Antiphospholipid Syndrome with Monoclonal Gammopathy—A Mechanism for Recurrent Thrombosis?

Andrew J. Doyle[1] Karen A. Breen[1] Beverley J. Hunt[1]

[1] Centre for Thrombosis and Haemostasis, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom

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Address for correspondence Andrew J. Doyle, Centre for Thrombosis and Haemostasis, St Thomas' Hospital, Westminster Bridge Road, London SE1 7EH, United Kingdom (e-mail: Andrew.Doyle@gstt.nhs.uk).

Recurrent thromboses are a feature of antiphospholipid syndrome (APS) despite anticoagulation.[1] The mechanism for the development of antiphospholipid (aPL) antibodies remains elusive. Circulating plasmablasts are thought to produce aPL antibodies to domain I of β2-glycoprotein when a cryptic epitope is exposed.[1,2]

Treatment for thrombotic APS is with long-term anticoagulation. Vitamin K antagonists are the preferred anticoagulant particularly in those with "triple-positive" aPL serology.[3] Khamashta et al described 20 to 40% rates of thrombosis recurrence per year without anticoagulation.[4] Crowther et al showed that with adequate warfarin treatment, the estimated recurrence is 3 to 10% per year.[5] Bazzan et al described rates of thrombosis recurrence after the initial thrombosis of 7.5% over 5 years although 45% were not receiving anticoagulation.[6] The mechanism(s) for thrombosis recurrence despite appropriate anticoagulation remain largely unclear.[1,6]

Monoclonal gammopathy producing a paraprotein can cause various renal conditions (monoclonal gammopathy of renal significance), AL amyloidosis, and type 1 cryoglobulinemia. In some cases, these may progress to myeloma or lymphoma although many remain within diagnostic thresholds of monoclonal gammopathy of undetermined significance. Paraproteins have been increasingly associated with numerous systemic conditions due to the paraprotein having functional autoantibody activity.[6] These include C1 inhibitor deficiency, acquired von Willebrand syndrome, cutaneous bullous diseases, immunoglobulin M (IgM)-associated peripheral neuropathy, and xanthomatosis.[7,8] The development of aPL antibodies in the setting of a monoclonal gammopathy may therefore be distinct from those with an autoimmune-driven syndrome. Case reports have described the presence of aPL antibodies in monoclonal gammopathies.[9–14] Some have had thrombotic events and others have described aPL activity attributed to the identified paraprotein.

We present a group of patients with thrombotic APS found to have an associated monoclonal gammopathy. We recognized this feature in a small number of patients who were found to have thrombosis recurrence despite appropriate anticoagulation.

Patients diagnosed with thrombotic APS at our center with an identifiable paraprotein from January 1, 2015 to January 1, 2020 were reviewed. Cases were age- and gender-matched to patients with thrombotic APS without a paraprotein over this period. Clinical records were reviewed retrospectively for medical history and treatments. Diagnosis was made by Sydney Criteria with methods for aPL detection described previously in accordance with current recommendations.[15–17] Protein electrophoresis was performed using Capillarys 2 system (Sebia, France).

Nine patients were identified with thrombotic APS with associated monoclonal gammopathy. Their clinical features and treatment are described in ►**Table 1**. Cryoglobulinemia and hyperviscosity syndrome were not seen. The median age at monoclonal gammopathy diagnosis was 55 years (range: 45–73 years) and median time from first thrombosis to monoclonal gammopathy diagnosis was 10.6 years (range: 2–26 years). The paraprotein immunoglobulin subtype was the same as immunoglobulin subtype of the identified anticardiolipin and/or anti-β2-glycoprotein-1 antibody in all patients.

Comparison was made between those with monoclonal gammopathy and matched controls (►**Table 2**). This showed lower rates of other autoimmune conditions and preponderance for arterial events at presentation. Lupus anticoagulant was largely present in both cases (100%) and control (92%). The rate of "triple-positive" serology was 4/9 (44%) versus 12/36 (33%) (Fisher's exact test, $p = 0.7$) with monoclonal gammopathy versus without.

The rates of thrombosis recurrence in all patients with a monoclonal gammopathy were 7/9 (89%) versus 15/36 (42%) in those without ($p = 0.058$; ►**Fig. 1A**). Rates of thrombosis

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Georg Thieme Verlag KG,
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Table 1 Clinical features and treatment of patients with monoclonal gammopathy-associated APS

Patient	Gender	Site/age of initial thrombosis	aPL serology	PP type	Monoclonal disorder	Anticoagulation	Treatment for monoclonal disorder	Response to treatment
1	Female	42, lower limb arterial	LA IgG β2GP-1	IgG κ	Lymphoplasmacytic lymphoma	Warfarin	DRC Ibrutinib Bortezomib	Lymphoma progression with increasing PP Further ischemic strokes
2	Female	Lower limb arterial	LA IgG ACL IgM β2GP-1	IgM κ	Lymphoplasmacytic lymphoma	Warfarin	R-CVP R-CVD Ibrutinib PEX	Lymphoma progression with increasing PP Further cerebral small-vessel disease with anticoagulation
3	Male	48, cerebral	LA	IgG λ	MGUS	Warfarin	Nil	Further cerebral ischemic events with anticoagulation
4	Female	65, upper limb arterial	LA IgM ACL IgM β2GP-1	IgM λ	MGUS	Warfarin	Nil	No recurrence
5	Female	18, DVT	LA IgG β2GP-1	IgG κ	Smoldering myeloma	Warfarin	Nil	DVT recurrence with anticoagulation
6	Female	40, DVT	LA IgG ACL IgG β2GP-1	IgG κ	MGUS	Warfarin	Nil	CAPS with DOAC
7	Female	47, cerebral	LA	IgG λ	Smoldering myeloma	Warfarin	Nil	No recurrence
8	Male	46, cerebral	LA IgG ACL IgG β2GP-1	IgG κ	MGUS	Warfarin	Nil	Progressive neurocognitive deterioration
9	Male	40, splanchnic vein	LA	IgG κ	MGUS	Warfarin	Nil	Recurrence with anticoagulation (CVST)

Abbreviations: ACL, anticardiolipin antibody; APS, antiphospholipid syndrome; β2GP-1, anti β2GP-1 antibody; CAPS, catastrophic antiphospholipid syndrome; CVST, cerebral venous sinus thrombosis; DOAC, direct oral anticoagulant; DRC, dexamethasone, rituximab, cyclophosphamide; DVT, deep vein thrombosis; LA, lupus anticoagulant; MGUS, monoclonal gammopathy of unknown significance; PEX, plasma exchange; PP, paraprotein; R-CVP, rituximab, cyclophosphamide, vincristine, prednisolone; R-CVD, rituximab, cyclophosphamide, dexamethasone.

recurrence with monoclonal gammopathy while on anticoagulation were 6/9 (67%) versus 4/36 (8%) without ($p = 0.002$; ►**Fig. 1B**). Two patients received multiple lines of cytoreductive treatment for lymphoplasmacytic lymphoma. Both patients had a reduction in their IgM paraprotein levels with cytoreduction corresponding to >50% decrease in their IgM aPL titers. One patient received both anticoagulation and ibrutinib resulting in intracranial hemorrhage. Further thrombosis occurred with temporary cessation of anticoagulation. One patient also received monthly plasma exchange in conjunction with anticoagulation, stopping the progression of cerebral small-vessel disease.

We describe a novel finding of monoclonal gammopathy in a small group of patients with thrombotic APS, who demonstrated higher rates of recurrent thrombosis when receiving anticoagulation when compared with those without a paraprotein. In our clinical management of APS with recurrent thromboses, protein electrophoresis is now performed. The overall incidence of paraprotein associated with thrombotic APS is unclear as they are not routinely assessed in APS. This should be the subject of further evaluation. In the interim, we feel that analysis for a paraprotein and subsequent histopathological studies if present should be considered in APS with unexplained recurrent thrombosis, particularly those on appropriate long-term anticoagulation.

Previous case reports have described the presence of aPL antibodies in both plasmacytic and lymphocytic disorders. These cases have demonstrated either incidental aPL antibodies in patients with monoclonal gammopathy or following thrombotic events, for which aPL antibodies were considered as a contributing or causative factor.[9–14] Other aPL-antibody-mediated conditions such as lupus anticoagulant hypoprothrombinemia syndrome presenting with a bleeding diathesis have been described with multiple myeloma.[18,19] Paraproteins with aPL-antibody activity in patients with a variety of monoclonal disorders, including myeloma and Waldenström's macroglobulinemia, have been described.[20–25] Both monoclonal gammopathy and APS are independently associated with an increased risk of thrombosis and therefore thrombotic events may be due to this cumulative effect.[1,26] However, we suspect that in some patients, the paraprotein has an aPL-antibody activity and therefore is potentially driving this thrombotic tendency particularly in those with higher levels of paraprotein. The next step to test this hypothesis would be to isolate these paraproteins and assess their aPL activity.

Long-term anticoagulation with vitamin K antagonists is advised in patients with thrombotic APS.[26] In those with a paraprotein, targeting the monoclonal disorder may be an additional treatment option. Two patients in our case series

Table 2 Clinical features of patients with monoclonal gammopathy-associated APS in comparison to those with thrombotic APS without a detectable paraprotein

Clinical features	Monoclonal gammopathy-associated APS ($n = 9$)	Thrombotic APS with no gammopathy ($n = 36$)
Median age (range)	57 y (47–75)	58 y (47–77)
Gender (male:female)	3:6	12:24
Diagnosis of SLE	2/9 (22.2%)	6 (16.7%)
Diagnosis of other AI condition	1/9 (11.1%)	11 (30.5%)
Median age at first thrombosis (range)	42 y (19–65)	47 y (19–65)
Site of first thrombosis		
Venous	3 (33%)	19 (53%)
Arterial	6 (67%)	17 (47%)
Microvascular	0	0
Obstetric complications		
Early pregnancy loss	0/6	0/24
Late pregnancy loss	0/6	1/24
Other morbidities	2/6	1/24
aPL serology		
Lupus anticoagulant	9 (100%)	33 (92%)
IgG/IgM anticardiolipin	4 (44%)	19 (53%)
IgG/IgM anti-β2-glycoprotein 1	6 (67%)	13 (36%)
Triple positive	4 (44%)	12 (33%)
Recurrence of thrombosis	8 (89%)	15 (42%)
Recurrence of thrombosis with anticoagulation	6 (67%)	3 (8%)

Abbreviations: AI, autoimmune; aPL, antiphospholipid antibody; APS, antiphospholipid syndrome; SLE, systemic lupus erythematosus.

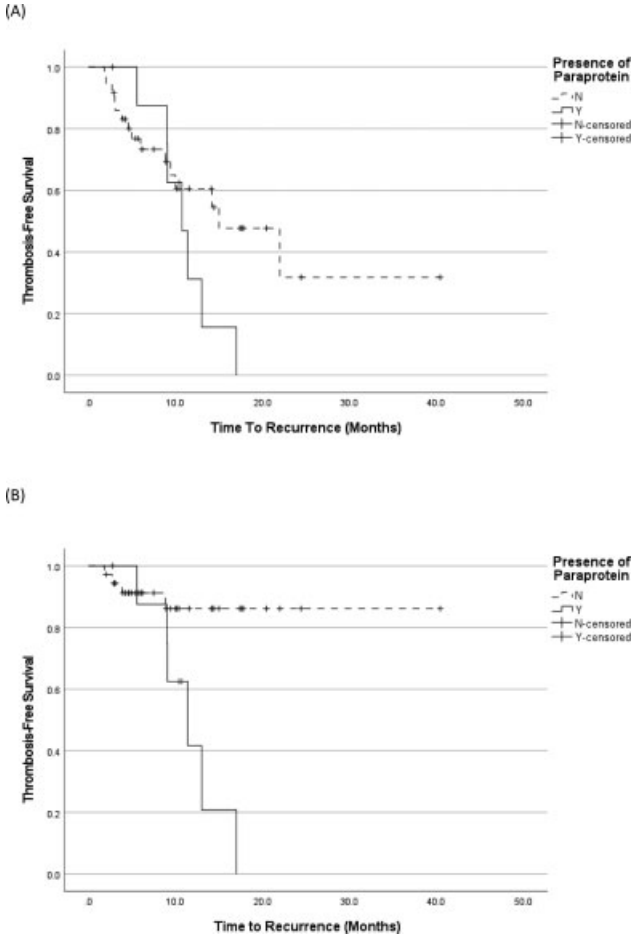

Fig. 1 (**A**) Thrombosis-free survival in those with monoclonal gammopathy in comparison to those without ($p = 0.175$). (**B**) Thrombotic recurrence on anticoagulation ($p = 0.004$).

received cytoreductive therapy for their associated hematological malignancy with thrombosis recurrence in one patient following lymphoma progression. Considerations of drug interactions, bleeding, and prothrombotic risk must be considered due to the recognized adverse effects of some cytoreductive therapies.

To conclude, the investigation of APS with recurrent thrombosis despite anticoagulation should include protein electrophoresis. This could be considered as a potentially distinct mechanism of thrombotic APS. Optimization of anticoagulation and consideration for cytoreduction to reduce paraprotein levels may be tentative treatment options. This is being explored in other disorders with monoclonal gammopathy causing end-organ damage.[7] Further research is required to define this association: these include the frequency of paraproteins in APS, whether these paraproteins have aPL activity, and lastly, what optimal treatment options are.

Author Contributions
A.J.D. designed the study, collected the data, and wrote the manuscript. K.A.B. and B.J.H. designed the study and critically reviewed the manuscript.

Conflict of Interest
None declared.

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