Case report - Cardiopulmonary bypass

Aortic valve replacement and coronary revascularization in paroxysmal nocturnal hemoglobinuria

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Abstract

Cardiac surgery in patients with paroxysmal nocturnal hemoglobinuria (PNH), which is an acquired hemolytic anemia associated with thrombocytopenia and an abnormal susceptibility to venous thromboses, requires special perioperative measures. PNH is based on a clonal defect of hematopoietic stem cells characterized by deficiency in glycosyl-phosphatidylinositol-anchored surface proteins. The major mechanism of hemolysis consists of unregulated complement activation. In cardiac surgery, PNH-induced granulocytopenia increases the risk of postoperative infection. PNH-induced complement activation is further exaggerated by extracorporeal circulation in cardiac surgery leading to putative hemolytic crisis. Here, we report on a patient who developed PNH after severe aplastic anemia undergoing aortic valve replacement and coronary revascularization using extracorporeal circulation and discuss the special perioperative management and the relevant literature on this issue. Special emphasis should be given to optimal preoperative patient preparation including G-CSF administration and red blood pack transfusions, perioperative platelet substitution, fluid management, and antibiotic prophylaxis.

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1. Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hemolytic anemia associated with an increased risk of developing thrombocytopenia, atypical venous thrombosis and hypoplastic bone marrow. Hemolytic crisis and venous thrombosis are known to precipitate in clinical conditions associated with complement activation such as systemic infections. PNH is based on a clonal defect of hematopoietic stem cells characterized by deficiency in glycosyl-phosphatidylinositol (GPI)-anchored surface proteins due to mutations within the X-chromosomal PIG-A gene [1,2]. Due to the lack of GPI-linked complement regulating surface proteins such as CD59 (membrane inhibitor of reactive lysis), erythrocytes become abnormally sensitive to the activation of especially the autologous complement [3,4]. As a result, PNH is an acquired hemolytic anemia associated with an increased risk to develop thrombocytopenia, atypical venous thrombosis and hypoplastic bone marrow. Hemolytic crisis and venous thrombosis are known to precipitate in clinical conditions associated with complement activation such as systemic infections.

Here, we report on a patient with a severe aortic valve regurgitation and coronary artery disease undergoing prosthetic aortic valve replacement and coronary revascularization with extracorporeal circulation who suffers from PNH.

2. Case report

A 72-year-old man was admitted to hospital due to acute shortness of breath without typical angina. The patient’s history included treatment for severe aplastic anemia with anti-thymocyte globulin, prednisone and cyclosporine 8 years previously. Two years later he developed PNH with increasing hemolytic activity. Furthermore, he suffered compensated renal insufficiency, and arterial hypertension.

Echocardiography revealed reduced left ventricular function and a severe combined aortic vitium with leading aortic valve regurgitation (III–IV°) with aortic annulus...
measuring 26 mm. Angiography and right heart catheter confirmed severe aortic regurgitation, and moderate pulmonary hypertension (PA mean 26 mmHg). Coronary angiography revealed significant stenosis of the left anterior descending artery. Therefore, indication for aortic valve replacement and coronary revascularization was scheduled.

On admission, laboratory tests exhibited leucocytopenia (1900/μl), hemoglobin 5.27 mmol/l, thrombocytopenia 89 G/l, complete-bilirubin 22 μmol/l [<17 μmol/l], haptoglobin <0.06 g/l [0.3–2.0 g/l], and LDH 1215 U/l [80–240 U/l]. Differential blood count revealed 26% neutrophils [50–70%], 46% lymphocytes [25–40%], 27% monocytes [2–8%], and 1% eosinophils [2–4%]. Flow cytometric analysis resulted in a marked GPI-anchoring defect on different cell lineages including neutrophils (about 75% deficient cells), monocytes (about 96% deficient cells), and erythrocytes (about 25% deficient cells) (Fig. 1).

Therapy included oral cyclosporin (CsA levels 100–150 ng/ml) for cytopenia. Seven days before the scheduled procedure treatment with G-CSF (Neupogen™ 300 μg, Amgen™, subcutaneously three times a week) was started. On the day before the surgical procedure, blood counts were 11,600/μl leucocytes with a marked increase in the neutrophil population (58%), but apart from 2% myelocytes, without further granulocytic precursors under G-CSF stimulation. In order to avoid perioperative hemolytic crisis the patient was transfused with five units of packed red blood cells (RBC) when he had a hemoglobin level of 5.27 mmol/l resulting in a hemoglobin level of 8.18 mmol/l preoperatively.

After initiation of anesthesia including the use of etomidate, fentanyl, isoflurane, and pancuronium, the aortic valve was completely excised and a 23 mm porcine aortic valve prosthesis (Mosaik™, Medtronic™) was inserted. Furthermore, the left anterior descending coronary artery was revascularized with the left internal mammary artery. Intraoperatively, three units of packed RBC, two units of fresh frozen plasma, and one unit of thrombocytes were transfused. Antibiotic prophylaxis was performed using ceftriaxone (Rocephin™, Roche™) 2 g intravenously over 5 days. The patient was transferred to the ICU with hemoglobin of 5.02 mmol/l, hematocrit of 25%, and leucocytes of 6600/μl. Perioperatively, the patient twice received 125 ml of mannitol 10% prophylactically in order to avoid acute renal failure due to hemolytic crisis. Maximal enzymes postoperatively were elevated for LDH (910 U/l [80–240 U/l]), CK (144 U/l [<80 U/l]), CKMB (28 U/l [<10 U/l]), and Troponin T (0.13 μg/l [<0.10 μg/l]), which all decreased to normal values within 48 h. No further RBC transfusion was needed; G-CSF (300 μg) was administered only on postoperative day (POD) 3 due to leucocytopenia. Thoracic drainage produced 1120 ml and extubation was performed after 14 h.

On POD 4, the patient was discharged from ICU. On POD 5, complement analysis (CH 50, C5a, C3a) was in a normal range. No signs of hemolysis were detected with normal haptoglobin values over all days and no thrombosis was evident under intravenous heparin prophylaxis for 11 days with PTT ranging between 50 and 60 s. G-CSF was applied three times within 1 week postoperatively and stopped thereafter. The patient was discharged from hospital on POD 15 with a leucocyte count of 6500/μl, hemoglobin of 5.7 mmol/l, hematocrit of 27%, and a platelet count of 149,000/μl. Cyclosporin therapy was continued and further hematological supervision was performed on an outpatient basis every 8 weeks.

3. Discussion

PNH is an acquired hemolytic anemia, which often exhibits an association with aplastic anemia. The underlying mechanism is a clonal expansion of hematopoietic progenitors with a defect in the surface expression of GPI-anchored surface proteins [1,2] due to mutations within the PIG-A gene. Due to an abnormal sensitivity especially to the alternative complement cascade, intravascular hemolysis results. Clinically, an increased risk of atypical thrombosis and hypoplastic bone marrow besides hemolytic crisis due to unspecific complement activation are the main problems in PNH leading to a significantly lower life expectancy [3,4]. There have been some reports on immunosuppressive

![Fig. 1. Flow cytometry studies 6 months before cardiac surgery. Partial loss of GPI-anchored antigens on (A) granulocytes (defined as CD15<sub>high</sub>SSC<sub>high</sub>, 75% CD55 negative), (B) monocytes (defined as CD15<sub>high</sub>SSC<sub>low</sub>, 96% CD55 negative), and (C) erythrocytes (glycophorin A<sup>-</sup>, 67% CD59 negative).](https://academic.oup.com/icvts/article-abstract/2/4/647/707598/fig1)
therapy in combination with cytokines, such as G-CSF, useful for patients with pancytopenia and GPI-deficient blood cells, leading to even a trilineage response [5].

Cardiac surgery in PNH patients is associated with several possible complications. (1) PNH-induced granulocytopenia increases the risk of postoperative infection. Therefore, the prophylactic use of antibiotics appears to be mandatory. Furthermore, the use of G-CSF (Neupogen™ 300 μg, Amgen®, subcutaneously) to stimulate neutrophil counts is an option in this setting. (2) The aggravation of hemolysis by extracorporeal circulation in cardiac surgery due to complement activation from either contact of blood with the foreign material surfaces during cardiopulmonary bypass circuit, or use of protamine to neutralize systemic heparin after cardiopulmonary bypass and tissue injury is well known [6–8]. Therefore, such a treatment in patients with PNH is expected to result in consecutive hemolytic crisis. We mainly prevented intraoperative hemolytic crisis by preoperative transfusion up to a normal hemoglobin level in order to decrease GPI-deficient RBC. As a result, over the postoperative course we even observed a normal haptoglobin level indicating that hemolysis was almost absent due to the preoperative treatment. In this patient with associated cytopenia this would be a feasible treatment approach. For patients with primary hemolytic PNH without cytopenia this cannot be directly concluded. However, it may be speculated that even in these patients a preoperative transfusion program might dramatically decrease intravascular hemolysis leading to an acceptable risk in perioperative management. (3) The risk of acute renal failure after cardiac surgery due to hemolysis in PNH is further increased by preexisting renal insufficiency. In this clinical setting, adequate fluid administration and the use of diuretics, in this case mannitol pre- and perioperatively, appears to be essential. (4) Thrombocytopenia in PNH and the use of extracorporeal circulation may lead to an increased risk of bleeding. Furthermore, substitution of platelets perioperatively supposedly reduced bleeding complications.

To our knowledge, literature on PNH patients undergoing surgery consists of visceral surgical procedures, such as laparoscopic cholecystectomy, and renal and liver transplants. Only one case of a successful percutaneous transluminal coronary angioplasty in a PNH patient has been reported [9]. Besides our report on a combined aortic valve replacement and coronary revascularization procedure, an Ontario working group reported recently on a successful coronary artery bypass procedure in a 62-year-old woman [10].

We conclude that cardiac surgery can be done in patients with PNH even with the use of extracorporeal circulation. Special emphasis should be given to optimal preoperative patient preparation including G-CSF administration and red blood pack transfusions, perioperative platelet substitution, fluid management, and antibiotic prophylaxis.

References