How I treat anticoagulant-refractory thrombotic antiphospholipid syndrome

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Abstract

The standard treatment of thrombotic antiphospholipid syndrome (APS) is oral anticoagulation with a vitamin K antagonist, generally warfarin. In a minority of APS patients, achieving successful anticoagulation is more complicated as they continue to re-thrombose despite seemingly adequate anticoagulation. These patients are deemed anticoagulant-refractory. The management of anticoagulant-refractory APS is largely empirical and extrapolated from other situations with clinical similarities, to optimise patient outcomes. For affected patients, additional measures are required, either in the form of increased intensity VKA anticoagulation or alternative antithrombotic strategies, including low molecular weight heparin, fondaparinux, the addition of antiplatelet therapy, as well as consideration of other approaches, including vasodilators or vascular intervention. Anticoagulant-refractory thrombotic APS patients may have APS-associated thrombocytopenia, which requires great care in balancing the risk of recurrent thrombosis versus bleeding, with dose titration of anticoagulation based on platelet counts. Finally, APS patients may also have systemic lupus erythematosus (SLE), which can greatly add to the complexity of managing their thromboembolic disease. However, with great attention to detail and an individualised approach, it is possible to minimise the morbidity resulting from anticoagulant-refractory thrombotic APS.

Introduction

Antiphospholipid syndrome (APS) is characterised by thrombosis (arterial, venous, microvascular) and/or pregnancy morbidity in association with persistent antiphospholipid antibodies (aPL): one or more of lupus anticoagulant (LA), anticardiolipin antibodies (aCL) or anti-beta 2 glycoprotein I antibodies (aß2GPI), present on two occasions at least 12 weeks

apart.[1] Approximately 50% of thrombotic events are lower limb deep venous thrombosis, and pulmonary embolism, with stroke and transient ischaemic attack (TIA) accounting for around 30%.[2] The overall prevalence of APS is estimated to be 40-50/100,000 of the population,[3] with the female:male ratio approximately 5:1.[2] Catastrophic APS has a 37% mortality and accounts for 1% of cases.[4]

What is anticoagulant-refractory thrombotic antiphospholipid syndrome?

Anticoagulant-refractory thrombotic APS can be broadly defined as breakthrough thrombosis on standard treatment, i.e. oral anticoagulation with warfarin or an alternative vitamin K antagonist (VKA). Some patients who have re-thrombosed at standard-intensity VKA (target INR 2.5, range 2.0-3.0) will be protected from further thrombosis with high-intensity VKA (target INR 3.5, range 3.0-4.0), whereas others re-thrombose even at high-intensity oral anticoagulation. When optimal anticoagulant intensity is not established, e.g. APS-related stroke, recommended options are standard-intensity VKA,[5-6] with or without low dose aspirin (LDA)[7,8] or high-intensity VKA.[7,8] In this instance, defining what constitutes anticoagulant-refractory is somewhat controversial. The management of anticoagulant-refractory APS is empirical and extrapolated from other situations with clinical similarities.

Recurrent thrombosis may occur while on subtherapeutic VKA anticoagulation. This could be secondary to patient non-adherence and necessitates patient education. The majority of commercial thromboplastins can be safely used in LA positive patients,[9,10] but in a small minority, LA can interfere with the action of thromboplastin so that the International Normalised Ratio (INR) is falsely elevated.[9,10] An LA-insensitive thromboplastin should be used to monitor the INR and the prothrombin time checked before starting a VKA wherever possible.[9,10] Point-of-care INRs are variably affected by LA and results must be interpreted with caution.[9-11] Chromogenic factor X levels provide an LA-independent assessment of VKA intensity, however, therapeutic ranges are not established.[9,10,12]

The annualised risk of recurrent thrombosis in APS patients on VKA was 1.3-4.0 in two randomised controlled trials (RCTs);[13,14] 4.3 in the Euro-phospholipid prospective cohort study of 1000 patients;[15] and 4.8% in a retrospective cohort study on triple aPL-positive APS patients.[16] In the past decade, direct oral anticoagulants (DOACs) have been introduced as a potential alternative to VKAs. The precise place of these agents in APS is not established. They offer several advantages compared to warfarin, including: being prescribed in fixed dose with more predictable anticoagulant effect and, therefore, no routine anticoagulation monitoring required, having fewer drug interactions and no interactions with food or alcohol. These advantages are desirable for thrombotic APS patients who require indefinite anticoagulation. However, some of the recent trial data[17-19] have raised concern about re-thrombosis occurring on DOACs,[18,19] although earlier reports indicated that re-thrombosis is also a feature of warfarin therapy.[13-16] These emerging data prompted the European Medicines Agency (EMA) to issue a recommendation against the use of DOACs in APS patients, especially those who are triple aPL-positive.[20] The EMA safety warning has been incorporated into the DOAC manufacturer summary of product characteristics (SPCs) and endorsed by the United States of America (USA) Food and Drug Administration (FDA).[21] The EMA recommendations have been adopted in several guidelines, including the European League Against Rheumatism (EULAR) recommendations,[8] with guidance on DOAC use in APS patients in preparation by the International Society on Thrombosis and Haemostasis (ISTH).

Synopsis of pathophysiology mechanisms in thrombotic antiphospholipid syndrome

It is generally assumed that the hypercoagulability associated with APS is based upon a “two hit” phenomenon.[22] The first hit is dependent upon the presence of aPL and the second to a subsequent precipitating event with causes including surgery, immobilisation or exogenous oestrogens and pregnancy. The precise mechanisms leading to the development of thrombosis are, however, complex and are discussed in detail in a recent review.[23] In brief,

pathogenic aPL are thought to bind ß2GPI leading to exposure of a cryptic domain 1 Arg39-Arg43 epitope, i.e. its more open oxidised form - this form lacks free thiols, which are increased in the presence of oxidative stress, is thought to be increased with patients with APS.[24] The aPL complex with this open oxidised form of ß2GPI, can then cause cross-linking to many surface receptors, with subsequent activation of effector cells, in turn leading to release of prothrombotic and proinflammatory mediators.

Figure 1 provides more detail about the individual receptors and the molecules which are (mostly) upregulated as a consequence. Diverse cells including endothelial cells, monocytes, neutrophils and platelets are involved in this process. Intracellular signalling in particular through mitogen-activated protein kinases (MAPKs) and the key transcription regulator nuclear factor kappa B (NF-κB), is integral in activating these target cells. In addition, increasing evidence supports the concept that the complement system is involved in the pathogenesis of APS. Thus, lower levels of both C3 and C4 are present in primary APS patients, with concomitant increased levels in C3a-desArg and C4a,[25] suggesting complement activation is occurring. Aberrant activation of the coagulation cascade of serine proteases [SP] may also be contributory,[20] perhaps through antibodies which cross-react with SPs and factor-Xa. Other possible contributory factors include coagulation cascade abnormalities, notably enhanced activation of the tissue factor (TF) pathway and impaired activation of protein C.[26] The multiple mechanisms involved in the generation of the thrombotic phenotype in APS suggest that anticoagulation alone may not control thrombosis.

The ‘second-hit’ may be provided by a variety of external or patient-related factors. Venous thromboembolism may be precipitated in individuals with aPL during prothrombotic situations, including infection, trauma, surgery, immobilisation, exogenous oestrogens, pregnancy, or SLE and other autoimmune disease, as discussed elsewhere.[26,27] The risk of arterial thromboembolism is also increased in SLE.[26] Application of the adjusted Global AntiphosPholipid Syndrome Score (aGAPSS) in a prospective study on the AntiPhospholipid

Syndrome Alliance For Clinical Trials and InternatiOnal Networking (APS ACTION) cohort indicates that hypertension and hyperlipidaemia, in addition to aPL status, exacerbate the risk of arterial thrombosis.[28] This emphasises the importance of active management of conventional cardiovascular risk factors.

Case 1: Anticoagulant-refractory recurrent venous thromboembolism

A 28-year-old woman had a right popliteal vein DVT at 20 weeks' gestation, treated with standard therapeutic dose subcutaneous low molecular weight heparin (LMWH), during the remainder of the pregnancy, followed by a three month post-partum course of standard-intensity warfarin, target INR 2.5. In her next pregnancy two years later, she received prophylactic dose (LMWH) throughout pregnancy and for six weeks postpartum. She had pre-eclampsia, onset at 28 weeks' gestation. When 40, she had an unprovoked left popliteal vein DVT and received initial therapeutic dose LMWH followed by standard-intensity warfarin. Triple positive aPL, with high titre IgG aCL and ab2GPI, were identified. She was started on life-long standard-intensity warfarin and adherent to treatment. Four months later, she developed symptomatic extension of the DVT to the left common femoral vein, while the (venous) INR was therapeutic. She had bridging standard-intensity LMWH and the target INR was increased to 3.5. Eight months later, despite good anticoagulant control, she developed new proximal DVT in the left external iliac vein, INR 3.4 [Figure 2]. The warfarin was switched to split-dose high-intensity LMWH at approximately 20% above standard therapeutic dose. A year later, she developed a left sigmoid sinus thrombosis associated with an upper respiratory tract and ear infection. Brain imaging suggested a fistula, not confirmed by magnetic resonance angiography (MRA). The MRA was complicated by a small acute frontal embolic infarct, thought to be procedure-related. LMWH was escalated to approximately 30% above standard dose, split-dose, with target peak anti-factor Xa levels 1.0-1.20. A year later, an unprovoked right middle lobe segmental pulmonary embolism (PE) occurred. LMWH was switched to fondaparinux and had rituximab. She did not re-thrombosis over the next four

years. Vitamin D was insufficient with replacement treatment instituted. Lipid status was normal. Serial dual energy x-ray absorptiometry (DEXA) scanning remained normal.

Comments about Case 1

After an initial first pregnancy-provoked proximal DVT, this patient developed early pre-eclampsia, a manifestation of APS-associated obstetric morbidity, in her next pregnancy.[1] APS classification criteria are being updated.[29]

The history raises the critical question of whether APS patients with recurrent/anticoagulant-refractory thrombosis can be identified early in their clinical course. Although there is no uniformly agreed definition of "high risk", it is notable that she was triple aPL-positive, the phenotype associated with the highest risk of thrombosis.[30] Other factors may include anti-ß2GPI antibodies that bind to a limited epitope (Arg39-Arg43) on domain 12[31,32] and anti-protein C antibodies linked to acquired activated protein C resistance.[33] VTE is multifactorial and therefore, standard risk factors for VTE, e.g. age of onset, body mass index may be contributory to recurrent thrombosis (Figure 1),[27] although their role, or that of ethnicity, in APS-related VTE is not fully defined.

This case illustrates the progression of anticoagulation options for APS-related recurrent VTE (Figure 3). After a first unprovoked VTE, APS patients require life-long anticoagulation, when aPL and D-dimer are independently associated with recurrence,[34] although the optimal duration of anticoagulation following provoked APS-associated VTE is undefined. Management is based on assessment of the reason for the recurrence and extrapolated from other situations, particularly cancer. Points to consider when re-thrombosis occurs are summarised in Table 1. Suspected re-thrombosis must be confirmed objectively while bridging LMWH is started. It is also important to consider potential provoking factors for VTE, detailed above, or a concomitant prothrombotic condition, such as cancer[35] or myeloproliferative neoplasm,[36] which were not implicated here. Measurement of the INR with assessment as to

whether it is representative of anticoagulant intensity, informs an optimal anticoagulation plan. If the INR is subtherapeutic, under 1.5, the warfarin/VKA may be resumed at standard-intensity, with close INR monitoring. If re-thrombosis occurs at standard-intensity VKA, high-intensity VKA anticoagulation, INR range 3-4, is widely used, although formal studies regarding this approach are lacking. Re-thrombosis at an INR between 3-4, as occurred in this patient, necessitates a switch to LMWH. High-intensity LMWH was used, as recurrent DVT occurred, despite a therapeutic high-intensity INR. This approach was associated with no VTE recurrence in 91% and major bleeding in one patient, in a retrospective study in 70 cancer patients with recurrent VTE following oral anticoagulation, who either switched from VKA to LMWH (23 patients) or had their LMWH increased by 20-25% (47 patients), followed up for 3 months.[37] Dose escalation of high-intensity LMWH was undertaken after the unprovoked PE. This approach accords with ACCP guidelines that recommend an increase of approximately 25%, then 33% for re-thrombosis on LMWH (grade 2C).[27] In APS patients, two small retrospective studies in 24 and 23 patients, 14 and nine of whom had failed warfarin therapy, one and three patients, respectively had recurrent thrombosis.[38,39] Thus, LMWH offers an option in some patients who have had recurrent thrombosis on oral anticoagulation.

Prolonged LMWH, between 6-24 months, is associated with a decrease in bone mineral densitometry (BMD). Furthermore, 1alpha,25-dihydroxyvitamin D3 downregulated TF upregulated thrombomodulin expression *in vitro*[40] and vitamin D inhibits the expression of TF in monocytes stimulated by aβ2GPI from APS patients. Low vitamin D levels correlate with arterial/venous thrombosis in APS patients[41] and the 14th and 15th International Congress on Antiphospholipid Antibodies Treatment Trends Task Force recommended that vitamin D deficiency is corrected, based on general population guidelines. They also recommended consideration of hydroxychloroquine as adjunctive treatment in refractory APS; and statins for hyperlipidaemia.[42,43] Hydroxychloroquine reduced clot formation and thrombin generation in animal models; and improved nitrous oxide production with subsequent endothelial-dependent relaxation.[44] It reduces the risk of thrombosis in SLE patients and animal models

of APS[45] and was reported to reduce aPL levels and arterial thrombosis recurrence in primary APS patients.[46] Statins have immunomodulatory, anti-inflammatory, and antithrombotic properties, in addition to their lipid-lowering effect.[47] Fluvastatin reduces aPL-mediated tissue factor (TF) and monocyte adhesion to endothelial cells *in vitro*.[48] A prospective open-label pilot study of fluvastatin for three months in 24 APS patients showed reduction in proinflammatory and prothrombotic biomarkers, including interleukin-1 beta (IL1β), vascular endothelial growth factor (VEGF), tumour necrosis factor alpha (TNFα) and soluble TF.[49]

Following re-thrombosis on high-intensity LMWH, it was switched to fondaparinux. This synthetic analogue of heparin pentasaccharide, used mainly for the treatment of heparin induced thrombocytopenia,[50] has specific anti-factor Xa activity seven-fold higher than LMWH.[51] A prospective cohort study in 30 patients with DVT or PE, 13 with hypercoagulable states including APS and 13 with recurrent VTE despite a therapeutic INR, showed no re-thrombosis or major bleeding after 90 days follow-up.[52] Fondaparinux has also been used successfully in two patients with APS and microvascular thrombosis, in combination with mycophenolate mofetil (MMF), with no re-thrombosis after four years follow-up.[53] *In vitro* studies show no significant inhibitory effect on osteoblast proliferation or activity observed with fondaparinux,[54] although whether prolonged fondaparinux use is associated with preservation of bone mass is unknown. Consideration of IVC filters should be reserved for patients at high risk of PE when anticoagulation is contraindicated,[55] although a recent RCT of IVC filter placement in this situation showed no overall benefit.[56]

Case 2: Anticoagulant-refractory persistent microvascular thrombosis, recurrent VTE, thrombocytopenia and bleeding

This patient was diagnosed aged 18 years with SLE, characterised clinically by arthritis and membranous glomerulonephritis, treated successfully with a course of intramuscular steroids and started on hydroxychloroquine.[57] When aged 30, she had an unprovoked proximal lower

limb DVT and after initial LMWH was maintained on warfarin, target INR 2.5. She was found to be triple aPL-positive with high titre IgG aCL and ab2GPI. Aged 39, she had an early miscarriage. Three months later she developed severe pain from ulcers in the right shin (biopsy showed microvascular thrombosis) and dorsum of the right foot, and a blue right second toe. A computerized tomographic (CT) angiogram showed right dorsalis pedis artery occlusion and a small right common iliac artery mural thrombus. The platelet count, previously stable at >150,000/uL, was 44,000/uL with haemoglobin 77g/L and no red cell fragmentation. Renal and hepatic function tests, lactate dehydrogenase and ADAMTS13 activity were normal. Her SLE was serologically active, with raised anti-double stranded (ds)-DNA antibodies and reduced C3 at 0.80 (NR 0.90-1.8) g/L, but clinically quiescent. The warfarin was switched to split treatment dose LMWH; and intravenous methyl prednisolone (IVMP), plasma exchange (PEX) and rituximab, with clinical improvement and platelets >100,000/uL.

Over the next six months, she was treated with intravenous methylprednisolone (IVMP), plasma exchange (PEX), rituximab and iloprost (platelet count target >75,000/uL, with 2/3 split therapeutic dose LMWH during iloprost infusion, in view of its platelet inhibitory effect). However, the skin ulcers became necrotic, treated with antibiotics and debridement, with subsequent epidermal grafting, with a good result. She was readmitted with worsening necrotic skin ulcers and platelets 26,000/uL. She received IVMP, PEX, rituximab, IVIG and iloprost. She had skin debridement and epidermal grafting, with a good result (Figure X). Fifteen months after her initial presentation with skin ulcers, she was admitted with Citrobacter bactaraemia, platelets 9,000/uL. Treatment included IVMP, PEX, IVIG and platelet transfusions. Subsequently, she underwent terminalisation of an ischaemic right hallux, and fourth and fifth toes followed by angioplasty, PEX and iloprost. She developed a post-operative left iliac vein catheter-associated DVT and received IVIG and platelet transfusions, to elevate platelet counts sufficiently for anticoagulation. She was started on MMF for the thrombocytopenia without effect. To limit IVIG, this was switched to eltrombopag. She underwent a temporary, followed by two permanent lumbar sympathectomies. She

subsequently received a six-month course of eculizumab and hyperbaric oxygen therapy (HBOT; 50 sessions over 10 weeks), with healing/improvement in the surgical wounds and ulcers (Figure X). The thrombocytopenia improved, with platelets generally maintained >50,000/uL and lengthened intervals between IVIG infusions.

During the initial iloprost infusion, she had a small intracerebral haemorrhage (platelets 66,000/uL), with subsequent diagnosis of a transverse sinus occlusion. Approximately a year later, she had seizures associated with spontaneous acute on chronic subdural haemorrhage, new saggital sinus thrombosis and acute frontal intraparenchymal haemorrhage (platelet nadir 48,000/uL in the preceding fortnight). During a complicated three month admission, she developed a spontaneous left cerebellar haematoma with mild mass effect (platelet nadir 64,000/uL in the preceding fortnight). Platelet thresholds for LMWH dosing were individualised to: platelets >70,000/uL: treatment dose; platelets 50,000-70,000/uL: 75% treatment dose; platelets 25,000-50,000/uL: prophylactic dose with platelet transfusion if platelets <35,000/uL. She gradually improved and returned to work.

Comments on Case 2

This case demonstrates approaches to the management of microvascular thrombosis, which was anticoagulant-refractory, occurring while on therapeutic warfarin. It also highlights the challenge of optimal management of recurrent intracranial haemorrhage associated with cerebral venous sinus thrombosis and thromocytopenia. The case demonstrates the major challenges of optimal management of anticoagulation in the presence of recurrent critical site bleeding as well as persistent microvascular thrombosis, with skin ulcers (reported in 5.5% of APS patients).[2] APS in SLE patients (approximately 15%) is associated with a more complicated course and increased organ damage.[58,59] Mild thrombocytopenia, platelets <150,000/uL, is associated with a two- to four-fold increased risk of thrombosis in APS patients.[60,61] The pathophysiology of thrombocytopenia in APS is not clear, probable mechanisms including autoantibodies against platelet glycoproteins as in immune

thrombocytopenic purpura (ITP), aPL-mediated platelet activation and consumption; and thrombotic microangiopathy. Our patient did not fulfil preliminary classification criteria for definite or probable CAPS.[4,62] Management was pragmatic, with IVMP, PEX, IVIG and rituximab. The first three modalities are recommended by the McMaster RARE-Bestpractices guideline for CAPS, with rituximab, an anti-CD20 chimeric monoclonal antibody, suggested for refractory cases.[62] In the CAPS registry, 15/20 rituximab-treated patients survived.[63] In the RITuximab in APS (RITAPS) phase 2 open-label prospective pilot study, 5/19 patients had skin ulcers, with complete and partial remission in three and one respectively.[64]

Anticoagulation is central to this patient's management, with options VKA or LMWH. The latter is preferable in individuals with thrombocytopenia, because of the shorter half-life of LMWH, 3-6 hours,[65] compared with 36-42 hours for warfarin.[66] LMWH dosing is largely extrapolated from the cancer literature. International Society on Thrombosis and Haemostasis,[67] National Comprehensive Cancer Network,[68] American Society of Clinical Oncology[69] and British Society for Haematology[70] consensus guideline statements recommend full-dose anticoagulation in cancer patients with a high risk of thrombus propagation and a platelet count >50,000/uL, with platelet transfusion support to maintain platelet counts of 40,000-50,000/uL.[67-70] However, recent analysis of pooled data on >400,000 patients from US healthcare organizations suggests that bleeding incidence was increased in cancer versus non-cancer patients with a platelet count of <100,000/uL on LMWH (13.2% vs 9.7%, $P < 0.001$).[71]

Initially, LMWH doses were titrated in general accordance with international guidelines, but the recurrent intracerebral bleeds necessitated an individualised approach. The balance of thrombotic and haemorrhagic risk in critical sites can be very challenging and enhanced by concomitant thrombocytopenia. In this particular patient, IVIG and eltrombopag, a thromopoietin agonist, were helpful. These therapies are widely used in the treatment of ITP,[72] however reports suggest that both may be associated with thrombosis,[73-75] although a review

of 35 studies suggested that IVIG could be useful, in addition to standard therapy, to prevent recurrent thrombosis in anticoagulant-refractory APS patients.[76] The addition of antiplatelet treatment, suggested by the EULAR guidelines as an option in APS-related refractory thrombosis,[8] was precluded by thrombocytopenia. Iloprost, a prostacyclin analogue, was used frequently to try and improve the peripheral circulation.[77] Its potential benefit in APS may go beyond vasodilation, possibly mediated by platelet function inhibition and endothelium-stabilising properties.[78] Epidermal grafting for wound healing involves the transfer of the epidermis from a healthy location to cover a wound and is a promising alternative to the more invasive conventional surgical techniques.[79]

We used eculizumab, a humanised monoclonal antibody, that binds complement protein C5 and prevents activation of the membrane attack complex leading to tissue injury. Case series suggest that eculizumab is beneficial for patients with SLE and/or APS with thrombotic microangiopathy (TMA).[80-82] A phase 2a study of a C5a inhibitor ALXN1007, in persistently aPL-positive patients with non-criteria APS manifestations including thrombocytopenia, nephropathy, and/or skin ulcers, was terminated early after 9 patients were recruited, due to slow enrollment.[83] Complement-inhibition may be beneficial in APS patients with refractory microvascular thrombotic states, including TMA or, as in this case, chronic persistent microvascular thrombosis. There are no published studies on HBOT, which was also used, in APS. The largest RCT, in diabetic foot ulcers, showed a 26% (95% CI 10-38) improvement in amputation-free survival in those who finished a protocol of 90 minutes over 40 sessions.[84] However, as many did not complete treatment, the overall intention to treat analysis showed no benefit. HBOT may be an option for refractory APS-related ischaemic cutaneous ulceration or tissue loss.

Case 3: Anticoagulant-refractory digital ischaemia with concomitant active SLE

A female aged 22 years was diagnosed with SLE manifested by a skin rash, fever, serositis and arthritis. Serologically, she had antibodies to DNA, Ro, Sm and RNP. She developed bilateral avascular necrosis, requiring bilateral total hip replacements, and hypothyroidism. Her principal therapies included prednisolone, hydroxychloroquine, methotrexate and MMF. Having previously been negative for all three aPL, aged 41, she had a stroke and was found to have isolated persistent high titre IgG aß2GPI. She was commenced on warfarin, target INR 3.5. Aged 46, she developed digital ischaemia and severe alopecia. Her platelet count, previously normal, dipped to 51 x 10^9/L. Although anti-DNA antibody levels were normal, her complement C3 was low, 0.49 (NR 0.90-1.8) g/L. The warfarin was switched to LMWH and iloprost added after platelet recovery, with LMWH dose reduced to 75%. She also received IV MP, followed by oral prednisolone; and rituximab, with subsequent MMF. The digital ischaemia was persistent and painful. A digital sympathectomy was performed, but did not prevent subsequent autoamputation of the first fingertip (Figure X).

Comments on Case 3

This case highlights the challenge of managing two diseases with different aetiopathogenesis. SLE patients with concomitant APS present a major challenge. Thirty-forty percent of SLE patients have aPL, but only approximately one-third develop relevant clinical features.[85] This patient highlights a particular practical issue. When she first presented, she had no detectable aPL, but aged 41, nearly 20 years after her diagnosis, she had a stroke accompanied by high titre isolated IgG aß2GPI. It is likely that she developed these antibodies during this two decade gap, begging the question how often in an asymptomatic SLE patient should aPL be checked? Furthermore, once they have been detected, what is their optimal management? A further question arises as to how she might have been managed differently had aPL been detected during the two-decade hiatus. The recent EULAR APS guidelines recommend low dose aspirin (LDA) 75-150mg daily in this situation.[8] This recommendation was based upon a meta-analysis of seven observational studies involving 460 asymptomatic patients mainly with a ‘high risk’ aPL profile.[86] Pooled data from two cohort studies in SLE patients indicate that

LDA was linked to a lower risk of thrombosis even in those deemed to have a 'low risk' aPL profile.[87,88]

This patient had a digital sympathectomy to try and improve vasodilation. In this procedure, all neural connections between the digital nerve and artery are divided and the adventitia stripped from the main digital artery. This may improve blood flow by interrupting sympathetic vasoconstrictor supply to the digital arteries and removing the external constrictive cuff or peri-adventitial fibrosis from around the digital arteries.[89] Although no formal studies of this therapy in APS patients have been undertaken, we have noted partial improvement in several patients.

Although it is generally agreed that triple aPL-positive patients are at increased risk of thrombotic complications in APS and APS/SLE, as this case illustrates, even single aPL positive patients may develop major thrombotic manifestations.

Conclusions

As these three cases illustrate, managing patients with anticoagulant-refractory thrombotic APS can be a major challenge. However, with great attention to detail, morbidity related to complex and severe thrombotic situations can be contained. Even the second patient, the most severely affected, returned to full-time work. The extent of the refractory nature of APS patients is highly variable. Thus, some patients can be managed successfully with increased VKA anticoagulation intensity of INR 3-4, whereas others will require anticoagulation with LMWH or fondaparinux and consideration of the addition of antiplatelet therapy. Additional options include iloprost, rituximab, PEX, IVIG, and vascular intervention including epidermal grafting, digital sympathectomy and HBOT. When anticoagulant-refractory patients have the additional burden of thrombocytopenia, balancing the risk of recurrent thrombosis versus bleeding becomes critical, with dose titration of anticoagulation based on platelet counts. An individualised approach is required. There is a pressing need to undertake multicentre studies

to guide the sequence of interventions and their comparative efficacy in APS patients with anticoagulant-refractory thrombotic APS.

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Authorship

Contribution: HC and DAI contributed equally to the first draft of the manuscript, concept, design and writing of the manuscript.

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Table 1: Factors to consider when assessing patients with suspected venous thromboembolism recurrence on standard-intensity warfarin/vitamin K antagonist

1. Confirmation by imaging of new thrombosis or thrombosis extension
2. Review of the preceding International Normalised Ratio (INR) prior to the thrombosis to help in the assessment of patient adherence
3. Test for heparin-induced thrombocytopenia is re-thrombosis occurs within 21 days of starting low molecular weight heparin
4. Checking that the patient's INR assessment has been performed using an appropriate assay
5. Consideration of additional risk factors for thrombosis e.g. malignancy, systemic lupus erythematosus or other autoimmune disease
6. Consideration of bleeding risk factors, e.g. gastrointestinal or uterine, or thrombocytopenia, as such factors may limit anticoagulation intensity

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