CASE REPORT

An extraordinary case of recurrent stroke, disseminated thrombosis and endocarditis

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SUMMARY

A 43-year-old woman with no known cardiovascular risk factors was admitted with a second episode of ischaemic stroke. She was not a known case of connective tissue disease like systemic lupus erythematosus or antiphospholipid syndrome (APS). During the current episode, she was found to have markedly deranged coagulation parameters and laboratory evidence of microangiopathic haemolysis, but no evidence of sepsis or active bleeding. Further investigation revealed multiple organ infarcts. A diagnosis of probable catastrophic APS was made and she improved dramatically with a combination of plasmapheresis, corticosteroids and therapeutic anticoagulation. Serological markers of APS were negative. Her hospital course was complicated by Libman Sacks endocarditis with significant aortic regurgitation that improved markedly with anticoagulation obviating the need for high-risk cardiac surgery. At discharge, she was stable and well and was advised long-term anticoagulation and rheumatology follow-up.

BACKGROUND

Catastrophic antiphospholipid syndrome (CAPS) is a rare entity and prompt diagnosis is critical for definitive management of this otherwise fatal condition. Manifesting in less than 1% of those known to have APS, it has a mortality approaching 50%. In those not known to have APS, an initial presentation as CAPS is an extremely challenging diagnosis, not only due to its rarity but also because of its myriad multisystemic manifestations.

Here we aim to shine the spotlight on seronegative CAPS (SCAPS), an even rarer entity. SCAPS, though described in a handful of cases previously, has not yet established itself in the lexicon of rheumatology. This particular case stands out as a unique case, where prompt diagnosis of CAPS in a patient not previously known to have Connective Tissue Disease (CTD) or APS with treatment initiation within the first 72 hours of the patient's presentation to the hospital resulted in rapid improvement in the deranged parameters averting a full blown catastrophe. Thus, through this case we aim to emphasise three important learning points: first, CAPS may be the initial manifestation of APS; second, CAPS may be SCAPS and finally, prompt diagnosis and aggressive management based on the clinical presentation can be lifesaving.

This case also demonstrated that therapeutic anticoagulation in certain selected scenarios is a

reasonable and maybe even better alternative to cardiac surgery for management of cardiac valvular lesions.

CASE PRESENTATION

A 43-year-old, unmarried woman of Egyptian origin presented to the hospital with a history of sudden-onset left-sided weakness and numbness which was preceded by dizziness and nausea. There was no history of headache, diplopia or seizures. There was no history of fever, chest pain or shortness of breath.

She had a history of stroke with weakness involving her left side, 3 months back for which she had been thrombolysed, with subsequent recovery of her motor power to near normal. She had no history suggestive of arthritis/ulcers and no systemic symptoms. She had no history of previous abortions.

Her medical history was significant for hypothyroidism for the past 5 years, for which she was on thyroxine supplementation and regular follow-up. She also had a history of uterine fibroid diagnosed 3 years back and had menorrhagia and consequently, iron deficiency anaemia. She was a non-smoker and did not consume alcohol. She had no significant family history. On examination, she had stable vital signs, mild pallor and neurological signs of left hemianopia, left upper motor neuron facial palsy and left hemiparesis. Abdominal examination revealed right lower abdomen fullness, and a palpable, firm, rounded, non-tender mass, around 5×7 cm, in the suprapubic and right iliac fossa, arising from the pelvis. A CT scan brain showed an acute ischaemic right temporo-occipital infarct (figure 1). She was admitted in the stroke unit, kept under careful neuro-observation, started on antiplatelet and statin as per the protocol. She was found to have deranged coagulation parameters, low platelets and a blood film showing schistocytes. Provisional diagnosis of Disseminated Intravascular Coagulation (DIC) complicating a possible underlying malignancy was considered and an abdominal CT scan performed. The CT scan revealed a large uterine fibroid (figure 2) with red degeneration and haemorrhagic ovarian cysts (likely endometriosis) but significantly and unexpectedly revealed multiple splenic and bilateral renal infarcts (figures 3 and 4).

In summary, this 43-year-old woman with two strokes in the absence of conventional cardiovascular risk factors had deranged coagulation, DIC like laboratory picture with no clinical bleeding

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Figure 1 CT brain images showing acute right temporo-occipital and chronic temporoparietal and basal ganglia infarct. Above: at presentation. Below: at discharge.

and a CT scan suggesting multiorgan thrombosis. Thus, a diagnosis of probable CAPS was seriously considered. With haematology consultation, plasmapheresis, pulse methylprednisolone,

Figure 2 CT abdomen showing multiple uterine fibroids in the uterus extending into the abdominal cavity.

Figure 3 CT abdomen showing hepatomegaly and multiple hypodense lesions in the spleen showing multiple splenic infarcts.

therapeutic anticoagulation and mycophenolate mofetil were initiated simultaneously. Over the next 3 days, her coagulation parameters, and DIC like blood picture improved dramatically ([table 1](#)).

Echocardiography, as part of stroke work up revealed severe aortic regurgitation (AR) due to malcoaptation of the valves secondary to aortic valve masses suspected to be either infective or marantic vegetation ([figure 5](#)). In the clinical scenario, it was more likely to be non bacterial thrombotic endocarditis (NBTE) or Libman Sacks endocarditis. A cardiothoracic consultation was done and surgery with valve replacement was advised once her condition stabilised.

A Computed tomography Pulmonary Angiogram (CTPA) done revealed bilateral segmental and subsegmental pulmonary embolism and Doppler ultrasound of lower limbs showed left saphenous vein thrombosis. Her autoimmune profile and APS antibody serology reported after 1 week were all negative. CA-125 was significantly high at 1359 U/mL. Other tumour markers notably Alpha fetoprotein (AFP), Beta Human Chorionic Gonadotropin (B HCG) and carcinoembryonic antigen (CEA) were negative.

Figure 4 CT abdomen showing bilateral renal infarcts.

Table 1 Trend of haematological parameters from day 1 to 5

	Day 1	Day 2	Day 4	Day 5
Hb (MCV)	8.3 (74.9)	7.6		7.7
Platelets	50 000	27 000	48 000	94 000
PT/INR	25.2/2.27	33/3.27	23/2.02	19/1.63
APTT	75.2	87.2	40	34
Dimer (0.5 mg/L)		17.5		0.64
Fibrinogen (200–400 mg/dL)		60		

APTT, activated partial thromboplastin time; Hb, haemoglobin; INR, international normalised ratio; MCV, mean corpuscular volume; PT, prothrombin time.

INVESTIGATIONS

Haematology

Blood film: RBCs— NCNC, anisopoikilocytosis, occasional fragmented cells.

WBCs—neutrophilia. Platelets—reduced, presence of giant forms.

Autoimmune markers

- ▶ Anticardiolipin-immunoglobulin (Ig)G/IgM: <2 GPL U/mL
- ▶ AntidsDNA:negative
- ▶ Antinuclear factor (ANF): negative
- ▶ Beta 2 glycoprotein (B2GLY) IgG/IgM: negative
- ▶ Phosphatidyl serine/phosphatidylglycine: <2 RU/mL negative
- ▶ p-ANCA Myeloperoxidase (MPO), c-ANCA (PR 3): <5 U/mL(negative)
- ▶ ADAMTS 13 abs. (cp) 0.9 U/mL
 - (**) ADAMTS-13 activity (cp) 41.8% 40.0–130.0
 - (**) ADAMTS-13 antigen (cp) 0.68 µg/mL 0.60–1.60

Tumour markers

- ▶ AFP-TM: 0.5IU/mL
- ▶ CEA: 4.9 ng/mL
- ▶ CA-125: 1359 U/mL
- ▶ B HCG: negative

CT brain ([figure 1](#)): acute right temporo-occipital non-hemorrhagic infarct. Chronic right temporal, parietal and basal ganglia infarction.

CT abdomen with contrast ([figures 2, 3 and 4](#)): hepatomegaly. Multiple renal and splenic infarcts.

Figure 5 Transoesophageal echocardiogram showing large, pedunculated, friable vegetation on the aortic valve leaflet.

Red degeneration of uterine fibroids. Haemorrhagic ovarian cysts/endometrioma in pelvis.

Transoesophageal ECHO heart ([figure 5](#)): There are multiple masses attached to the aortic valve, pedunculated and friable, largest measuring 2 by 1 cm. These masses result in malcoaptation of the aortic valve leaflets with severe highly eccentric Aortic regurgitation (AR). These masses represent either a thrombus or vegetations. A less likely possibility would be a tumour (either primary cardiac like fibroelastoma or even less likely a secondary tumour (ie, metastasis). Intact interatrial septum with no evidence of a shunt.

DIFFERENTIAL DIAGNOSIS

- ▶ Endocarditis: systemic emboli.
- ▶ Malignancy: DIC.
- ▶ Thrombotic thrombocytopenic purpura (TTP).

There were a number of differential diagnosis based on her clinical presentation and subsequent investigations. However, none of them could satisfactorily explain the complex and unusual presentation except CAPS, which in this case also happened to be seronegative (SCAPS).

1. Endocarditis/valvular mass/and systemic emboli: the echocardiography described multiple masses attached to the aortic valve. From the clinical scenario, they are unlikely to be infective because of absent evidence of infection, both clinical and laboratory. These then could most likely be thrombi or primary cardiac tumours (though rare cannot be definitely ruled out without a biopsy). Emboli from these masses could explain the stroke as well as the multiple systemic infarcts (including pulmonary assuming a patent foramen ovale (PFO)) and the schistocytes. It would not however explain the saphenous vein thrombosis and the deranged coagulation. Therefore, the cardiac valves probably have thrombi, which are likely part of the disseminated systemic thrombosis that is seen in this patient.
2. Malignancy and DIC: an underlying malignancy could probably explain the multiple thrombosis in various organs, deranged coagulation and DIC like picture observed in this patient including the marantic valvular vegetations. Tumour markers were done and did reveal a high CA-125, and CT scan showed uterine mass and ovarian cyst. However, despite laboratory features of DIC, there are no bleeding manifestations in this patient. Notably, DIC in malignancies are features either of advanced malignancies or of specific haematological malignancies. Moreover, they are usually resistant to treatment other than directed specifically at the underlying malignancy.
3. TTP: an entity which can manifest as a disseminated thrombosis with schistocytes in the blood film. However, the similarity ends there because the coagulation in this case is impaired, which is not a feature of TTP and there is no renal involvement. It does not explain the cardiac manifestations and the strokes. Moreover, ADAMTS 13 was done and was negative.

The differences between CAPS, TTP and DIC are summarised in [table 2](#).

To summarise, we have a young female with recurrent stroke, with an acute onset of disseminated thrombosis in spleen, bilateral kidneys, superficial vein thrombosis, pulmonary embolism, DIC like picture, thrombocytopenia and valvular thrombi. No condition can explain this except catastrophic APLA. This could be primary or secondary. And though it is more likely to be primary we cannot at this stage definitely rule out an

Table 2 Differences between CAPS, TTP and DIC. Guntz *et al*²⁸

	CAPS	TTP	DIC
Thrombotic mechanism	Antibody mediated	Antibody mediated	Sepsis, drugs, malignancy...
Thrombotic site	Microvascular	Microvascular	Microvascular
Haemorrhagic manifestations	Absent/–	Maybe present +/-	Present++
Haematological manifestations			
Anaemia	+/-	+	+/-
Schistocytes	+/-	++	+/-
Thrombocytopenia	+/-	++	+
Labs			
Prolonged PT	+	–	+
Prolonged APTT	+	–	+
FDP/dimer	+	–	++
Immunological			
Antiphospholipid Ab	++	+/-	+/-

Ab, antibody; APTT, activated partial thromboplastin time; FDP, fibrin degradation product; PT, prothrombin time.

underlying malignancy presenting with catastrophic Antiphospholipid Antibodies (APLA).

TREATMENT

Therapeutic clexane, plasmapheresis, pulse steroids, mycophenolate initiated simultaneously on day 2 of presentation.

OUTCOME AND FOLLOW-UP

The thrombocytopenia and deranged coagulation parameters improved by day 3 of therapy. The cardiac valvular lesions and AR) were followed up with a repeat ECHO heart after 22 days and showed significant improvement in the AR and decrease in size of the valvular thrombi (figure 6).

Her neurological status was stable with no recovery of power in the left upper limb and 3/5 power in the lower limb. She had one episode of GTCS presumably scar epilepsy secondary to previous Middle cerebral artery (MCA) territory stroke.

Regarding her large uterine mass, likely fibroid and ovarian cysts, gynaecologists were not in favour of urgent intervention and advised routine outpatient follow-up.

She was continued on therapeutic clexane to be changed to warfarin at a later date (as she was keen to travel and follow-up in her home country) and a target INR between 3 and 4 advised.

At discharge, she was conscious, oriented, with persisting left hemiparesis but able to mobilise with support. She had no cardiac symptoms and cardiovascular examination was unremarkable. She was advised lifelong high-intensity anticoagulation and

Figure 6 Transthoracic ECHO showing significant resolution of the aortic valve vegetation. Left panel: August 18. Right panel: September 7.

Box 1 Criteria for diagnosis of APS (Sydney, 2006) Updated Sapporo APS classification criteria.³ APS, antiphospholipid syndrome.

Clinical criteria

1. Vascular thrombosis: 1 clinical episodes of arterial, venous or small vessel thrombosis, in any tissue or organ
2. Pregnancy morbidity:
 - a. ≥ 1 unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, or
 - b. ≥ 1 premature births of a morphologically normal neonate before the 34th week of gestation because of: eclampsia, severe pre-eclampsia, or recognised features of placental insufficiency, or
 - c. ≥ 3 unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

Laboratory criteria

1. Lupus anticoagulant present in plasma, on more than equal to two occasions at least 12 weeks apart.
2. Anticardiolipin antibody of IgG and/or IgM isotype, in medium or high titre (>40 GPL or MPL, or $>$ the 99th percentile), on more than equal to two occasions, at least 12 weeks apart.
3. Anti- $\beta 2$ -glycoprotein-I antibody of IgG and/or IgM isotype, in medium or high titre ($>$ the 99th percentile), on more than equal to two occasions, at least 12 weeks apart.

Definite APS is present if at least one of the clinical criteria and one of the laboratory criteria are met.

APS, antiphospholipid syndrome; Ig, immunoglobulin.

mycophenolate mofetil for a period of 3 months, until further rheumatological review.

DISCUSSION

From the introduction of the APS or Hughes syndrome,¹ in 1983 to a decade later when CAPS was described by Asherson,² till the latest addition of an entity called SNAPS in 2003 by Hughes and Khamashta, this syndrome continues to evolve, paralleling advancements in lab technology and our understanding of the disease. In this paper we bring into the spotlight yet another terminology, SCAPS, which though described before, has not been officially defined.

A diagnostic criterion for APS originally proposed by Sapporo in 1996 was later updated in the Sydney classification in 2006 (box 1).³ CAPS was defined and classified as per international consensus in 2003 (box 2), and included a definition of 'probable' CAPS,⁴ emphasising the need for a high index of clinical suspicion, to facilitate prompt treatment initiation for this otherwise rapidly fatal condition.

Despite the revised and updated classifications, the complex nature and highly variable manifestations of the disease, make it extremely challenging to diagnose, especially when the initial presentation is a catastrophic episode, without history of thrombosis, and negative antiphospholipid (aPL) antibodies.^{5 6}

SNAPS first introduced in 2003, by Hughes and Khamashta, is a terminology used for patients who have clinical features of APS but are negative for the *conventional* antibodies described in the Sapporo criteria, namely anticardiolipin (aCL) antibodies, anti- $\beta 2$ -glycoprotein -I antibodies and lupus anticoagulant. Three possible explanations for the existence of such

Box 2 Preliminary classification criteria for CAPS (Asherson *et al* 2003).⁴

1. Evidence of involvement of three or more organs, systems and/or tissues.
2. Development of manifestations simultaneously or in less than a week.
3. Confirmation by histopathology of small-vessel occlusion.*
4. Laboratory confirmation of the presence of APA.†

*Definite CAPS

► All four criteria present

*Probable CAPS

- All four criteria, except only two organs, systems, and/or tissues involved.
- All four criteria, except for the absence of lab confirmation of (APA).
- Criteria 1, 2 and 4.
- Criteria 1, 3 and 4, with the development of a third event >1 week but within 1 month of presentation, despite anticoagulation.

*Vasculitis may coexist, but significant thrombosis must be present as well.

†'Positive aPL' twice 12 weeks apart.

APA, antiphospholipid antibodies; aPL, antiphospholipid; CAPS, catastrophic antiphospholipid syndrome.

'seronegative' cases have been proposed: the diagnosis is wrong, previously positive aPL tests have become negative or, as seems most likely, the current range of tests is inadequate.⁷ Conclusions from a study by⁸ Fabrizio *et al* exploring the 'mosaic of SN-APLA' suggest that in sera from patients with SNAPS, antibodies may be detected using 'new' antigenic targets (mainly vimentin/cardiophilin) or methodological approaches different from traditional techniques (mainly thin-layer chromatography immunostaining). *Thus, SNAPS represents a mosaic, in which antibodies against different antigenic targets may be detected.*⁸

Similar to classical APS, SNAPS can also have a fulminant or catastrophic course with accelerated and disseminated thrombosis.⁹ Apart from the possible explanations mentioned previously for 'seronegative' APS, it is possible that transient seronegativity could be due to consumption of antiphospholipid (aPL) antibodies during thrombotic episodes which would be even more pronounced during the disseminated thrombosis as seen in CAPS.^{10–12}

Though there have been several cases of CAPS reported in patients with pre-existing APS or cases that initially presented with suspected CAPS and were later confirmed to be CAPS by positive antibodies, *this case is one of a handful of cases which were not known to have pre-existing APS or connective tissue disorder and was diagnosed and reported as SCAPS.*^{13–15}

- In the case reported by Losonczy *et al*,¹³ a 29-year-old woman initially presented with headache due to cerebral venous thrombosis and aortic and splenic artery thrombosis in the background of diabetic ketoacidosis and hyperthyroidism. The patient recovered with a combination of steroids, plasma exchange and intravenous Ig but the work up and diagnosis is not clear, and the multivessel thrombosis had other contributing factors notably diabetic ketoacidosis.
- Another case reported by Park *et al*,¹⁴ in a 20-year-old man, discussed a case of DIC and multiple thrombosis in portal, hepatic, mesenteric and renal veins, with no aPL antibodies. He was started on steroids, but the diagnosis was suspected

only on day 8, and intravenous Ig initiated. This was followed by rituximab and eventual recovery of the patient.

Our patient was a 43-year-old woman who presented with stroke and was found to have a haematological picture of DIC with no bleeding manifestations. On day 2 of admission, CT imaging was done showing infarcts in the spleen and both kidneys. At this early juncture, CAPS was suspected and aggressive management initiated with plasmapheresis, anticoagulation, pulse methylprednisolone and mycophenolate. *To the best of our knowledge, such a prompt diagnosis and management has not been reported in the literature in a patient who is not a known case of APS or autoimmune disease like systemic lupus erythematosus (SLE). The patient improved dramatically with haematological manifestations resolving rapidly over the next 72 hours.*

In a descriptive analysis done by Cervera *et al* published in 2009, from data of around 280 patients in the CAPS registry established by the European forum in 2000, it was reported that a majority suffered from primary APS as opposed to SLE, lupus-like disease and other autoimmune diseases. Precipitating factors were observed in 40% and noted to be infections, surgery and withdrawal of anticoagulation, medication, obstetric complications, neoplasia and lupus flare. Pertinent to our case report, it was also found that CAPS was the first manifestation of APS in 46% of the patients.¹⁶

Over the course of her stay, she was also found to have bilateral segmental and subsegmental PE, as well as saphenous vein thrombosis. Further complicating her hospital course was the discovery of aortic 'vegetations, valvular masses' on echocardiography, which in the clinical context was most likely 'Libman Sacks' or thrombotic non-bacterial endocarditis (initially described in SLE in 1924, and later in APS in 1985).^{17,18} However, their larger size 2×0.5 cm, and description as 'friable', pedunculated and causing 'severe eccentric AR' posed major management challenges. The role of cardiothoracic intervention in view of high risk of a recurrent cardio-embolic stroke was discussed and debated. There is currently no consensus on this issue and no clear guidelines. The use of corticosteroids is controversial, as it has been implicated in accelerated healing causing leaflet thickening and scarring of valves leading to progressive valvular dysfunction.¹⁹ Anticoagulation has been reported to facilitate resolution of the valvular lesions/vegetations.^{20,21} Immunosuppressants may be beneficial. In a prospective study of patients with primary APS, new cardiac lesions were significantly related to high IgG levels and aCL antibody titres, suggesting that lowering these titres with immune-modulating therapy may prevent the development of cardiac lesions.²¹

Our patient was haemodynamically stable, with no cardiac symptoms. Furthermore, there was no valvular destruction and the AR was a result of malcoaptation of the valves. Considering these factors, it was decided to continue conservative management with anticoagulation and mycophenolate and defer potentially complicated and high-risk cardiac surgery in the setting of a prothrombotic state, with mortality rates up to 25%.²²

She had no further thrombotic episodes. A repeat echocardiography done 22 days later showed significantly reduced size of vegetation (from 2×0.5 cm to 1.3×0.4 cm) and only a mild AR.

A case report of cardiac surgery with valve replacement in Libman Sacks endocarditis²³ typifies the dilemma faced by the treating team and under the circumstances, surgery may be justified. But it is worthwhile to consider that thrombotic masses would respond to anticoagulation and as demonstrated in our case, a close follow-up and therapeutic anticoagulation may be equally if not more appropriate in the setting of hypercoagulable state and high-risk surgery.

Treatment and prognosis

Management of CAPS include a combination of anticoagulants, corticosteroids, plasma exchange, intravenous Ig and immunosuppressants.

The prognosis for patients with CAPS is poor with 25%–50% mortality unless treated aggressively. Various modalities of treatment have been tried (no randomised trials), mainly targeting the accelerated thrombosis and the cytokine cascade. The combination of anticoagulation, glucocorticoids and plasma exchange with or without intravenous Ig has been associated with recovery rates ranging from 50% to 8%.

Retrospective study of data from the CAPS Registry found that recovery rates of up to 75% was achieved by a combination of anticoagulation, glucocorticoids and plasma exchange.²⁴ Newer modalities CAPS, notably rituximab and eculizumab, have been tried in refractory or resistant cases and reported to be of benefit.^{25 26}

Prognosis

Patients who survive the catastrophic thrombotic episode usually do fairly well on long-term anticoagulation specifically warfarin. Newer oral anticoagulants have not yet been approved for this subset of patients. In a study by Erkan *et al*, assessing long-term outcome of 58 survivors of CAPS,²⁷ over a 5-year period, it was observed that only around 20% of them developed recurrent thrombotic events, and a majority of these events occurred perioperatively.

Learning points

- Catastrophic antiphospholipid syndrome (CAPS) could be the initial manifestation of APS.
- CAPS can be seronegative CAPS.
- Suggestive clinical features, with no likely alternative diagnosis should alert the physician to the possibility of CAPS triggering prompt and aggressive management.
- Combination of anticoagulation, high-dose corticosteroids and plasmapheresis initiated promptly and simultaneously seems to be highly effective.
- Conservative management with anticoagulation for cardiac valvular lesions may be a reasonable option in the absence of compelling indications for cardiac surgery.

Contributors LMT: the first author was closely involved in patient care, diagnosis and decision making in the reported case. She has done the research, drafted and reviewed the final case report. NAS: has provided guidance and support throughout the patient's hospital course, in crucial management decisions. He has critically analysed the draft and helped review and finalise it. RP: significantly contributed to edit and revise the manuscript.

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