HEMOSTASIS AND THROMBOSIS

Review

Autoimmune disorders of platelet function: systematic review of cases of acquired Glanzmann thrombasthenia and acquired delta storage pool disease

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Acquired platelet function disorders (PFD) are rare bleeding diseases that should be suspected in all patients with unexplained mucocutaneous bleedings of recent onset, with no previous history of haemorrhages, and with normal coagulation test and platelet count. Drug-induced platelet function bleeding disorders are the most frequent PFDs and can easily be identified on the basis of recent administration of platelet-inhibiting drugs. Apart from these, the most challenging acquired PFDs are those caused by autoimmune mechanisms. In fact, demonstration of autoantibodies inhibiting platelet function may be difficult in most non-specialised centres. Among autoimmune PFDs (aPFDs), acquired Glanzmann thrombasthenia (aGT), which is caused by autoantibodies that bind to platelet αIIbβ3 integrin, inhibiting its function, is the most frequent. aGT can be associated with underlying haematological malignancies or autoimmune diseases but can also be idiopathic. More rarely, other immune-mediated PFDs can occur, such as acquired delta storage pool disease (aδSPD). Treatment of aPFDs must rely on the control of acute and chronic bleedings, treatment of the underlying disease in secondary forms, and immunosuppressive treatment for autoantibody reduction or eradication. aPFDs may completely resolve upon treatment of any underlying disease that may be present. In primary aPFDs, and in the majority of secondary forms, treatment relies on immunosuppressive therapies.

Here we present a systematic review of previously described immune-mediated aGT and aδSPD cases. Clinical and laboratory characteristics, treatments for the control of bleedings and for the eradication of autoantibodies, and responses to treatments are also discussed. Although no guidelines are available for the management of these very rare conditions, presentation of all cases reported so far can help clinicians in the diagnosis and treatment of these life-threatening diseases.

Keywords: *acquired platelet function disorders, Glanzmann thrombasthenia, delta storage pool disease, immune-mediated platelet disorders, rituximab.*

Arrived: 11 April 2021
Revision accepted: 7 June 2021
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INTRODUCTION

Acquired platelet function disorders (PFD) encompass a group of heterogeneous conditions characterised by platelet function defects causing moderate-to-severe bleedings. Acquired

Blood Transfus 2022; 20: 420-432 DOI 10.2450/2021.0119-21

PFD are rare bleeding disorders that should be suspected in all patients with unexplained mucocutaneous bleedings of recent onset, with no previous history of haemorrhages, and with normal coagulation test and platelet count[1]. The most frequent acquired PFD are those which are drug induced; these can easily be identified on the basis of recent administration of platelet-inhibiting drugs. Occasionally, platelet dysfunction can be related to medications and health supplements that affect platelet function non-specifically[1]. Acquired PFDs caused by autoimmune mechanisms can also occur. Autoantibodies against various platelet receptors may block them and cause platelet dysfunction. This condition can be suspected in patients who may have also mild/moderate thrombocytopenia but their bleeding is out of proportion to platelet count. Autoimmune PFD (aPFD) are commonly associated with autoimmune or lymphoproliferative diseases; however, several cases of primary aPFDs cases have been reported[2,3]. Bleeding symptoms might precede or occur simultaneously to primary disease; in both cases, diagnosis can be missed because of the rarity of aPFD. aPFDs must be suspected in patients with: 1) unexplained mucocutaneous bleeding occurrence and no prior bleeding history; 2) absent antiplatelet drug intake; 3) normal coagulation results; and 4) normal or moderately reduced platelet count.

A rapid and accurate diagnosis, as well as appropriate therapy, are both crucial to stop bleedings. The following laboratory tests can be used to identify aPFDs: 1) platelet function testing to identify any platelet defects; 2) mixing tests to evaluate antiplatelet activity in patient's plasma/serum, and 3) positive antiplatelet antibody testing. Therapy of these bleeding disorders includes haemostatic therapies for the control or treatment of bleedings, treatment of primary disease, if present, and immunosuppressive treatment for the eradication of antibodies. Response to treatments is variable and unpredictable.

Among aPFDs, acquired Glanzmann thrombasthenia (aGT) is the most frequently diagnosed platelet dysfunction. More rarely, other immune-mediated PFDs can occur with characteristics of acquired delta storage pool disease (aδSPD). We performed an updated systematic literature review on immune-mediated platelet function disorders. We discuss here the clinical characteristics, treatment modalities, and outcomes of bleedings in patients with autoimmune PFDs reported so far.

LITERATURE REVIEW

We carried out a search in the electronic databases PubMed, Embase, Scopus and Google Scholar. We used "acquired Glanzmann Thromboasthenia" and "acquired delta storage pool disease" to retrieve all relevant articles published in English. All clinical studies and case reports reporting aPFDs sustained by demonstrated or suspected autoimmune mechanisms published up to April 2020 were included. Studies reporting acquired GT or δSPD cases associated with myeloproliferative diseases were excluded because the mechanism causing the platelet dysfunction was the abnormal proliferation of haematopoietic cells. In some acquired δSPD cases, the presence of concomitant sepsis or disseminated intravascular coagulation suggested a consumption mechanism; these cases were excluded from this review. When studies or case series included aPFDs based on different mechanisms, only those cases of aGT and aδSPD where the presence of antiplatelet antibodies and/or bleeding response to immunosuppressive therapy suggested immune-mediated mechanisms, were considered; these are reported in **Table I**. In **Table I**, few studies are reported as "aPFDs of uncertain/mixed diagnosis" as they appeared among papers selected by the query above. However, those studies reported cases of immune-mediated aPFDs not better identified[4] or with mixed diagnosis[5,6]. We included in this category also a few studies describing aPFDs in lymphoproliferative disorders or rheumatological disorders where an autoimmune mechanism for the bleedings could not be confirmed by the presence of antiplatelet antibodies or the response to immunosuppressive therapy, but was considered likely because of the underlying disorder.

Authors EDC, MB, AFe, and MAA screened titles and abstracts of all articles obtained through the search strategy.

CLINICAL PHENOTYPE AND LABORATORY CHARACTERISTICS

Symptoms

Physicians should suspect aPFDs in case of spontaneous mucocutaneous bleeding in patients without previous bleeding history and normal coagulation tests.

Table I - *Summary of reported cases of acquired Glanzmann's thrombasthenia, acquired delta-storage pool disease and immune-based platelet function disorders*

aGT	Reference	Cases (n)	Age (yrs)	Sex	Associated disease	Bleeding/platelet count	Test to demonstrate anti-platelet antibodies	Treatment of PFD and of bleedings	Response/progress	Long term outcome
1	Greaves *et al.* (1983)[50]	1	64	F	ITP, splenectomy	GIB with anaemia, bruising and epistaxis/normal after splenectomy	Platelet autoantibody/ positive mixing test	n.r.	Recurrency of bleedings despite normal platelet count after splenectomy and ITP remission	Persistence of bleedings for 9 yrs
2	Niessner *et al.* (1986)[31]	1	42	F	None	Fluctuating spontaneous ecchymosis and haematomas, episodes of epistaxis and menorrhagia over 7 yrs/normal	IgG1 antibody to GP αIIb-β3	IvIg and PDN	No response to treatment	Spontaneous remission after a 7-year period
3	Di Minno *et al.* (1986)[30]	1	62	M	MM	Easy bruising, diffuse petechiae of the arms and legs/moderate reduction	IgG1 kappa monoclonal paraprotein anti GP IIIa	None	Massive GIB	Died from massive GIB 8 weeks after presentation
4	Balduini *et al.* (1987)[37]	1	33	F	HL, chronic ITP, splenectomy	Petechiae, spontaneous ecchymoses, menorrhagia, epistaxis, gum bleeding/ normal after splenectomy	Autoantibodies to GP αIIb-β3	PDN	Good response to steroids	Persistent remission 3 yrs after treatment
5	Kubota *et al.* (1989)[40]	1	38	F	Previous NHL of the stomach, later relapse at cervical glands	Bleeding and severe thrombocytopenia at the relapse of NHL/low	IgG anti-GP αIIb-β3	Radiation therapy to cervical lymph nodes	Resolution of bleedings and thrombocytopenia after radiotherapy	Persistent remission of bleedings after radiotherapy
6	Meyer *et al.* (1991)[42]	1	62	F	Castleman disease and paraprotein 2 yrs before bleedings, ITP, splenectomy	GIB, epistaxis, anaemia persistent after splenectomy/normal after splenectomy	Autoantibodies to GP αIIb-β3	n.r.	Severe bleedings despite normalisation of platelet count	Persistent bleeding tendency
7	Bertolino *et al.* (1991)[41]	1	19	M	NHL 15 months after onset of bleeding symptoms and ITP	Mucocutaneous bleeding symptoms/moderate reduction	n.r.	PDN, splenectomy	No response of bleedings to PDN and splenectomy	Remission of bleedings after CHT for NHL
8	Balduini *et al.* (1992)[34]	1	27	F	ITP	Mucocutaneous bleeding symptoms/normal after PDN	Autoantibodies to GP IIIa	PDN, PDN + AZA	No response to PDN, response to PDN+AZA	Remission of bleedings after PDN + AZA
9	Mc Millan *et al.* (1996)[28]	1	60	M	None	Bruising, epistaxis, melena/ normal	IgG4 autoantibody to GPαIIb-β3	PDN	Normalisation of bleeding symptoms and platelet function after PDN	Persistent remission after PDN
10	Malik *et al.* (1998)[38]	1	53	F	HL 14 months before bleedings onset	Ecchymoses, rectal bleeding, prolonged bleeding time 14 months after successful treatment of HL/mild reduction	Putative IgM autoantibody to GPαIIb-β3	Platelet transfusions	Resolution of bleeding diathesis after left hemicolectomy, removal of atypical lymphoid hyperplasia	Persistent CR after hemicolectomy
11	Macchi *et al.* (1998)[16]	1	63	F	Recurrent ITP, splenectomy	Epistaxis and gum bleeding/recurrence of severe thrombocytopenia. Severity of bleeding unrelated to platelet count during ITP recurrency	Autoantibodies to GP αIIb-β3	PDN, splenectomy, IvIg	No response to steroids and splenectomy, transitory responses to periodic IvIg	n.r.
12	Fuse *et al.* (1998)[33]	1	33	F	Evans syndrome, splenectomy	Extensive bruising on the trunk and limbs, menorrhagia, cutaneous petechiae, ovarian bleeding/normal after splenectomy	IgG autoantibody anti IIb	Prednisolone + IvIg, prednisolone + AZA, platelet transfusions	Severe bleeding despite normalisation of platelet count	Died of cerebral haemorrhage 6 yrs after splenectomy
13	Granel *et al.* (1998)[43]	1	65	F	ITP and splenectomy, MGUS, LAC	Extensive ecchymosis 5 yrs after splenectomy/normal after splenectomy	Autoantibodies to GP αIIb-β3	PDN	Resolution of bleedings and of platelet dysfunction after PDN	Relapse of bleedings after 8 yrs
14	Thomas *et al.* (2002)[36]	1	60	F	None	Easy bruising, life-threatening GIB/normal	Autoantibodies to GP αIIb-β3	Prednisolone+AZA, plasma exchange	Resolution of bleeding diathesis, after 12 plasma exchanges, HIT developed after one week of femoral line insertion and intraluminal heparin	Persistent remission after 18 months form plasma exchange, gradual discontinuation of immunosuppression over 1 year
15	Rawal *et al.* (2003)[7]	1	20	F	Heart transplant, tacrolimus + AZA immunosuppressive therapy, recurrent AIHA and cytopenia	Mucosal and GI bleedings 5 yrs after transplant/ thrombocytopenia	Autoantibodies to GP αIIb-β3 in plasma and platelet eluate	PDN and IvIg	Three relapses of bleedings and thrombocytopenia	Responses of each relapse to PDN and IvIg
16	Dinakaran S. *et al.* (2003)[11]	1	79	F	None	Intraocular bleeds during eye surgery, recurrent GI bleedings, epistaxis, vaginal bleeding/normal	n.r.	None	Cauterisation and suture of the conjunctiva were unsuccessful	Local haemostatic measures (oxidised regenerated cellulose) stopped bleeding
17	Tholouli E. *et al.* (2004)[25]	1	52	M	Renal transplant, cyclosporin A, AIHA and NHL 8 months after bleeding onset	Spontaneous bruising, mucocutaneous bleedings, subconjunctival haemorrhage/normal	Antiplatelets antibodies	CTX and prednisolone, CHT	Remission of bleedings after PDN+ CTX	CR from lymphoma, AIHA and aPFD after cht
18	Tholouli E. *et al.* (2004)[25]	1	88	M	None	Easy bruising, severe epistaxis and prolonged bleeding after surgery/ normal	Autoantibodies to GP αIIb-β3	None	n.r.	Died two yrs later with normal platelet function and count and extensive DVT

δSPD: acquired Delta storage pool disease; ADP/ATP: adenosin diphosphate/adenosine triphosphate; aGT: acquired Glanzmann thrombasthenia; AIHA: autoimmune haemolytic anaemia; ALL: acute lymphoblastic leukemia; aPFD: autoimmune platelet function disorder; aVWF: acquired von Willebrand disease; AZA: azathioprine; CHT: chemoterapy; CHT: chemotherapy; CLL: chronic lymphocytic leukemia; CR: complete remission; CTX: cyclophosphamide; DDAVP: desmopressin; DEXA: dexamethasone; DVT: deep vein thrombosis; GIB: gastrointestinal bleedings; HCL: hairy cell leukemia; HL: Hodgkin lymphoma; ICH: intracranial haemorrhage; ITP: immune thrombocytopenia; IvIg: intravenous immunoglobulin; LAC: lupus anticoagulant; LTA: light transmission aggregometry; MGUS: monoclonal gammopathy of unknown significance; MM: multiple myeloma; MTX: methotrexate; NHL: non-Hodgkin lymphoma; PAR1-AP: protease activated receptor 1- activating peptide; PDN: prednisone; RA: rheumatoid arthritis; rFVIIa: recombinant factor VII activated; RTX: rituximab; SLE: systemic lupus erythaematosus; TA: tranexamic acid; WD: Waldenstrom disease; yrs: years; n.r.: not reported.

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Table I - *Summary of reported cases of acquired Glanzmann's thrombasthenia, acquired delta-storage pool disease and immune-based platelet function disorders* *(continued from previous page)*

aGT	Reference	Cases (n)	Age (yrs)	Sex	Associated disease	Bleeding/platelet count	Test to demonstrate anti-platelet antibodies	Treatment of PFD and of bleedings	Response/progress	Long term outcome
19	Andrè *et al.* (2005)[12]	1	14	F	ALL	Severe cutaneous haemorrhagic syndrome, epidural haematoma after intrathecal injection, severe bleeding during surgical decompression of haematoma, haematuria/ severe reduction	Autoantibodies to GP αIIb-β3 on platelets	CHT, prednisolone + multiple platelet and plasma transfusions, rFVIIa for biopsy of cerebral lesions	Refractoriness of bleedings to treatments and platelet transfusions. Bleeding remission at ALL remission.	Died with relapse pf ALL and persistent bleeding
20	Morath *et al.* (2005)[23]	1	46	F	Renal transplant, tacrolimus therapy, hepatitis C	Easy bruising, epistaxis, mucocutaneous bleeding, intraperitoneal bleeding, ICH/mild reduction	MAIPA autoantibodies to GP αIIb-β3	Plasmapheresis,IvIg, PDN and CTX, rFVIIa	Temporary response to IvIg. Stop of bleeding after rFVIIa.	Died from severe intracerebral haemorrhage 12 yrs after transplantation and 7 yrs after tacrolimus therapy
21	Bloor A.J.C. *et al.* (2006)[8]	1	4	M	None	Spontaneous bruising/ normal	MAIPA autoantibodies to GP αIIb-β3	Prednisolone	Normalisation of platelet function	Persistent remission after two yrs of follow up
22	Yee NS *et al.* (2006)[35]	1	43	F	AIHA, splenectomy, SLE, ITP	Bruising, epistaxis, gum bleedings, menorrhagia after splenectomy/severe thrombocytopenia	MAIPA IgG autoantibody to GP αIIb-β3	Steroids, IvIg, Prosorba column pheresis, low-dose MTX for SLE	Persistence of bleedings despite platelet count normalisation after corticosteroids and apheresis. Remission of bleedings after continuous PDN and MTX for lupus pneumonitis	Complete and persistent remission after 28 months of low-dose MTX
23	Tubman *et al.* (2007)[9]	1	11	F	Heart transplant 6 yrs before bleedings onset, tacrolimus, cyclosporine and AZA chronic treatment	Epistaxis, bruising, petechiae, acute GIB/mild thrombocytopenia	Serum autoantibodies to GP αIIb-β3	Platelet transfusions, IvIg, high-dose PDN, RTX	Lack response to high-dose of PDN and IvIg. Remission of bleeding symptoms after RTX	Persistent remission of bleedings and anti-αIIb-β3 antibodies after 10 months of RTX, died 2 months later from a severe allograft vasculopathy
24	Giannini S. *et al.* (2008)[17]	1	27	M	NHL 4 yrs after occurrence of bleedings	Mucocutaneous bleedings, ecchymosis, haematemesis/normal	Positive indirect MAIPA, anti-GPIIb IgG3 antibody	CHT for NHL; steroids and CTX	No significant improvement of the bleeding symptoms despite NHL remission. No response to steroids and CTX	n.r.
25	Porcelijn L. *et al.* (2008)[29]	1	59	F	Diclophenac use for nephrolithiasis	Haematomas/normal	Positive direct and indirect MAIPA, IgG2 antibodies to GP αIIb-β3	None	Spontaneous resolution of bleedings after 2 months of diclofenac stop	No recurrency
26	Porcelijn L. *et al.* (2008)[29]	1	77	F	None, ITP 5 months after aGT	Epistaxis, haematomas, melena/normal at the onset, 5 months later severe reduction	Positive direct and indirect MAIPA, IgG4 platelet autoantibody, later IgG1 platelet autoantibody	Platelet transfusion and DDAVP for melena, splenectomy for ITP	Resolution of melena after plt trasnfusions and DDAVP, resolution of bleedings and thrombocytopenia after splenectomy	Remission of bleedings and thrombocytopenia 5 months after splenectomy
27	Porcelijn L. *et al.* (2008)[29]	1	24	F	HL 7 months before bleedings	Petechiae and epistaxis/ high	Positive direct and indirect MAIPA to αIIb-β3, IgG2 platelet autoantibody	High-dose corticosteroids + aza	Resolution of bleeding symptoms	Resolution of bleeding symptoms after immunosuppressive treatment
28	Porcelijn L. *et al.* (2008)[29]	1	85	M	NHL 2 yrs earlier, NHL relapse together with bleeding symptoms	Epistaxis and haematuria/ normal	Positive direct and indirect MAIPA to αIIb-β3, IgG2 platelet autoantibody	Prednisolone and TA	No response of bleeding symptoms to PDN and TA	Bleeding stopped after local radiotherapy on NHL relapsed mass
29	Porcelijn L. *et al.* (2008)[29]	1	67	F	Chronic ITP, splenectomy	Severe haemorrhagic diathesis 2 months after splenectomy/normal after splenectomy	Positive direct and indirect MAIPA to αIIb-β3, IgG1 platelet autoantibody	PDN	Resolution of bleeding symptoms	Chronic PDN therapy with no other bleedings
30	Porcelijn L. *et al.* (2008)[29]	1	51	F	ITP, splenectomy	Bleedings, not specified/ mild reduction	Positive direct and indirect MAIPA to αIIb-β3, IgG1 platelet autoantibody	IvIg and RTX, antibiotics for sepsis	Temporary improvement of bleedings and thrombocytopenia	Relapse of thrombocytopenia and of bleedings after 8 months
31	Kannan M. *et al.* (2009)[18]	1	51	M	HCL	Epistaxis, gum bleedings; occasional GIB/normal	n.r	n.r.	n.r.	n.r.
32	Sohl *et al.* (2011)[19]	1	52	F	None	Increased bruising after minimal trauma, severe epistaxis/normal	Positive direct and indirect MAIPA to αIIb-β3	Dexamethasone, platelet transfusions, RTX	Transitory resolution of bleedings and platelet function tests after dexamethasone, stable complete response after RTX	Temporary response to dexa, persistent remission 6 months after RTX.
33	Blickstein D. *et al.* (2014)[45]	1	75	F	SLE and antiphospholipid syndrome at 55 yrs, ITP at 60 yrs, splenectomy	Mucocutaneous and GIB 15 yrs after splenectomy/ normal	Patient's serum inhibited GpIIb-IIIa antibodies binding to normal platelets	Steroids, CTX, AZA, IvIg, RTX	Lack of response to steroids, AZA, CTX, IvIg. Normalisation of platelet aggregation and of bleeding manifestation after RTX	Relapse of bleedings 8 months after RTX, complete response to a second course of RTX. Complete remission six yrs after second cycle of RTX
34	Raman V. *et al.* (2014)[15]	1	44	M	HL (Stage IVB)	Haematemesis, melena, epistaxis/normal	Direct antiplatelet IgG to αIIb-β3	ABVD	Resolution of bleeding symptoms after 1 week of CHT	Remission of bleedings and normalisation of platelet aggregation after CHT

δSPD: acquired Delta storage pool disease; ADP/ATP: adenosin diphosphate/adenosine triphosphate; aGT: acquired Glanzmann thrombasthenia; AIHA: autoimmune haemolytic anaemia; ALL: acute lymphoblastic leukemia; aPFD: autoimmune platelet function disorder; aVWF: acquired von Willebrand disease; AZA: azathioprine; CHT: chemoterapy; CHT: chemotherapy; CLL: chronic lymphocytic leukemia; CR: complete remission; CTX: cyclophosphamide; DDAVP: desmopressin; DEXA: dexamethasone; DVT: deep vein thrombosis; GIB: gastrointestinal bleedings; HCL: hairy cell leukemia; HL: Hodgkin lymphoma; ICH: intracranial haemorrhage; ITP: immune thrombocytopenia; IvIg: intravenous immunoglobulin; LAC: lupus anticoagulant; LTA: light transmission aggregometry; MGUS: monoclonal gammopathy of unknown significance; MM: multiple myeloma; MTX: methotrexate; NHL: non-Hodgkin lymphoma; PAR1-AP: protease activated receptor 1- activating peptide; PDN: prednisone; RA: rheumatoid arthritis; rFVIIa: recombinant factor VII activated; RTX: rituximab; SLE: systemic lupus erythaematosus; TA: tranexamic acid; WD: Waldenstrom disease; yrs: years; n.r.: not reported.

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Table I - *Summary of reported cases of acquired Glanzmann's thrombasthenia, acquired delta-storage pool disease and immune-based platelet function disorders* *(continued from previous page)*

aGT	Reference	Cases (n)	Age (yrs)	Sex	Associated disease	Bleeding/platelet count	Test to demonstrate anti-platelet antibodies	Treatment of PFD and of bleedings	Response/progress	Long term outcome
35	Tuffigo M. *et al.* (2015)[20], Pillois X *et al.* (2019)[21]	1	50	M	Chronic ITP and Crohn's disease, splenectomy for ITP (Tuffigo), IgM MGUS development (Pillois)	Severe GIB/mild reduction	IgM monoclonal autoantibody to αIIb-β3 causing complex internalisation	AZA, platelet transfusions, artery embolisation for active GIB, rFVIIa + TA for emergency surgery (Tuffigo); RTX, IvIg (Pillois)	No response to azathioprine; no response to platelets, no bleedings during two surgeries after rFVIIa and tranexamic acid (Tuffigo); no response to rituximab, response to IVIG (Pillois)	Diagnosed IgM MGUS, development of macrothrombocytopenia with reduced αIIb-β3expression and constitutive integrin activation, no response to RTX and AZA, partial and reversible response to IvIg (Pillois)
36	Mayne E.S. *et al.* 2018[44]	1	81	F	MGUS, aVWD	Melena, haematemesis and lethargy, duodenal angiodysplasia/normal	n.r.	Blood transfusions, anti-fibrinolytic agents, IvIg	Response of bleedings to IvIg	Clinical stabilisation, partial improvement of platelet aggregation
37	Akuta K. *et al.* (2018)[2]	1	72	M	Chronic ITP, chronic thyroiditis, splenectomy for ITP 22 yrs before bleedings, cyclic thrombocytopenia after splenectomy	GIB and epistaxis/moderate reduction	Serum and platelet eluate IgG1 and IgG2 anti αIIb-β3 causing complex internalisation	n.r.	Spontaneous improvement of bleedings associated with reduction of anti αIIb-β3 titres and increase of αIIb-β3 expression on platelet surface	n.r.
38	Rostami *et al.* (2018)[39]	1	28	F	HL, bleeding symptoms occurred at the second relapse 8 yrs later	Ecchymosis on the legs, menorrhagia/normal	n.r	CHT for HL	Remission of bleedings after CHT	CR after CHT
39	Alberelli M.A. *et al.* (2019)[10]	1	42	M	None	Bruising, severe spontaneous epistaxis, gum bleedings, post-trauma haemarthrosis and extensive haematomas/ moderate reduction	Indirect MAIPA autoantibodies to αIIb-β3, Inhibitory activity in patient's plasma	PDN+CTX, RTX	Temporary response to PDN and CTX, persistent response to RTX	CR of bleedings and platelet dysfunction during a follow up of 4 yrs from RTX
40	Alberelli M.A. *et al.* (2019)[10]	1	68	F	Cutaneous B-cell lymphoma, ITP, bleeding symptom at the relapse of LNH after 6 yrs	Severe mucocutaneous symptoms/normal	Autoantibodies to αIIb-β3, Inhibitory activity in patient's plasma	Steroids, RTX, RTX +CTX+PDN	Resolution of bleedings after RTX, relapse of bleedings 8 months after 1st cycle of RTX	Resolution of bleeding symptoms and of platelet function after RTX + CRP treatment
41	Compton F. *et al.* (2020)[14]	1	64	F	None	Significant bleeding during surgical repair of an enterocutaneous fistula and multiple subcutaneous haematomas and petechiae, bruising tendency for 2 yrs before surgery/mild reduction	IgG autoantibodies to platelet αIIb-β3 and GPIa/IIa, mixing studies with impedance whole blood aggregation	rFVIIa recommended for surgery, surgery not performed	nr	nr
42	Zheng SS *et al.* (2020)[32]	1	55	M	ITP, splenectomy	Recurrent epistaxis and prolonged bleeding from minor injuries despite normal platelet count/ normal after splenectomy, ITP recurrency	IgG1-4 anti-platelet antibodies, indirect MAIPA positive for anti αIIb-β3, mixing platelet aggergeometry	Steroids, rituximab, plasmapheresis, IvIg	Partial response to rituximab, response to plasmapheresis, response to IvIg of ITP relapse	Persistence of self-limiitng epistaxis

aδSPD	Reference	Cases	Age (yrs)	Sex	Associated disease	Bleeding/platelet count	Serum plasma Ab	Treatment of PFD and of bleedings		Long-term outcome
1	Zahavi J. and Marder V.J. (1974)[26]	1	33	M	Nephritis, polyarthralgia, chondritis, recurrent thrombophlebitis, Raynoud's phenomena	Prolonged bleeding time/ moderate reduction	Antiplatelets antibodies	Steroids	Clinical response with normalisation of bleeding time and platelet count	Normalisation of platelet aggregation and disappearance of antiplatelet antibodies 3 months after corticosteroid therapy
2	Weiss HJ *et al.* (1980)[13]	1	35	F	SLE, thrombocytopenia	Prolonged bleeding time/ mild reduction	Platelet associated IgG	PDN for SLE	n.r.	n.r.
3	Weiss HJ *et al.* (1980)[13]	1	59	F	SLE	Multiple spontaneous ecchymoses/normal	Platelet associated IgG	PDN for SLE	n.r.	n.r.
4	Weiss HJ *et al.* (1980)[13]	1	65	M	Symptoms suggestive for connective tissue disorders with specific test negative	Easy bruising, bleeding after superficial cuts/mild reduction	Platelet associated IgG	None	n.r.	Development of acute myelomonocytic leukemia 6 yrs after bleedings occurrence
5	Weiss HJ *et al.* (1980)[13]	1	70	F	Chronic ITP started at the age of 38 yrs	Easy bruising, excessive bleeding after superficial cuts and tooth extraction/ moderate reduction	Platelet associated IgG	Cycles of PDN for ITP since the age of 38, discontinued for osteoporosis	n.r.	n.r.
6	Weiss HJ *et al.* (1980)[13]	1	26	F	None	Easy bruising, vaginal bleedings and epistaxis, excessive bleeding after tonsillectomy and tooth extraction/normal	Platelet associated IgG	None	n.r.	n.r.
7	Lewandowski K *et al.* (1991) Pol Arch Med[46]	1	64	F	RA	Generalised haemorrhagic diathesis/moderate reduction	n.r.	n.r.	n.r.	n.r.

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aδSPD	Reference	Cases	Age (yrs)	Sex	Associated disease	Bleeding/platelet count	Serum plasma Ab	Treatment of PFD and of bleedings		Long-term outcome
8	Carr M.E. *et al.* (1997)[27]	1	51	M	CLL	No bleeding, prolonged bleeding time/moderate to severe reduction	n.r.	None	n.r.	n.r.
9	Selle F. *et al.* (2017)[3]	1 (#9)	94	M	Waldenstrom	Leg haematoma/n.r.	n.r.	None	n.r.	n.r.
10	Selle *et al.* (2017)[3]	1 (#12)	82	F	Chronic ITP	Bruising, purpura, oral haemorrhagic bullae/ reduction	n.r.	Red blood transfusion after appendicectomy	n.r.	n.r.
11	Alberelli M.A. *et al.* (2019)[10]	1 (#2)	65	M	CLL	Subdural haemorrhages/ moderate reduction	Not done	Bendamustine, RTX	Recurrent ICH after bendamustine therapy. No other haemorrhages or bleedings during RTX	Progressive improvement of platelets function during RTX and normalisation at the end of therapy. No other bleedings and no other platelet defects during 2 yrs of observation
aδSPD or aGT	Cortelazzo S. *et al.* (1984)[4]	1	58	F	ITP, splenectomy	Ecchymoses, haematoma, epistaxis, bleeding gums after splenectomy/ fluctuations of platelet count after splenectomy	Platelet associated IgG	PDN	Response of bleedings and of platelet aggregation after PDN	Persistent partial normalisation of platelet aggregation one month after stop PDN
4 acquired PFDs	Naresh K.N. *et al.* (1992)[5]	4	n.r.	n.r.	4 CLL and CLL-related disorders	Various bleeding in 2 out of 4 patients/reduced in 2 out of 4 patients		none	n.r.	n.r.
1 acquired defective response to collagen	Beer JH *et al.* (1993)[42]	1	24	F	None	Gum and skin bleeding, easy bruising, and heavy menses/moderate reduction	Autoantibodies to GP αIIb-β3, Ia/IIa, GP IV	Steroids	Moderate improvement of platelet count and platelet function, no reduction of the bleedings	After 1 yr, the clinical bleeding symptoms persisted and the antibody titres were again high
Various acquired platelet function disorders	Sharma P *et al.* (2011)[6]	109	from 2 to 78	n.r.	34 idiopathic, 1 CLL, 2 WD, 4 MM, 1 MGUS, 1 SLE	82.6% with heterogeneous range of bleedings (71.1% WHO grade 1/2- 28.9% WHO grade 3/4). 13.8% non-bleeding patients/n.r.	n.r.	Treatment of underlying disease, platelet transfusion in severe bleeding	Resolution according to underlying disease	n.r.
Delta storage pool deficiency	Rosove MH *et al.* (1980)[47]	1	65	F	HCL	Easy bruising, petechiae, epistaxis, excessive bleeding during dental extraction/mild reduction	No platelet-associated IgG	Splenectomy (during surgery platelets transfusion)	Resolution of bleedings after splenectomy	Resolution
aδSPD	Nieuwenhuis	55 total aδSPD	2 CLL, 1 HL, 1 WD, 7 SLE	n.r.			n.r.	n.r.		n.r.

aδSPD: acquired Delta storage pool disease; ADP/ATP: adenosin diphosphate/adenosine triphosphate; aGT: acquired Glanzmann thrombasthenia; AIHA: autoimmune haemolytic anaemia; ALL: acute lymphoblastic leukemia; aPFD: autoimmune platelet function disorder; aVWF: acquired von Willebrand disease; AZA: azathioprine; CHT: chemoterapy; CHT: chemotherapy; CLL: chronic lymphocytic leukemia; CR: complete remission; CTX: cyclophosphamide; DDAVP: desmopressin; DEXA: dexamethasone; DVT: deep vein thrombosis; GIB: gastrointestinal bleedings; HCL: hairy cell leukemia; HL: Hodgkin lymphoma; ICH: intracranial haemorrhage; ITP: immune thrombocytopenia; IvIg: intravenous immunoglobulin; LAC: lupus anticoagulant; LTA: light transmission aggregometry; MGUS: monoclonal gammopathy of unknown significance; MM: multiple myeloma; MTX: methotrexate; NHL: non-Hodgkin lymphoma; PAR1-AP: protease activated receptor 1- activating peptide; PDN: prednisone; RA: rheumatoid arthritis; rFVIIa: recombinant factor VII activated; RTX: rituximab; SLE: systemic lupus erythaematosus; TA: tranexamic acid; WD: Waldenstrom disease; yrs: years; n.r.: not reported.

There is no correlation with gender (female: male ratio) (**Table I**). Nor is there any correlation with age; in fact, primary and secondary forms have also been reported in children[7,8,9].

Symptoms are those typically associated with platelet defects and encompass mild to severe spontaneous mucocutaneous bleeding symptoms (**Figure1**). Ecchymosis, haematomas, petechiae, nose and gum bleedings, upper and lower gastrointestinal bleedings, menorrhagia, subconjunctival haemorrhage, haematuria may occur in patients with aPFDs. Intracranial haemorrhage is the most severe spontaneous bleeding complication of platelet disorders; however, this is very rare in aPFDs. In one patient with aδSPD associated with chronic lymphocytic leukaemia (CLL), three episodes of subdural haematoma were the presenting symptoms of CLL[10]. In this patient, bleeding symptoms persisted in spite of a dramatic CLL response to therapy and disappeared together with improvement of platelet dysfunction and platelet count only after rituximab therapy. Therefore, early recognition of an acquired platelet dysfunction is crucial to prevent and adequately treat such severe bleeding complications. Other reported symptoms include surgery or trauma-induced bleedings, such as intraocular bleedings during eye surgery[11], epidural haematoma after intrathecal injection[12], excessive bleedings after tonsillectomy and tooth extraction[13], post-trauma elbow haemarthrosis[10], significant bleeding during surgical repair of an enterocutaneous fistula[14].

Laboratory tests

The most frequently diagnosed autoimmune PFD is aGT. The disease should be suspected through the clinical

picture and the laboratory finding of a platelet function defect mirroring the congenital GT, i.e., severe reduction or absence of aggregation by all platelet agonists except for ristocetin. Light transmission aggregometry (LTA) remains the preferred test to diagnose aGT, although platelet function analyzer (PFA), impedenziometric aggregometry and lumi-aggregometry can be useful for the identification and follow up of platelet defect[10] (**Figure 2**). LTA by epinephrine and low-dose adenosin diphosphate (ADP) are the most sensitive tests when platelet dysfunction has been investigated over time, and it was shown that these tests normalised several months after clinical remission of bleeding symptoms following successful therapy[10,15].

In contrast to congenital GT, in the majority of cases of aGT, with few exceptions, platelets express normal levels of αIIbβ3[7,16-20]. Recently, two aGT cases were reported to be caused by autoantibodies inducing reduction in αIIbβ3 expression on the platelets through two different mechanisms. In one case, anti-αIIbβ3 IgG antibodies induced active internalisation of the complex with only 5% of its residual surface expression. In this case, antibodies did not block platelet function and the platelet dysfunction was due to the absence of αIIbβ3 integrin on the platelet surface. In this patient, bleeding symptoms improved together with an increase in αIIbβ3 expression on platelets and a reduction in antibody titre in platelet eluate and plasma[2]. In the other case, an anti-αIIbβ3 IgM monoclonal autoantibody caused internalisation of αIIbβ3/IgM

SYMPTOMS IN PATIENTS WITH aPFDs

FREQUENT MANIFESTATIONS	RARE MANIFESTATIONS
• Prolonged epistaxis • Unexplained or extensive bruising • Menorrhagia • Gum bleeding • Petechiae • Haematuria • Bleeding after invasive procedures and dental extractions	• Muscle haematomas • Joint bleed • Intracranial haemorrhage

Figure 1 - Frequent and rare bleeding symptoms of autoimmune acquired platelet function disorders (aPFDs)

TESTS FOR THE DIAGNOSIS OF aPFDS	RESULTS
Platelet function testing demonstrating platelet defects	
☐ Blood smear	No abnormalities/reduction of granules
☐ Bleeding time	Prolongation
☐ Light transmission aggregometry (LTA)	Defective/absent response to all agonists except for ristocetin (aGT), defective response to low concentration of agonists (aδ SPD)
☐ Impedance platelet aggregometry	Defective/absent response to all agonists
☐ Platelet function analyzer (PFA)	Prolongation of CADP and CEPI closure times
☐ Lumiaggregometry	Defective/absent platelet aggregation and ATP secretion
☐ Assessment of platelet granule release	Defective/absent release of alpha and delta granules
☐ Analysis of major platelet surface glycoproteins by flow cytometry	Normal expression of major platelet GPs. Reduced binding of PAC1 on stimulated platelets in aGT
Mixing tests demonstrating antiplatelet activity in patient's plasma/serum	Inhibition of control platelet function when control PRP or whole blood is mixed 1:1 with patient's plasma or serum
Antiplatelet antibody test	Identification of antiplatelet antibodies or antibodies to glycoproteins in patient's plasma/serum/platelet eluate

Figure 2 - Laboratory test for the diagnosis of acquired autoimmune platelet function disorders (aPFDs)
CADP: collagen/ADP, CEPI: collagen/epinephrine, PRP: platelet rich plasma

Blood Transfus 2022; 20: 420-432 DOI 10.2450/2021.0119-21

complex with reduced αIIbβ3 membrane content[21]. This monoclonal IgM was also able to constitutively activate αIIbβ3 and trigger αIIbβ3 outside-in signalling, thus mimicking a gain-of-function phenotype similar to described germline mutations causing constitutive αIIbβ3 mediated outside-in signalling[22].

Exposure of activated αIIbβ3 after platelet stimulation by agonists, measured using flow cytometry and PAC1 binding to platelets, was defective in all cases in whom it has been investigated[2,10,16,17,20,23], most probably because the anti-αIIbβ3 autoantibody interferes with PAC1 binding and/or with complex activation. Thus, in the presence of normal amounts of αIIb and β3 integrins in resting platelets, the finding of reduced PAC1 binding on activated platelets may be useful to support the diagnosis. On the contrary, the exposure of membrane p-selectin upon activation, as measured by flow cytometry, can be either normal or defective[10].

A crucial step to confirm the diagnosis of aGT is the identification of antibodies with specificity against αIIbβ3 in patient serum/plasma or in platelet eluate[24]. Anti-platelet activity in aPFD patients can be functionally identified by mixing tests, where LTA of control platelets is inhibited by patient's plasma or serum[7,10,19,25]. Mixing of aGT patient plasma with normal whole blood could also show significative inhibition of platelet aggregation measured by whole blood impedence aggregometry, a simpler and faster method than LTA that does not require sample processing[14].

Acquired aδSPD should be suspected by the clinical picture and the defect of platelet function mirroring δSPD, i.e. mild-to-moderate aggregation reduction by low ADP and collagen concentration that can be overcome using higher agonist concentrations and/or absence of secondary aggregation waves. Severe reduction of aggregation by protease activated receptor1-activating peptide (PAR1-AP) and by epinephrine has also been described[3,10]. Measurement of ADP and adenosine triphosphate (ATP) content and of ATP release, as well as mepacrine or ^{14}C-serotonin platelet uptake, are needed to confirm the reduced content of delta granules. Electron microscopy can also be used to demonstrate lack or severe reduction of delta granules[3,26,27]. In aδSPD, major glycoproteins (GPs) are normally expressed[3,10], and exposure of p-selectin and of activated αIIbβ3 after stimulation are similar to control platelets.

While the mechanism for the antiplatelet antibody-mediated dysfunction is obvious for aGT, it is less clear for the acquired δSPD. It has been suggested that antiplatelet antibodies may cause direct platelet damage, promoting delta granule content release or an indirect release secondary to *in vivo* platelet aggregation[13,27].

PLATELET DYSFUNCTION WITH OR WITHOUT THROMBOCYTOPENIA

Several cases of autoimmune PFDs are sustained by antibodies that block platelet function and do not affect platelet count; in other cases, antibodies also cause thrombocytopenia. Therefore, when bleeding symptoms occur, platelet count can be within normal range or mild/moderate thrombocytopenia may be present (**Table I**). Discrepancy between bleeding symptoms and platelet count typically suggests that platelet dysfunction co-exists in those patients with mild/moderate thrombocytopenia.

Antibody isotype

Among the factors that may affect the platelet count, it has been hypothesised that the antibody isotype is relevant for the development of thrombocytopenia. In some cases, where isotype of antiplatelet IgG antibodies has been characterised, IgG4[28,29] and IgG2[25,29] were not associated with thrombocytopenia and it was speculated that these antibodies are poorly recognised by phagocytic cells. In contrast, IgG1 and IgG3 antibodies have a higher capacity to interact with macrophage Fc receptors, and these IgG isotypes were associated with thrombocytopenia[29,30]. Porceljin described one case with IgG4 identified at the onset of aGT with normal platelet count while IgG1 was later identified when the patient developed thrombocytopenia[29]. However, the presence of IgG1[31] and of IgG3[17] were reported in two patients without thrombocytopenia at the onset of bleedings. In some cases, concomitant presence of IgG1 and IgG2[2] and of all IgG subtypes (1-4)[32] have been reported, making it difficult to understand which IgG subtype caused the low platelet count. Thus, the isotype of IgG might only partially explain the presence of thrombocytopenia.

Immune thrombocytopenic purpura and platelet function disorders

An interesting finding from the literature review is that patients with aPFDs often have a previous history of immune thrombocytopenic purpura (ITP), or develop

ITP either simultaneously or after the occurrence of aPFD (**Table I**). Sixteen out of 42 aGT cases and 3 out of 11 aδSPD cases (including the case reported by Cortelazzo *et al.*[4]) had ITP before, during or after aPFD occurrence. In the majority of these patients, aGT developed following splenectomy for chronic ITP (n=12) or for other reasons (n=1). Porceljin *et al.* hypothesised that, in splenectomised patients, the spleen-mediated platelet destruction no longer occurs, hence persistent or relapsing anti-platelet antibodies blocking the platelet function can induce platelet dysfunction without thrombocytopenia[29]. In the case described by Fuse *et al.*, a 33-year old woman was splenectomised for Evans syndrome[33]. In spite of normalisation of platelet count, after splenectomy she presented extensive bruising which was only controlled by platelet concentrate transfusions. In this patient, a sharp increase in the activity of anti-GpIIb antibody was documented after splenectomy, suggesting a relationship between the antibody titre and the platelet dysfunction. Hence, in patients with a previous history of ITP and splenectomy, mucocutaneous bleeding with normal platelet count strongly suggest aPFD.

ITP may precede or follow the onset of aPFD even in the absence of splenectomy. ITP preceded the PFD in two aGT patients[10,34] and in two aδSPD patients[3,13] who had not undergone splenectomy. In one case described by Porcelijn (Patient n. 2), aGT sustained by anti-platelet IgG4 antibodies resolved spontaneously; however, four months later thrombocytopenia developed and IgG1 subclass antibodies were found. Eventually, the patient underwent splenectomy with resolution of both platelet dysfunction and thrombocytopenia[29].

Zheng *et al.* recently reported a patient who had undergone splenectomy for steroid intolerance. They identified an interesting mechanism by which an anti-αIIbβ3 antibody caused ITP and aGT post splenectomy. They demonstrated that the antiplatelet antibody, in addition to inhibiting fibrinogen and PAC-1 binding to activated platelets, was also able to induce neuraminidase and platelet desialylation, likely mediated via FcRIIa. This mechanism mediated platelet clearance by the spleen causing ITP, whereas after splenectomy the inhibitory effect of antibody became evident[32].

In one case only aGT developed in the presence of a very high platelet count (1,080×10^9/L). This patient had been treated for Hodgkin's lymphoma (HL) seven months before the occurrence of bleedings[29].

AUTOIMMUNE PLATELET FUNCTION DISORDERS SECONDARY TO OTHER DISEASES

Autoimmune PFDs may be primary or secondary to underlying disorders that induce an immune response, mostly haematological malignancies or immune diseases[2,13]. In secondary forms, more than one condition could be associated to aPFDs[7,20,25,35].

Primary and secondary acquired Glanzmann thrombasthenia

The review of aGT cases described in the literature showed that 9 were primary cases with no other disease prior or after the occurrence of bleedings[8,10,11,14,19,25,28,31,36]. Eighteen cases were associated to lymphoproliferative diseases diagnosed before or after the bleeding disorder. Among these, there were 5 HL[15,29,37-39], 7 non-Hodgkin's lymphoma (NHL)[10,17,25,29,40-42], 1 acute lymphoblastic leukemia (ALL)[12], 1 hairy cell leukemia (HCL)[18], 1 multiple myeloma (MM)[30] and 3 monoclonal gammopathy of unknown significance (MGUS)/paraprotein[21,43,44]. Nine aGT cases had concomitant autoimmune disorders, including 1 case of systemic lupus erythematosus (SLE) and 1 case of SLE with anti-phospholipid syndrome in the context of a multiple-autoantibody syndrome[35,45], 1 case of Crohn's disease[20], 1 chronic thyroiditis[2] together with other autoimmune manifestations, 3 cases of autoimmune haemolytic anaemia[7,25,35](AIHA), 1 Evans syndrome[33], 1 acquired vonWillebrand disease[44] (aVWF) (**Table I**). Among autoimmune disorders, we considered the group of patients (n=16) who developed ITP before or after the onset of the aGT separately (see above).

Four aGT cases were described in recipients of renal and heart transplant receiving tacrolimus or immunosuppressive therapy. Whether the cause of antibody production is related to organ transplants or to immunosuppressive therapy, such as tacrolimus, is controversial[9,24]. In one case, a 20-year old woman developed a multiple autoantibody syndrome characterised by thrombocytopenia, autoimmune haemolytic anaemia, and neutropenia five years after a cardiac transplant and immunosuppressive therapy with tacrolimus and azathioprine (AZA). Autoimmune diseases resolved after stopping tacrolimus and relapsed six months after

reintroduction of tacrolimus. During a 4-year follow up, the patient developed several episodes of bleedings that were independent of thrombocytopenia but that were instead associated to laboratory platelet dysfunction consistent with aGT[7]. Another case is of a 46-year old male who developed bleedings and aGT five years after tacrolimus therapy and 12 years after a second renal transplant. The authors reported that platelet count and haemoglobin (Hb) levels had begun to decline after initiation of tacrolimus therapy and bleeding symptoms had begun after five years of tacrolimus therapy despite a moderate reduction in platelet count[23]. Another renal transplanted 52-year old man under cyclosporine immunosuppressive treatment developed bleedings and autoimmune haemolytic anaemia 12 years after transplant. In this case, T-cell angioimmunoblastic lymphoma was diagnosed a few months after bleeding onset; chemotherapy resolved the lymphoma, AIHA and immune thrombocytopathy[25]. Finally, an 11-year old female developed bleedings six years after a heart transplant. This patient was under chronic immunosuppressive treatment with tacrolimus and AZA[9]. Tubman *et al.* presented another 2 cases of autoimmune cytopenias (AHIA and ITP) as late complications of paediatric cardiac transplantation. They suggested that, in their patients, chronic alterations in B-lymphocyte regulation caused by calcineurin inhibition (by tacrolimus or cyclosporine) may have been a predisposing factor to the development of autoantibodies[9]. At the same time, they made the point that among over 150 patients who had undergone cardiac transplantation in their institution, only one had developed aGT. Nevertheless, they concluded that immunosuppression may predispose patients to the development of autoreactive antibodies.

In one case only aGT was associated to drug use, for instance diclofenac; platelet dysfunction spontaneously recovered two months after diclofenac had been stopped[29].

Some patients may develop more than one condition associated with aGT, in the context of multiple autoantibodies syndromes. For instance, in one woman, SLE was diagnosed at 55 years of age, ITP was diagnosed at 60 and successfully treated with splenectomy, while 15 years later, bleedings and platelet dysfunction with normal platelet count developed[45]. Another woman was diagnosed with AIHA at 43 years of age; she required splenectomy for autoimmune haemolysis at 52, developed SLE at 55, ITP at 60, and aGT after resolution of ITP[35]. One man with Crohn's disease developed ITP at 43 years of age, and splenectomy failed to resolve the thrombocytopenia. In spite of a normal platelet count after romiplostin, he suffered from gastrointestinal bleedings and anaemia, and a diagnosis of aGT was confirmed[20].

Primary and secondary acquired delta storage pool disease

Among aδSPD, autoimmune disorders and connective tissue disorders (5 out of 11) are the most frequently reported underlying diseases with 2 SLE[13], 1 reumathoid arthritis (RA)[46], 2 unspecified connective tissue diseases[13,26], followed by lymphoproliferative disorders (3/11), 2 CLL[10,27], 1 Waldenstrom disease (WD)[3], with only 1 reported case of primary aδSPD[13] (**Table I**). Two cases of aδSPD were associated with chronic ITP[3,13].

Other autoimmune platelet function disorders

Among autoimmune PFD of uncertain/mixed diagnosis (**Table I**), Rosove described a case of HCL-associated δSPD with no platelet associated IgG, whose platelet dysfunction and bleedings improved but were not completely resolved after splenectomy. They hypothesised direct hairy cell-platelet interaction as a cause for platelet activation and granule release[47].

Cortelazzo described one patient splenectomised for ITP who developed an acquired platelet defect that was identified as storage pool deficiency; however, function abnormalities were strongly suggestive of aGT[4].

Nieuwenhuis *et al.* reported a cohort of congenital and acquired δSPD to demonstrate that platelet aggregation may be normal in up to 23% of subjects with this platelet disorder. Among acquired δSPD, there were 2 CLL, 1 HCL, 1 WD, and 7 SLE associated cases[48] .

Beer described one patient with acquired bleeding diathesis sustained by an isolated defect in platelet-collagen interaction that they attributed to the combination of heterozygous congenital GPVI deficiency and development of autoantibodies anti-GPIIb/IIIa, anti-GPVI, anti-GPIa/IIa. They concluded that the synergism of congenital defect of collagen receptor and autoantibodies against platelet GPs was required to induce bleedings in their patient[49].

Naresh reported 12 cases of acquired platelet defects in patients with chronic leukaemias. Four patients had CLL

and CLL-related disorders, and displayed aggregation responses that were compatible with aδSPD in 2 cases and with aGT in the other 2[5].

Sharma *et al.* described 109 patients with primary and secondary acquired PFDs diagnosed over five years. Among these cases, the following PFDs were likely to have been mediated by an immune-mediated mechanism: 34 were idiopathic, 15 were associated with myeloma, 4 with WM, 1 with CLL, 1 with SLE[6].

Timing of bleedings in secondary autoimmune platelet function disorders

In secondary aPFDs, bleedings due to platelet dysfunction may be the first manifestation of the underlying disorder or may appear several years after the diagnosis of the primary disease.

Four aGT patients developed NHL eight months to six years after the bleeding disease[10,17,25,41], and, in 4 cases, NHL had occurred before the onset of the bleedings[10,29,40,42]. In one HL case, aGT occurred at the relapse of the disease eight years after the first diagnosis[42].

Platelet dysfunction usually follows the clinical outcome of the underlying disease in most secondary aPFDs. In Patient n. 3 in the work by Alberelli[10], bleeding symptoms paralleled the clinical outcome of NHL and disappeared after the first cycle of rituximab therapy, only to relapse eight months later due to the persistence of stable untreated cutaneous lymphoma. Eventually, bleedings and platelet disorder rapidly responded to chemotherapy for NHL[10]. In one child with ALL-associated aGT, bleedings resolved when ALL complete remission was obtained[12]. In another patient with SLE-associated aGT, treatment of SLE with low-dose methotrexate resolved bleedings[35].

In other cases, the outcomes of the bleeding disorder and of the underlying disease are not to be considered associated. In one patient affected by CLL-associated δSPD, the first-line therapy for CLL with bendamustin and dexamethasone induced a dramatic response of CLL, whereas it was ineffective on platelet count and function, and another episode of intracranial haemorrhage occurred in this patient while under remission from CLL. In this case, rituximab therapy induced a complete remission of aPFD[10].

TREATMENT APPROACHES

With regard to treatment approaches, no recommendations to guide patient care have been developed so far because of disease heterogeneity and a lack of clinical trials. Indeed, therapies have been personalised on the basis of clinical phenotype (major/minor bleedings), clinical needs (surgery, anaemia), and underlying disease. The therapy should address controlling bleeding, antibody elimination, and treatment of the underlying disease.

Treatment of acute bleedings

Treatment of acute bleedings mostly relies on platelet transfusions and antifibrinolytics, similarly to congenital platelet function disorders (**Table I**). In patients with thrombocytopenia and bleedings, refractoriness to platelet concentrate transfusions should be considered a sign of the presence of antiplatelet antibodies causing platelet dysfunction[12]. In one case, also desmopressin has been used[29]. In 2 cases, recombinant factor VIIa (rFVIIa) has been used with successful control of bleeding during surgery. In one of these cases, rFVIIa was successfully used to perform ulcerated polyp resection and biliary sphincterotomy in combination with tranexamic acid[20], and in the other case, rFVIIa was successfully used to perform cerebral biopsy and ventriculostomy[12] (**Table I**). rFVIIa may represent a rational approach in the management of bleeding complications and emergencies, although this should be approached with caution because of the risk of thrombotic events, and the balance between efficacy and risk should be evaluated on an individual basis.

Eradication of antiplatelet antibodies

For the eradication of antiplatelet antibodies, corticosteroids, intravenous immunoglobulins (IvIg), immunosuppressive drugs, plasmapheresis and plasma exchange have all been used, in addition to treatment of the underlying disease. In many cases, standard immunosuppressive therapy with corticosteroids, AZA, cyclophosphamide was effective in controlling bl eedings[4,7,8,25,26,28,29,35,37,43]. In one case, IvIg successfully reversed acquired von Willebrand Disease (aVWD), but it was not effective on platelet dysfunction[44], whereas in other cases IvIg could, at least temporarily, control the bleedings[16,23,32]. In some cases, plasma exchange could revert the bleedings[36]. However, in other cases, standard immunosuppressive therapy was not effective in reverting the bleedings in aPFD[9,10,12, 16,17,20,31,41,45].

A more powerful immunosuppressive drug such as rituximab was successfully used in the treatment of aPFDs. The effective use of rituximab in the treatment of

refractory ITP has been well established. So far, 8 cases of aPFDs treated with rituximab have been reported in the literature. Of these cases, one patient had persistent remission after ten months[9], and another after six months, of rituximab therapy[19]. Another case responded completely after a first rituximab cycle, relapsed after eight months, but remained in stable remission for six years after the second rituximab cycle[45]. Porceljin *et al.*[29] reported a case of aGT with previous ITP and splenectomy whose bleedings responded to rituximab, but the patient developed sepsis and died. Recently, we described a primitive aGT case who was under stable complete remission after 40 months from rituximab therapy[10]. At the time of this review, the patient is under complete remission six years after diagnosis (De Candia E, *personal observation, 2021*). In another patient with LNH-associated aGT, platelet dysfunction and bleeding symptoms improved after the first rituximab cycle but relapsed after eight months due to persistence of cutaneous lymphoma; improvement was eventually achieved after chemotherapy associated with rituximab[10]. We described for the first time successful remission of platelet dysfunction and bleeding symptoms after rituximab treatment in a CLL-associated aδSPD case which had not responded to first-line corticosteroid treatment[10].

In a few cases, rituximab was less effective in the remission of aPFD. In one patient who developed aGT after splenectomy for ITP bleedings only partially responded to rituximab therapy[32]. In a recently reported aGT case associated with IgM MGUS, rituximab was ineffective[21]. Neverthless, rituximab should be considered for the treatment of these severe autoimmune conditions when first-line therapies fail to control haemorrhage. Unfortunately, rituximab cannot be used in emergency situations, given that it takes a few weeks after the first rituximab administration for platelet function to begin to normalise[10,19]. However, use of ritximab might prevent further life-threatening bleeding events or their relapse.

CONCLUSIONS

Autoimmune PFDs must be considered in bleeding patients with no coagulation abnormalities and normal to moderately reduced platelet count who are not taking any antiplatelet drug. These bleeding disorders are underdiagnosed due to lack of platelet function testing in many laboratories. When suspected, early recognition and treatment could prevent severe haemorrhages, and allow invasive and surgical procedures to be carried out safely.

For the control of bleedings, rFVIIa was safe and effective for the prevention of surgical bleedings in anecdotal cases where it has been used.

Rituximab was effective for the eradication of antiplatelet antibodies as a second-line immunosuppressive therapy and could induce long-term remission of autoimmune platelet dysfunction.

ACKNOWLEDGEMENTS

This paper was supported by the Università Cattolica del Sacro Cuore. The funder had no role in study design, data collection and analysis, or preparation of the manuscript.

AUTHORSHIP CONTRIBUTIONS

EDC, A.Fa. and CL conceived the idea, supervised the project, and wrote the manuscript. EDC, MB, AFe, MAA, and MM, analysed the literature.

The Authors have no conflicts of interest to declare.

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