CASE REPORTS

Antiphospholipid syndrome (APLS) – A thrombotic challenge to the cardiac surgeon

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CASE HISTORY

Case 1

A 54-year-old female patient, previously diagnosed with anti phospholipid syndrome (APLS) presented with severe mitral regurgitation with P2 prolapse. She had a history of deep vein thrombosis (DVT) complicated with pulmonary embolism involving femoral and tibial veins, 8 years back and she had three miscarriages. She was on warfarin 5mg daily with PT/INR maintained between 2.0 -2.5

As the patient was known to have APLS, a hematology opinion was taken, and she was started with bridging therapy by stopping regular warfarin treatment and converted to sub cutaneous lower molecular weight heparin (LMWH). LMWH was omitted 12 hours before the surgery and restarted after 8 hours of surgery. The mitral valve was repaired with triangular resection of the posterior leaflet (P2), medial and lateral commisuroplasty and annuloplasty with a semi flexible annuloplasty ring. Warfarin started on post operative day-1 and enoxaparin continued until PT/INR reached 2.5. A short course of prednisolone was started on the patient by hematology team during 1st post operative 3 days and omitted after PT/INR reached 2.5. As the caprine score was high the measures to prevent thromboembolism were taken, patient was mobilized early and closely monitored. A 2D echocardiographic evaluation showed successful valve repair.

Case 2

A 50-year-old male underwent aortic valve replacement and was on regular warfarin and followed up in monthly clinic with therapeutic range PT/INR. After being asymptomatic for nearly 4 months he presented with severe left lower limb pain. On admission the PT/INR was normal. There was a mild swelling in his left thigh. Following vascular surgical assessment multiple left calf muscle hematoma was suspected and no DVT was noted in pelvic and lower limb veins. Warfarin was omitted and sub cutaneous enoxaparin was started. Next day the patient had a sudden cardiac arrest in the ward and all resuscitation attempts failed. In autopsy it was found that the prosthetic aortic valve had been thrombosed and obstructed. Subsequent postmortem histological assessment of body tissues showed an SLE like picture and APLS.

INTRODUCTION

Coagulopathies can frequently throw unexpected challenges to cardiac surgeons as clotting pathways are frequently manipulated in cardiac surgery to achieve an optimal outcome. anti phospholipid syndrome (APLS) is one such rare noninflammatory autoimmune disease where autoantibodies are formed against subgroups of phospholipids which are involved in the clotting mechanism. Apart from antiphospholipid antibodies (aPL) other antibodies such as anticardiolipin antibodies (aCL) or lupus anticoagulant (LA) are present in APLS patients. Although antiphospholipid antigens are present in about 5% of the healthy general population the prevalence of APLS is about 2% of the general population[1,2,3].

CLINICAL PRESENTATIONS

APLS is associated with a spectrum of clinical mutations. Some of the commonest presentations of APLS are pregnancy related, namely intra uterine growth retardation (IUGR), pre-eclampsia, recurrent miscarriages, pregnancy induced hypertension, premature or still births, placental insufficiency etc. The hypercoagulability of APLS predisposes patients to arterial or venous thrombosis leading to DVT, pulmonary embolism, TIA, strokes, and other thrombotic phenomena. Renal failure, migraine, recurrent headaches and skin ulcers due to associated SLE like connective tissue disorders are some other manifestations. More than 2/3 of the APLS patients have valvular diseases and coronary artery disease as frequent manifestations[1].

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From a cardiac point of view, an APLS patient can have coronary artery thrombosis, valvular heart disease, intra cardiac thrombus, pulmonary hypertension, endocarditis and cardiomyopathy etc.[1,4]. The basic pathophysiology in APLS related cardiac conditions is governed by hypercoagulability. Several studies have shown the morbidity and mortality of percutaneous coronary interventions and CABG are high in APLS patients. This is because they are predisposed to pro-thrombotic events such as graft thrombosis and restenosis of coronary artery stents[5,6]. Vascular occlusive complications of APLS are a headache to both the cardiologist and cardiac surgeons. It can be due to reversal of anticoagulation before the surgical procedure or intervention or due to inadequate anticoagulation during cardiopulmonary bypass. Post operatively there can be occlusive complications before achieving optimal anticoagulation[4].

There can be acute presentations of APLS. This is resulting from simultaneous failure of several organs over a short period of time (days to week) due to multiple vascular and microvascular thrombosis. This is known as catastrophic APLS (cAPLS)[3,15]. The cAPLS has a mortality rate of nearly 50%. The clinical picture resembles DIC, SIRS, thrombotic thrombocytopenic purpura (TTP), heparin induced thrombocytopenia (HIT) or sepsis[3]. The cAPLS is usually precipitated by infections, surgical stress or changes of anticoagulation therapy[3].

Sometimes these patients are unfortunately not diagnosed and succumb to various complications of APLS or c-APLS[25]. These cases are diagnosed at autopsy based on high index on suspicion according to the clinical picture which led to the death of the patient. Postmortem diagnosis of APLS based on autopsy tissue samples has its own limitations and there are discussions among forensic scientists[26].

PATHOPHYSIOLOGY

APLS is caused by anticardiolipin antibodies which are autoantibodies. These antibodies work against phospholipid-protein complexes[5]. There are two types of APLS. In primary APLS thrombosis and other features occurs without clinical features of SLE. When anticardiolipin antibodies are present with other connective tissue disorders like SLE or rheumatoid arthritis it is called secondary APLS[5]. Triggering of thrombosis is usually due to two hits. The first hit is the endothelial cell injury due to the titer of aPL antibodies. Surgical stress, vascular trauma, pregnancy and infections act as second hits to cause the thrombosis[4,16]. It is interesting to know that diseases like syphilis and some drugs like phenothiazines can also produce antibodies against phospholipids. These are direct antiphospholipid antibodies. But in APLS, the antibodies are indirect Apl directed against phospholipid depending proteins which are abundant in plasma or vascular cells[17].

Cardiac valve pathologies in APLS are due to immune complex deposition. About 35% to 82% of APLS patients have valvular issues due to these immune complexes. Only 4%-6% patients out of them are requiring surgical interventions[7]. The most commonly affected valve is the mitral valve, followed by aortic valve and then the tricuspid valve[8]. Left sided valves are more prone to APLS as they are more vulnerable to high stress[4]. When the patient has primary APLS, these valve lesions are non-infectious and non-inflammatory but rather fibrotic or thrombogenic[11]. When APLS patients simultaneously have valve disease, the arterial embolization risk is around 77% [4]. As per literature, APLS is combined with other connective tissue disorders such as SLE in about 40%. In these cases, the pathology may be a little different[12]. Not all patients with APLS who have valve disease need surgical interventions to the valve. Only 4%-6% of patients develop severe mitral regurgitation jets to indicate surgical interventions[1]. The mortality of valve surgeries in APLS are as high as 10% -20%. This is due to the prothrombotic status of APLS patients[9]. Because of these surgical interventions are deferred to medical management if possible[10]. When it comes to surgical interventions, there is a choice between mechanical vs bioprosthetic valves and more importantly valve repair. Most of the APLS patients are younger, they anyway need long term anticoagulation for APS. The thromboembolic complications render a mechanical heart valve in danger of malfunction at any satge[11,13]. The general advantage of a bioprosthetic valve is patients don't have to take long term anticoagulation. But biological prosthetic valves are more vulnerable to excessive pannus formation and consecutive stenosis, which renders replacement of the valve mandatory after a few years. This risk is higher in APLS patients. If there is any possibility of valve repair as in the index case, it can save the patient from many possible complications. The decision is tailor made to the patient most of the time[11,14].

Thrombosis in APLS with cardiac disease is highest preoperatively during the time of bridging and withdrawal of warfarin, and during post operative hypercoagulable state (despite whether the patients are on anticoagulant or not) and during late post operative period while re-establishing warfarin therapy.

Thrombus can occur in any cardiac chamber, commonly on the right side. Because of that pulmonary embolism is commoner than systemic embolism where both are life threatening complications[4]. The thrombogenicity of APLS causes micro emboli into capillary beds of systemic circulation causing renal failure, cerebral damage, visual disturbances, myocardial infractions etc. There is accelerated atherosclerosis process associated with APLS which is more related with inflammatory and immunopathogenic factors seen in APLS. This makes them more prone to coronary artery disease[4].

APLS and challenges to the cardiac surgeon

Cardiac surgeries are associated with significant physiological stress to the body. They are commonly done on cardio-pulmonary bypass (CPB). APLS patients are at higher risk of thrombosis. Even minor alteration of anticoagulation therapy, infection and surgical insult can ignite thrombosis. On the other hand, they are at a high risk of bleeding due to APLS related long term anticoagulation treatments or APLS related clotting factor deficiencies like factor II or thrombocytopenia[19]. Some cardiac surgeries are done in deep hypothermic circulatory arrest (DHCA). Both the effect of extracorporeal CPB circulation circuit and DHCA can complicate the picture of coagulation balance. DHCA is associated with blood stasis, changes of body enzymes and cofactor activity due to extreme temperature fluctuations. A fine monitoring of anticoagulation is therefore essential in APLS patients undergo cardiac surgeries. In DHCA, an agent like bivalirudin can be used instead of heparin to achieve anticoagulation.

Monitoring of anticoagulation is a challenge as aPL antigens are interfering with tests for hemostasis. For Example, activated clotting time ACT is the usual test to monitor the heparin activity. It is a phospholipid dependent test. This may be falsely prolonged by LA antibodies[19]. Heparin needs a lot of monitoring by ACT as it has individualized action for a given dose while LMWH has more predictable action for a dose. Therefore, LMWH is more suitable in the setting of APLS as it needs less monitoring[19]. Suggested alternative methods for monitoring anticoagulation during bypass in APLS patients include empirically doubling the baseline ACT or to reach an ACT twice the upper limit of normal[11], obtaining heparin concentrations by protamine titration (hepcon), performing anti-factor Xa assays[20,21]. In cardiac surgeries of APLS patients, the use of protamine to antagonize the action of heparin should be done in smooth stepwise manner with close monitoring. APLS patients need higher INR rates (2.5 to 3.5) to be maintained after cardiac surgeries[23]. But there are many controversies about this. The INR may not corelate with the outcome of APLS patients[24].

It's reported there is 84.2% incidence of postoperative thrombosis or bleeding and 63.2% mortality being reported in APLS patients[22]. But the figures are variable in different studies.

MANAGEMENT

A successful outcome requires multidisciplinary management in order to prevent thrombotic or bleeding complications and to manage perioperative anticoagulation. A thorough preoperative assessment is essential to evaluate the patient's medical history, APLS manifestations, and overall health. Special attention is given to previous thrombotic events, presence of antiphospholipid antibodies, and any associated autoimmune conditions. Anticoagulation therapy is a critical component of managing APS during cardiac surgery. If the patient is on long-term warfarin therapy, the anticoagulant must be temporarily switched to low molecular weight heparin (LMWH) before surgery. Adequate anticoagulation is maintained during CPB to prevent clot formation within the bypass circuit. Postoperatively, anticoagulation therapy is carefully managed to balance the risk of thrombosis with the risk of bleeding. The transition from heparin to long-term anticoagulation (e.g., warfarin) is carefully coordinated.

Immunotherapy to manage effects of APLS and some new treatment strategies such as new oral anticoagulants, statins, hydroxychloroquine, steroids, coenzyme Q10, B-cell depletion, platelet and TF inhibitors, peptide therapy or complement inhibition are being proposed[27].

In valve pathologies making every attempt to repair a valve rather than replacing will always minimize the complexity of long-term post operative management as it will not require long term anticoagulation as for mechanical prosthetic valves.

Strategies to minimize bleeding risk include meticulous surgical techniques, monitoring for signs of bleeding, and avoiding interactions with other medications that may increase bleeding risk. Moreover, additional factors of thrombosis such as hypertension, diabetes mellitus, hyperlipidemia should be treated optimally or avoided (e.g. smoking). Generally, antiplatelet therapy may be added but the effectiveness of low-dose aspirin or the newer antiplatelet agents are yet to be well established. Collaboration with hematologists or rheumatologists is often beneficial for guidance on anticoagulation management and overall care. Patients should be educated about their condition, the need for anticoagulation, and signs of complications. Understanding the importance of adherence to postoperative medication is crucial. Close postoperative follow-up is essential to monitor for any signs of thrombosis, bleeding, or other complications. Adjustments to the anticoagulation plan may be made based on ongoing assessments.

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