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Cardiac surgery in a patient with paroxysmal nocturnal hemoglobinuria

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Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hemolytic anemia associated with thrombocytopenia and an abnormal susceptibility to venous thromboses. 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 potential hemolytic crises. In addition, resulting thrombocytopenia would lead to an increase risk of bleeding. Here, we report for the first time on a patient who developed PNH after severe aplastic anemia (SAA) undergoing aortic valve replacement and coronary revascularization using extracorporeal circulation.

Paroxysmal nocturnal hemoglobinuria (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.[1-4] 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.[5-8] As a result, PNH is an acquired hemolytic anemia associated with an increased risk of developing thrombocytopenia, atypical venous thrombosis and hypoplastic bone marrow.[4] Hemolytic crises and venous thrombosis are known to precipitate in clinical conditions associated with complement activation such as systemic infections. Here, we report for the first time on a patient with a severe aortic valve regurgitation undergoing prosthetic aortic valve replacement with extracorporeal circulation who suffers from PNH developed after aplastic anemia.

Case report. A 72-year old man was admitted to hospital due to acute shortness of breath without typical angina. The patients' history included treatment for severe aplastic anemia with anti-thymocyte globulin, prednisone and cyclosporine 8 years ago. Two years later he developed paroxysmal nocturnal hemoglobinuria (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. Coronary angiography revealed significant stenosis of the left anterior descending artery. Therefore, aortic valve replacement and coronary revascularization was scheduled. On admission, laboratory tests exhibited leukocytopenia (1.9 g/L), 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], LDH 1215U/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) (Figure 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 11.6 g/L leukocytes 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 procedure started with median sternotomy, preparation of the left internal mammary artery, and after initiation of cardiopulmonary bypass, aortotomy was performed. The aortic valve exhibited a tricuspid valve with a 1 cm perforation in the acoronary cusp. The valve was completely excised and a 23 mm porcine aortic valve prothesis (Mosaik®, Medtronic©) was inserted. Furthermore, the left anterior descending coronary artery was revascularized with the left internal mammary artery. Extracorporeal circulation was discontinued after 108 minutes with an aortic cross-clamp time of 67 minutes. Intraoperatively, three units of packed RBC, two units of fresh frozen plasma, and one unit of platelets were transfused. Antibiotic prophylaxis was performed using ceftriaxon (Rocephin®, Roche©) 2 g intravenously over 5 days. The patient was transferred to the ICU with a hemoglobin of 5.02 mmol/L, hematocrit of 25%, and leukocytes of 6.6 g/L. 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 LDH (910 U/L [80-240 U/L]), CK (144 U/L [<80 U/L]), CKMB (28 U/L [<10U/L]), Troponin T (0.13 µg/L [<0.10 µg/L]), which all decreased to normal values within 48 hours. No further RBC transfusion was needed, G-CSF (300 µg) was administered only on postoperative day (POD) 3 due to leukocytopenia. Thoracic drainage produced 1120 mL, extubation was performed after 14 hours. On POD 4, the patient was discharged from the ICU. On POD 5, complement analysis 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 50-60s. G-CSF was applied 3 times within one week postoperatively and stopped thereafter. The patient was discharged from hospital on POD 15 with a leukocyte count of 6.5 g/L, hemoglobin of 5.7 mmol/L, hematocrit of 27%, and platelet count of 149 g/L. Cyclosporin therapy was continued and further hematologic supervision was performed on an outpatient basis every 8 weeks.

Discussion. Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hemolytic anemia, which often exhibits an association with aplastic anemia.[9] The underlying mechanism is a clonal expansion of hematopoietic progenitors with a defect in the surface expression of glycosyl-phosphatidylinositol-(GPI)-anchored surface proteins[7,9] due to mutations within the PIG-A gene.[10] Due to an abnormal sensitivity especially to the alternative complement cascade, intravascular hemolysis results. Clinically the main problems in PHD are an increased risk of atypical thrombosis and hypoplastic bone marrow besides hemolytic crisis due to unspecific complement activation, leading to a significantly lower life expectancy.[5,6] The only curative therapy available is allogeneic bone marrow transplantation.[5,6,11] There have been some reports on immunosuppressive therapy in combination with cytokines, such as G-CSF, useful for patients with pancytopenia and GPI-deficient blood cells,[12,13] leading even to trilineage response. 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[12,13] 2) The aggravation of hemolysis by extracorporeal circulation in cardiac surgery due to complement activation from either contact of blood with foreign materials during passage through the cardiopulmonary bypass circuit, or use of protamine to neutralize systemic heparin after cardiopulmonary bypass and tissue injury is well known.[14-18] Therefore, such a treatment in patients with PNH is expected to result in hemolytic crisis. We mainly prevented intraoperative hemolytic crises by preoperative transfusion up to a normal hemoglobin level in order to decrease GPI-deficient red blood cells. 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 was a feasible treatment approach. For patients with primary hemolytic PNH without cytopenia this may not be the case. 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 reduces bleeding complications.
To our knowledge, literature on PNH-patients undergoing surgery describes of visceral surgical procedures, such as laparoscopic cholecystectomy,[19] renal and liver transplants.[20,21] Only one case of a successful percutaneous transluminal coronary angioplasty in a PNH-patient has been reported.[22] For the first time, we herein report on a PNH-patient undergoing cardiac surgery with the use of extracorporeal circulation. 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

1. Miyata T, Yamada N, Iida Y, et al. Abnormalities of PIG-A transcripts in granulocytes from patients with paroxysmal nocturnal hemoglobinuria. N Engl J Med 1994;330:249-55.
2. Bessler M, Mason P, Hillmen P, Luzzatto L. Somatic mutations and cellular selection in paroxysmal nocturnal haemoglobinuria. Lancet 1994;343:951-3.
3. Ostendorf T, Nischan C, Schubert J, et al. Heterogeneous PIG-A mutations in different cell lineages in paroxysmal nocturnal hemoglobinuria. Blood. 1995;85:1640-6.
4. Rosse WF. Paroxysmal nocturnal hemoglobinuria as a molecular disease. Medicine (Baltimore). 1997;76:63-93.
5. Hillmen P, Lewis SM, Bessler M, Luzzatto L, Dacie JV. Natural history of paroxysmal nocturnal hemoglobinuria. N Engl J Med 1995;333:1253-8.
6. Socie G, Mary JY, de Gramont A, et al. Paroxysmal nocturnal haemoglobinuria: long-term follow-up and prognostic factors. French Society of Haematology. Lancet 1996;348:573-7.
7. Schubert J, Alvarado M, Uciechowski P, et al. Diagnosis of paroxysmal nocturnal haemoglobinuria using immunophenotyping of peripheral blood cells. Br J Haematol 1991;79:487-92.
8. Schubert J, Ostendorf T, Schmidt RE. Biology of GPI anchors and pathogenesis of paroxysmal nocturnal hemoglobinuria. Immunol Today 1994;15:299-301.
9. Lewis SM, Dacie JV. The aplastic anaemia--paroxysmal nocturnal haemoglobinuria syndrome. Br J Haematol 1967;13:236-51.
10. Kinoshita T, Inoue N. Relationship between aplastic anemia and paroxysmal nocturnal hemoglobinuria. Int J Hematol 2002;75:117-22.
11. Bacigalupo A, Brand R, Oneto R, et al. Treatment of acquired severe aplastic anemia: bone marrow transplantation compared with immunosuppressive therapy--The European Group for Blood and Marrow Transplantation experience. Semin Hematol 2000;37:69-80.
12. Bacigalupo A, Bruno B, Saracco P, et al. Antilymphocyte globulin, cyclosporine, prednisolone, and granulocyte colony-stimulating factor for severe aplastic anemia: an update of the GITMO/EBMT study on 100 patients. European Group for Blood and Marrow Transplantation (EBMT) Working Party on Severe Aplastic Anemia and the Gruppo Italiano Trapianti di Midolio Osseo (GITMO). Blood 1993;95:1931-4.
13. Schubert J, Scholz C, Geissler RG, Ganser A, Schmidt RE. G-CSF and cyclosporin induce an increase of normal cells in hypoplastic paroxysmal nocturnal hemoglobinuria. Ann Hematol. 1997;74:225-30.
14. Kirklin JK, Westaby S, Blackstone EH, Kirklin JW, Chenoweth DE, Pacifico AD. Complement and the damaging effects of cardiopulmonary bypass. J Thorac Cardiovasc Surg 1983;86:845-57.
15. Videm V, Fosse E, Mollnes TE, Garred P. Complement activation by extracorporeal circulation: effects of precoating a membrane oxygenator circuit with human whole blood. Scand J Thorac Cardiovasc Surg 1988;22:251-6.
16. Kirklin JK, Chenoweth DE, Naftel DC, et al. Effects of protamine administration after cardiopulmonary bypass on complement, blood elements, and the hemodynamic state. Ann Thorac Surg 1986;41:193-9.
17. Fransen E, Maessen J, Dentener M, Senden N, Geskes G, Buurman W. Systemic inflammation

present in patients undergoing CABG without extracorporeal circulation. Chest 1998;113:1290-5.
18. Gu YJ, Mariani MA, Boonstra PW, Grandjean JG, van Oeveren W. Complement activation in coronary artery bypass grafting patients without cardiopulmonary bypass: the role of tissue injury by surgical incision. Chest. 1999;116:892-8.
19. Covey WG, Duerr S. Laparoscopic cholecystectomy in paroxysmal nocturnal hemoglobinuria. Conn Med 1992;56:63-4.
20. Vanwalleghem J, Zachee P, Kuypers D, et al. Renal transplantation for end-stage renal disease due to paroxysmal nocturnal haemoglobinuria. Nephrol Dial Transplant 1998;13:3250-2.
21. Schattenfroh N, Bechstein WO, Blumhardt G, et al. Liver transplantation for PNH with Budd-Chiari syndrome. A case report. Transpl Int 1993;6:354-8.
22. Fong PC, Tai YT, Lau CP, et al. Percutaneous transluminal coronary angioplasty in a patient with paroxysmal nocturnal hemoglobinuria. Cathet Cardiovasc Diagn. 1992;25:144-47.

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