döhle body-like inclusions" (Figure 3) [1, 10, 19, 24, 32–34]. In the other syndromes that yield neutrophil inclusions, Fechtner and Sebastian syndromes, the cytoplasmic inclusions are smaller, pale and more numerous [10].

The large platelets observed in Paris-Trousseau thrombocytopenia (Jacobsen syndrome) are characterised by abnormally large granules, caused by a mutation in the *FLI1* gene [1, 19].

Small platelets can be found in Wiskott-Aldrich syndrome/X-linked thrombocytopenia and some further rare hereditary conditions (Table 3) [16, 24, 29]. Inherited diseases showing agranular platelets are all uncommon. Agranular/hypogranular platelets that appear pale and grey are derived from an α-granule deficiency and are the characteristic morphological substrate of the grey platelet syndrome [12, 19, 24]. Hypogranular/agranular platelets can also be observed in other uncommon hereditary disorders such as the Chediak-Higashi, Hermansky-Pudlak and Griscelli syndromes due to a reduction or lack of dense granules, and Wiskott-Aldrich syndrome, thrombocytopenia with absent radii, thrombocytopenia in *GATA1* mutation and arthrogryposis renal dysfunction and cholestasis syndrome [16–19, 30]. Table 4 summarises the acquired and inherited causes of agranular/hypogranular platelets.

Circulating megakaryocytes, micromegakaryocytes and megakaryoblasts

Megakaryocytes (Figure 4A–E) are rarely observed in PB smears of healthy adults, because they are usually trapped in the pulmonary capillaries. However, some megakaryocytes are able to pass through the pulmonary capillaries and are thus detectable in PB smears, especially in buffy coat preparations or in leukocyte concentrates [1]. Their number is found between 5 and 7 cells per millilitre in healthy adult subjects, and is increased in neonates, young infants, after delivery, following surgery, in patients with inflammatory, infectious and solid malignant disorders,

disseminated intravascular coagulation, as well as in MPN and MDS [1, 35–39].

In healthy subjects, circulating megakaryocytes usually present as bare nuclei, nearly free from any cytoplasm, whereas megakaryocytes with plentiful cytoplasm are rarely found. Such forms may physiologically occur in infants, but are suggestive of a haematopoetic neoplasm in adults [1]. However, it has to be mentioned that bare megakaryocyte nuclei may be observed in cases with haematopoetic disorders as well [20].

The occurrence of abnormal megakaryocytes, micromegakaryocytes and megakaryoblasts on PB smears is usually restricted to pathological conditions.

Micromegakaryocytes (Figure 4F–H) are small atypical megakaryocytes with a diameter of 7–10 μm with characteristic morphological features. They are characterised by a round or slightly irregular, non-lobed or bilobular nucleus, similar or smaller in size to that of a promyelocyte, with a dense mature chromatin. The nucleo-plasmatic ratio can be high. The cytoplasm is weakly basophilic and may show vacuoles or granulation and may vary from scanty to moderate in amount. The cellular margins may show protrusions or "blebs" [1, 11, 20]. Occasionally, a "budding" of platelets from the surface can be observed [11]. Micromegakaryocytes can be apparent in various haematopoietic disorders such as MDS, acute megakaryoblastic leukaemia, transient abnormal myelopoiesis of Down syndrome, PMF, post polycythaemia or post thrombocythaemia myelofibrosis and chronic myeloid leukaemia (CML) [1, 38–40]. In CML, the occurrence of circulating micromegakaryocytes may indicate the transformation to blast crisis [39].

Megakaryoblasts (Figure 4I) are mostly large blast cells with a variable diameter of 10 to more than 20 μm, which have a diffuse chromatin pattern [1, 20]. Small megakaryoblasts may cytologically be indistinguishable from lymphoblasts [11]. Cytoplasm varies from scanty to moderate in amount, with a weak to strong basophilia, or may resemble the hyalomere of platelets. On the cellular surface, protrusions or "blebs", or even unseparated platelets may be observed [1, 20]. Megakaryoblasts are usually found in some cases of AML, but it is noteworthy that they are often not identifiable by cytology alone [1].

Reporting of the platelet morphology according to guidelines

Currently, there are several guidelines, that deal with the reporting of blood cell morphology in clinical laboratory routine, available in the literature. The International Council for Standardization in Haematology (ICSH) published guidelines for the standardization and grading of peripheral blood cell morphological features in 2015, including some recommendations for the reporting of qualitative platelet abnormalities. The authors stated that a comment about the platelet count and the presence of small, large and/or giant platelets can be made with an additional interpretive comment if appropriate, and recommended that giant platelets should be graded (few/1+; moderate/2+, 11–20%; many/3+, >20%). It was further recommended that a comment about the presence of hypogranular platelets, megakaryocytes, micromegakaryocytes and megakaryoblasts should be made if seen in the PB smear [11].

In 2018, the Working Group on Diagnostic Hematology of the Italian Society of Clinical Chemistry and Clinical Molecular Biology (WGDH-SIBioC) published recommendations on the harmonisation of interpretative comments in laboratory haematology reporting. The Working Group suggested that an occasional observation of giant platelets in healthy subjects should not be reported, and that the communication of cases with small megakaryocytes (small megakaryoblasts and naked megakaryocyte nuclei) to the clinicians is only necessary at the first observation. Furthermore, the presence of microplatelets should only be reported with thrombocytopenia and, if possible, in combination with data of the parameters generated by the haematology analyser. The presence of hypogranular/agranular platelets should also only be reported with thrombocytopenia, but should not be included in the report, when other significant abnormalities are lacking. The authors further stated that the comment "presence of dysplastic platelets" should be solely used in cases of thrombocytopenia with a platelet count $<100 \times 10^9/\mu L$ [41].

Whether the terms "dysplastic platelets" or "platelet dysplasia" should be used in laboratory routine is still a matter of debate. According to a consensus statement of the European LeukemiaNet (ELN) Morphology Faculty, the term "dysplasia" should be restricted to nucleated blood cells. It should not be used for platelets or erythrocytes, although dysplastic haematopoiesis may lead to the production of cytologically abnormal platelets or red blood cells [42].

Summary

The examination of a PB smear is mandatory in case of unexplained thrombocytopenia or thrombocytosis. In the diagnostic work-up of a patient with thrombocytopenia, the size of the platelets is of diagnostic relevance. Thrombocytopenia with small platelets is suggestive of

a defect in platelet production, whereas the presence of large platelets is more likely to be associated with enhanced platelet turnover or hereditary thrombocytopenias. Morphological platelet abnormalities may affect the granulation and the shape and are frequently accompanied by abnormalities of the platelet size. Platelet anomalies can be found in various inherited or acquired haematologic disorders, such as MDS, MPN, acute megakaryoblastic leukaemia or hereditary thrombocytopenias. The detection of circulating megakaryocytes, micromegakaryocytes or megakaryoblasts is of clinical relevance, because it may indicate malignant hematopoietic neoplasms.

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