ANAESTHETIC IMPLICATIONS OF THE ANTI-CARDIOLIPIN ANTIBODY SYNDROME

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SUMMARY
The anti-cardiolipin antibody syndrome (or anti-phospholipid antibody syndrome) is characterized by the presence of autoimmune antibodies to phospholipids. Its major association is with systemic lupus erythematosus. It is characterized further by in vitro prolongation of phospholipid-dependent coagulation tests. However, in vivo it is associated with a markedly increased incidence of thrombosis, both arterial and venous. We describe the case of a 36-yr-old female patient with the anti-cardiolipin antibody syndrome who presented initially for diagnostic laparoscopy and later for exploratory laparotomy. Her postoperative course after the first general anaesthetic was complicated by disseminated intravascular coagulation and adult respiratory distress syndrome. After the second operation, she deteriorated further with worsening cardiac, renal and respiratory function and eventually died. As far as we are aware, this is the first reported case of the anti-cardiolipin antibody syndrome in anaesthetic literature. Further aspects of this puzzling condition and its anaesthetic implications are discussed. (Br. J. Anaesth. 1993; 70: 587-590)

KEY WORDS
Complications: anti-cardiolipin antibody syndrome.

These patients may present to the anaesthetist for routine and emergency operations, and in the intensive care unit. In addition, as SLE occurs primarily in women in the childbearing age group, with a female: male ratio of approximately 10:1, there is a greater incidence in obstetric patients [9]. The anaesthetist may be involved in the care of these high risk parturients, especially as operative delivery is common. The anaesthetic literature lacks any references on this subject. We present a case report of this condition.

CASE REPORT
A 36-yr-old Indonesian female, gravida 2, para 0, presented to the gynaecologists with a 1-week history of lower abdominal pain, high grade pyrexia and a brief episode of vaginal bleeding. An ultrasound scan demonstrated a pelvic mass consistent with a necrotic ovarian tumour. SLE had been diagnosed 10 years earlier ("lupus like", rather than classical SLE). She was receiving warfarin 3 mg and aspirin 75 mg daily. There was a history of a stroke in the past, but the patient was unable to provide further details because of her and her family's inability to speak English. There were no residual signs of a stroke except for partial blindness in one eye. In addition, her old notes from another hospital were not available at the time. Investigations revealed a haemoglobin concentration of 8.0 g dl⁻¹ and a greatly prolonged prothrombin time (PT) and activated partial thromboplastin time (APTT), with normal platelets. Before diagnostic laparoscopy, the warfarin was stopped and the coagulation profile corrected with fresh frozen plasma (FFP) to bring the International normalized ratio within the therapeutic range. Anaesthesia was induced with thiopentone and suxamethonium and maintained with enflurane, fentanyl and vecuronium. Laparoscopy confirmed the presence of a large ovarian fibroma or a sub-serous fibroid.

After operation in the recovery room, the patient was clinically stable, but developed significant hypoxaemia when oxygen was discontinued. Oxygen therapy was re-commenced and she was transferred back to the ward. In the ward, anticoagulation was...
recommenced with heparin infusion. The patient developed further hypoxaemic episodes in the ward over the next 1 week, accompanied by pleuritic chest pains and shortness of breath. However, ventilation—perfusion scans were not consistent with pulmonary embolism. She continued to have persistent pyrexia (> 39 °C) while receiving broad spectrum antibiotics. All investigations for the cause of the fever were inconclusive (blood cultures, viral serology, malarial parasites etc.).

At this point, the patient’s old notes became available from another hospital. The records revealed a significant history of major thrombotic episodes. Aged 20 yr, the patient had developed sudden unexplained venous thrombosis of her left leg. At the age of 26 yr, after an appendicectomy, she developed retinal vein thrombosis. Investigations led to a diagnosis of SLE although she was anti-nuclear antibody negative. At the age of 32 yr, when 27 weeks pregnant, she underwent emergency Caesarean section under general anaesthesia. Three days post-partum she developed a brain-stem infarct. At this time, she was found to be strongly anti-cardiolipin antibody positive and anticoagulation was commenced with warfarin. Her next presentation was at the age of 35 yr when, after dilatation and curettage for a miscarriage, she developed a cerebellar infarct.

In the light of this history of major thrombotic events and a diagnosis of the anti-cardiolipin antibody syndrome now available, full heparinization was continued. In spite of this, the patient deteriorated further with continuing high pyrexia, becoming semi-conscious with neck stiffness and a blood picture suggestive of disseminated intra-vascular coagulation. CT scan of the head demonstrated old cerebellar and basal ganglia infarcts, but no new changes. The cause of her sudden neurological deterioration was unclear. High-dose steroid therapy was started and antibiotics were continued.

The patient was admitted to the intensive care unit for monitoring of her cardiovascular and neurological state. She made a rapid neurological recovery with resolution of neck stiffness and recovery of full consciousness. However, she remained tachycardic (> 150 beat min⁻¹), pyrexic (> 39 °C), tachypnoeic and hypoxaemic. Echocardiogram was normal. While receiving full heparinization, the patient developed further episodes of pleuritic chest pain. Plasmapheresis was commenced to decrease her concentration of anti-cardiolipin antibody. She continued to deteriorate, with decreasing renal and respiratory function. A pulmonary artery thermodilution catheter was inserted and revealed a central venous pressure of 9 mm Hg, pulmonary artery pressures of 30/18 mm Hg, pulmonary artery wedge pressure of 19 mm Hg, and cardiac index of 1.2. A repeat echocardiogram (within 24 h of the previous one) revealed a large, poorly functioning left ventricle with poor global systolic contraction. Treatment with inotropes and vasodilators (dopamine, dobutamine, adrenaline, nitrates) produced some improvement in cardiac index. In view of the patient’s deterioration and intra-abdominal signs suggestive of a necrotic ovarian/uterine fibroid, it was decided to proceed to exploratory laparotomy.

Heparin was stopped 2 h before operation and anaesthesia induced in the operating theatre with full haemodynamic monitoring. A rapid-sequence induction was performed with etomidate and suxamethonium and anaesthesia maintained with atracurium and incremental doses of fentanyl. The intraoperative course was uneventful. The patient remained haemodynamically stable, with good gas exchange. Laparotomy confirmed the presence of a necrotic ovarian fibroid which was removed. Blood loss was estimated at 300 ml. However, in view of the continuous oozing and decreasing haemoglobin concentration, she was transfused with 1 unit of blood, 6 units of platelets and 2 units of FFP.

The patient was transferred back to the intensive care unit after operation, with full circulatory and ventilatory support. On arrival in the unit, she developed increasing facial oedema with mottled, blueish macular discolouration of the skin and congested neck veins. However, central venous pressure and lung inflation pressures were normal and an echocardiogram did not reveal any new changes. There were no signs of superior vena cava obstruction or cardiac tamponade. Blood-gas analyses revealed severe metabolic acidosis, but normal gas exchange.

Her general condition continued to deteriorate with worsening renal, cardiac and respiratory function in spite of haemodialysis, full inotropic support and continued ventilation. She died 10 days after admission for the initial complaint.

Postmortem revealed only the presence of numerous scattered petechial haemorrhages over the myocardium with left ventricular hypertrophy. The coronary arteries were normal. The cause of death was recorded as cardiac failure. There was pulmonary oedema in the lungs, but no evidence of infarct or emboli. Apart from old infarcts in the basal ganglia and cerebellum, the rest of the postmortem examination was unremarkable.

**DISCUSSION**

The unfortunate demise of this patient prompted us to search the anaesthetic literature on the anaesthetic implications of the anti-cardiolipin syndrome. We were unable to find any information on this subject, apart from one reference to the lupus anticoagulant [10]. A search of the general medical literature revealed a large number of conflicting facts, reports and ideas [1–8].

The anti-cardiolipin antibodies may be part of a family of autoantibodies. A cause and effect relation between presence of antibodies and complications has not been established. About 50% of patients with this syndrome have SLE, although the prevalence of these antibodies in SLE patients may vary from 5 to 55% [7, 8].

Patients with this syndrome who have SLE are usually “lupus like” [11]. The revised American Rheumatism Association criteria for diagnosis of classical SLE requires the presence of four or more typical symptoms (e.g. malar rash, arthritis, photo-
sensitivity, renal involvement) [12]. Most of the patients with classical SLE (> 90%) are antinuclear antibody (ANA) positive. Patients who have fewer than four of the above criteria are labeled “lupus-like” and are usually ANA negative (similar to our patient).

The diagnosis of this syndrome is confirmed by specific tests:

(a) The presence of these antibodies blocks the activity of the X_2-V_Ca^{2+} phospholipid complex required to convert prothrombin to thrombin. In vitro, the phospholipid-dependent coagulation tests (APTT and kaolin cephalin clotting time (KCCCT)) are prolonged, although prothrombin time (PT) and thrombin clotting time are usually normal.

(b) The most sensitive and specific test for the presence of the anti-cardiolipin antibodies is an enzyme-linked immunosorbent assay (ELISA) [13]. The combination of these two tests gives the greatest degree of sensitivity and specificity.

In vivo, these patients have a markedly increased incidence of thromboses. There are many theories on the aetiology of thromboses, but so far none has been substantiated. Current knowledge suggests that these antibodies mediate thrombosis by acting at several sites of action. When platelets are pre-activated by a variety of stimuli, they expose the negatively-charged phospholipids on their surface to the antibodies, resulting in platelet aggregation.

The antibodies also react with surface phospholipids in endothelial cells, inhibiting the production of prostacyclin and interfering with the action of thrombomodulin and protein C in endothelial cells. Thus platelet aggregation is promoted. The clinical manifestations of platelet aggregation and thrombosis could lead to thrombocytopenia [8].

In 40–50% of patients with this syndrome, there is a history of thromboses, both arterial and venous, often recurrent, at unusual sites and occurring spontaneously. This picture was typical of our patient. The venous system involved may be at unusual sites such as the renal, retinal and adrenal venous systems. In addition, one case of superior vena caval occlusion in anti-cardiolipin antibody syndrome has been described [14]. Our patient developed a similar picture after operation, with increasing facial oedema and congested neck veins. Venography to confirm thrombosis is not recommended in these patients.

The obstetric history may show recurrent spontaneous abortions. Presence of circulating anti-cardiolipin antibodies is associated with increased fetal loss in all trimesters and approaches 80% in patients with high titres of antibodies. This was again typical of our patient. The presence of the anti-cardiolipin syndrome in patients with SLE makes the pregnancy a high-risk one. There is an increased incidence of pre-eclamptic toxemia in patients with this syndrome [15].

A prospective study looked at the incidence of cardiac complications in patients with SLE with and without the anti-cardiolipin antibody syndrome [16]. There was a 54% incidence of cardiac complications in the SLE group. However, in the presence of SLE and the anti-cardiolipin syndrome, the incidence was close to 80%. The myocardial changes seen in our patient were those characterized in this study—global and left ventricular dysfunction.

Neurological complications in the anti-cardiolipin antibody syndrome comprise transient ischaemic attacks, strokes and neuropsychiatric disturbances [17]. Our patient showed such a picture, with a sudden neurological deterioration followed by recovery.

In addition, there is another presentation described recently [18], with acute, widespread, non-inflammatory vascular occlusions resulting in major organ dysfunction. The trigger factor seems to be infection, changing the anticoagulation regimen, or both [19]. Patients with this syndrome have a tendency to develop thromboses even while receiving full anticoagulation. Our patient had classical signs suggestive of multiple pulmonary emboli even while receiving full heparinization.

Patients with SLE present a significant morbidity and mortality. The 5-yr survival rate is approximately 75%. The morbidity and mortality is increased substantially in the presence of the anti-cardiolipin antibody syndrome, although no figures are available as yet.

We recommend the following management regimen in patients with the anti-cardiolipin antibody syndrome:

All patients with SLE and a history of recurrent abortions, thrombotic episodes, or both, should be screened for the antibody. If positive, and in the presence of high titres, the complications are increased substantially.

In patients with SLE and in the presence of anti-cardiolipin antibodies but with no history of thrombosis and a normal coagulation screen (except for prolonged APTT), appropriate s.c. preoperative doses of unfractionated heparin or low molecular weight heparin are recommended.

Patients with a history of one or more thrombotic events require permanent anticoagulation and there should be close liaison with haematologists for this purpose. It is important to maintain these patients in their anticoagulated state, with warfarin or aspirin. In the perioperative period, carefully controlled heparin therapy by infusion or given s.c. is recommended.

Regional anaesthesia is generally contraindicated in patients receiving high-dose warfarin. The use of regional techniques in those receiving low-dose aspirin, even with a normal bleeding time, is debatable. The safety of regional blocks in a patient who has the anti-cardiolipin antibody syndrome and prolonged APTT is unknown. The use of regional techniques in the uncomplicated syndrome is probably not associated with any complications. Regional techniques would naturally be contraindicated in the presence of an overt coagulopathy, decreased platelet concentrations, or both.

Patients who have the diffuse coagulopathy, vasculopathy picture (of our patient) need intensive haemodynamic monitoring in the intensive care unit with plasmapheresis (to decrease the titre of the anti-cardiolipin antibody), high-dose steroids, full heparinization and, if disseminated intravascular
coagulation is present, appropriate replacement. In the presence of a circulating anticoagulant, the adequacy of heparinization is monitored preferably with a heparin assay.

From this case history and available literature, the following anaesthetic recommendations would seem appropriate:

(a) All prophylactic measures should be taken to prevent thromboses. Use of anti-embolic stockings, avoiding dehydration and maintaining normothermia should be mandatory.

(b) Drugs likely to precipitate or exacerbate the condition (e.g. hydralazine) should be avoided.

(c) Infection, which is another trigger source for lupus and for initiating coagulopathy, should be prevented by routine antibiotic therapy.

(d) Blood transfusion should be avoided if possible, as this has also been implicated as a trigger factor.

(e) Standard monitoring (heart rate, oximetry, capnograph, ECG, etc.) may be all that is needed for routine cases. In addition, patients may need CVP/pulmonary artery monitoring in the presence of severe cardiac, renal or pulmonary artery involvement.

(f) Postoperative hypoxaemia, when it occurs, may be indicative of ARDS or pulmonary thromboembolism and needs investigation and monitoring in an intensive care unit. If signs of acute widespread coagulopathy occur, early aggressive plasmapheresis with high-dose steroids and immunosuppression may be indicated.

ACKNOWLEDGEMENT

We thank Dr Parker-Williams, Consultant Haematologist, St George's Hospital for his advice.

REFERENCES