Hemolytic Anemia in Native Valve Infective Endocarditis
—— A Case Report and Literature Review ——

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Hemolytic anemia is a rare manifestation of infective endocarditis. A 19-year-old man with a small ventricular septal defect developed right-sided infective endocarditis with huge vegetations involving the tricuspid valve, the ventricular septal defect, and the pulmonary valve. Intravascular hemolysis was suggested by the presence of numerous fragmented erythrocytes, giant platelets and polychromasia of the red blood cells. The direct Coombs test was positive, and there were spherocytes and splenomegaly, findings that suggested an immune-mediated mechanism also played a role in the hemolysis. The hematological picture persisted despite antibiotic therapy and recovered only after surgical removal of the vegetations, tricuspid and pulmonary valvectomy, and patch closure of the ventricular septal defect. (Jpn Circ J 1999; 63: 400–403)

Key Words: Hemolytic anemia; Infective endocarditis; Valvectomy

Mild normocytic anemia without reticulocytosis frequently accompanies conditions such as infective endocarditis, malignancy and chronic inflammations, and is generally recognized as the ‘anemia of chronic disorder’. Hemolytic anemia associated with native valve infective endocarditis has been noted only in a few previous reports. We describe an unusual case of endocarditis-induced hemolysis that resolved after removal of the vegetations, valvectomy and repair of a congenital defect.

Case Report

A 19-year-old man was admitted to hospital with a 3-month history of general malaise, low-grade fever and lower leg edema. Five months before admission, he had symptoms of an upper respiratory tract infection. At that time, a complete blood cell count revealed mild leukocytosis (white blood cell count, 10.9×10⁹/mm³) without anemia (hemoglobin 12.9 g/dl) or thrombocytopenia (platelet count, 210×10³/mm³). The red cell distribution width was less than 140% and the peripheral blood smear disclosed normal morphology of erythrocytes without spherocytes or polychromasia. Physical examination was normal. Progressive dyspnea, swelling and petechiae over the lower legs developed 3 days before admission.

On admission, the patient was pale and febrile with a temperature of 37.8°C, a heart rate of 104/min and a respiratory rate of 24/min. He denied any history of intravenous drug abuse, sexual contact or family history of hematological disease. Physical examination revealed a grade IV/VI holosystolic murmur at the left lower sternal border, a grade III/VI diastolic blowing murmur at the pulmonic area and hepatosplenomegaly with palpable systolic pulsation of the liver. The hemoglobin was 5.8 g/dl and reticulocytes 153%; lactate dehydrogenase was 543 U/L (normal: 47–140) and haptoglobin less than 24.3 mg/dl (normal, 53–170); the platelet count was 23×10⁹/mm³. A peripheral blood smear displayed numerous fragmented erythrocytes, spherocytes, giant platelets and polychromasia of red blood cells. Bone marrow aspiration revealed hypercellular marrow without evidence of hemophagocytosis. His liver and renal function remained normal throughout the course, although a mild elevation of unconjugated bilirubin was noted (4.7 mg/dl).

Anti-nuclear antibody, anti-HIV antibody, sucrose hemolysis test, Ham’s test and other examinations for abnormal hemoglobin were negative. The direct Coombs test was positive (IgG, complement (−)) and the circulating immune complexes was 25 μg/ml (normal, <20 μg/ml). Three separate blood cultures revealed Streptococcus oralis. Two-dimensional echocardiography and color flow mapping disclosed multiple vegetations on the tricuspid valve, right ventricle and pulmonary valve with severe tricuspid and pulmonic regurgitation (Fig 1A,B) as well as a small ventricular septal defect, which was occluded almost completely by the vegetations (Fig 2). Therapy with intravenous aminoglycoside antibiotics (18 meg-units per day) and gentamicin (240 mg/day) was initiated. Three days later the petechiae faded and the platelet count rose to 165×10³/mm³, but the fragmented erythrocytes, reticulocytosis and positive direct Coombs test persisted despite antibiotic treatment for 6 weeks. The patient then underwent surgical therapy. The tricuspid and pulmonary valves were excised, the vegetations removed, and the ventricular septal defect was closed with a patch. One month after the surgery, 2-dimensional echocardiography revealed the absence of the tricuspid and pulmonary valves with only tiny vegetations in the right ventricle (Fig 1C,D). The hemogram improved with a hemoglobin of 10.4 g/dl, reticulocytes of 28%, an erythrocyte sedimentation rate of 20 mm/h and a haptoglobin of 45.7 mg/dl. The peripheral blood smear was also normal and the direct Coombs test was negative. The patient was discharged 3 months after admission with no
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Discussion

Infective endocarditis involving the right side of the heart is less common comparing with that involving the left-side. Most patients with a right-sided endocarditis have an underlying congenital heart disease such as ventricular septal defect, atrial septal defect, pulmonary stenosis or patent ductus arteriosus. An increase in the incidence of right-sided infective endocarditis with involvement of the tricuspid valve due to drug abuse has been reported. In the cases of right-sided infective endocarditis reported by Grover et al, the tricuspid valve was affected in more than 50% of the patients whereas the pulmonary valve alone or other sites in the right heart were affected in less than 10% of the patients. In the present patient, vegetations occurred on the tricuspid valve, the right ventricle and the pulmonary valve; the underlying ventricular septal defect was almost occluded by vegetations. Transesophageal echocardiography accurately detected the vegetations and the presence of the ventricular septal defect.

Anemia is a common manifestation of infective endocarditis and is generally normochromic and normocytic. Hemolytic anemia has been reported in only a few previous cases. Maeda et al reported a 65-year-old female with hemolysis associated with streptococcal endocarditis of the mitral valve. That patient had an underlying obstructive hypertrophic cardiomyopathy with a 115-mmHg pressure gradient in the left ventricular outflow tract and a moderate mitral regurgitation due to mitral valve prolapse. The infection improved after antibiotic treatment, but the hemolysis persisted. A reduction in the pressure gradient in the left ventricular outflow tract following propranolol administration resulted in an improvement of the hemolysis, probably due to a decrease in the shearing stress on the red blood cells. Nishiu et al described hemolytic anemia with Aspergillus endocarditis involving the mitral valve in a patient with acute lymphocytic leukemia. Postmortem examination of their patient showed huge vegetations on the mitral valve, and they postulated that the rapid progression of vegetations resulted in a powerful turbulent flow that caused intravascular hemolysis. Naidoo et al also reported intravascular hemolysis with fragmented erythrocytes in a patient with isolated endocarditis of the pulmonary valve. Neither an underlying heart disease nor a specific microorganism was identified in that patient. The hematological abnormalities improved after 1 week of empiric antibiotic treatment. Inada et al also demonstrated improvement of hemolytic anemia after antibiotic therapy in a patient with Streptococcus sanguis endocarditis. In contrast, the patient with staphylococcal endocarditis involving the tricuspid valve due to drug abuse, reported by Gradon et al, required surgical removal of the vegetations for control of the hemolytic process. In an infant with further complications. Four months after operation, a follow-up hemogram showed a hemoglobin of 14.4 g/dl, reticulocytes of 10‰ and a normal red cell distribution width. He has remained well during follow-up.

Fig 1. Two-dimensional echocardiograms before (A, B) and after surgery (C, D). (A) Parasternal short axis view and (B) apical 4 chamber view. Note multiple vegetations (arrowheads) occurring on the pulmonary valve, the tricuspid valve and the right ventricle before surgery. The pulmonary and tricuspid valves were absent after the operation and only a few vegetations were seen on the right ventricle. AO, aorta; PA, pulmonary artery; RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle.
hemolysis reported by Hsu et al, the right ventricle was occupied by a huge fungal ball and there were spherocytes, splenomegaly, and a positive direct Coombs test. The hemolysis improved after the surgical removal of the vegetations and tricuspid valvuloplasty, but the patient subsequently died of multiple organ dysfunction. The presence of fragmented erythrocytes in all of these patients suggests that mechanical destruction of the red blood cells was responsible for the intravascular hemolysis. Obstruction of the right heart chamber by huge vegetations or obstruction in the high pressure system of the left heart may provide an adequate shearing stress on the erythrocytes leading to hemolysis. However, an immune-mediated mechanism is also suggested by the spherocytes, splenomegaly and a positive direct Coombs test. In an experimental study on extravascular hemolysis due to infective endocarditis in rabbits, Joyce and Sande demonstrated that the half-life of the red blood cells of the rabbits with infective endocarditis and intact spleen was significantly shorter than in the rabbits without endocarditis or the rabbits with endocarditis and splenectomy, which suggests that hypertrophy of the reticulo-endothelial system with hypersplenic sequestration is the major mechanism of extravascular hemolysis. In addition, invading microorganisms also contribute to the production of anti-erythrocyte antibodies by cross-reaction with erythrocyte antigens, by modifying the antigenicity of erythrocyte antigens, or by unmasking antigens that are not normally available. The antibody-coated erythrocytes then are broken down in the spleen, leading to acute hemolysis.

In the present patient, intravascular hemolysis was suggested by the numerous fragmented red blood cells, the low level of haptoglobin and the presence of hemosiderinuria. The presence of a positive direct Coombs test, spherocytes and splenomegaly also suggests that an immune-mediated mechanism could also have contributed to the hemolysis. After surgery, only tiny vegetations were left in the heart. The reduction in shearing stress and loss of ability to produce enough antibodies due to the removal of the antigenetic material resulted in the disappearance of the hemolytic anemia.

In summary, we have described intravascular and extravascular hemolysis in a patient with a congenital ventricular septal defect who had infective endocarditis with vegetations that involved the tricuspid and pulmonary valves. Hemolysis persisted despite antibiotic therapy and resolved only after removal of the vegetations and the valves, and repair of the ventricular septal defect.

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References


