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Case Report

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Acquired platelet dysfunction as a cause of bleeding diathesis: two case studies

Abstract

The aims are to highlight the importance of recognizing that clinically significant platelet dysfunction can develop in the background of known causes of bleeding disorders. In this paper, we discuss two patients who developed acquired platelet dysfunction due to eosinophilia with underlying mild Hemophilia A and IgA paraproteinemia that complicated a clinical picture of acquired von Willebrand disease.

Case 1: An 8-yr-old boy with known mild haemophilia A presented with abdominal pain and gross haematuria that partially response to Factor VIII concentrate and cryoprecipitate. Tests revealed significant peripheral eosinophilia (AEC 3200/mm^3), prolonged bleeding time >15seconds, FVIIIc 31%, normal vWF: Ag and RICOF assays. Functional platelet studies were abnormal and a diagnosis of Acquired Platelet Dysfunction with Eosinophilia (APDE) was made. His symptoms resolved with standard treatment of eosinophilia with anti-histamines, diethylcarbamazine and albendazole.

Case 2: A 57-year-old lady was admitted with malena following commencement of oral prednisolone for recently diagnosed Sjogrens syndrome. UGI showed multiple gastric erosions with no response to standard treatment. She was a known diabetic and treated for carcinoma breast 4years ago. A year before this admission, she had her first bleeding episode with epistaxis following septoplasty (APTT prolonged at 40s, not investigated). She finally responded to fresh frozen plasma and cryoprecipitate. Investigations showed APTT 55sec, protein electrophoresis/immune fixation-small spike with IgA lambda and normal SFLC ratio. The mucosal bleeds with partial response to cryoprecipitate and FFP was suggestive of aVWD. Functional platelet studies were abnormal and a diagnosis of paraprotein associated acquired platelet dysfunction was made. She responded to rituximab with reduction in IgA levels and no further bleeds and remains on bortezomib. Identification of acquired platelet dysfunction and knowledge of how that may affect bleeding risk with existing complex autoimmune/hematological disorders are important in optimizing patient care.

Keywords: bleeding disorders, acquired platelet dysfunction, eosinophilia, paraprotein

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Abbreviations: APDE, acquired platelet dysfunction with eosinophilia; AEC, absolute eosinophil count; ADP, adenosine diphosphate; RiCof, platelet ristocetin cofactor; APTT, activated partial thromboplastin time; PT, prothrombin time; SFLC, serum free light chains; IgA, immunoglobulin A; aVWD, acquired von willebrand disease; FVIII, factor VIII; FIX, factor IX; ANA, antinuclear antibody; ECMO, extracorporeal membrane oxygenation; RISTO, ristocetin

Introduction

Haemorrhagic diathesis is usually caused due to a defect in coagulation or hypocoagulability due to deficiency in coagulation factors. The overall hemostatic process, however, is a complex phenomenon and not only involves coagulation factors, fibrinolysis including optimum platelet number and function. The diagnostic approach to patients with bleeding tendencies usually involves a detailed history taking, clinical examination and standard laboratory tests before considering highly specialized tests that is not available to most routine laboratories. Clinicians generally would not consider an alternative explanation to bleeding diathesis in a patient who already has a condition known to cause hypocoagulability. We present two cases each of whom had an underlying bleeding disorder but did not respond to standard treatment and an alternative explanation was required to be made to prevent serious complications and unwarranted treatment.

Case presentation

Case 1: A previously well 8-yr-old boy was diagnosed with mild haemophilia A after he presented with haemorrhagic itchy lesions on the scalp and ecchymosed forearm. A few weeks later, he presented with abdominal pain and gross haematuria which only partially response to Factor VIII concentrate and cryoprecipitate. Investigations revealed peripheral eosinophilia (AEC of 3200/mm^3), microbiological investigations for stool parasites, blood tests for malaria/filarial were negative. Total IgE level 314kU/L (normal reference range (<12years): 2-325kU/L, specific IgE to house dust mite/cockroach were negative (<0.35kUA/L) and mast cell tryptase level was normal (<11.5ng/ml). He had a prolonged bleeding time >15seconds, FVIIIc was border line at 31%, but had normal level of vWF: Ag with normal responsiveness to ristocetin (RiCof). Functional platelet studies done at this time (platelet aggregometry) showed absent response to collagen (2.0mcg), epinephrine (10mcgM), thromboxane receptor agonist and subnormal response to ADP. The platelet function studies and significant

peripheral eosinophilia was consistent with the diagnosis as Acquired Platelet Dysfunction with Eosinophilia (APDE) that was responsible for his symptoms and not the haemophilia A. Parents were counseled to avoid severe trauma and the child's symptoms resolved with fexofenadine, montelukast, diethylcarbamazine for 21days and two stat doses of albendazole.

Case 2: A 57-year-old lady was admitted with malena following commencement of hydroxychloroquine, oral prednisolone for recently diagnosed Sjogrens syndrome. Prior tests had revealed coarse speckled pattern antinuclear antibody 4+(1:100 dilution, HEp-2000 cell line, EUROIMMUN) confirmed with anti-SS-A+++ and Schirmer's test revealed <5mm wetting. Upper gastrointestinal endoscopy done at admission showed multiple gastric erosions. Investigations showed raised APTT at 55sec. FVIII activity was 24%, FIX activity was 105%, FVIII inhibitor assay was negative with normal vWF Ag level at 64(50-160). She was given 2000 IU of Haemate P but had no clinical response (one vial of Haemate P contains 1000 IU human coagulation factor VIII (FVIII) and 2400 IU human von Willebrand Factor (VWF). The malena continued for 8th admission day and then had an episode of epistaxis. ENT review did not reveal a structural cause for the epistaxis. She then had a partial response to fresh frozen plasma and cryoprecipitate. She was a known diabetic and treated for carcinoma breast 4 years ago. There was no personal or family history of bleeding disorders. A year before this admission with malena, she had her first bleeding episode with epistaxis following septoplasty at which time APTT was 40s, PT 20s. The mucosal bleeds were suggestive of acquired von Willebrand disease (aVWD), but still did not explain the poor response to Haemate P. She was therefore investigated further that showed no evidence of circulating anti-phospholipid antibodies: anti-cardiolipin IgG<0.5 GPL-U/ml, anti-cardiolipin IgM<0.5 MPL-U/ml, anti-β2GPI IgG/IgM-negative with absent lupus anticoagulant. Bone marrow showed iron deficiency anemia and reactive plasmacytosis while serum protein electrophoresis showed a small spike in early gamma region (3g/L) with IgA lambda on immune fixation. Serum free light chain levels with SFLC ratio was normal. Platelet aggregometry showed decreased response to ristocetin (1.5mg/ml) and collagen and absent response to ADP highlighting the possibility of paraprotein associated acquired platelet dysfunction. She responded to rituximab with reduction in IgA levels and had no further bleeds. She remains on bortezomib since the IgA level remains high.

Discussion

The two cases described aims to convey the message that acquired platelet dysfunction (APD) should be suspected when the nature of the bleed is out of proportion to the coagulation defect identified.[1] It is not that the two causes of acquired platelet dysfunction described is new, but that this had developed in the background of bleeding disorders in both patients is highlighted, such as in Case 1 where the bleeding did not respond to therapy directed against the disorder (FVIII infusion for hemophilia A) and in Case 2 where infusion of Haemate P (vWF rich and FVIII concentrate) did not control mucosal bleeds as is expected to be seen in acquired vWD. The syndrome of Acquired Platelet Dysfunction with Eosinophilia (APDE) was described in detail by Suvatte et al.[2] in 62cases, with the very first description by Mitrakul.[3] Since then this syndrome has been described in children in the Asian subcontinent and appears to be the commonest cause of purpura in Thai children,[4] but also recognized that APDE can affect anyone who resides or visits the tropics.[5] In a study of 168 children aged 13months to 12.6years with APDE, while parasitic infection was proven in only 56% of children eosinophilia was seen in 86%, raised IgE >100IU/ml in 83% of children and prolonged bleeding time in half of them (53%), but there was no correlation between eosinophil count, serum total IgE and the severity of bleeding symptoms.[6] Abnormal platelet adhesiveness was found in 33% of cases. Abnormal platelet aggregation induced by collagen was the most sensitive test in these patients, while Ristocetin-induced platelet aggregation was normal in all children. Decreased or absence of platelet dense granules was detected in some patients that led to the hypothesis of acquired storage pool deficiency of platelets as the cause of APDE.

The hallmarks of APDE are recurrent spontaneous bruising, eosinophilia, normal hematocrit, normal platelet counts, normal routine coagulation assays but prolonged bleeding time, abnormal platelet adhesiveness and associated parasitic infection. Platelet aggregometry with abnormal aggregation to collagen is seen in most of these patients that helps to differentiate with aspirin induced defects and vWD.[3–6] Antibodies to platelet factors are not detected. As intestinal parasitic infection is the most common cause of eosinophilia, anti-helminthic therapy is usually helpful as an adjunct treatment in the Asian subcontinent. Stool examination shown common parasites, such as ascaris, hookworm, enterobius in 50-60% of cases. The bleeding tendency in APDE is transient and usually last for 3-6months but may last longer. If bleeding is severe or patients require urgent surgery then platelet concentrate infusion is required. There is no role of FFP or cryoprecipitate in the management of this condition. No mortality related to bleeding has been observed in any of the 150+ cases described so far in the medical literature. Patients and their parents need to be reassured about the prognosis and transient nature of symptoms.

In paraprotein associated APD, nonspecific immunoglobulin adherence to the platelet surface results in platelet dysfunction.[7,8] Therefore, platelet transfusion has limited efficacy as the transfused platelets quickly become dysfunctional. Certain drugs[9,10] and procedures[11,12] that can affect platelet function need to be considered in these complicated patients (Table 1), but removal of the paraprotein is generally effective in improving platelet function and helps in correcting the bleeding diathesis. Djunic et al.[13] showed that paraproteins bind to specific platelet receptors such as the platelet vWF receptor GPIb and platelet collagen receptor GPVI (decreased CD42b and CD36 expression on flow cytometry, respectively. On addition of paraprotein to platelet-rich plasma from normal healthy donors), thereby affecting their function.[13] New generation instruments such as multiplate multiple electrode aggregrometry using whole blood impedancemetry allow multiple functional studies to be performed on platelets using agonists (such as ADP test, RISTO test, COL test among others) using the help of multiple channels on the analyzer.[14] In paraprotein associated aVWD, the laboratory reports will show a normal PT and prolonged APTT which corrects on mixing. The FVIII level may be low normal and vWF function analysis using RiCof assay clinches the diagnosis. While aspirin treatment causes abnormal platelet aggregation with ADP, collagen and arachidonic acid, in von Willebrand disease the platelet agglutination with ristocetin is absent. When there is life threatening bleeds or when the paraprotein cannot be completely eliminated, intravenous gamma globulin infusions can be tried as this prolongs vWF survival and increases vWF levels (for about 3 weeks) but is recommended to be tried in combination of VWF-containing factor concentrate and depending on the severity of bleeding and baseline vWF levels. Intravenous gamma globulin will possibly work best when the paraprotein is IgG and in the setting of IgG auto antibodies. However, it is important to realize that these treatment options are short-lived, therefore proper patient counseling is required in the management of this challenging disorder.

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Table 1 Causes and abnormalities identified in acquired platelet dysfunction

Cause	Description of cause	Abnormalities identified
Drugs	Aspirin, COX-1 inhibitors (Ibuprofen, Diclofenac), ADP receptor antagonists or thienopyridines (clopidogrel, prasugrel), GPIIb/IIIa inhibitors (Abciximab, Tirofiban, Eptifibatide), Dipyridamole, Cilostazol, Beta lactam antibiotics, Selective Serotonin Reuptake Inhibitors, Nitrates, Alcohol, Phenothiazines, Prednisolone (long-term)	Aspirin, COX-1 inhibitors: inhibit formation of thromboxane A2 SSRIs reduce platelet serotonin and aggregation on functional tests (effect enhanced with Aspirin/ NSAIDs) Nitrates: inhibit platelet aggregation by increasing cGMP
Procedure-related (temporary)	Cardio-pulmonary bypass, extracorporeal membrane oxygenation (ECMO), splenectomy, left ventricular assist devices	Cardiopulmonary bypass: P-selectin expression decreases affecting platelet activation11 ECMO: platelet aggregation defective with ADP12
Hematological and hematological malignancies	Acquired platelet dysfunction with eosinophilia (APDE)	APDE: Abnormal platelet storage pool with no aggregation with ADP, collagen, ristocetin
	Myeloproliferative disorders	Myeloproliferative disorders: loss of high molecular weight vWF multimers lead to bleeding
	Myelodysplasia	Myelodysplasia: abnormal thrombopoiesis lead to dysfunctional platelets
	Paraproteinemia-induced APD	Paraprotein-induced APD: Nonspecific immunoglobulin adherence to the platelet surface7; paraprotein binding onto platelet receptors13
	Amyloidosis	Amyloidosis: acquired deficiencies of vitamin K–dependent factors, particularly factor X, through adsorption to the amyloid fibrils7
Renal disorder	Uremia	Impaired platelet-vessel wall interaction
Autoimmune	Immune thrombocytopenia with platelet dysfunction	Antibodies against gpIIb/IIIa or gpIb-IX receptor

Conclusion

Identification of acquired platelet dysfunction and isolating the cause with knowledge of how that may affect bleeding risk are important in optimizing patient care with existing complex autoimmune and hematological disorders. The presence of slightly low platelet count or abnormal coagulation does not exclude APD from the diagnostic conundrum particularly as other bleeding or coagulation disorders can coexist in the same patient as it occurred on both our patients.

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Conflict of interest

The author declares no conflict of interest.

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