Urgent replacement of a mechanical mitral prosthesis in an anticoagulated patient with Bombay red blood cell phenotype

Remplacement urgent d'une prothèse mitrale mécanique chez un patient anticoagulé ayant un phénotype érythrocytaire Bombay

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Abstract

Purpose *Bombay red blood cell phenotype is an extremely rare blood type for which patients can receive only autologous or Bombay phenotype red blood cells. We report a case of urgent repeat sternotomy for replacement of a mechanical mitral prosthesis in a patient with Bombay phenotype anticoagulated with warfarin, to emphasize the transfusion challenges in such patients.*

Clinical features *A male of Indian descent presented to hospital with New York Heart Association IV symptoms. His medical history revealed previous mitral valve replacement with a mechanical prosthesis in 2005 and Bombay phenotype blood. Preoperative transthoracic echocardiography demonstrated thrombus obstruction of the mitral prosthesis despite anticoagulation with warfarin. Right ventricular systolic pressure was >100 mmHg with 3+ tricuspid regurgitation. The patient's condition was temporized with diuretics, bronchodilators, and bi-level positive airway pressure ventilation while transfusion medicine and cardiac surgery were consulted for urgent surgery. The patient received vitamin K and prothrombin complex concentrate prior to repeat sternotomy and successful mitral prosthesis*

replacement. After cardiopulmonary bypass, heparinization was corrected with protamine and followed by a second dose of prothrombin complex concentrate and recombinant activated factor VIIa. Postoperatively, the patient received four units of packed red blood cells, two autologous units and two units of Bombay specific red blood cells. Right ventricular pressures stabilized at 40 mmHg following surgery. The patient recovered following several days of inotropic support with milrinone, diuretics, and bronchodilators.

Conclusion *Patients with Bombay phenotype red blood cells present as type O, but they are unable to receive red blood cells from any phenotype other than Bombay phenotype. They are able to receive all other blood products, including fresh frozen plasma, cryoprecipitate, platelets, prothrombin complex concentrate, and recombinant activated factor VIIa. Coordination between Canadian Blood Services, transfusion medicine, surgery, and anesthesia is important in managing these patients.*

Résumé

Objectif *Le phénotype érythrocytaire Bombay est un groupe sanguin extrêmement rare; les patients possédant ce groupe sanguin ne peuvent recevoir que des érythrocytes autologues ou de phénotype Bombay. Nous rapportons ici un cas de deuxième sternotomie urgente pour le remplacement d'une prothèse mitrale mécanique chez un patient avec le phénotype Bombay et anticoagulé à la warfarine afin de mettre en exergue les défis transfusionnels pour de tels patients.*

Éléments cliniques *Un homme d'origine indienne s'est présenté à l'hôpital avec des symptômes de score IV sur l'échelle de la New York Heart Association. Ses antécédents médicaux comprenaient un remplacement de la valve mitrale avec une prothèse mécanique en 2005 et un groupe*

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sanguin de phénotype Bombay. L'échocardiographie transthoracique préopératoire a révélé une obstruction thrombotique de la prothèse mitrale en dépit d'une anticoagulation à la warfarine. La pression systolique ventriculaire droite était >100 mmHg avec une régurgitation tricuspide de 3+. L'état du patient a été maintenu à l'aide de diurétiques, de bronchodilatateurs et d'une ventilation à pression positive à deux niveaux pendant que les départements de médecine transfusionnelle et de chirurgie cardiaque étaient consultés pour réaliser une chirurgie urgente. Le patient a reçu de la vitamine K et du concentré de complexe prothrombique avant une deuxième sternotomie et le remplacement réussi de la prothèse mitrale. Après la circulation extracorporelle, l'héparinisation a été corrigée avec de la protamine et suivie d'une deuxième dose de concentré de complexe prothrombique et du facteur VIIa activé recombinant. Après l'opération, le patient a reçu quatre unités de concentré d'érythrocytes, soit deux unités autologues et deux unités d'érythrocytes Bombay. Les pressions ventriculaires droites se sont stabilisées à 40 mmHg après la chirurgie. Le patient s'est rétabli après plusieurs jours de soutien inotropique avec de la milrinone, des diurétiques et des bronchodilatateurs.

Conclusion Les patients avec un phénotype érythrocytaire Bombay sont en apparence de groupe O, mais ils ne peuvent recevoir des érythrocytes d'un phénotype autre que le Bombay. Ils peuvent recevoir tous les autres produits sanguins, y compris du plasma frais congelé, des cryoprécipités, des plaquettes, du concentré de complexe prothrombique et du facteur VIIa activé recombinant. La coordination entre la Société canadienne du sang et les départements de médecine transfusionnelle, de chirurgie et d'anesthésie est cruciale pour la prise en charge de ces patients.

Bombay is a rare autosomal recessive phenotype within the ABO blood group.¹ The estimated prevalence is 1:10,000 in India and 1:10⁶ outside of India.² ABO grouping is characterized by the presence or absence of A and B antigens attached to an H antigen. The Bombay phenotype differs in that it is antigen H deficient and thus presents as type O but with a positive antibody screen. Further investigation would reveal incompatibility with all panel cells other than the Bombay phenotype³ prompting Canadian Blood Services (CBS) to initiate a search of their national database for frozen units and/or compatible donors. Fortunately, persons with Bombay phenotype may receive other blood products, including fresh frozen plasma, cryoprecipitate, platelets, prothrombin complex concentrate, and recombinant activated factor VIIa.⁴ We discuss the case of a patient with Bombay phenotype who developed

New York Heart Association (NYHA) IV congestive heart failure and severe right ventricular hypertension secondary to obstruction of a mitral valve prosthesis in the setting of warfarin anticoagulation. The patient required urgent repeat sternotomy for mitral prosthesis replacement. The patient provided written consent for publication of the submitted article.

Case report

A male patient of Indian descent of slight stature in his fifth decade presented to the emergency department following a two-week period of progressively increasing shortness of breath, NYHA IV with orthopnea. Of significance, he was born in Hyderabad, AP, India to consanguineous parents and immigrated to Canada in the 1980s. He was identified with Bombay phenotype red blood cells by transfusion medicine in 2005 during preoperative investigations for mitral valve replacement for rheumatic mitral valve disease. At that time, the transfusion medicine service recommended a preoperative course of erythropoietin injections to accommodate autologous blood donation of three units prior to his mitral valve surgery. However, since none of his autologous blood was required in 2005, it remained frozen and stored with CBS. His medical history was significant for normal coronary arteries, moderately well-controlled chronic obstructive pulmonary disease, and one episode of a generalized tonic-clonic seizure secondary to a left parietal infarct in 2008.

Preoperatively, he had only moderate clinical evidence of right heart failure. His jugular venous pressure was normal with no evidence of hepatomegaly, ascites, or peripheral edema. However, there was a right ventricular heave and severe orthopnea. His respiratory rate was >20 breaths·min⁻¹ with quiet air entry bilaterally. There were no murmurs on auscultation, but neither was there an expected click from the mechanical mitral prosthesis. Cardiovascular hemodynamics demonstrated sinus tachycardia and normal blood pressure. Chest *x-ray* revealed hyperinflation suggestive of chronic obstructive pulmonary disease but minimal evidence of pulmonary edema. His electrocardiogram (ECG) showed ST depression in V₅₋₆, II, III, and the augmented voltage right arm. A transthoracic echocardiogram confirmed a diagnosis of obstruction of the mechanical mitral prosthesis with possible thrombus. The mean gradient was 33 mmHg. There was moderate to severe right ventricular dysfunction with an estimated right ventricular systolic pressure of 108 mmHg, 3+ tricuspid regurgitation, and mild left ventricular dysfunction. Laboratory investigations demonstrated normal hemoglobin, increased creatinine of 131 $\mu\text{mol}\cdot\text{L}^{-1}$, normal creatine kinase, and only a slight elevation in troponin I at 0.05 $\mu\text{g}\cdot\text{L}^{-1}$. Total bilirubin

was elevated at $58 \mu\text{mol}\cdot\text{L}^{-1}$ with slight increases in aspartate aminotransferase (AST) ($87 \text{ U}\cdot\text{L}^{-1}$) and alanine aminotransferase (ALT) ($99 \text{ U}\cdot\text{L}^{-1}$), but normal gamma-glutamyl transpeptidase and alkaline phosphatase. These abnormalities in bilirubin and transaminases may have been secondary to a combination of hepatic congestion and intravascular hemolysis from the stenotic valve prosthesis. Anticoagulation was therapeutic on warfarin. Due to ECG changes, the patient was treated initially as having an acute coronary syndrome, which included heparin intravenous. The patient was temporized overnight with diuretics, bronchodilator therapy, and bi-level positive airway pressure ventilation as needed, in order to provide time to consult cardiac surgery, anesthesia, CBS, and transfusion medicine. Fortunately, three units of frozen autologous red blood cells were available that the patient had donated prior to his first surgery. There were no other units of Bombay phenotype red blood cells in the immediate area. Approximately three hours would be required to thaw and wash the autologous units.

Given the concerns of an increased risk of postoperative coagulopathy in an emergency, re-do sternotomy for valve surgery, and the limitations to transfusion, the perioperative approach to hemostasis was to give vitamin K 8 mg *po* 12 hr prior to surgery, prothrombin complex concentrate 40 mL *iv* in the immediate preoperative period, and a second dose of prothrombin complex concentrate plus 2.4 mg of recombinant activated factor VIIa following protamine reversal of heparin. Although it is not the norm to give factor VIIa prophylactically, in this unique case, it was felt that the benefits of attempting to prevent a coagulopathy rather than treating one would outweigh any potential thrombotic risks. Fresh frozen plasma, cryoprecipitate, and platelets would be given in the postoperative period, as per both laboratory and clinical indications. The patient was also given a post induction bolus of tranexamic acid $10 \text{ mg}\cdot\text{kg}^{-1}$ *iv* followed by a $2 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ infusion throughout surgery. The patient received 25 KU of heparin in preparation for a cardiopulmonary bypass, which was reversed with 250 mg of protamine following separation from cardiopulmonary bypass.

The anesthetic and surgical plans were as follows: Given that the patient was intolerant of the supine or Trendelenburg positioning, peripheral venous and arterial access were secured prior to induction, but right internal jugular cannulation for a continuous cardiac output pulmonary artery catheter was secured post induction. Surgery was immediately available for femoral-femoral bypass. Induction included midazolam 2 mg *iv* and ketamine 50 mg *iv* followed by sufentanil 25 μg *iv*, propofol 30 mg *iv*, and rocuronium 100 mg *iv*. Post-induction hemodynamics was complicated by a decrease in systolic pressure to 60 mmHg and an increase in systolic pulmonary artery pressure to

Fig. 1 Stenotic mitral prosthesis

150 mmHg. Hemodynamic stability was obtained with phenylephrine $1,000 \mu\text{g}$ *iv* in divided doses, norepinephrine at $0.5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, and rapid initiation of femoral-femoral bypass that unloaded the right ventricle dramatically. Anesthesia was maintained with sevoflurane and infusions of propofol and sufentanil. The intraoperative transesophageal echocardiography before cardiopulmonary bypass was essentially unchanged from the preoperative report. The mechanical prosthesis (Figure 1) was replaced with a size 33 tissue prosthesis without complication. Total blood loss was approximately 700 mL, and no blood transfusion was required intraoperatively. Post cardiopulmonary bypass transesophageal echocardiography showed continued moderate right ventricular dilation and severely reduced systolic function despite a normal gradient across the new prosthesis. Right pulmonary artery pressures were greatly improved at approximately 40 mmHg. The patient was transferred to the cardiac surgical intensive care unit when hemodynamically stable on milrinone, norepinephrine, and vasopressin infusions. On the first postoperative day, the patient received two of the three available units of autologous red blood cells; one unit broke during thawing. He also received two units of Bombay phenotype red blood cells from an outside institution, two units of platelets, and two units of fresh frozen plasma. Pathology confirmed that one of the leaflets on the mechanical prosthesis was immobilized by both an organizing thrombus and the pannus around the sewing ring (Figure 1). The patient's trachea was extubated on postoperative day 1 on inotropic support, diuretics, and bronchodilators.

Hematology followed the patient postoperatively and began darbepoetin injections until his hemoglobin was $> 100 \text{ g}\cdot\text{L}^{-1}$. By postoperative day 3, alterations in hepatic function were characterized by further increases in AST and ALT ($360 \text{ U}\cdot\text{L}^{-1}$ and $235 \text{ U}\cdot\text{L}^{-1}$, respectively),

both total and direct bilirubin (170 and 102 $\mu\text{mol}\cdot\text{L}^{-1}$, respectively), and lactate dehydrogenase (461 $\text{U}\cdot\text{L}^{-1}$). Haptoglobin levels were low/normal at 0.35 $\text{g}\cdot\text{L}^{-1}$. These levels normalized by postoperative day 12. The patient's only other postoperative complication was development of a third degree atrioventricular block with a high junctional rhythm. Despite normal hemodynamics, the decision was made to insert a permanent pacemaker.

Discussion

Bombay red blood cell phenotype (O_h or hh) was first described by Bhende *et al.* in 1952 who documented the incompatibility of a patient with group O blood with multiple group O donors.⁵ The Bombay phenotype has since been determined to be a rare autosomal recessive phenotype confined mostly to the Southeast Asian countries.⁶ The estimated prevalence is 1:10,000 in India and 1:10⁶ outside of India.² However, the regional prevalence of Bombay phenotype in India varies, as it does have a higher prevalence in Indian states where consanguineous marriages are acceptable, such as the state from which our patient originated. The prevalence in Reunion Island, a region outside of India, is estimated at 1:1,000.⁷ Further cases of Bombay phenotype outside of India may become more prevalent with global redistribution.

According to the International Society for Blood Transfusions, there are over 700 documented erythrocyte antigens and twenty-nine blood grouping systems. Karl Landsteiner's ABO blood typing system remains the single most important group for blood transfusions. Briefly, the A, B, AB, and O blood types refer to specific antigenic sugar moieties attached by an alpha 1-2 linkage to short oligosaccharide chains that exist as the carbohydrate moiety of glycolipid and glycoprotein molecules located on red blood cells.⁸ This linkage is controlled by the action of glycosyltransferase enzymes that specifically select for N-acetyl-D-galactosamine (GalNAc) for type A and for D-galactose (Gal) for type B. The glycosyltransferase enzyme for type O blood cross-reacts immunologically with the A and B transferase enzymes but is functionally silent. These transferase enzymes are the product of four major alleles located on the long arm of chromosome 9.⁹ In addition, there is another glucose antigenic moiety, fucose, the H antigen, which serves as the precursor of the A, B, and O antigens.¹⁰ The responsible transferase for fucose is the product of a very common H gene that is lacking in the Bombay phenotype. Since the fucose moiety is a necessary precursor for the A and B antigens, Bombay blood will type as O, but will have hemolytic auto-antibodies to the H antigen.³

Identification of the Bombay phenotype occurs during the antibody screen interpretation of blood.¹¹ The patient will appear to have group O blood, but all type O blood will be reactive to the patient's plasma. Rare cells that are negative for common high incidence antigens are tested against the patient's plasma, k^- , Kp^b -, Js^b -, Lu^b -, and H-. All cells will be reactive except for the one lacking the H antigen. This negative reaction points to the patient being Bombay phenotype and having anti-H. Subsequently, the patient's red blood cells are tested with anti-H antisera and found to be negative, further proving that the patient is Bombay phenotype. The patient's phenotype is fully tested for the other common blood group antigens, and the sample may be sent to a reference lab where more O_h cells are available for antibody exclusions. Red blood cell transfusions for persons with Bombay phenotype must be either autologous or from another Bombay phenotype donor.³ CBS would normally require a minimum of 24 hr to obtain red blood cells from local compatible donors or to locate and obtain frozen units through their national database.

Although red blood cells can be stored for ten years at -65°C , this process is not without its complications. Due to the use of glycerol as a cryopreservative agent, cells must be thawed and deglycerolized, a two- to three-hour process performed at CBS. Furthermore, the process may increase red cell fragility and reduce the hematocrit to 50% compared with normal packed red blood cells with a hematocrit of 75%.¹² Thus, perioperative management of transfusion with frozen autologous red blood cells is challenging given the conflicting concerns of a limited supply of available blood and the need for an advanced but accurate prediction of intraoperative need. It is fortunate that patients with Bombay phenotype can receive any fresh frozen plasma and cryoprecipitate for the treatment of coagulopathies. However, platelet transfusion should probably be limited to type A because ABH antigens are also expressed on platelets, and most platelet preparations also contain a small amount of donor red blood cells. Group A donors have the least amount of H antigen of all the ABO blood groups.⁴ There is no well-documented disease association with Bombay phenotype.⁷ However, all patients with type O blood, including Bombay phenotype, have been described with higher rates of bleeding complications.¹³⁻¹⁵

There are numerous anesthetic considerations for this particular case including: 1) presence of Bombay phenotype that severely limits or even negates the possibility of red blood cell transfusion; 2) use of frozen red blood cells with concomitant lower hematocrit, delayed availability, and increased red blood cell fragility; 3) urgent repeat sternotomy for prosthetic valve surgery; 4) relatively acute severe right heart failure and pulmonary hypertension that causes hepatic congestion and places the patient in extreme risk of

major hemodynamic instability on induction of anesthesia necessitating rapid initiation of cardiopulmonary bypass; 5) increased risk of perioperative coagulopathy secondary to emergent surgery, hepatic congestion, and therapeutic warfarin anticoagulation requiring reversal with prothrombin complex concentrate;¹⁶ and finally 6) intolerance of even minimal pulmonary edema because of chronic obstructive pulmonary disease.

The approach of pre-donating and deep freezing autologous red blood cells has been used successfully in a patient undergoing elective bypass surgery.¹⁷ Patients with Bombay phenotype red blood cells present as type O, but they are unable to receive red blood cells from any phenotype other than Bombay phenotype. Fortunately, they are able to receive all other blood products, including fresh frozen plasma, cryoprecipitate, platelets, prothrombin complex concentrate, and recombinant activated factor VIIa. Coordination between Canadian Blood Services, transfusion medicine, surgery, and anesthesia is important in managing these patients.

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Competing interests None declared.

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