Case Report

Disseminated intravascular clotting associated with Fc-receptor IIa-mediated platelet activation in a patient with endocarditis after aortic valve replacement

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This report describes fatal disseminated cardiovascular thrombosis associated with Fc-receptor IIa-mediated platelet activation during surgery for aortic valve replacement in a patient with endocarditis. The patient's serum contained antibodies which strongly activated platelets via the Fc-receptor IIa. Antibodies did not bind to platelet factor 4 or aprotinin and binding was independent of heparin. The mechanisms and differential diagnosis for such a complication are discussed. Our data show for the first time in a patient with endocarditis that, beside HIT, other immune complexes can induce massive intravascular coagulation via platelet Fc-receptor IIa activation.

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Case report

A 46-yr-old woman (50 kg body weight) with aortic valve insufficiency (III) because of endocarditis was admitted for aortic valve replacement. She was on intermittent haemodialysis six times per week after bilateral nephrectomy secondary to polycystic renal disease. Approximately 12 weeks before surgery she had shown thrombosis of the right subclavian vein and multiple shunt thrombosis despite anticoagulation with the vitamin K antagonist phenprocoumon. An infected demers catheter had been removed before 5 weeks.

After 4 weeks of i.v. antibiotic treatment with metronidazol, imipenem, gentamicin and linezolid the patient was transferred for aortic valve replacement. She had normal white blood cell count and normal C-reactive protein concentration. Anticoagulation with heparin (800 iu h−1) had been administered for weeks. The day before surgery variables of haemostasis were as follows: platelet count of 141 nl−1 (normal: 149–409 nl−1), thrombin time 52 s (normal: 14–21 s), INR 1.4, activated thromboplastin time (aPTT) >180 s (normal: 26–36 s) while on i.v. heparin (800 iu h−1).

On the morning of surgery she presented awake and conscious, and no vasoactive drug support was required. For continuous measurement of arterial pressure, a radial artery catheter was inserted under local anaesthesia. General anaesthesia was induced by midazolam 2 mg, sufentanil 150 μg, etomidate 20 mg, followed by rocuronium 50 mg, and maintained with sufentanil and isoflurane 0.6–0.8% end-tidal, as required. A triple-lumen central venous catheter was inserted via the left internal jugular vein, and its position close to the right atrium was confirmed by intravascular electrocardiography. A pulmonary artery catheter was advanced via the left internal jugular vein. Transoesophageal echocardiography (TEE) showed severe aortic valve insufficiency with vegetations and destruction of the aortic valve.

Baseline activated clotting time (ACT) was 122 s. Before initiation of cardiopulmonary bypass (CPB), aprotinin [1 000 000 kallikrein inactivation units (KIU), i.v.] after sternotomy and heparin (400 iu kg−1 i.v.) were administered in preparation for CPB resulting in an ACT of 517 s. During CPB a second dose of aprotinin (1 000 000 KIU) was given (Fig. 1). ACT, measured at 30 min intervals, ranged between 472 and 517 s and no further heparin administration was required. Initial haematocrit during CPB was 22% and three units of packed red blood cells were added to the extracorporeal circuit. The aortic valve showed thrombotic material and
endocarditis-related destruction, and was replaced by a St Jude Medical valve (23 mm).

TEE showed good valve and biventricular function, and surgery and anaesthesia progressed uneventfully after an uncomplicated separation from CPB. There was some diffuse bleeding after reversal of heparin effects by protamine sulphate (15 mg, ACT 152 s) and a third dose of aprotinin (500,000 KIU) was given. Accordingly, the patient received two more units of packed red blood cells, two units of virus inactivated pooled frozen plasma and an additional 2 mg of protamine sulphate. This was effective clinically in controlling bleeding and the ACT was 125 s when the thorax was closed. The patient’s vital signs were stable with a heart rate of 99 min⁻¹, an arterial blood pressure of 124/95 mm Hg, a central venous pressure (CVP) of 14 mm Hg, a mean pulmonary artery pressure (mPAP) of 23 mm Hg and a cardiac index of 2.7 litre min⁻¹ m⁻². During skin closure, for no apparent reason, the patient’s arterial pressure suddenly decreased to 50/30 mm Hg, and CVP and mean PAP increased to 19 and 30 mm Hg, respectively (Fig. 1). During immediate sternotomy the patient was given heparin (25,000 i.v.) and a total of epinephrine 1 mg. On aortic recannulation, despite an ACT greater than 800 s, blood was seen clotted and an intraaortic thrombus was recognized. After re-initiation of CPB, TEE also showed large intracardiac thrombi in both atria, in both the right and left ventricle, and in the superior caval vein.

As a rescue therapy tissue plasminogen activator (rt-PA, 100 mg i.v.) was given into the extracorporal circuit. Remarkably, this did not result in any bleeding. However, intracardiac thrombi did not resolve either. After rt-PA injection, coagulation variables were as follows: aPTT > 180 s, thrombin time > 60 s, fibrinogen 48 mg dl⁻¹, d-dimer > 2800 µg litre⁻¹ and antithrombin (AT) 30%. The patient died after a futile attempt to wean her from bypass.

Autopsy, performed 72 h after death, showed large thrombi in both atria and ventricles, and, in addition, in the inferior caval vein, superior mesenteric artery and coeliac trunk extending into both hepatic arteries. Furthermore, evidence of acute purulent native aortic valve endocarditis and multiple infarcts in the spleen were seen.

Post hoc analysis of blood samples obtained before surgery revealed Fc-receptor-mediated platelet activation. In the heparin-induced platelet activation assay (HIPA)
The patient had no clotting abnormalities; AT, protein C and S deficiencies, activated protein C (APC) resistance (factor V Leiden), anti-phospholipid and cardiolipin antibodies were excluded.

There was neither evidence for any incompatibility of the red blood cells as judged by detailed immunohaematological screen nor for any abnormalities of the transfused plasma units (virus inactivated pooled plasma from approximately 800 donors). The blood products had been from frequent donors. Blood products obtained from previous donations of these donors were never reported to have caused any adverse effects. A sample of the plasma pool was tested with washed platelets in the HIPA test in the presence and absence of heparin, and with platelet rich plasma (PRP) of normal donors (60 µl plasma, 120 µl PRP) in the presence of buffer, heparin (0.5 u/ml), adenosine diphosphate and collagen. The plasma did not cause platelet aggregation in vitro.

Discussion
This case describes fatal generalized disseminated thrombosis mediated by platelet activation independent of heparin. We demonstrated that the serum strongly activated platelets. This reaction was completely inhibited by the monoclonal antibody IV.3, which strongly indicates that the reaction was antibody mediated. Fc-receptor IIa is expressed on platelets and is usually activated by IgG immune complexes. The best known hypercoagulable syndrome caused by Fc-receptor IIa-mediated intravascular platelet activation is heparin-induced thrombocytopenia (HIT). In HIT, immune complexes of antibodies bound to platelet factor 4/heparin complexes are responsible for Fc-receptor IIa activation. Although patients undergoing open heart surgery are at particular risk for HIT it is very unlikely that HIT was the underlying cause. First, the vast majority of patients with HIT have antibodies against platelet factor 4/heparin complexes. We excluded these antibodies by a sensitive ELISA test. Second, a few patients may develop HIT as a result of antibodies against interleukin-8 or neutrophil-activating peptide. While we did not test for these, specific binding of these antibodies to platelets is inhibited typically by very high heparin concentrations (100 u/ml) as heparin in this concentration displaces proteins with a heparin binding side from the platelet surface. Third, the patient was treated with heparin for frequent dialysis for years and received heparin i.v. for weeks before surgery at a dose sufficient for causing HIT-related platelet activation which obviously did not occur. Sufficient boosting of low presurgery HIT antibody titres during CPB surgery can be excluded because of the short period of time. Within the 4 h between start of surgery and onset of disseminated clotting, B cells could not have produced sufficient amounts of antibodies to increase the titres significantly. In our patient, the preoperative platelet count of 141 x 10^9/L was almost within the reference range, not suggesting evidence for HIT. The borderline low platelet count was most likely caused by aortic valve endocarditis and frequent haemodialysis.

We hypothesize that intravascular coagulation in our patient was induced by massive platelet activation. It is well known that Fc-receptor-mediated intravascular platelet activation and microparticle generation can induce massive generation of thrombin. Indeed, we have shown that in acute HIT this mechanism leads to excessively increased thrombin–antithrombin (TAT) levels. In the present case the patient’s plasma induced Fc-receptor IIa [CD32]-dependent activation, which could be abolished by blocking Fc-receptor IIa with a monoclonal antibody (anti-CD32, IV.3). This strongly indicates that immune complexes other than IgG/platelet factor 4/heparin complexes gave rise to fulminant platelet activation.

Unfortunately, we cannot pinpoint the specificity of the antibodies responsible for platelet activation because of lack of further patient plasma, but can discuss the potential antigens. Anti-phospholipid antibodies are able to activate platelets via the Fc-receptor IIa. However, we found no evidence for these antibodies. As massive coagulation occurred after termination of CPB, both preformed antiprotamine or anti-aprotinin antibodies may have formed IgG immune complexes with these drugs. However, anti-aprotinin antibodies are a very unlikely cause as the patient’s serum did not contain IgG anti-aprotinin antibodies, and two sera with known high titre IgG
anti-protamin antibodies did not cause platelet activation in vitro. Although the patient had no diabetes and insulin use, we cannot rule out the presence of anti-protamin antibodies as she may have received previously protamin to neutralize heparin after dialysis out of hospital. However, involvement of anti-protamin antibodies is unlikely as no immediate response was seen after the first protamin administration.

Another possibility could be that the patient had antibodies against the bacteria or soluble bacterial products causing endocarditis. Considering the recurrent shunt occlusions when endocarditis manifested several weeks before surgery, this is a plausible concept. We suspect that this young patient was able to compensate for coagulation activation by exposure to minor amounts of bacterial proteins for a long time while under a continuous heparin infusion before operation. Although the patient had negative blood cultures before surgery, it is likely that bacterial proteins had been released during surgery. Only reversal of procoagulant state with widespread thrombosis. However, a similar mechanism may have prevented anti-aprotinin antibodies to induce massive clotting while the patient was fully anticoagulated.

Neither intracardiac nor systemic clots resolved in response to a large dose of rt-PA and heparin while on CPB. Possibly, intracardiac thrombi did not resolve because insufficient amounts of rt-PA may have reached the cardiac chambers as a result of minimal right ventricular and pulmonary blood flow during bypass.

Only a few patients of massive thrombosis have been described during or after cardiac surgery.16–18 Unfortunately, in none of these patients further investigations were made into the underlying mechanisms. Our study shows for the first time that such a catastrophic event can be mediated by antibodies, which induce massive intravascular coagulation via platelet Fc-receptor IIa activation. These antibodies have to be present before surgery. This provides the perspective to identify patients at risk before surgery once the involved antigens are identified. This report should alert clinicians to obtain serum samples for this purpose in patients with sudden intracardiac and systemic thrombosis related to surgery.

References


