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Invited Commentary

The platelet-skin connection

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ABSTRACT

This review looks at how the hemostatic function links platelets to skin and then discusses the under-recognized non-hemostatic function of platelets, which may be much more important in the dermatology context.

Keywords: Platelets, Skin, Hemostasis, Inflammation, Platelet-rich plasma

INTRODUCTION

It may be surprising for the readers of this article to think how at all is it possible for the least well-known blood cells originally called the "blood dust" can be linked to the most ubiquitous structure and often considered the largest organ in the body, the skin. We could begin by thinking that the skin and platelets both form the barrier which stops the escape of the most nutritious fluid and the blood from the human body; the skin being the protective outer body layer and platelets by forming a clot on vessel injury. Another fundamental property of both these often unsung heroes is their ability to stop microbial invasion – the dermatological barrier with its immune cell repertoire is of course the best defense mechanism to any environmental pathogen. However, platelets also serve the purpose of antimicrobial defense with an increasing recognition in the last two decades of its highly specialized immune function.[1] Thus, the skin and platelets serve many similar purposes. In this review, we look at how the hemostatic function links platelets to the integumental structure and then discuss the under-recognized non-hemostatic function of platelets which may be much more important in the dermatology context.

CUTANEOUS BLEEDING AND PLATELETS

The characteristic dermatological and often the only clinical finding in patients with severe thrombocytopenia are varying grades of cutaneous bleeding. The spectrum of these bruises starts from the tiny red dots called "petechiae" through to "purpura" which denotes blood collection in larger areas and even larger circumference bleeding termed "ecchymosis." Why do these occur? A recently understood function of platelets is its crucial role in the maintenance of basal endothelial barrier function.[2] In other words, platelets are a key factor which helps in keeping the endothelial gap junctions tightly closed. It is well-known to the readers that during inflammatory processes, there is transmigration of the immune cells through the endothelial gap junctions to the subcutaneous tissue. The widening of the endothelial gaps secondary to inflammation can be further worsened if there is associated moderate-to-severe thrombocytopenia, due to the lack of endothelial barrier protective function of platelets

[Figure 1].[3] This explains the larger ecchymosis in patients with severe thrombocytopenia in severe sepsis (e.g., dengue) and the mixing of subcutaneous bruising with edema due to the extravasation of several intravascular components in conditions like purpura fulminans.[4] The exact mechanisms for the endothelial stabilizing effects of platelets have yet not been defined but sphingosine-1-phosphate has been suggested to play a significant role.[5] An interesting research angle in dermatology based on this knowledge is the role of platelets in allergic skin diseases wherein platelet dysfunction may contribute to localized itching and edema.[6] However, then, the question is how can circulating platelets localize to an allergic trigger site?

SITE OF PLATELET PRODUCTION AND CLUBBING

To understand more about the versatility of platelets, we need to look closely at where it is made, and a "minor" clinical sign called clubbing may help in this regard. Clinical examination is becoming an "ancient" art and many of the newly qualified medical professionals would rather depend on scans and imaging modalities than use their eyes and hands in the investigative purposes. The author remembers the time when the different degrees of clubbing would need to be correctly assessed to be allowed to continue his medical posting by professors with unparalleled clinical acumen. The question here is what has clubbing got to do with platelets? This brings to a lesser-known aspect of platelet production. It is well established that platelets are produced from the megakaryocytes and this manufacturing process occurs in the bone marrow. However, several scholars dispute the bone marrow origin and postulate that platelets are produced in the lungs.[7] This was based on the studies where the platelet number was noted to be higher on the left side of the heart compared to the right when blood was sampled from these chambers during open heart surgeries.[8] Hence, in clinical situations, where there is right-to-left shunt, the megakaryocytes which would have normally got stuck in the lung capillaries escape into the circulation and get lodged in the smaller vessels of the fingers and toes.[9] These megakaryocyte fragments and platelets which get stuck in these tiny vessels would burst and release several of the vascular and growth factors (see later), leading to the bulbous and spongy appearance termed clinically as "clubbing."[10] Does this mean the megakaryocytes are floating around in the blood and producing platelets not just in the lungs, but at the sites where they may be needed, including the sites of skin injuries? Can megakaryocytes reach the site of inflammation or infection or allergen and produce large amounts of platelets to participate in these physiological, and in some cases, pathological processes?

NON-HEMOSTATIC FUNCTION OF PLATELETS AND THE SKIN

As mentioned before, to understand more about the skin-platelet connection, we need to understand how platelets behave more than just a cell which participates in blood clotting. It also has several non-hemostatic functions. Platelets are anucleate cells and thus cannot synthesize any new proteins. However, they have over 300 granular constituents packaged into three (possibly four) well-defined granules; the alpha, dense, and lysosomal granules.[11] These granular components play myriad roles which include the well-known hemostatic function, but also immunological

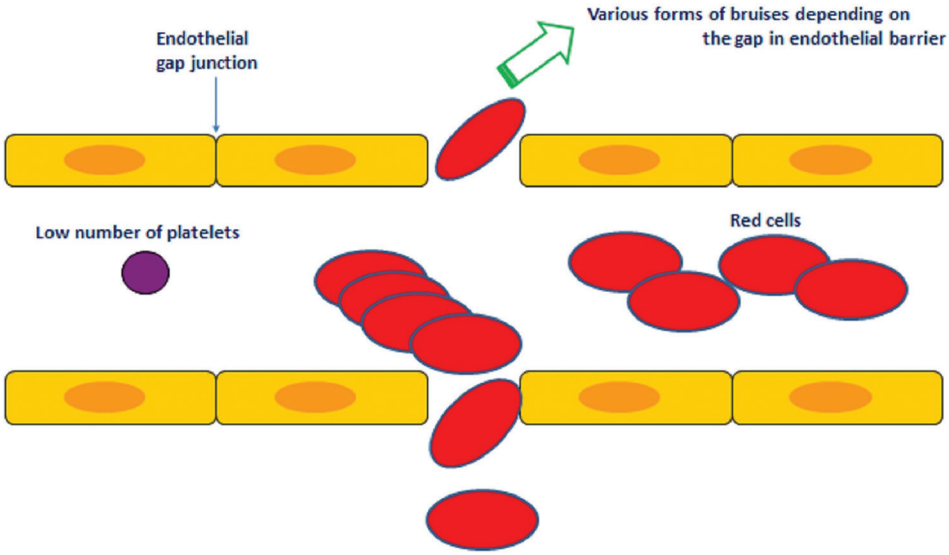

Figure 1: The important role of platelets in maintaining vascular integrity.

effects, antimicrobial defense, wound repair, and cell growth and differentiation.[1] Since the platelets, in the process of hemostasis, adhere to the vessel wall, it only become logical for them to continue their work after clot formation in the next important steps, which is wound healing. In this role of repair and the accompanying inflammation, they synchronize with leukocytes and other cells of the immune system [Figure 2]. When it comes to inflammation and specifically, for our current discussion, the inflammatory skin diseases, the key components are the chemokines which are small chemoattractant proteins that stimulate the activation of inflammatory cells such as phagocytic cells and lymphocytes, which then contribute to the pathogenesis of these cutaneous inflammatory conditions.[12-14]

CLINICAL APPLICATION OF "INFLAMMATORY" PLATELETS – PLATELET-RICH PLASMA (PRP)

Hence, we have learned that there are many beneficial proteins inside platelet granules which are released into the blood after injuries following platelet activation. These proteins actively participate in the wound healing process and thus are found to be of much clinical significance. In comes, PRP, which is increasingly being used in various clinical specialties including dermatology practice. It may be useful to see how PRP is prepared and used for these clinical purposes. Blood is obtained from the patient who needs PRP treatment (they should ideally be not receiving antiplatelet drugs such as aspirin or clopidogrel).[15] The obtained blood is centrifuged at slow speed to obtain a supernatant layer of PRP while the red cells get suspended at the bottom. After obtaining the PRP, just before it is ready to be injected into the desired area, a small dose of thrombin is added to the PRP to stimulate the platelets.[15,16] The activated platelets would then release the granular content of growth factors and inflammatory proteins required for wound healing or anti-inflammatory purposes, respectively. A different method to this autologous PRP preparation (which clearly has a low risk of immunological or infectious risks) is the allogenic PRP method.[17] The latter involves PRP being prepared from blood obtained from donors at the blood banks and is usually through commercial companies.[17]

The first trial using PRP was in the use of maxillofacial surgeries, where PRP was shown to help in quicker healing.[18] Wider applications arose including in sports injuries and more recently, in skin diseases. In particular, PRP has been used in dermatology as beauty or rejuvenation therapy and also for treating alopecia.[19,20] It has been trialed in the setting of accelerated wound healing techniques.[21]

Although very popular in an outpatient setting and been used by some prominent athletes, there has been some controversy about PRP use highlighted by some of the platelet research gurus (Harrison and Alsousou).[22] One of the key issues noted is the lack of definition for the quality and contents of the PRP, especially if obtained commercially.[22] Non-autologous methods use various devices for preparing the sterile PRP which may use different separation principles and thus may contain other blood cells and occasionally activated

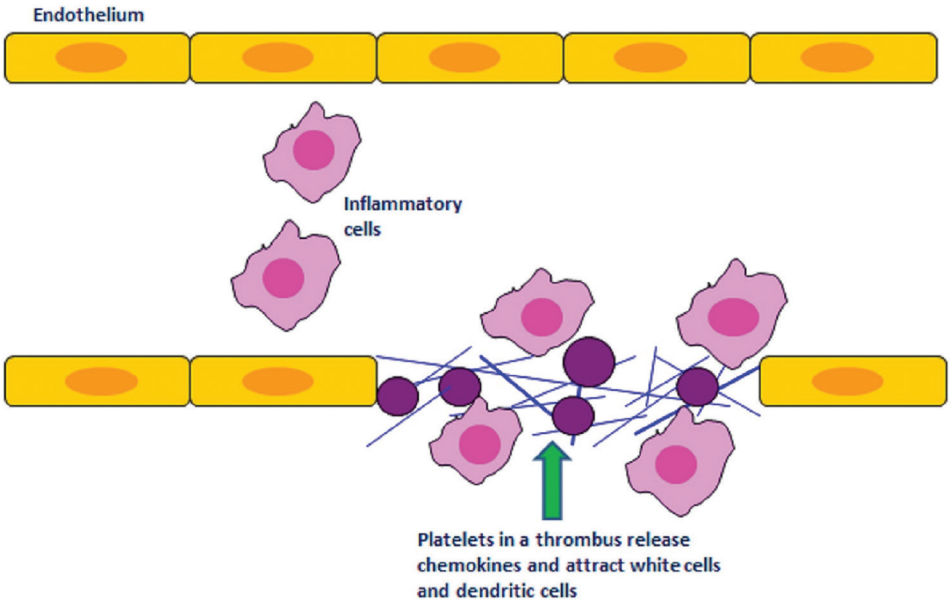

Figure 2: Platelets in immune reaction. After participating in clot formation, it releases chemokines which attract immune cells to the site of endothelial damage to work in wound healing and immune response.

platelets even before the use.[22] Standardization of PRP preparation process may be the cornerstone for good and bad scientific results.

PLATELETS IN SKIN DISEASES

Platelet granule contents have been demonstrated to be involved in contact sensitivity, immediate-type hypersensitivity response, and chronic allergic inflammation.[23-26] Platelets also contain pruritogenic factors like histamine which participate in vasodilation associated with allergic responses. Much of the body's serotonin content is also inside platelets. Low serotonin has been recognized as a risk factor for psoriasis and possibly atopic dermatitis.[26,27] An important clinical pointer here is the link between mental health states such as depression and anxiety, where serotonin levels are low, and the development of various dermatological conditions such as eczema and worsening of already existing problems like psoriasis.[27,28] In this respect, an improvement in the skin disease status can often be measured with the patients' taking antidepressants for their psychological well-being.

Moving away from inflammation and allergens, another fascinating platelet function is its antimicrobial role. The concentration of megakaryocytes in the lungs is very likely to be due to the need for producing copious amounts of platelets which can directly attack the bacteria, viruses, or fungi which may invade the respiratory tract on a regular basis. In a similar manner, platelets have been shown to be stimulated by *Staphylococcus aureus*, a very common infectious agent affecting the skin.[29] Activated platelets can directly disrupt bacterial membranes. Some of the other platelet antimicrobial contents impair bacterial growth, while others can recruit leukocytes to sites of infection demonstrating the importance of multipronged attack in our body's defense repertoire.[30]

CARDIOVASCULAR DISEASE AND SKIN – THE PLATELET CONNECTION

Platelet aggregation is sine qua non of the pathophysiology of cardiovascular diseases. In the recent years, it has become increasingly clear that certain skin diseases like psoriasis are associated with an increased risk of cardiovascular disease.[31] It is possible, low-grade activation of platelets which may be occurring in these dermatological conditions may contribute to the higher incidence of ischemic disease and related problems noted in such patients.[32,33] Acute flares may also mean activation of larger amount of platelets and a higher risk of such vascular problems. Low-dose aspirin has clearly been shown to reduce markers of vascular endothelial inflammation. Several interesting questions arise – will aspirin benefit patients with psoriasis both to reduce cardiovascular events and possibly reduce severity of the skin effects? Will all patients with psoriasis need to take aspirin or can we identify risk factors and tailor the treatment? In acute flares, should higher doses be considered to prevent cardiovascular disease? What is the role of antiplatelet agents in other dermatological conditions?

CONCLUSION

We have looked at the several different ways how platelets participate in a beneficial and also harmful manner in relation to the skin. How can we take this knowledge forward? Yes, the application of PRP is a big advance but with its own methodological issues. But what about blocking platelet activation when it can contribute to the pathogenesis of these diseases? Can we plan a drug trial like randomizing patients to receive antiplatelet agents like aspirin to prevent acute flares in various dermatological conditions? Another approach is to analyze how those with similar conditions may behave once they had to start antiplatelet drugs for alternate conditions like cardiovascular disease prevention. One of the caveats here is that the currently available antiplatelet agents may not block the specific signaling pathways which may be responsible for the pathogenesis of these diseases. This means research into discovering new drugs; for example, those which may specifically block the inflammatory mediator release but does not affect the hemostatic function – a safe and effective approach certainly. All in all, it is fair to say, better understanding of and more research into platelet-skin connection is sure to reap rewards.

Declaration of patient consent

Not required as there are no patients in this article.

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Conflicts of interest

There are no conflicts of interest.

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