CASE REPORT

Antiphospholipid syndrome masquerading as a case of infective endocarditis

Sarah Micallef,¹ Charles Mallia Azzopardi²

¹Department of Medicine, Mater Dei Hospital, Msida, Malta
²Infectious Diseases, Mater Dei Hospital, Msida, Malta

Correspondence to
 Dr Sarah Micallef,
 sarah.a.micallef@gov.mt

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SUMMARY

A 54-year-old Caucasian woman presented with an episode of loss of consciousness and dysphasia. MRI revealed a number of ischaemic foci indicating an embolic source. Echocardiography showed a mitral valve vegetation. After taking three sets of blood cultures, she was started on empirical treatment for infective endocarditis. The blood cultures remained negative and a presumed diagnosis of culture-negative endocarditis was entertained. However, despite the antibiotic therapy, the patient deteriorated further. Subsequently the patient was found to be positive for antiphospholipid antibodies. Eventually, after a convoluted hospital stay, a diagnosis of antiphospholipid syndrome complicated by Libman-Sacks endocarditis was reached. The patient was treated with steroids and anticoagulation with dramatic improvement.

BACKGROUND

Antiphospholipid syndrome (APS) is an autoimmune condition characterised by the occurrence of pregnancy loss and venous or arterial thrombosis, among other features.¹ One recognised complication of APS is Libman-Sacks endocarditis, which consists of non-infectious thrombotic vegetations.² A more severe form of APS is catastrophic APS (CAPS), which constitutes 1% of patients with APS.³ CAPS represents a devastating condition with multiorgan involvement and an associated significant mortality rate.

CASE PRESENTATION

A 54-year-old Caucasian woman, with a history of anxiety and depression, presented to the emergency department after being found unconscious at home by her daughter. She lost consciousness for about 10 min, and this was followed by a 30 min period of confusion. There was no evidence of tongue biting or urinary incontinence, no jerking movements were witnessed, and the patient was amnesic to the event. Prior to presentation, the patient had complained of a 6-week history of malaise, fatigability, joint pains and fevers. These symptoms had been accompanied by anorexia and loss of appetite. The patient had been started on low-dose prednisolone 4 weeks prior to admission to the hospital by a rheumatologist, who had suspected polymyalgia rheumatica. The patient gave a family history of maternal rheumatoid arthritis. On examination, she was hypertensive with a systolic of 175 mm Hg, but otherwise the

other parameters were normal and the patient was afebrile. A full examination including a cardiovascular and neurological examination revealed no abnormality.

INVESTIGATIONS

CT scan of the brain on admission showed a focal hypodense area in the right parietal lobe measuring 10 mm in diameter. MRI of the brain performed the following day showed scattered foci of restricted diffusion in both hemispheres, in keeping with embolic infarctions; some were described as acute (figures 1–3), whereas some were described as chronic (figure 4). Subacute infective endocarditis (IE) was suspected, and a transthoracic echocardiogram performed on the third day of admission showed mitral regurgitation, although no obvious vegetations were noted.

Blood investigations taken during the first few days of admission included complete blood count, renal profile, erythrocyte sedimentation rate (ESR), C reactive protein (CRP), multiple sets of blood cultures, antinuclear antibodies (ANA), anticardiolipin antibodies, rheumatoid factor and complement levels. No organisms were grown after prolonged blood culture incubation. Both ESR and CRP were raised at 94 mm during the first hour (17–21 mm first hour) and 93 mg/L (0–10 mg/L), respectively. Full blood count and renal profile were normal. Complement levels and rheumatoid factor came back normal. The ANA and anticardiolipin antibodies were made available 2 weeks into her admission and showed positive ANA at 1:160 with a homogeneous pattern, while anticardiolipin IgG was positive at 34.7 IgG Phospholipid (GPL) U/mL (0.0–10.0 GPL U/mL).

EVOLVING CLINICAL COURSE AND DIFFERENTIAL DIAGNOSIS

Four days into her stay, the patient suffered an episode of expressive dysphasia, associated with mild right-sided facial weakness and upper limb drift. Infectious diseases were consulted and the patient was started on empirical teicoplanin and gentamicin in view of a working diagnosis of IE with septic embolisation. A transoesophageal echocardiogram was performed on the following day. This identified a vegetation measuring 1.3×0.8 cm attached to the base of the A1 segment of the anterior mitral valve leaflet, together with moderate mitral regurgitation. The cardiothoracic surgeons

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Figure 1 Focus of restricted diffusion in the right hemisphere (arrow), diffusion-weighted image. AFR, Anterior Foot - Right; LFA, Left foot - Anterior; PHL, Posterior head - Left; RHP, Right Head - Posterior.

were consulted, who felt that there was no indication for acute surgical intervention.

During the subsequent days, her dysphasia gradually improved, but she remained febrile, with fevers up to 38°C, despite persistently negative blood cultures. In view of the positive ANA and anticardiolipin antibodies, the diagnoses of systemic lupus erythematosus (SLE) and APS were entertained. After discussion, the raised ANA and anticardiolipin antibodies

Figure 2 Foci of restricted diffusion in both hemispheres (arrows), diffusion-weighted image. AFR, Anterior Foot - Right; LFA, Left foot - Anterior; PHL, Posterior head - Left; RHP, Right Head - Posterior.

Figure 3 Two foci of restricted diffusion in the left hemisphere (arrow), diffusion-weighted image. AFR, Anterior Foot - Right; LFA, Left foot - Anterior; PHL, Posterior head - Left; RHP, Right Head - Posterior.

were thought to be false positives, possibly raised due to the presumed IE. The absence of any history of miscarriages, thrombotic events or migraines, rashes, mouth ulcers, alopecia, pleuritic pains, or Raynaud's made SLE or APS less likely. On the

Figure 4 Hyperintensity in the right occipital lobe on axial FLAIR (arrow), in keeping with a chronic infarct. AFR, Anterior Foot - Right; FLAIR, Fluid-attenuated inversion recovery; LFA, Left foot - Anterior; PHL, Posterior head - Left; RHP, Right Head - Posterior.

other hand, starting the patient on anticoagulation and possibly steroids was then thought to be too risky.

The patient gradually developed a normochromic normocytic anaemia of 8 g/dL with no evidence of haemolysis. Her platelet count remained normal throughout and her renal function remained stable. Her urine microscopy and biochemistry remained normal. The patient underwent an ophthalmic review where no Roth's spots were identified. Dental review identified two carious molars described as a possible source of infection, although the patient remained too unwell to undergo extraction.

Despite ongoing treatment with intravenous teicoplanin and gentamicin, the patient's fever continued to spike. A central line was inserted to facilitate the administration of intravenous antibiotics. On day 30 of admission, a repeat transoesophageal echo was performed, which showed no change in the size of the vegetation. In view of persistently negative blood cultures, culture-negative endocarditis was suspected, and thus her antibiotic spectrum was widened with the addition of ceftriaxone, doxycycline and hydroxychloroquine to cover for HACEK endocarditis (*Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Echinella*, *Kingella* species) and *Coxiella* endocarditis. *Coxiella* serology was also taken.

Coxiella serology eventually proved negative. Further investigations included Bartonella and syphilis serologies, which also resulted negative. Repeat ANA, anticardiolipin antibodies and complement levels taken 4 weeks into admission showed a persistently positive anticardiolipin IgG at 35.4 GPL U/mL and a rising ANA titre from 1:160 to 1:320. Complement levels remained normal.

Six weeks into admission, the patient remained febrile and her general condition continued to deteriorate. She developed fluctuating consciousness and a transient monoplegia of the right upper limb. Suspicion of possible epileptic episodes with subsequent Todd's palsy led to the patient being started on levetiracetam. Electroencephalogram (EEG) showed diffuse bihemispheric slowing consistent with non-specific encephalopathy, but no seizure activity. The patient's general condition deteriorated to the extent that a nasogastric tube had to be inserted to sustain the patient's caloric intake.

Seven weeks into her admission, a CT of the thorax/abdomen/pelvis was performed, specifically looking for a collection of pus or a neoplastic process that could be the possible cause of her fever. This revealed a long thrombus involving the right internal jugular vein and superior vena cava, and thrombosis involving the lower lobar branches of the left pulmonary artery. A small infarction in the upper pole of the spleen was also noted. No fluid collections or abscesses were visualised. Repeat MRI of the brain showed several new bilateral small embolic infarcts compared with the MRI performed 6 weeks previously. A lumbar puncture showed normal opening pressures, biochemistry and cytology. Cerebrospinal fluid (CSF) investigations for *Cryptococcus*, tuberculosis, microscopy and culture came back negative. CSF viral PCR was also negative for herpes zoster, enterovirus, mumps, parechovirus and varicella zoster.

Further blood tests showed a normal serum protein electrophoresis, and ANA and anticardiolipin antibodies were repeated. The results subsequently showed an increasingly positive anticardiolipin IgG at 45.9 (0.0–10.0 GPL U/mL), a positive ANA at 1:320 (this time with a speckled pattern) and persistently normal complement.

In view of the progressive deterioration despite broad-spectrum cover for IE, and the rising ANA titre and anticardiolipin antibody levels, the diagnosis of APS became much more likely. Lupus anticoagulant as well as anti-B₂ glycoprotein levels were

taken. Lupus anticoagulant (by dilute Russell viper venom test) subsequently came back positive, and anti-B₂ glycoprotein levels were found to be elevated at 8.7 (0.0–5.0 U/mL).

Given this new evidence, the final diagnosis was changed to that of APS, possibly CAPS, complicated by Libman-Sacks endocarditis.

TREATMENT

The patient was started on intravenous unfractionated heparin and intravenous methylprednisolone 1 g daily. The unfractionated heparin was subsequently stopped in view of a high Activated Partial Thromboplastin Time (APTT) ratio of 7. The patient was switched to enoxaparin at 0.75 mg/kg twice daily. She was given intravenous methylprednisolone for 2 days and eventually switched to oral prednisolone 20 mg twice daily.

OUTCOME AND FOLLOW-UP

The patient showed dramatic improvement, with resolution of the fever and the encephalopathy within 24 hours of starting anticoagulation and steroids, thus supporting the diagnosis of APS, possibly catastrophic, complicated by Libman-Sacks endocarditis. The patient was subsequently switched to warfarin and discharged a few days later.

The patient's CRP, anti-B₂ glycoprotein IgG and anticardiolipin antibodies normalised within 1 month from discharge. Subsequent follow-up at outpatients revealed a very good recovery. The patient remains well. She has no residual weakness and only mild occasional residual word-finding difficulties. She remains asymptomatic from a cardiology point of view with a stable left ventricular systolic function and resolution of the mitral regurgitation. Repeat blood tests showed a normal ANA and anticardiolipin antibody levels up to 7 months after discharge, although they were noted to rise once again a year after discharge, while the patient was asymptomatic and still on steroids.

DISCUSSION

This case is of significant clinical interest because of its rarity and because of the diagnostic dilemmas that it poses. The patient presented with features highly consistent with subacute IE: fever, new-onset mitral regurgitation, mitral valve vegetation associated with embolic phenomena, as well as elevated inflammatory markers.

The Infective Diseases Society of America (IDSA) Duke Criteria was developed to facilitate the diagnosis of IE.⁴ This includes major and minor criteria as listed below:

Major criteria

- ▶ Blood culture positive for IE: typical micro-organisms consistent with IE from two separate blood cultures, or micro-organisms consistent with IE from persistently positive blood cultures, or a single positive blood culture for *Coxiella burnetii* or antiphase 1 IgG antibody titre $\geq 1:800$.
- ▶ Evidence of endocardial involvement on echocardiogram.

Minor criteria

- ▶ Predisposition: predisposing heart condition and intravenous drug use.
- ▶ Fever: temperature $>38^{\circ}\text{C}$.
- ▶ Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial haemorrhage, conjunctival haemorrhages and Janeway lesions.
- ▶ Immunological phenomena: glomerulonephritis, Osler nodes, Roth's spots and rheumatoid factor.

► Positive blood culture that does not meet a major criterion.

A definite diagnosis of IE is made if there are two major criteria present, or one major criterion and three minor criteria present, or all five minor criteria present. A possible diagnosis of IE can be made if one major and one minor criterion are present, or if three minor criteria are present. Using the IDSA Duke Criteria, one could classify this as a case of possible IE based on the presence of one major and at least two minor criteria: evidence of endocardial involvement, fever and vascular phenomena.

With no history of thrombosis, miscarriages or SLE, a diagnosis of APS was not considered as the most likely diagnosis at the outset. The persistently negative blood cultures led to a working diagnosis of possible culture-negative IE, and the patient was started on doxycycline, ceftriaxone and hydroxychloroquine as empirical therapy to widen the antibiotic spectrum. Early in the patient's work-up, both the positive ANA and anticardiolipin antibodies were believed to be false positives secondary to the presumed underlying infection. Failure to improve despite what was believed to be optimal antibiotic therapy and the rising antiphospholipid antibody titres finally led to the realisation that the diagnosis was APS rather than an infectious pathology.

APS is an autoimmune condition characterised by the occurrence of pregnancy loss and venous or arterial thrombosis. Other features may include cardiac valve abnormalities, renal impairment, livedo reticularis and skin ulcers.¹ The cause of APS is unknown. In the minority of cases, it occurs in isolation and is known as primary APS, whereas in the majority of cases it occurs on the background of SLE and is known as secondary APS. With no history of rheumatological manifestations such as rashes, joint problems, alopecia or systemic manifestations, normal complement levels and a negative antidual-stranded DNA antibody on admission, our case was likely to be primary APS.

The pathogenesis of APS seems to involve the interaction of antiphospholipid antibodies with phospholipid surfaces and secondary activation of endothelial cells, platelets, monocytes and a myriad of other cells, resulting in thrombosis.³ The antiphospholipid antibodies are believed to target mainly B₂ glycoprotein I and prothrombin, which subsequently interact with further mediators of haemostasis, causing a disruption of natural anticoagulant systems and fibrinolysis.⁵

One recognised complication of APS is Libman-Sacks endocarditis, also known as non-bacterial thrombotic endocarditis. This consists of the deposition of sterile platelet plugs on valves, causing non-infectious thrombotic vegetations. Libman-Sacks endocarditis may also be associated with malignancy and SLE. The mitral valve is often the most commonly affected valve, mitral regurgitation being the usual result,² as was observed in our case.

The presence of circulating antiphospholipid antibodies, such as anticardiolipin IgG or IgM, anti-B₂ glycoprotein I IgG or IgM, as well as lupus anticoagulant, is required for a diagnosis of APS. False positives may occur in the presence of infection, cancer and catecholamine administration.³ Activated partial thromboplastin time is also occasionally elevated in APS as the antiphospholipid antibodies interfere with phospholipid-dependent clotting tests.

A more severe manifestation of APS is CAPS. CAPS was first described in 1984, affecting about 1% of patients with APS. CAPS is characterised by multiple small vessel occlusions affecting multiple organs.⁵ Data from the CAPS registry show that pulmonary complications can be found in 24% of cases, neurological complications in 18% and renal complications in 18%. The liver, gastrointestinal tract, spleen, adrenal gland and pancreas can also be affected.⁶ This occurs in the presence of a systemic inflammatory response syndrome, secondary to the

release of cytokines from necrotic tissue.⁷ Interestingly, almost 46%–50% of patients with CAPS have no history or manifestations of APS.¹³ Our patient, in fact, had no history or symptoms suggestive of APS.

The salient features of CAPS include the following³:

1. Evidence of involvement of three or more organs, systems or tissues.
2. Development of manifestations simultaneously or in less than a week.
3. Confirmation by histopathology of small vessel occlusion in at least one organ or tissue.
4. Laboratory confirmation of the presence of antiphospholipid antibodies.

A definite diagnosis of CAPS can be made if all four criteria are present.³ A probable diagnosis of CAPS can be made if:

- All four criteria are met but only two organs or tissues are affected.
- All four criteria except for the absence of laboratory confirmation at least 6 weeks apart due to the early death of a patient who was never tested for phospholipids prior to CAPS.
- Presence of features 1, 2 and 4.
- Presence of features 1, 3 and 4 and the development of a third event in more than 1 week but less than 1 month, despite anticoagulation.

Our case easily fits the diagnosis of primary APS complicated by Libman-Sacks endocarditis, based on the thrombotic events, the echocardiographic findings, the antiphospholipid serology (rising ANA titres, anticardiolipin antibody levels, positive lupus anticoagulant and anti-B₂ glycoprotein I antibodies) and the absence of any evidence of infection. On the other hand, the case does not clearly fulfil the above criteria for a diagnosis of CAPS. While multiorgan involvement was observed in our patient, it is difficult to say whether this is a direct outcome of underlying APS or not. For example, the thrombus within the jugular vein and superior vena cava may well have been secondary to the insertion of the jugular venous line, rather than a direct outcome of APS. The pulmonary embolism was likely a direct result of APS, but it could also have been due to embolisation from the central vein thrombosis mentioned above.

Despite this, a diagnosis of CAPS is still a reasonable possibility in view of a number of points. First, the rapidly deteriorating clinical condition in the context of a prominent systemic inflammatory response syndrome is suggestive of CAPS. Second, the fact that such a devastating condition came on suddenly within the space of a few weeks, with no history to suggest SLE or APS, is also in keeping with CAPS. Finally, the dramatic response to steroids and anticoagulation, the recommended treatment for CAPS, makes the diagnosis of CAPS even more convincing.

In one study,³ 65.4% of CAPS cases were precipitated by particular insults—infection was the most common precipitant accounting for 46.7% of cases.⁸ A 'second hit' hypothesis has been proposed in such cases explained as follows: the presence of antiphospholipid antibodies causes a procoagulant state, this being the 'first hit'. The 'second hit' is the inciting factor, namely infection, inflammation or trauma, which leads to thrombus formation.⁵ Organisms implicated include a number of pathogens, including *Streptococcus*.

The treatment of thrombotic APS is usually dependent on antiplatelets or anticoagulants. Antiplatelets such as low-dose aspirin are particularly useful for preventing arterial thrombosis, whereas anticoagulants such as vitamin K agonists and heparin are particularly useful to prevent and treat venous thrombosis.⁷ The treatment of CAPS, on the other hand, is more aggressive

and typically involves a combination of anticoagulants, systemic glucocorticoids, plasma exchange and intravenous immunoglobulins (IVIGs).⁸ Data on treatment in CAPS have largely been compiled from the CAPS registry.³ Survival has been shown to be better in patients with CAPS who receive anticoagulation (63% vs 22%, $p < 0.0001$).⁶ There is no evidence to favour unfractionated heparin over low molecular heparin or warfarin. There is no evidence supporting the use of antiplatelet agents or novel anticoagulants in this condition.³ Steroids blunt the inflammatory response and are recommended by most experts. As steroids are usually used in combination with anticoagulation, there is little evidence to support their use independently. Consensus suggests the use of high-dose steroids such as methylprednisolone for 3 days.³ In our case, starting the patient on intravenous methylprednisolone and heparin resulted in a very significant improvement in the patient's condition within 24 hours.

Of interest is the fact that expert consensus has recently advocated the use of 'triple therapy' in CAPS, advising a strong consideration for plasma exchange and/or IVIG, in addition to anticoagulation and steroid therapy.³ This stems from the fact that plasma exchange has been successfully used to treat other microangiopathies. Studies have shown a survival of 77.8% vs 55.4% ($p = 0.083$) in patients treated with combination anticoagulants, steroids and plasma exchange.⁹ IVIGs can be used instead of plasma exchange in patients with thrombocytopenia, but some experts advocate a combination of IVIGs and plasma exchange. Further treatments that may be of benefit include

cyclophosphamide, particularly for CAPS occurring on a background of SLE, rituximab and eculizumab.³

In conclusion, this case posed a number of clinical dilemmas. The patient presented with sufficient clinical manifestations to meet the criteria for a diagnosis of possible IE complicated by recurrent embolic phenomena. With no pointers to suggest APS or SLE in the patient's history, the positive ANA and anticardiolipin antibodies were thought to be false positives, secondary to the presumed underlying infection. After weeks of broad-spectrum antibiotics and a worsening clinical status, the diagnosis of APS was again revisited. Given all the evidence, a diagnosis of APS, possibly CAPS, was finally made, however only after long weeks of investigation.

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Learning points

- ▶ Antiphospholipid syndrome is characterised by widespread thrombosis that may affect a number of organ systems, including the heart.
- ▶ A high index of suspicion for the condition must therefore be kept in mind.
- ▶ A diagnosis of Libman-Sacks endocarditis should always be borne in mind in patients presenting with endocarditis that is refractory to optimal antibiotic therapy, including targeted therapy for culture-negative endocarditis.
- ▶ Antiphospholipid antibodies should be taken in cases where a diagnosis of Libman-Sacks endocarditis is being considered.
- ▶ Catastrophic antiphospholipid syndrome may be the first ever manifestation of antiphospholipid syndrome.
- ▶ The treatment of catastrophic antiphospholipid syndrome typically involves a combination of anticoagulants, systemic steroids, plasma exchange and intravenous immunoglobulins.

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