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Novel therapeutics & emerging technology in haemostasis & thrombosis

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Clinical Education Session speaker summaries

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Clinical education session speaker summary and biography

Common Clinical Dilemmas in Management of APS

Dr Karen Breen
London

Covering common presentations and clinical conundrums in APS, diagnostic testing and discuss many of the complexities of making a diagnosis of APS.

Dr Karen Breen
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London

Dr Karen Breen is a consultant haematologist with a specialist interest in thrombosis and is joint clinical director of Haematology and supporting services at Guys and St.Thomas' NHS foundation Trust.

She trained in haematology in Ireland and moved to the UK to conduct research in antiphospholipid syndrome leading to an MD.

Her main area of clinical interest is in thrombosis and in particular, in the field of antiphospholipid syndrome. She is currently involved in several clinical trials and in translational research in antiphospholipid syndrome.

Clinical education session case studies 01

Acquired Glanzmann's Thrombasthenia with IgG and IgA against activated aIIbb3

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Glanzmann's Thrombasthenia (GT) is a rare haemostatic disorder characterised by an impaired function of integrin aIIbb3. It is usually caused by mutations in ITGA2B or ITGB3 genes that encode this platelet receptor (congenital GT) or, more rarely, it can be triggered by the presence of autoantibodies (acquired GT). Acquired GT is often associated with the presence of another autoimmune disease or haematological malignancy disorder.

We present the case of an 85 year old male suffering from small lymphocytic leukaemia (SLL), who developed spontaneous extensive bruising. His platelet counts were normal. Initial aggregometry analysis revealed a severe defect in platelet aggregation with ADP, collagen, epinephrine, arachidonic acid, as well as Ristocetin. The platelet function analyser (PFA-100) revealed severely prolonged bleeding time. The patient started treatment with high-dose steroids and subsequently rituximab as well as CLL based therapy, as the presence of autoantibodies against platelets was suspected. Following treatment initiation, citrated plasma was stored longitudinally and used in flow cytometric analysis to confirm the presence of autoantibodies and investigate their target.

Platelets isolated from healthy controls (n=6) were washed (in the presence or absence of platelet inhibitors) and resuspended in either control plasma or plasma from the patient collected on different dates (n=5). Thereafter, platelets were analysed using flow cytometry, under resting or activated conditions. Platelets were labelled with CD41, CD42b and CD61 markers and further incubated with an antibody against IgG or IgA. Results clearly revealed that the patient had autoantibodies (both IgG and IgA) binding to the platelets. The level of detection was highest when platelets were gated using the CD42b marker, suggesting a competition between patient autoantibodies and CD41/CD61 (aIIbb3). Importantly, IgG and IgA were only detected on the surface of activated platelets and not in their resting state, suggesting that the autoantibodies target activated aIIbb3. Longitudinal analysis revealed a decrease in the percentages of platelets positive for IgG and IgA, in line with the stable condition of the patient and normalising aggregometry results following treatment.

Together, these data confirm, using a new flow cytometric approach, that this patient developed an acquired GT disorder following SLL, having detected both IgG and IgA against aIIbb3 in its active conformation.

Clinical education session case studies 02

Acquired Haemophilia A in the COVID era – building the case for Emicizumab?

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Until now treatment options for bleeding in Acquired Haemophilia A (AHA) have been limited to the FVIII-bypassing agents (BPA) and recombinant porcine FVIII combined with immunosuppressive therapy (IST) to restore tolerance. The bypassing agents have a number of limitations including, short half-lives, intravenous administration, no means of monitoring and are not always sufficient to gain haemostatic control. In addition, IST is associated with often fatal toxicity secondary to infection - a considerably heightened concern in the COVID pandemic.

The use of the recombinant, humanised, bispecific monoclonal antibody emicizumab in AHA remains off label in the UK but theoretically, its mechanism of action as a FVIII mimetic should also make it a favourable option for AHA - providing a novel alternative therapeutic approach in this setting. We report the first case of its use in post-partum Acquired Haemophilia and the 17 month follow up of this case that proved refractory to conventional therapy,

A 41 year old female presented in March 2021 14 days post-partum, with severe PV bleeding and a prolonged APTT of 77.3 seconds. Further investigation revealed a FVIII level of 0.01 IU/mL and an inhibitor titre of 72BU. There was minimal clinical response to BPA necessitating switch to Obizur. Further bleeds had a diminishing response to Obizur and an anti-porcine antibody was detected at 32.3BU. Ongoing bleeding prompted consideration of Emicizumab which achieved an immediate and excellent control of bleeding.

In its first use in the post-partum setting emicizumab provided several advantages for a new mother during the pandemic including a return home to her newborn, contact with family support and minimal attendance at hospital. Its route of administration is subcutaneous, thus avoiding the need for intravenous access and its half-life of 4 weeks is significantly longer than that of the bypassing agents, allowing for up to 4 weekly administration. Furthermore, emicizumab allowed for low intensity immunosuppression at a time of heightened risk whilst also providing excellent haemostatic efficiency. In the 17 months since the initiation of emicizumab in this patient, there have been no further bleeding episodes. Factor VIII became detectable at 7 months post emicizumab.

Since this case we have managed a further four AHA cases with Emicizumab which has conferred rapid and efficacious haemostatic control in all patients with no thrombotic events observed.

Clinical education session case studies 03

A challenging case of refractory ITP in and after pregnancy

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A 30 years old woman was diagnosed with ITP outside of pregnancy with a good response to romiplostim. When she got pregnant she started on prednisolone and romiplostim was stopped. In the 3rd trimester her platelet count dropped to 0×109/L. Romiplostim was restarted following extensive discussion. Additionally, she received weekly IVIG. She gave birth at 38 weeks to a healthy baby through an uneventful induced normal vaginal delivery. Although her platelet count remained 1×109/L, there was no significant bleeding and she was discharged on weekly romiplostim.

One day after discharge, she developed severe haematuria causing renal obstruction, hydronephrosis, and acute kidney injury requiring ITU admission. She had platelet transfusions in addition to IVIG with no improvement. Bilateral nephrostomies were inserted urgently. Her platelet count remained 1×109/L and she continued to bleed through nephrostomy tubes. Subsequently, the MDT decision was to start her on weekly rituximab for 4 weeks. She also received vincristine and continued on twice daily platelet transfusions throughout.

Few days after her first rituximab dose she developed major GI bleeding, requiring several units of blood and platelet transfusions. Due to major bleeding events both mycophenolate and eltrombopag were added to her medications. Despite the high risk of splenectomy, it was decided by the MDT to start plasma exchange (PLEX) for 3 days and do urgent splenectomy after. Before initiating PLEX she developed right sided diplopia and brain imaging showed micro-haemorrhages. She continued 3 PLEX then urgent splenectomy was done.Splenectomy was uneventful; however, no rise in platelet count was observed. She continued to bleed from nephrostomies and GI tract. Moreover, she developed PV bleeding.

Fostamatinib was added to her other medications. Additionally, she received cyclophosphamide and mycophenolate was replaced by cyclosporine. Although her platelet count did not improve, her bleeding settled and her platelet count started to show initial improvement (19×109/L). This was 5 days after completing the 4th rituximab dose, 8 days after cyclophosphamide and 13 days after fostamatinib initiation.
This case highlights the importance of giving the maximal medical intervention to patient with ITP and bleeding symptoms. Patient with refractory ITP may be resistant to numerous lines of treatment. Pregnancy may exacerbate pre-existing mild ITP and MDT approach to management is crucial.

Clinical education session case studies 04

Running low on adrenaline

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We report on the case of a 19-year-old teaching assistant, with a demonstrable platelet function defect and a BAT score of 7.

This young woman was referred to the Haemostasis and Thrombosis Centre prior to planned nasal cauterisation surgery for an assessment of her bleeding history. She had left secondary education early due to recurrent epistaxis of varying severity occurring 2-3x per week. Previous events required ambulance dispatch, A&E attendance, cauterisation and nasal packing.

Past medical history includes heavy menstrual bleeding, endometriosis, female androgenetic alopecia and a ventricular septal defect repair requiring blood transfusion as an infant.

Current medication includes tranexamic acid, desogestrel, vitamin D and spironolactone. She had recently received IV iron.

The BAT score of 7 is reached by scoring 3 for epistaxis and 4 for heavy menstrual bleeding. Pertinent negatives include no history of tooth extraction and no history of pregnancy. There was no bleeding following laparoscopic surgery for an ovarian cyst 2 years ago.

She is the middle (5th) of 9 sisters. Her parents are not related. Her second sister has had heavy periods, whilst two younger sisters have epistaxis, one being advised to have cauterisation. There is no family history of bleeding in the extended family.

Blood tests showed: Hb 140g/L, WCC 6.5 x 10^9/L, Plt 275 x 10^9/L, MCV 80.9 fL, Blood Group O RhD+.

PT 11.3s, APTT 28.8s, TT 16.7s, Fibrinogen 3.5g/L, vWFAg 0.53 IU/ml, vWF Act 0.47 IU/ml, vWF CB 0.54 IU/ml, fVIII 0.68 IU/ml, fIX 1.19 IU/ml, fXI 1.20 IU/ml.

Platelet function aggregometry showed the following:

- Ristocetin 0.6mg/ml No response
- Ristocetin 1.2mg/ml Typical Sigmoidal Shape 80%
- Collagen 1.25ug/ml = Typical Sigmoidal Shape 80%
- Arachidonic Acid 1.0mM = Typical Sigmoidal Shape 80%
- ADP 5uM = Primary Wave 40%
- ADP 10uM = Reduced 50%
- Adrenaline 5uM = No response
- Adrenaline 10uM = No response
- Normal ATP release on lumiaggregometry

No mutations in a 107 gene panel for common bleeding disorders were detected.

A peri-operative plan was provided, however, in light of the above history and discussion with the patient, the ENT surgeon decided to defer the surgery pending a further trial of tranexamic acid 1g TDS for 1 month.
Key learning points:
-Investigative approach for a patient with a high BAT score -Perioperative plan for a patient with a platelet function disorder -Potential causes of a reduced platelet adrenaline/ADP response

Clinical education session case studies 05

A case of coagulation testing disparity in alcohol related hepatitis

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Introduction: We describe a case of clinically significant disparity of results in using two PT reagents in an acute admission setting, due to transient interference with an Innovin-based PT assay.

Case: Mrs. D had a history of alcohol excess and two previous admissions with alcohol related hepatitis.

At admission she had mildly abnormal coagulation screen with PT ratio of 1.2-1.4 on our standard Innovin-based assay. Liver function tests were not particularly raised above her baseline.

Within a few days she became septic and hepatitic.

At the time that sepsis was diagnosed, repeat coagulation screen showed a PT of >122 seconds and PT ratio of 10.1, with little change in other parameters.

There was a transient, partial improvement following treatment with vitamin K. However, severe prolongation of the PT recurred.

This was felt to be inconsistent with the level of liver impairment and other coagulation screen parameters, so a decision was made to test her PT with an alternative reagent (Thromborel). The resultant PT ratio was 2.2, much closer to her baseline.

Factor assays returned normal levels other than a low FVII level at 0.10 iu/ml (Recomboplastin-based assay), which fitted better with the PT seen when tested with Thromborel.

She had no bleeding complications and required no blood product support. Later in her admission, after over a week of discrepant results, Innovin-based PT was again concordant with the Thromborel-based PT. No previously reported culpable medications were administered to explain this.

Discussion and Learning Points: There have been documented interfering agents with Innovin PT reagent, in particular strong lupus anticoagulants and the phospholipid-binding antibiotic telavancin. However, we are not aware of any reports of such transient interference outside of the use of telavancin.

Had the Innovin-based PT been accepted as accurate, consequences could have included exposure of the patient to unnecessary blood products and inappropriate management decisions.

Learning Points: This case was interesting in that it required consideration of non-clinical factors in interpretation of coagulation tests. This specific cause of interference with the Innovin-based PT does not appear to have been described before.

It showed that knowledge of reagents is important when considering incongruous or inconsistent laboratory results.

Finally, it illustrated the difficulties and dangers that the patient might face should these factors be missed.

Clinical education session case studies 06

Therapeutic efficacy of Emicizumab in type 3 von Willebrand Disease

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Emicizumab is a monoclonal bispecific antibody which binds to activated Factor IX and Factor X, mimicking the FVIII cofactor functionality. Emicizumab is licensed for use in patients with haemophilia A and FVIII inhibitors, and severe Haemophilia A without inhibitors. We report an off label use of Emicizumab in a patient with Type 3 VWD and a history of severe allergic reactions to von Willebrand Factor (VWF) concentrates as well as a Factor VIII and VWF inhibitor.

The patient had a lifelong history of recurrent episodes of mucocutaneous bleeding. His baseline VWF ristocetin cofactor activity was 7% and Factor VIII:C activity 4%. He had a genotype consistent with type 3 VWD. He received intermediate purity VWF concentrate (Haemate-P) for bleeds, but in 2009 developed chest pain and dyspnoea following an infusion. He also developed an inhibitor with both anti FVIII and anti VWF activity. Following withdrawal of VWF concentrate the inhibitor disappeared. However there was recrudescence of the inhibitor within a week of re-exposure to Haemate-P in 2012. He was given an alternative intermediate purity VWF concentrate (Wilate) but again developed chest pain and dyspnoea shortly after an infusion. Since 2013 he has been treated with recombinant Factor VIIa (Novoseven) for moderate to severe bleeding.

There had been a significant increase in the number of mucocutaneous bleeding episodes over the past few years. In 2020 he used 144mg of Novoseven whilst in 2021 he used 361mg. He also had a hospital admission of several days in November 2021 following a traumatic thigh haematoma. Furthermore the patient was diagnosed with depression which he indicated was driven to an extent by the increased frequency of bleeding. Approval was granted by the local health board for off label use of Emicizumab given the worsening bleeding phenotype. Since commencing this in March 2022, the patient has had a dramatic reduction in bleeding symptoms. He no longer is troubled by oral cavity bleeding or epistaxis. Furthermore, he is not bruising as easily as before. This is reflected in the dramatic reduction in Novoseven use since he started Emicizumab, having only used 7 mg of Novoseven in the last 7 months.

Key learning points

- Emicizumab enables thrombin generation despite a severe reduction or absence of FVIIIa
- Patients with type 3 VWD have near undetectable levels of both VWF and FVIIIa
- Emicizumab demonstrates efficacy in reducing bleeding in type 3 VWD

Clinical education session case studies 07

The FX of AL Amyloid

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Factor X (FX) deficiency is a rare clotting disorder with variable bleeding phenotype, from mucosal bleeding to life-threatening haemorrhage. When acquired, the most common cause is AL amyloidosis. Factor replacement includes FFP, aPTC and rVIIa, however fluid overload and thrombotic complications are reported. In recent years, FX concentrate has been developed for inherited FX deficiency. Experience of such concentrates in acquired deficiency is very limited. We present a case highlighting the use of FX concentrate in acquired FX deficiency.

A 69-year-old male presented with melaena, weight loss, ankle swelling and macroglossia. He had no comorbidities and no personal/family history of bleeding. Initial assessment found a significant upper gastrointestinal (GI) bleed. Haemoglobin had dropped to 83 g/dL with haemodynamic instability. Prothrombin time (PT) was elevated at 36.9s with normal aPTT and fibrinogen. Historical coagulation screens were normal. Mixing studies showed correction of PT to 15.0s and FX was quantified at 7.0%.

With the constellation of symptoms, amyloidosis was suspected, with a resulting FX deficiency. To try to control GI bleeding, he was given prothrombin complex concentrate, which caused in an improvement in PT to 23.8s and FX to 18%, but with no improvement in clinical symptoms. He was transferred to a haemophilia comprehensive care centre. Coagadex™ (human coagulation FX) was commenced and dosed according to inherited FX deficiency, once daily. This resulted in a post dose FX of 24.0% and an improvement in clinical bleeding. To achieve higher FX levels for invasive procedures, subsequent doses were increased by 100%, achieving a post dose FX level of 36.7%. The patient did not experience any thrombotic complications.

A diagnosis of AL was confirmed on Congo-red staining of biopsies. The patient was commenced on velcade, thalidomide and dexamethasone.

In inherited FX deficiency, bleeding symptoms typically occur <10%, but the threshold for bleeding in acquired disease seems lower, with one study demonstrating an increased risk of haemorrhage <25%. This may be due to other amyloid associated changes. The major underlying mechanism is postulated to be adsorption of FX by amyloid deposits. Coagadex™ is a single factor concentrate licensed for the treatment of inherited FX deficiency. This case report highlights its use in the acquired FX deficiency, for the management of bleeding or to facilitate procedural interventions.

Clinical education session case studies 08

A case report of relapse of immune-mediated thrombotic thrombocytopenic purpura after SARSCoV-2 vaccination

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We report the case of a 39-year-old Caucasian female who experienced a relapse of immune mediated thrombotic thrombocytopenic purpura (iTTP) in close association with the first dose of Pfizer-BioNTech COVID-19 vaccine (BNT162b2). She was diagnosed with primary iTTP in 2018 and treated with plasma exchange procedures (PEX) plus IV methylprednisolone. Nine months later her disease relapsed, and was managed with PEX, steroids and Rituximab. Remission was achieved following this. In 2021, a decision was made to proceed with COVID-19 vaccination. 2 months prior to receiving her first dose of BNT162b2, and over two years after last treatment for iTTP, she was in remission with ADAMTS13 activity of 72.8% (normal range: 60.6-130.6%). 48 hours after vaccination she presented with a new headache and visual disturbance. Her platelet count was 195 x109/L, but ADAMTS13 activity had fallen to 2.6% and anti-ADAMTS13 antibody level was 22%. No triggering event was identified. She was treated with 4 doses of Rituximab, 7 PEX sessions and 2 weeks of Caplacizumab. After reaching a nadir of 91x109/L, her platelet count normalised on day 6 of treatment. ADAMTS13 activity subsequently normalised and, to date, she remains in remission. It is known that iTTP can be triggered by viral infection and vaccination. A small number of cases of de novo and relapsed iTTP after COVID-19 vaccination have been reported. Several small cohort studies have shown different relapse rates amongst iTTP patients who are vaccinated against COVID-19. Some identify a relationship between low ADAMTS13 activity and increased risk of relapse, and advise an activity level of >20% before vaccination is considered. This is the first case where ADAMTS13 levels were monitored closely around the vaccination with a normal result shortly before, demonstrating continued remission of over two years in duration, followed by an abrupt fall on post-vaccination testing. In addition, the patient's neurological symptoms developed at 36-48 hours post vaccination, closely followed by new onset thrombocytopenia. Whilst causation is impossible to prove, this close association is highly suggestive. Consideration should therefore be given to monitoring of ADAMTS13 activity pre and post COVID-19 vaccination in patients with prior iTTP to allow early detection of disease relapse. This case also highlights that that an ADAMTS13 activity level of >20% may not necessarily be a safe threshold for proceeding with vaccination.