Antiphospholipid syndrome: the burden of inadequate anticoagulation management

Sirs,

Current guidelines on thrombotic antiphospholipid syndrome (APS) recommend prolonged anticoagulation by vitamin K antagonist (VKA), sometimes combined with antiplatelet (1). However, the long-term risk of thrombotic recurrence is not well known and VKA usage increases bleeding risk and requires regular blood tests. Therefore, one may be tempted to stop VKA or switch with direct oral anticoagulant (DOAC). We report four new illustrative cases demonstrating that anticoagulant discontinuation does not only increase the risk of recurrence but may also trigger a severe complication of APS, the catastrophic antiphospholipid syndrome (CAPS) (Table I).

The first patient was a 47-year-old woman with arterial and obstetrical APS with lupus anticoagulant (LA), anti-cardiolipin (aCL), anti-β2-glycoprotein-1 (aβ2GP1) and anti-DNA antibodies. Her anticoagulation by warfarin was switched to low molecular weight heparin before injection by botulinum toxin to counter thigh spasticity. One week later, chest pain with dyspnoea and fever ensued. Computed-tomography (CT) images showed bilateral pleural effusions, pulmonary emboli and bilateral adrenal haemorrhages. Laboratory analyses revealed non-obstructive acute renal insufficiency, thrombocytopenia, adrenal insufficiency and increased C-reactive protein. These rapidly appearing multiple symptoms were consistent with CAPS and she was treated with unfractionated heparin, steroids and therapeutic plasma exchanges (tPEXs). Her status further deteriorated leading to respiratory insufficiency and death.

The second patient was a 59-year-old woman with APS characterised by three unexplained, consecutive miscarriages and non-infectious aortic endocarditis (Libman-Sacks) with high titre antibodies (aCL IgG and aβ2GP1 IgG). She underwent mechanical valve replacement, and took aspirin and acenocoumarol. They were stopped to perform colonoscopy and gastroscopy for microcytic anaemia. Several days later, abdominal pain and mild rectal bleeding appeared followed by bilateral thoracic pain and acute respiratory distress syndrome requiring intensive care. She then suffered remitting events: haemodynamic collapse, renal insufficiency and thrombocytopenia. Imaging revealed alveolar haemorrhage, bilateral adrenal haemorrhages and cardiac akinesia without prosthetic valve dysfunction. She was treated with danaparoid, vasopressors and after haemodynamic stabilisation, tPEXs and steroids were started. Respiratory distress recurred and CT images showed multiple pulmonary abscesses. Broad-spectrum antimicrobials and mechanical ventilatory support were implemented. She succumbed to uncontrolled septic shock and multiple organ failure two

Table I. Clinical characteristics of the four cases.

Characteristics	Case 1	Case 2	Case 3	Case 4
Age at APS diagnosis (yrs.)	23	23	41	28
Age at relapse (yrs.)	47	59	43	48
Sex	F	F	F	F
Thrombotic phenotype	Ischaemic stroke	None	Deep venous thrombosis	Deep venous thrombosis and pulmonary embolism
Obstetrical events	Pre-eclampsia and HELLP	3 Unexplained consecutive miscarriages	None	None
Other	None	Non-infectious aortic endocarditis, mechanical valve replacement	Moderate thrombocytopenia	Heterozygous factor-V (Leiden) mutation
Antibody profile	Triple-positive: LA, aCL (91 UGPL) and aβ2GP1 (71 USG)	Double-positive: aCL IgG 365GPL and aβ2GP1 IgG 233 U/mL	Triple-positive: LA, aCL IgG 171 UGPL and anti-β2GP1 IgG 593 UGPL	Single-positive: LA
Cardiovascular risk factors	Hypertension	None	None	None
SLE clinic/ biology	Anti-DNA, anti-SM, anti-RNP antibodies	Anti-DNA antibodies, arthralgia, pericarditis	Anti-DNA, anti SM, anti-SSA antibodies	Anti-DNA antibodies, Evans syndrome
Treatment	Warfarin	Acenocoumarol and aspirin	Fluindione and hydroxychloroquine	Warfarin and hydroxychloroquine
Clinical events at relapse	Pulmonary emboli, renal failure, adrenal haemorrhage with adrenal insufficiency, haemorrhagic stroke	Liver, gastric and colic necrosis with renal failure and necrosis, pulmonary haemorrhage, cardiogenic shock, bilateral adrenal haemorrhages with adrenal insufficiency	Ischaemic stroke	Livedo reticularis and digital ischemia, acute coronary syndrome without ST elevation, adrenal necrosis without adrenal insufficiency
CAPS	Yes	Yes	No	Yes
VKA stop-to-thrombotic relapse interval	5 days	4 days	1 month	2 weeks
Treatment at relapse	LMWH (VKA stopped)	None	Rivaroxaban	None
Other precipitating factors	None	Colonoscopy and gastroscopy, context of disseminated aspergillosis	None	None
Treatment of relapse	UFH, Methylprednisolone, tPEXs	Danaparoid, steroids, tPEXs, antibiotics and antifungal	Warfarin	UFH, steroids, tPEXs
Outcome	Died	Died	Resolution without sequelae	Resolution with mild ischaemic sequelae

aCL: anticardiolipin; aβ2GP1: anti-β2-glycoprotein-1; HELLP: haemolysis with elevated liver enzymes and low platelet count; LA: lupus anticoagulant; LMWH: low molecular weight heparin; tPEXs: therapeutic plasma exchanges; UFH: unfractionated heparin; VKA: vitamin K antagonist.

months later. Autopsy found multiple organ necroses and aspergillosis in lungs, myocardium and endocardium.

The third patient was a 41-year-old woman with APS characterised by two deep venous thrombophlebitis (DVT) associated with LA, aCL IgG and aβ2GP1 IgG. Initial treatment comprised hydroxychloroquine and fluindione. For personal convenience fluindione was switched to rivaroxaban (20 mg/day). One month later, aphasia and right upper limb apraxia appeared. Magnetic resonance imaging confirmed left middle cerebral artery occlusion causing global sylvian infarct. There was no evidence of Libman-Sacks endocarditis. Warfarin replaced rivaroxaban and her clinical status improved without sequelae.

In the last case, a 48-year-old woman developed APS characterised by venous thromboembolic disease (five unprovoked DVT and pulmonary emboli) associated with persistent LA. Warfarin and hydroxychloroquine were prescribed. She was hospitalised for meningeal syndrome that revealed chronic left subdural haematoma, it was drained and anticoagulation was discontinued. Two weeks later, she was hospitalised for chest and abdominal pains. Physical examination found livedo reticularis and digital ischaemia. Laboratory analyses revealed elevated troponin and electrocardiographic changes compatible with ischaemia. CT images showed adrenal necrosis. CAPS was suspected; effective anticoagulation was restarted, combined with tPEXs and steroids. She rapidly improved and was discharged under warfarin. Only mild digital ischaemic lesions persisted.

We described four women with different APS clinical phenotype and antibody profile in whom VKA interruption led to APS relapse (ischaemic stroke) or CAPS (three cases), 5-to-14 days later. The CAPS-Registry analysis identified precipitating factors for 65% of cases, with the three most common precipitating being infections (49%), surgery (17%) and malignancy (16%) (2). In our cases, the main precipitating factor identified was recent VKA discontinuation. Hence, anticoagulation misuse alone may trigger CAPS more frequently than previously thought. Additionally, accumulating precipitating factors increases the CAPS risk. This led to devising CAPS prevention (3) and suggesting perioperative APS-management strategies: whenever possible minimise the time without anticoagulation and consider any unusual event possibly APS-related (4). DOACs are as effective as VKA at reducing the risk of recurrent venous thromboembolism with a lower risk of major bleeding (5). They are the treatment-of-choice in the general population, but not APS (6). In the first randomised, controlled trial (RAPS) against warfarin, rivaroxaban did not reach the non-inferiority threshold (7). Furthermore, rivaroxaban was associated with more arterial thrombotic and haemorrhagic complications than warfarin in triple positive patients (8, 9). Finally, the most recent trial comparing apixaban *versus* warfarin was amended to exclude arterial and triple positive APS but was terminated prematurely due to low patient accrual and increased stroke risk (10).

Interruption of VKA in APS patient may be the sole trigger of severe APS complications and must be avoided. Besides, DOAC use seems at risk of increased recurrence, especially in arterial and triple positive APS.

K. Nassarmadji[1], *MD*
A. Brigante[1], *MD*
C. Larroche[2], *MD*
P. Cacoub[3], *MD*
N. Costedoat-Chalumeau[1], *MD, PhD*
V. Le Guern[1], *MD*
L. Guillevin[1], *MD, PhD*

[1]Department of Internal Medicine, Assistance Publique-Hôpitaux de Paris (APHP), Hôpital Cochin, Université Paris Descartes, Paris, France;
[2]Department of Internal Medicine, APHP, Hôpital Avicenne, Université of Paris, Bobigny, France;
[3]Department of Internal Medicine, APHP, Hôpital Pitié-Salpêtrière, Université Pierre et Marie Curie, Paris, France.

Please address correspondence to:
Loïc Guillevin,
Service de Médecine Interne, Hôpital Cochin, Université Paris Descartes, 27 Rue du Faubourg Saint-Jacques, 75014 Paris, France.
E-mail: loic.guillevin@aphp.fr

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