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Ethylenediaminetetraacetic acid-dependent pseudothrombocytopenia in complex cardiac surgery

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ABSTRACT

Pseudothrombocytopenia is an unusual hematological disorder, which develops in response to ethylenediaminetetraacetic acid-dependent anti-platelet autoantibodies in blood, leading to platelet clumping. It is only an *in vitro* phenomenon, which presents with low platelet counts in routine hematology analysis. The definitive diagnosis should be established to avoid a delay in surgery and unnecessary blood transfusion in patients undergoing cardiovascular surgery. Herein, we present a 51-year-old female case with ethylenediaminetetraacetic acid-dependent pseudothrombocytopenia, who underwent a successful aortic root and valve surgery, and discuss perioperative management of this rare disorder.

Keywords: Cardiac surgery; ethylenediaminetetraacetic acid-dependent; ethylenediaminetetraacetic acid; pseudothrombocytopenia; pseudothrombocytopenia.

Pseudothrombocytopenia is a rare hematological disorder of platelet clumping related to ethylenediaminetetraacetic acid (EDTA)-dependent antiplatelet autoantibodies in blood.[1-4] The EDTA is a safe anticoagulant for a complete blood count analysis. However, this agent may induce the clumping, which causes the automatic hematology analyzers to undercount platelets, thereby, resulting in low platelet counts. Pseudothrombocytopenia is only an *in vitro* effect, which does not cause any hemostatic complications, as all platelet functions and coagulation tests are normal.[5] It can be seen in some patients with autoimmune diseases, malignancies, chronic liver diseases, viral infections, and cardiovascular diseases. In addition, pregnant women and healthy individuals may rarely present with this disorder.[5] The diagnosis of pseudothrombocytopenia is of unique clinical importance to avoid a delay in surgery and unnecessary blood transfusion in patients undergoing cardiac surgery.

Although EDTA-dependent pseudothrombocytopenia has been previously described in patients undergoing cardiac surgery,[2-4] its clinical features and management approaches still remain controversial for cardiac surgeons. Herein, we present a case of pseudothrombocytopenia who underwent aortic root replacement, mitral valve replacement, and tricuspid valve repair and discuss perioperative management of this entity.

CASE REPORT

A 51-year-old female was referred to our hospital with progressive dyspnea due to valvular heart disease. Her medical history revealed chronic renal failure and hypertension. She was also on medical treatment for hypertension with angiotensin-receptor blockers. On admission, her vital signs were stable. Physical examination revealed aortic, mitral, and tricuspid diastolic murmur. In the biochemical analysis, low platelet counts (65,000/mm^3) were observed. There was no skin lesion such as petechiae, ecchymosis, or purpura. Other than thrombocytopenia, biochemical and serological test results were normal without any indicator of an infection, inflammatory disease or coagulation disorder. Electrocardiography revealed sinus rhythm with a left-axis deviation. A chest X-ray showed cardiomegaly with enlarged left chambers. Echocardiography revealed an ejection fraction of 45%

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with a severe aortic and mitral valve regurgitation and moderate tricuspid valve regurgitation. Pulmonary artery pressure was 40 mmHg. It also showed enlarged left cardiac chambers, mild pericardial effusion, and an aneurysm of the ascending aorta. Thoracic computed tomography revealed an aortic annulus of 30 mm, sinus of Valsalva of 43 mm, sinotubular junction of 36 mm, and ascending aorta of 51 mm in size. Coronary angiography demonstrated no abnormality of coronary arteries. The patient was decided to undergo the Bentall procedure with mitral valve replacement and tricuspid valvuloplasty. Preoperatively, she was referred to a hematology consultant. EDTA-dependent pseudothrombocytopenia was diagnosed with a peripheral blood smear which showed platelet clumping (Figure 1). Clumping was not observed after analysis of heparinized blood sample. Surgery was decided based on the discretion of the consultant hematologist.

The operation was performed with a median sternotomy and systemic heparinization. Cardiopulmonary bypass was initiated through the cannulation of the ascending aorta and both vena cava. Cardiac arrest was established with antegrade infusion of isothermic blood cardioplegia through the coronary ostia. First, right atriotomy incision was performed and, using transseptal incision, the mitral valve was explored. It was degenerated and replaced with a No. 29 bileaflet mechanical valve, preserving the posterior mitral leaflet. Then, the Bentall procedure with a No. 21 mechanical aortic valve conduit was performed. Finally, the tricuspid valve annuloplasty was made using a No. 29 flexible annuloplasty ring. The valve showed a good coaptation on saline test. The operation was completed uneventfully. Cardiopulmonary bypass and aortic cross-clamp times were 169 and 137 min, respectively. She was transferred to the ward on postoperative Day 1 with a platelet count of 74,000/m^3. No platelet suspension was delivered postoperatively.

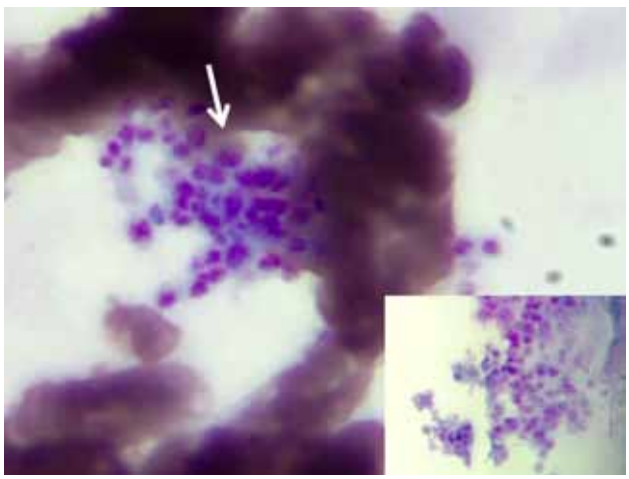

Figure 1. Hematoxylin and Eosin stained EDTA-blood smear showing platelet clumping (arrow, inset) (H-E x 40).
EDTA: Ethylenediaminetetraacetic acid.

The patient was discharged home with a favorable outcome on postoperative Day 6. The platelet count ranged between 65,000 and 87,000/mm^3. Routine anticoagulation was delivered, including early delivery of low-molecular-weight heparin and warfarin with an international normalized ratio of ranging between 2.5 and 3.5. At four months of follow-up, she is still disease-free.

DISCUSSION

Acquired platelet disorders are mainly classified into disorders of the platelet count and function.[1] The etiology of low platelet count includes decreased production by bone marrow and increased peripheral destruction due to immunological causes, non-immunological disorders, hemodilution, and pseudothrombocytopenia. The prevalence of EDTA-dependent pseudothrombocytopenia is reported to be between 0.1% and 2% among hospitalized patients and up to 17% in patients with isolated thrombocytopenia.[3,5] The EDTA is an anticoagulant, which is frequently used for hematological tests, and may induce platelet clumping. However, some other anticoagulants such as heparin, oxalate, hirudin, citrate, or abciximab may also cause pseudothrombocytopenia, although their actual incidence is still unclear.[5]

The underlying mechanism of platelet clumping in pseudothrombocytopenia includes an immunological process which was first described by Shreiner and Bell in 1973.[6] The authors proved that EDTA caused a new type of platelet agglutinin, which was active at 37 °C, as well as at room temperature. The EDTA-dependent antiplatelet antibodies recognize and activate different receptors, such as glycoprotein IIb-IIIa and thrombospondin, resulting in platelet clumping in the *in vitro* setting. Previously, Bizzaro[1] reported antiplatelet antibodies in 83% of the patients with pseudothrombocytopenia.[1] These antibodies were majorly immunoglobulin (Ig) M or IgG. In addition, a small number of patients had an IgA class.[1] Although

platelet clumping occurs during hematological tests, the number and function of the platelets can be normal in patients with pseudothrombocytopenia in the *in vitro* setting.[1] Previous reports also showed that low platelet counts were not associated with an increased risk of bleeding in the perioperative period of cardiac surgery.[2-5]

Although the cardiac surgical practice is itself associated with hemorrhagic complications, EDTA-dependent pseudothrombocytopenia presents with a benign course.[2-4] Preoperatively, patients usually have low platelet counts in the routine blood tests. Due to platelet clumping, conventional automated hematology analyzers count each clump as one and do not show the actual number of platelets. Therefore, the visual assessment of blood smears for clumping is considered as the gold standard for the diagnosis of this phenomenon.[1-5] Unawareness of this entity may lead to a delay in cardiac procedures or unnecessary transfusion in the perioperative period. These may, eventually, lead to severe complications, particularly in high-risk patients with a critical coronary or valve disease.

In the literature, pseudothrombocytopenia in cardiovascular operations has been described in few reports; however, it is still an unusual entity for cardiac surgeons.[2-4] The first report by Dalamangas et al.[3] described an uneventful coronary revascularization and aortic valve replacement using cardiopulmonary bypass. Then, Wilkes et al.[2] presented a patient with anticoagulant-induced pseudothrombocytopenia who underwent a successful coronary artery bypass grafting. The authors confirmed the low platelet count and clumping with microscopic examination, and concluded that clumping was associated with both EDTA and citrate on hematological analysis in the postoperative period. On the other hand, Nair et al.[4] reported that EDTA-dependent pseudothrombocytopenia could be easily diagnosed by repeating platelet counts in citrate and heparin-anticoagulated blood samples. These reports confirm that any type of anticoagulant can be associated with clumping. To the best of our knowledge, our case is the first report of a complex cardiac surgery with a prolonged cardiopulmonary bypass time in pseudothrombocytopenia.

The diagnostic approaches in such cases include blood smears which are simple and valuable tests to show an abnormality of clumping or hemostasis. Laboratory tests such as thromboelastography, which shows specifically the function of platelets, can be also used to reveal an abnormality of coagulation related to platelets. It is a simple and rapid tool for the diagnosis of hemostatic disorders; however, the availability of this tool is limited. Beyond the diagnostic tests, clinical experience is also important for hemostasis in complex and prolonged cases. In our case, if the duration of the procedure prolonged, which means coagulation can be affected from the cardiopulmonary bypass time, we could use platelet suspensions after weaning from cardiopulmonary bypass. Indeed, there is no known drawback of using platelets in prolonged and complex cardiac surgery procedures.

In conclusion, ethylenediaminetetraacetic acid-dependent pseudothrombocytopenia is a rare disorder of platelet clumping during hematological testing. It is a benign phenomenon and does not pose an increased risk for perioperative bleeding. The definitive diagnosis of pseudothrombocytopenia prevents unnecessary testing for thrombocytopenia, a delay in surgery, and unnecessary platelet transfusions.

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