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 which only partially respond to Factor VIII concentrate and cryoprecipitate. Tests revealed significant peripheral eosinophilia (AEC 3200/mm3), prolonged bleeding time >15 seconds, 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 melena 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 4 years 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

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...
Acquired Platelet Dysfunction as a Cause of Bleeding Diathesis: Two Case Studies

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 here are rare, but that 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) that was responsible for his symptoms and not the haemophilia A. Patients and their parents need to be reassured about the prognosis and transient nature of symptoms.

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%, FDX 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 (aWBD), 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-F2GPI 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.

(Table 1), but removal of the paraprotein is generally effective in improving platelet function and helps in correcting the bleeding diathesis. Djunic I 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 aggregometry using whole blood impedanceometry 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.

Table 1: Causes and abnormalities identified in acquired platelet dysfunction.

<table>
<thead>
<tr>
<th>Cause</th>
<th>Description of cause</th>
<th>Abnormalities identified</th>
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<tbody>
<tr>
<td>Drugs</td>
<td>Aspirin, COX-1 inhibitors (Ibuprofen, Diclofenac), ADP receptor antagonists or thienopyridines (clopidogrel, prasugrel), GPIb/IIIa inhibitors (Abciximab, Tiropiban, Eptifibatide), Dipyridamole, Cilostazol, Beta lactam antibiotics, Selective Serotonin Reuptake Inhibitors, Nitrates, Alcohol, Phenothiazines, Prednisolone (long-term)</td>
<td>Aspirin, COX-1 inhibitors: inhibit formation of thromboxane A2</td>
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<td>Procedure-related (temporary)</td>
<td>Nitrates: inhibit platelet aggregation by increasing cGMP</td>
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<td></td>
<td>Acquired platelet dysfunction with eosinophilia (APDE)</td>
<td>Cardiopulmonary bypass: P-selectin expression decreases affecting platelet activation</td>
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<tr>
<td>Hematological and hematological malignancies</td>
<td>Myeloproliferative disorders</td>
<td>Myeloproliferative disorders: loss of high molecular weight vWF multimers lead to bleeding</td>
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<tr>
<td></td>
<td>Myelodysplasia</td>
<td>Myelodysplasia: abnormal thrombopoiesis lead to dysfunctional platelets</td>
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<td>Paraproteinemia-induced APD</td>
<td>Paraprotein-induced APD: Nonspecific immunoglobulin adherence to the platelet surface; paraprotein binding onto platelet receptors</td>
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<td>Amyloidosis</td>
<td>Amyloidosis: acquired deficiencies of vitamin K-dependent factors, particularly factor X, through adsorption to the amyloid fibrils</td>
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<td>Renal disorder</td>
<td>Uremia</td>
<td>Impaired platelet-vessel wall interaction</td>
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<td>Autoimmune</td>
<td>Immune thrombocytopenia with platelet dysfunction</td>
<td>Antibodies against gpIIb/IIa or gpIIb-IX receptor</td>
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</table>

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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References