Coexistent antiphospholipid syndrome and myeloproliferative neoplasm

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Abstract

Antiphospholipid syndrome (APS) and myeloproliferative neoplasms (MPN) are associated with an increased risk of thrombosis. The optimal management of patients with coexistent APS and MPN has not been defined. A single centre and systematic literature review of patients with coexistent APS and MPN was performed. Cases were divided into two groups based on whether they met international consensus criteria for APS. Of the 12 studies identified, eight were excluded (leaving five of a total 54 patients), as although antiphospholipid antibodies (aPL) were documented, the diagnosis of APS was not conclusively demonstrated. Another ten patients with definite APS were identified at our centre. Fifteen patients (ten females, five males) were therefore included in this analysis (eleven definite APS and four likely), median age 44 (range: 13–71) years. Nine had polycythaemia vera and six, essential thrombocythaemia. Amongst the 15 patients there were six venous, six arterial, two microvascular events, and two cases of obstetric morbidity. Nine patients were single-positive, and six double-positive for aPL. None were triple aPL-positive. Four thrombotic patients at our centre had recurrent thrombotic/obstetric events, including while on anticoagulation/antiplatelet treatment. Identification of MPN in APS patients can inform thrombotic risk assessment.

Keywords: *Myeloproliferative neoplasm, antiphospholipid syndrome, antiphospholipid antibodies, venous thromboembolism, arterial thrombosis, microvascular thrombosis*

Introduction

Antiphospholipid syndrome (APS) is an acquired autoimmune thrombophilia defined by thrombosis (venous, arterial or microvascular) and/or obstetric complications in the context of persistent antiphospholipid (aPL) antibodies: lupus anticoagulant (LA), IgG and/or IgM anti-beta-2 glycoprotein-1 (aβ2GP1) and/or anticardiolipin antibodies (aCL) (1). The standard treatment of arterial and venous thrombosis in APS is anticoagulation with warfarin or an alternative vitamin K antagonist (VKA). For venous thromboembolism (VTE), standard intensity warfarin (target 2.5 [range 2.0-3.0]) is the preferred treatment option. The European Medicines Agency (EMA) states that direct oral anticoagulants (DOACs) are not recommended for APS patients, especially those who are triple aPL-positive, i.e. have LA, IgG and/or IgM aβ2GP1 and aCL (2). British Society for Haematology and International Society on Thrombosis and Haemostasis guidance advise that DOACs may be considered following a first VTE in single- and double aPL-positive APS patients, and should be avoided in those who are triple-positive (3, 4). There is a lack of substantive data on the management of APS and arterial thrombosis, however standard intensity VKA, with or without an antiplatelet agent, or high-intensity VKA (target 3.5 [range 3.0-4.0]) is advocated (5-7). The annual risk of recurrent thrombosis in APS while taking a VKA was up to 4.0% and 3.1% in two randomised controlled trials (RCTs);(8, 9) 4.3% in a prospective observational cohort study of 1,000 APS patients;(10) and 4.8% in a retrospective cohort study of triple aPL-positive APS patients (11).

The commonest *BCR-ABL* negative myeloproliferative neoplasms (MPN) are polycythaemia vera (PV), essential thrombocythaemia (ET) and primary myelofibrosis (PMF). Patients with MPN are at increased risk of venous and arterial thrombosis, sometimes combined with a significant bleeding risk (12). Thrombotic events are more frequent in PV than in ET and MF, and venous thrombosis can occur in unusual sites such as splanchnic vein thrombosis, even

in those with a normal full blood count (13). These events significantly contribute to morbidity and mortality (14). Adverse pregnancy outcomes are more common in patients with MPN: in a study of 151 women with ET and no previous history of thrombosis, 26.5% (n=40/151) had a miscarriage (15). This is compared with a reported risk of miscarriage in the general population of between 11-22% (16).

The risk of thrombotic events for patients with MPN can be stratified into low-, intermediate- and high-risk categories, primarily based on the patient's age and history of previous thrombosis (17). For those in the high-risk group, there is clear evidence that cytoreduction reduces the rate of thrombotic complications (18). In a randomised study of 114 high-risk ET patients, hydroxycarbamide plus aspirin significantly lowered the incidence of thrombotic events compared to aspirin alone (n=2/56, 3.6%, vs. n=14/58 patients, 24%, p = 0.003) (19). In the PT-1 trial, 809 patients with high-risk ET were randomised to receive either anagrelide or hydroxycarbamide (in addition to aspirin) (20). After a median follow-up of 39 months, the rates of arterial thrombosis and serious haemorrhage were significantly higher, and the rate of VTE significantly lower, in the anagrelide arm compared to the hydroxycarbamide arm, despite equivalent long-term control of platelet counts (20).

For MPN patients who develop VTE, the use of antithrombotic treatment should be coupled with special care to manage bleeding risk factors, particularly considering that thrombocytosis is associated with platelet function defects (21). The risk of recurrent VTE in MPN was reported as 6% per patient/year in a single-centre, retrospective study including 526 patients. In those with recurrent events, only three of 35 (9%) occurred on anticoagulation, suggesting a prolonged period of anticoagulation may be beneficial in this cohort (22). In a single retrospective study, recurrence after TIA/stroke in patients with MPN was estimated at 1.18 per 100 patient-years (23).

A small number of studies have reported aPL as a potential biomarker to assess thrombotic risk in MPN patients. In these studies a diagnosis of APS is not confirmed. In a study of 160 patients with primary Budd Chiari Syndrome were assessed for an underlying thrombotic disorder. 50/103 (49%) had MPN (PV n=27, ET n=9, idiopathic myelofibrosis n=2, unclassified n=11) and 37/150 (25%) had aPL (24). One cohort study of 68 patients with ET identified a higher prevalence of aPL (IgM aCL and aβ2GP1, titres unreported) compared with healthy controls, suggesting that aPL levels may aid in identifying MPN patients at highest risk of thrombosis, particularly IgM aβ2GP1 (25). Assessment of aPL in 50 patients with MPN compared with 30 controls demonstrated that IgM aCL were present in 11/50 (22%) compared with 1/30 (3%) in the control arm ($p<0.021$) (26).

In summary, both APS and MPN are associated with an increased risk of thromboembolism, venous, arterial and microvascular. However, coexistence of both disorders would expect to confer a higher risk of thrombosis or recurrence. We report herein a single centre and literature review of patients with coexistent APS and MPN.

Methods

Systematic review

A literature search was conducted in line with the PRISMA guidelines to search for all published articles up till and including January 2019. Three independent researchers (SN, ZS, ME) performed searches of the world literature using the databases PubMed, Cochrane Library, and Web of Knowledge. The PubMed MeSH terms were: ‘antiphospholipid syndrome’, ‘anti-phospholipid syndrome’, ‘lupus anticoagulant’, ‘anticardiolipin’, ‘myeloproliferative disease’, ‘myeloproliferative neoplasm’, ‘MPN’, ‘polycythaemia rubra

vera', 'polycythaemia', 'PCV', 'essential thrombocytosis', 'essential thrombocythaemia', 'ET', 'myelofibrosis'. We applied the following filters: English language, abstract available. References from original articles were also examined; no further relevant publications were identified, thus ensuring quality of the initial search. Patients were included if they met the criteria for APS i.e persistent positivity (>12 weeks apart) for medium positive IgG and/IgM aCL and/or aβ2GP1 and/or LA (1). Patients were considered to have 'highly likely' APS if: i) positive aPL but persistence of aPL (>12 weeks apart) and/or titre or isotype of antibody was not documented; ii) or if it was likely that the international consensus criteria were met for vascular thrombosis, but not confirmed. Electronic clinic records were searched using the terms 'APS', 'MPN', 'PV' and 'ET' at University College Hospital (UCLH), London. Data was extracted and reviewed.

Results

Our systematic review identified 12 abstracts that reported cases with concurrent MPN and aPL. The full texts of these articles were analysed carefully by two researchers (ZS & SN). Eight studies (49 patients) were excluded due to incomplete APS diagnosis. Although these articles mentioned the presence of aPL, it was not clear whether the criteria to fulfil APS diagnosis were fulfilled e.g. persistent aPL 12 weeks apart (1) (Figure 1). Five cases from four publications were assessed to have either fulfilled or were highly likely to have a diagnosis of APS. Ten further cases were identified in our own cohort of patients based at UCLH.

Patient demographics, aPL status and clinical histories are summarised in table 1. Ten of the 15 patients were female, with a median age of 44 (range 13 - 71) years. Nine had a diagnosis of PV and 6 ET. None had PMF. Thirteen of the 15 patients (86.7%) had

thrombotic APS (seven with initial venous events and six arterial) and two (13.3%) had obstetric APS.

Nine patients were single aPL-positive, and six double aPL-positive. None were triple-positive. Eight of the 15 patients had aLA, with IgG and IgM aβ2GP1 in 2/15 and 4/15, respectively, and IgG and IgM aCL antibodies in 4/15 and 3/15, respectively (the isotype of one aCL was not stated). Two patients at our institution fulfilled the criteria for obstetric APS, both single-positive for LA.

Venous thromboembolic events

Five patients experienced only venous events, with one in combination with obstetric morbidity and another with arterial thrombosis. The seven venous thromboses included; cerebral thrombosis (n=2), deep vein thrombosis (DVT) (n=3), Budd Chiari syndrome (n=1) and portal vein thrombosis (n=1). Four were LA positive, one had moderate/high titre IgM aβ2GP1 antibodies and three IgG aCL antibodies. Three patients had ET and four PV. Treatment included: five patients with standard intensity warfarin target INR 2.5 (range 2.0-3.0) without antiplatelet therapy, one with apixaban 5mg twice daily and one with warfarin target 3.0 (range 2.5-3.5) and low dose aspirin (LDA) 75mg once daily.

Arterial and microvascular events

Six patients had seven arterial events (one in combination with a venous event). These comprised cerebral infarct (n=3), splenic artery occlusion (n=1), transient ischaemic attack (n=1), aortic valve thrombus (n=1) and brachial artery thrombosis (n=1). Five had a diagnosis of PV and one ET. Three patients had moderate/high titre aβ2GP1 (two with IgM and one with IgG). Moderate/high titre aCL were present in five patients (two with IgM, one

with IgG and one unknown isotype). Three were LA positive. Two patients were treated with standard-intensity warfarin and LDA, one with intermediate-intensity warfarin, target INR 3.0 (range 2.5-3.5) plus LDA and one with high-intensity warfarin target INR 3.5 (range 3.0-4.0) without the use of aspirin. Two patients received VKA (without LDA) with no information on target INR range provided as not treated at UCLH.

Two patients had microvascular events including erythromelalgia and necrotic toe. One had a diagnosis of PV and the other ET. Both patients had moderate/high titre aCL (one with IgG and the other with IgM) and one patient also had IgG aβ2GP1. Erythromelalgia was treated with 100mg aspirin alone and the necrotic toe was treated with warfarin (target INR not documented) and an antiplatelet agent.

APS-related obstetric morbidity

Two patients had obstetric APS manifested by second trimester miscarriages. Patient five (table 1) presented with a miscarriage at 19 weeks gestation and patient 12 (table 1) is reported to have previously had 20 miscarriages between 12 and 16 gestation weeks. Both patients had ET with LA positivity. They were both carriers of the JAK2 V617F mutation.

Recurrent events

Four patients (table 1) at our centre had recurrent events, including while on anticoagulation (together with LDA in a patient with obstetric morbidity). Patient 3 presented with an extensive cerebral venous sinus thrombosis (CVST) initially, and had a recurrent CVST two years after her initial presentation, associated with a subtherapeutic INR on warfarin at 1.1 (target range 2.0-3.0). After a period on LMWH, the target INR range was increased to 2.5-3.5 but due to erratic INRs, she was subsequently switched to rivaroxaban 20mg od (weight

62.5kg), following which, she developed splenic vein thrombosis. Again, a period of LMWH was followed by reinitiating warfarin at high intensity.

Patient 6 presented with an arterial event (ischaemic stroke), and subsequently had a further ischaemic stroke ten years later while on warfarin and LDA. The INR was subtherapeutic at 1.4, target range 3.0-4.0, 3.0-3.5 ideal) on the day of this event during bridging prior to a colonoscopy. The target INR range was subsequently modified to 3.5-4.0 ideal following this second event, at which point the LDA was discontinued.

Patient 12 developed TIAs while on warfarin target INR range 2.0-3.0 for previous VTE (prior to diagnosis of APS) , but on admission with her first TIA, the INR was subtherapeutic at 1.4. She was discharged on bridging LMWH but represented seven days later with recurrent TIA (INR 2.5). Her INR range was subsequently increased to INR range 3.0-4.0, 3.0-3.5 ideal.

Patient 5 with obstetric APS initially presented with a miscarriage at 19 weeks gestation. An ultrasound scan demonstrated fetal growth restriction. At autopsy, a placental biopsy showed infarction. During a subsequent pregnancy she was treated with LDA and prophylactic dose LMWH, initiated at four weeks gestation. Despite this, she experienced a first trimester miscarriage at nine weeks gestation. Her third pregnancy was treated with aspirin 150mg once daily and intermediate dose LMWH started at four weeks gestation, despite which she had a further miscarriage at eight weeks. There was no chromosomal analysis of the fetus.

Bleeding events

Three patients experienced bleeding complications (table 1). Patient 3 was re-warfarinsed, aiming for a high intensity INR. A week after starting warfarin, while also on once daily

standard therapeutic dose bridging LMWH, presented at the hospital with back pain and was found to have bilateral adrenal haemorrhages. The INR at the time was 2.7. The antiplatelet agent had been discontinued when warfarin was initiated.

Patient 4 experienced recurrent episodes of mild macroscopic haematuria with her urine described as being pink for two months while on standard-intensity warfarin, with no identifiable cause on CT scan. This resolved spontaneously.

Patient 12 experienced minor intermittent epistaxis while on standard-intensity warfarin. She had two to three episodes in one year so was referred for an ear, nose and throat specialist opinion.

Discussion

This systematic review and service evaluation in a single institution has identified 15 patients with coexistent APS (10 confirmed, 5 highly likely) and MPN, nine with PV and six with ET. The majority (13/15, 86.7%) had thrombotic APS, seven with initial venous events and six arterial; and two (13.3%) had obstetric APS. The aPL phenotype was single aPL-positive in nine patients and double aPL-positive in six. Identification of coexistent APS and MPN may influence patient management such as in the case of arterial events where antiplatelet agents, rather than anticoagulation is standard treatment (5-7, 27).

The pathophysiological basis for an association between aPL and MPN is undefined. MPN is reported to be significantly associated with prior autoimmune disease such as polymyalgia rheumatica and Crohn's disease (28, 29). It has been suggested that patients with ET may be more likely to form aPL due to increased negative charge on platelet phospholipid

membranes (30). β2GP1 binds to membrane phospholipids, which subsequently undergo a conformational change, exposing epitopes for certain aPL subtypes (31). Exposure of phospholipid binding proteins such as β2GP1 and endothelial damage may trigger aPL formation (32). The aPL-β2GP1 complex can bind to and activate endothelial cells, platelets and monocytes and aPL binding to these cells can upregulate monocyte expression of tissue factor, a potent initiator of coagulation (30, 32, 33). Neutrophil extracellular traps (NETs) play a key role in the development of both arterial and venous thrombosis (34). Anti-NET antibodies in patients with primary APS are elevated and they may impair NET clearance as well as activating the complement cascade (35). JAK2 V617F expression has been linked to the formation of NETs and thrombosis and it has been suggested that inhibiting JAK2 V617F may reduce thrombosis in MPN (36).

The potential clinical consequences of coexistent APS and MPN merits consideration. No patients were found to be triple aPL-positive, the aPL phenotype considered to be associated with the highest thrombotic risk (37, 38). Four patients had recurrent events, including while on anticoagulation (together with LDA in a patient with obstetric morbidity). Recurrent events were predominantly in the same arterial or venous system as the initial event, which has been demonstrated in APS and MPN patients (39-41). One patient had a recurrent event while on a DOAC (3, 42, 43). The nature of the association between APS and MPN, as well as potential clinical consequences requires definition. This is clinically relevant to guide optimal management of antithrombotic strategies. Identification of underlying pathophysiological mechanisms could inform management approaches.

A key strength of this work is its novelty. It provides direction for studies to elucidate the relationship between APS and MPN and define the impact on clinical practice. Limitations are the retrospective nature of data collection and the small number of patients.

In conclusion, patients with a new thrombosis, particularly arterial, and MPN should be considered for APS assessment as this could lead to a change in management, namely with the use of a VKA rather than antiplatelet agents alone.

Acknowledgments

ZS, SN and ME performed the literature review, collected and analysed the data. All authors contributed to writing the paper

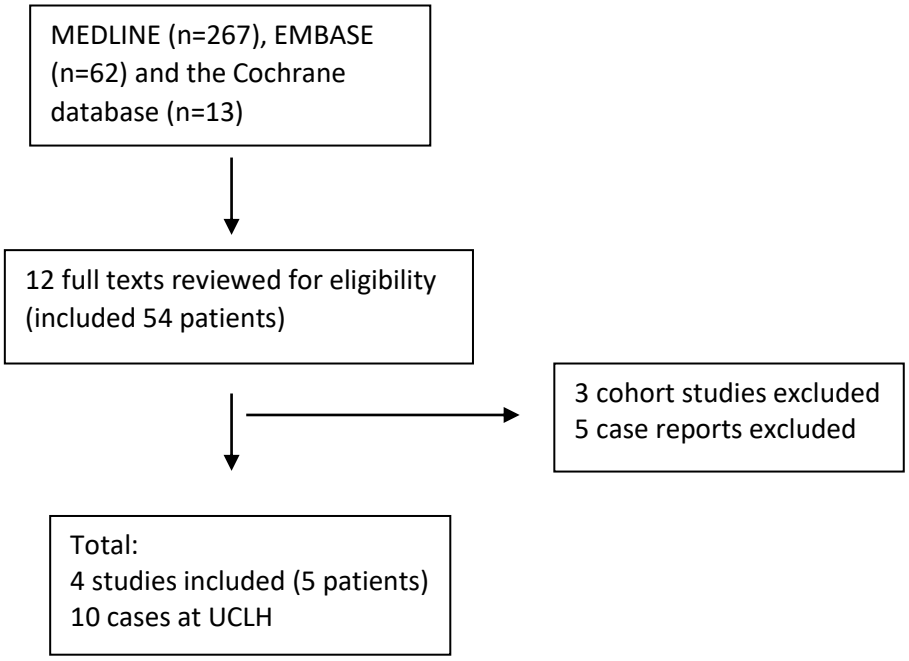

Figure 1: Study flow diagram

Table 1. Baseline characteristics										
No	**Sex**	**Age**	**MPN type**	**Mutation**	**MPN Treatment**	**LA**	**aCL**	**aß2GP1**	**Presenting arterial/venous event or obstetric morbidity**	**Blood results at time of thrombotic event**	**Initial treatment for thrombosis/obstetric morbidity**
1.^	M	71	PV	JAK2 V617F	HU	-	-	IgG	Arterial: Splenic artery occlusion	Hct 0.44 Plt 440 x 10^9/L	Warfarin (target INR 3.5)
2.^	M	21	ET	MPL Exon 10 MPL W515K	HU	+	-	-	Venous: Transverse/sigmoid sinus thrombosis	Plt 689 x 10^9/L	Warfarin (target INR 2.5)
3.^	F	46	PV	JAK2 V617F	Venesection HU	+	-	IgM	Venous: Sagittal sinus thrombosis	ND	Warfarin (target INR 2.5)
4.^	F	36	PV	JAK2 V617F	HU, aspirin	-	IgM	IgM	Arterial: TIA	ND	Warfarin (target INR 2.5)
5.^	F	33	ET	JAK2 V617F	PEG-IFN aspirin	+	-	-	Obstetric morbidity	Plt 900 x 10^9/L	Aspirin 75mg OD
6.^	F	28	PV	JAK2 V617F	HU, anagrelide PEG-IFN aspirin	+	-	IgM	Arterial: Cerebral infarct	ND	Warfarin (target INR 2.5)
7.[1]	F	44	ET	NA	HU	+	IgM	-	Arterial: Cerebral infarct	ND	Warfarin (target INR ND)
8.*[1]	F	62	ET	NA	HU, aspirin	-	IgM	-	Microvascular: Erythromelalgia[ŧ]	Platelets 1000-1200 x 10^9/L	NA
9.*[2]	F	47	PV	NA	Anagrelide	+	+[¥]	-	Arterial: Aortic valve thrombus	Hb 119g/L Plt 384 x 10^9/L	Warfarin (target INR ND)
10.*[3]	F	31	PV	JAK2 V617F	HU, antiplatelet (ND)	-	IgG	IgG	Microvascular: Necrotic toe	Hb 182 g/L Hct 0.538 Plt 552 x 10^9/L	VKA (target INR ND)
11.*[4]	M	13	ET	NA	NA	+	-	-	Venous: Budd Chiari syndrome	Hb 59 g/L (microcytic, hypochromic) Plt 689 x 10^9/L	Warfarin (target INR 2.5)
12^	F	70	ET	JAK2 V617F	HU	+	-	-	Venous: Portal vein thrombosis Obstetric morbidity	ND	Warfarin (target INR 2.5)
13^	M	71	PV	JAKV617F	PEG-IFN, aspirin	-	IgG	-	Arterial: Cerebral infarct, Brachial artery thrombosis Venous: DVT	ND	Warfarin (target INR 3.0)
14^	M	46	PV	JAKV617F	NA	-	IgG	-	Venous: DVT	Hb 133g/L Hct 0.385 Plt 281 x 10^9/L	Apixaban 5mg twice daily

15^	F	44	PV	JAKV617F	PEG-IFN	-	IgG	-	Venous: DVT	Hb 135g/L Hct 0.418 Plt 380 x 10^9/L	Warfarin (target INR 2.5)

aß2GP1: anti-beta 2 glycoprotein 1 antibodies; aCL: anticardiolipin antibodies; ET: Essential thrombocythaemia; F: Female; HU: Hydroxycarbamide; LA: lupus anticoagulant; M: Male; MPN: Myeloproliferative neoplasm; NA: not applicable; ND: not documented; OD: once daily; PEG-IFN: pegylated interferon alpha; PV: Polycythaemia vera; TIA: Transient ischaemic attack; VKA: vitamin K antagonist; ^ University College London Hospital patient; * Likely APS, but unable to confirm if aPL testing to confirm persistence was >12 weeks apart and/or titre of antibodies; ˟ Likely International consensus criteria met for vascular thrombosis, but unable to confirm; ¥ Isotype not documented

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