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Platelets and Platelet transfusions: Challenges for today and tomorrow

Spontaneous bleeding in thrombocytopenia: Is it really spontaneous?

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Abstract

Spontaneous bleeding is a clinical hallmark of thrombocytopenia and can take multiple forms including petechiae, epistaxis, gum bleeding, or, in worst cases, intracranial hemorrhage. Those bleeding events are called " spontaneous " because they occur in the absence of overt trauma. Spontaneous bleeding manifestations have long been considered to be a direct consequence of low platelet counts. Nevertheless, although low platelet counts may lead to ultrastructural endothelial alterations, those alterations and the associated state of vascular fragility are unlikely sufficient to cause spontaneous rupture of the microvessel wall. Indeed, in addition to endothelial injury, factors capable of damaging the basement membrane are required to allow escape of red blood cells in the extravascular space. Therefore, despite their misleading name, spontaneous bleeding events in thrombocytopenia are most likely provoked and involve subclinical biological processes in which platelets normally intervene to ensure hemostasis. In this review, we discuss past and more recent studies on the possible triggers of spontaneous bleeding events in thrombocytopenia, with a particular focus on the role of inflammatory reactions.

Keywords: Thrombocytopenia; Vascular integrity; Spontaneous bleeding; Platelets; Inflammation; Petechial bleeding; Angiogenesis

1. Introduction

Thrombocytopenia defined as a platelet count below the lower limit of 150,000 platelets/μL blood can be caused by a variety of reasons, one of the foremost being immune thrombocytopenia, formerly known as idiopathic thrombocytopenic purpura (ITP) [1]. Thrombocytopenia can be an isolated disorder or develop secondary to or in association with drug treatments [1–5] or conditions such as viral or bacterial infections [1,6–8]. Whatever the etiology of thrombocytopenia, thrombocytopenic patients have an increased risk of bleeding, which can be fatal in rare cases [1,9,10]. Nevertheless, not all thrombocytopenic patients share the same bleeding risk. Thrombocytopenia is considered mild if the platelet count remains above 70,000/μL and, generally, patients with counts greater than 50,000 platelets/μL are asymptomatic and may not need treatment [1,11–13]. Severe thrombocytopenia occurs when the platelet count falls below 20,000–30,000/μL. Patients with a count lower than 30,000/μL have an increased susceptibility to trauma-induced bleeding, and those with counts below 10,000/μL are regarded as the most at risk of so-called spontaneous bleeding, which represents a hematologic emergency. Those bleeding events are clinical hallmarks of thrombocytopenia and are called "spontaneous" because they occur in the absence of overt trauma. They can take the form of seemingly benign manifestations like petechiae, epistaxis, or gum bleeding, but also of more alarming signs like genitourinary, gastrointestinal, or, in worst cases, intracranial hemorrhage.

Causes of spontaneous bleeding in thrombocytopenic patients are often not investigated or at least rarely mentioned in published reports. This is perhaps partly because manifestations such as petechial pupura or epistaxis are not regarded as severe enough to warrant further examination. Another explanation for this lack of clinical investigation is that, as illustrated by the clinical term "thrombocytopenic purpura", thrombocytopenia in itself is largely considered as a sufficient explanation. While purpura is the collective term for bleeding into the skin and mucous membranes, "thrombocytopenic" purpura implicitely designates a particular form of purpura associated with, or caused by decreased platelet numbers. Nonetheless, from a mechanistic

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perspective, this raises the question of why would low platelet counts lead to the escape of red blood cells (RBCs) into tissues through a presumably uninjured vessel wall? Over the years, several non-exclusive explanations have been advanced to account for this intriguing aspect of thrombocytopenia. In this short review, we discuss past and more recent studies on the mechanisms underlying spontaneous bleeding events in thrombocytopenia.

2. Endothelial abnormalities and spontaneous bleeding in thrombocytopenia: Myth or reality?

A commonly given and widely accepted explanation is that thrombocytopenia compromises vascular resistance and causes vascular fragility related to the loss of the endothelial supporting functions of platelets. The concept of vascular fragility in thrombocytopenia arose very early [14] and was principally strengthened by electron microscopy analyses of the microvascular changes occurring in thrombocytopenic animals and patients. In 1970, Gore et al. described widespread alterations of the endothelium of small blood vessels in thrombocytopenic guinea pigs [15]. In line with those observations, in 1975, Kitchens and Weiss reported that extensive ultrastructural changes of the endothelium occurred within hours of thrombocytopenia induction in rabbits [16]. Changes in the endothelium affected capillaries and post-capillary venules, and included marked endothelial thinning as well as the formation of numerous fenestrations [16]. Kitchens and Pendergast later made comparable observations of ultrastructural endothelial alterations in skin and muscle biopsies of patients with severe thrombocytopenia [17]. Endothelial alterations were quite frequent as thin spots and fenestrations were observed in 43% and 6%, respectively, of the capillaries analzyed [17]. Remarkably, in both humans and rabbits, glucorticoid treatment corrected endothelial abnormalities together with the bleeding phenotype associated with severe thrombocytopenia [17,18]. From these observations, a model was proposed in which extravasation of RBCs partly occurs through endothelial gaps forming when platelet counts fall below a critical threshold of approximately 10,000–20,000 platelets/μL (Fig. 1). Despite some controversies, this model still resonates nowadays [19,20]. A matter of debate relates to whether or not endothelial gaps in thrombocytopenia form through disassembly of interendothelial junctions. Whereas Gore [15] and others [19,21] suggested that extravasation of RBCs took place between loosened interendothelial junctions, Kitchens emphasized that interendothelial junctions in thrombocytopenic rabbits and humans were normal [16–18]. Instead, he proposed that RBCs extravasate from sites of profound endothelial thinning and transcellular fenestrations, by a yet-to-be-defined mechanism that might involve increased vesicular transport and/or because of decreased mechanical strength of the endothelium in those spots [16–18]. A maybe more contentious aspect is the fact that several notable contemporaries of Kitchens, like David Shepro [22] and John V. Hurley [21,23], did not detect any consistent differences in the structure of endothelial cells between control and thrombocytopenic animals. All controversies left aside, there is evidence that low platelet counts and even gaps in the endothelial lining might not be sufficient to cause bleeding. First, there is variability in the bleeding risk and severity of thrombocytopenic patients with severe thrombocytopenia. In fact, patients with equally low platelet counts do not all bleed and bleeding severity also varies among patients [24–26]. Moreover, even in a given thrombocytopenic patient, bleeding is not widespread to the entire body but limited to certain areas. Clinical bleeding in thrombocytopenia is therefore likely affected by additional factors besides the platelet count. Variablity of the bleeding phenotype in thrombocytopenia was also observed in a recent experimental study, in which only 2 out of 5 severely thrombocytopenic dogs (< 3% of baseline platelet counts) developped cutaneous bleeding [19]. The authors observed that endothelial junctions in thrombocytopenic dogs who did not develop cutaneous hemorrhage appeared normal, while large interendothelial gaps and widened endothelial junctions were found in the skin of those who did bleed. From these observations it was suggested that variability in the degree of endothelial damage may account for differences in the bleeding phenotype in thrombocytopenia. Nonetheless, although opening of endothelial junctions and gaps surely permit plasma leakage, they are unlikely sufficient to allow the escape of RBCs beyond the inner endothelial layer of blood vessels, unless they are concomitant with alterations of the underlying basement membrane. However, with the exception of the initial study by Gore et al., in which disruptions of basement membrane portions adjacent to endothelial gaps in myocardial venules of thrombocytopenic guinea pigs were noted [27] (but later interpreted as possible tissue preparation artefacts [21]), none of the other electron microscopy studies on the origins of bleeding in thrombocytopenia found defects in the basement membrane of microvessels from thrombocytopenic animals or patients [16–19,21–23]. In the absence of such defects, one should expect to find RBCs escaping through endothelial junction being eventually retained by the basement membrane underneath the endothelium. Remarkably, electron microscopy micrographs of RBCs lying between the endothelium and the basement membrane of microvessels in the constricted cremaster of thrombocytopenic rats are shown in the 1976 study by Dale and Hurley [21]. Finally, in support of the idea that loosening of endothelial junctions is not the cause of bleeding in thrombocytopenia, recent studies have shown that injection of the pro-permeability factors histamine or VEGF did not induce skin bleeding in severely thrombocytopenic mice [28,29]. Taken together, these data strongly suggest that, although endothelial alterations might favor RBC extravasation and sensitize microvessels to injuries by weakening the first vascular barrier, second “hits” capable of inducing damage to the basement membrane are required for spontaneous bleeding during thrombocytopenia. If in addition to low platelet counts and possible associated endothelial alterations, second hits are needed to trigger “spontaneous” bleeding in thrombocytopenia, why did thrombocytopenic animals bleed in ultrastructural studies where, in most cases, induction of thrombocytopenia was supposedly the only challenge [6,16,18,21,27,31]? Could there be surreptitious causes? Mild trauma represents an obvious possible cause of basement membrane injury, but as presented

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