Journal of Clinical & Experimental Cardiology

Wang et al. J Clinic Experiment Cardiol 2012, 3:1
DOI: 10.4172/2155-9880.1000174

Case Report Open Access

# One Case of Anemia after the Implantation of A Drug-Eluting Stent Into Coronary Artery

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This 50-year-old male patient was admitted into this hospital for a chief complaint of intermittent chest pain for 2 years with aggravation for 3 days.

Since the last two years he felt chest pain without precipitation radiating to left shoulder which lasted for several minutes. No full medical therapy was offered. Over the last 3 days, the patient has recurrent chest pain for no apparent precipitating factor. The pain radiated toward both shoulders and back region and lasted around 7-8 minutes twice daily. He came to our emergency clinic for recurrent chest pain with cold sweat. Electrocardiograph (ECG): V3-V6 ST segment depressed for 0.2 mv and cardiac troponin T (cTnT) 0.21ng/ml. With the impression of non-ST segment elevation myocardial infarction, he was admitted into our CCU (cardiac care unit).

**Past history**: Resection of hip bone tumor was performed 35 years ago. There was intra-operative blood transfusion.

**Personal history**: As an occasional drinker, he consumed 15 cigarettes per day for 20 years. His father suffered coronary heart disease. There was no recent history of toxic substance exposure or medication.

## Admission Physical Examination

Temperature 36.8°C, respiratory rate 20 breaths/min, pulse 80 beats/min, blood pressure 109/64 mm Hg. No conjunctival hyperemia or pallor. No enlarged superficial lymph node was palpated. No jugular distention. No neck vascular bruit was heard. Respiratory sounds were clear throughout both lungs. No dry or moist rale was heard. Cardiac border was normal. Heart rate 80 beats per minute, even rhythm, A2=P2, no pathologic murmur. Soft abdomen, infra-xiphoid mild tenderness, no rebound tenderness or muscular tension, bowel sound at 3 times per minute, no edema in lower extremities.

Emergency ECG (2011-3-9): Sinus rhythm, V3-V6 ST segment depressed by 0.2 mv; Emergency blood routine (2011-3-9): WBC (white blood cell) $9.08\times10^9$/L, granulocytes 76.6%, RBC (red blood cell) $5.34\times10^{12}$/L, Hbg (hemoglobin) 167g/L, PLT (platelet) $254\times10^9$/L.

Echocardiographic findings: LA inner diameter was at the normal upper limit (LA 3.5cm) and the inner diameters of other atria and ventricles were normal (EDD 4.7cm). The left ventricular ejection fraction was normal (EF 0.69). No valvular abnormality. The basal part of interventricular septum became thicker at 1.4cm. And the motion of ventricular wall was coordinated.

Blood biochemistry (2011-3-9): Total protein (60-80g/L) 71.1 g/L, albumin (35-55g/L) 43.1g/L, potassium (3.5-5.5mmol/L) 3.99mmol/L, creatinine (53-115mmol/L) 94umol/L, BUN (1.43-7.14mmol/L) 5.62mmol/L, Glucose (3.93-6.16mmol/L) 5.49mmol/L, creatine kinase (22-180U/L) 98 U/L, creatine kinase-MB (0-24U/L)10.4U/L.

cTnT (2011-3-9 Emergency visit at this hospital) : 0.21ng/ml.

NT-pro BNP (N-terminal pro brain natriuretic peptide, <300 pg/ml): 499pg/ml.

DIC (Disseminated Intravascular Coagulation): normal.

After admission, the patient received the anti-platelet drugs of aspirin, clopidogrel and the coronary-dilating nitroglycerins along with symptomatic therapies. The patient had no more recurrence of angina pectoris.

On March 14, a selective coronary angiography was performed. The results indicated that triple vessels had lesions involving LAD (left anterior descending coronary artery), LCX (left circumflex) & RCA (right coronary artery)), LM (left main) (-), LAD p-m50% segmental stenosis, antegrade flow Class TIMI3, LCXp90-95% diffusive stenosis, thrombotic shadow visible, antegrade flow Class TIMI2, RCAm 50% segmental stenosis, antegrade flow Class III, collateral branch Grade III of RCA into LCX. 2.5×15mm Maverick balloon 12atm×5s, 16×5 dilation, thrombotic shadow visible on repeated angiography, residual stenosis 70%, antegrade flow Class TIMI3, 3.5×30mm Endeavor Resolute stent delivered to the LCXp lesion, stent balloon dilated with 16atm×5s, thrombotic shadow still visible at re-angiography, antegrade flow Class TIMI3, 4.0×12mm Quantum Balloon into LCXp stent, balloon dilated with 12-18atm×5s, re-angiography performed, slight thrombotic shadow visible at proximal stent end, no dissection found, residual stenosis 0%, excellent stent wall-adhering, antegrade flow Class TIMI3. Blood loss during PCI was about 20ml. The post-operative medications included aspirin 100mg/qd, clopidogrel 75mg/qd for anti-platelet and low-molecular-weight heparin (enoxaparin) of standard dose for anti-coagulation.

At a medical round, the patient had pale appearance without any hemorrhagic sign on 2011-3-16. The blood, stool and urine routines were re-examined. During the period of March 16-18, his hemoglobin level declined progressively. On soliciting his disease history, this patient had a habitual postprandial infra-xiphoid burn-like pain. At night, there was infra-xiphoid hunger-like pain. Thus the initial possibilities of peptic ulcer and upper gastrointestinal tract hemorrhage could not be ruled out. The anti-platelet and anti-coagulation drugs were withdrawn. And 2 units of erythrocyte suspension were infused. The examinations of stool routine and occult blood were repeated. All results were negative. Repeated examinations of urine routine found no erythrocyte in urine samples. Based upon the clinical symptoms and signs, no hemorrhagic sign of other sites was discovered. On March

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**Received** October 31, 2011; **Accepted** January 26, 2012; **Published** January 29, 2012

**Citation:** Wang P, Wang Y, Shen A, Wang Y, Chen H, et al. (2012) One Case of Anemia after the Implantation of A Drug-Eluting Stent Into Coronary Artery. J Clinic Experiment Cardiol 3:174. doi:10.4172/2155-9880.1000174

22, 2011, chest pain recurred. Physical examination: Blood pressure: 90/60 mm Hg, pulse: 70 beats permin. **ECG:** V1-V3 ST segment became depressed. Re-ischemia was considered. Thrombosis was not ruled out. Based upon clinical observations and examinations over the last several days, there were no definite hemorrhagic foci in this patient. While offering coronary dilation and symptomatic therapies, enoxaparin 0.6ml q12h ih was added. And erythrocyte suspension 2U was administered in emergency. 2011-3-23: Washed erythrocyte suspension 2U was infused. 2011-3-25: On physical examination, there was dull percussion in bilateral lower pulmonary lobes with weak respiratory sounds; On thoracic ultrasound Type B, there was bilateral pleural effusion. A diagnostic thoracentesis yielded a pale yellowish liquid without erythrocyte. There was a strong possibility of pleural effusion caused by cardiac insufficiency and hypoproteinemia. 2011-3-27: Fresh frozen plasma 200ml and washed erythrocyte suspension 2U were infused. 2011-3-28: Fresh frozen plasma 200ml was infused.

The relevant anemic examinations were as follows:

Count of peripheral fragmented erythrocyte (2011-3-22): fragmented erythrocyte rarely seen, polychromatic erythrocyte mildly increased and basophilic stippling erythrocyte visible in mature erythrocyte. Serum iron, Total iron binding capacity (TIBC), Unsaturated iron binding capacity (UIBC), Ferritin, Folic acid (FA) and Vitamin $B_{12}$ (2011-3-22) were normal. Urine hemosiderin test (2011-3-25): negative, Antinuclear antigen (2011-3-26): negative, Antineutrophil cytoplasmic antibody (2011-3-28): negative, Immunoglobulins and complements (2011-3-28): normal, Stool occult blood (2011-3-12/16/18/19/21/26/27/28): negative. Ultrasound Type B of abdominal cavity: normal, No obvious CT abnormality of abdomen was found. (Table 1, Figure 1, 2, 3, 4)

## Discussion

For this patient, one is puzzled at the cause of anemia after his interventional procedure. The common causes of anemia are hemorrhage, hemolysis and abnormal hematopoiesis of bone marrow. After the implantation of a drug-eluting stent (DES), combined anti-platelet drugs are routinely prescribed to prevent the occurrence of thrombosis. Especially for the patients with a heavy thrombotic burden within coronary artery, low-molecular-weight heparin and/or platelet II b/ III a receptor antagonist are often used in combination. Thus it carries a higher hemorrhagic risk. Therefore, with regards to a post-PCI decline of hemoglobin in a patient, a physician should first of all consider its cause to be hemorrhage. But a definite proof of hemorrhage was absent here. And, even after adding low-molecular-weight heparin for anti-coagulation, such evidence remained lacking. Therefore hemorrhagic anemia may be excluded. If due to abnormal hematopoiesis of bone marrow, such as pure RBC aplastic anemia, an anemic patient should have a normal or reduced count of reticulocyte. But in this patient, the percentage of reticulocyte was inversely correlated with the level of hemoglobin. Furthermore, his level of hemoglobin was self-restored at 20 days after a sharp decline. Therefore abnormal hematopoiesis of bone marrow seemed implausible.

After excluding hemorrhage and abnormal hematopoiesis of bone marrow, the common cause of a sharp decline of hemoglobin is hemolysis. Despite a sharp decline of hemoglobin in this patient, his urobilinogen was positive but blood bilirubin remained normal. Yet, in some instances, the level of bilirubin showed no increase during hemolysis. Thus the possibility of hemolysis can not be ruled out. What are the causes of hemolysis? This patient had no family hereditary history of hematological diseases. There was no previous history of hemolysis. Furthermore the smear of peripheral blood revealed no abnormal erythrocyte. Thus hemolysis due to inherent erythrocyte abnormality might be ruled out. During hospitalization, the patient had no contact history of other special substances. He only took some

| | TnT | urobilirubin | URO | Tbil. | Ibil | Dbil |
|---|---|---|---|---|---|---|
| 2011-3-9 | | | | 22.8 | 5.85 | 16.95 |
| 2011-3-11 | 0.3 | 1+ | 2+ | 11.9 | 4.34 | 7.56 |
| 2011-3-13 | 0.928 | | | | | |
| 2011-3-14 | 0.694 | | | | | |
| 2011-3-15 | 0.479 | | | | | |
| 2011-3-22 | 0.26 | | - | 3.6 | 2.1 | 1.5 |
| 2011-3-23 | 2.19 | | - | | | |
| 2011-3-24 | 5.5 | | 1+ | | | |
| 2011-3-25 | 4.41 | | 2+ | | | |
| 2011-3-26 | 4.06 | | 1+ | 6.13 | 2.52 | 3.61 |
| 2011-3-27 | 3.68 | | 1+ | | | |
| 2011-3-28 | 2.89 | | - | | | |
| 2011-3-29 | 1.87 | | - | | | |
| 2011-4-6 | | | - | 2.96 | 1.11 | 1.85 |

TnT (<3ng/ml): Troponin T, URO: Urobilinogen Qualitative, Tbil (42-17.1umol/L): total bilirubin, Ibil (0-6.84umol/L): indirect bilirubin, Dbil (0-12umol/L): direct bilirubin

**Table 1:** Blood and urine bilirubin examinations.

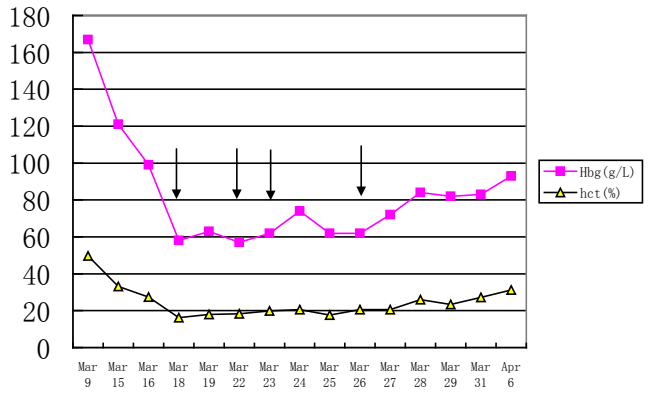


**Figure1:** The changes of Hbg and Hct level.

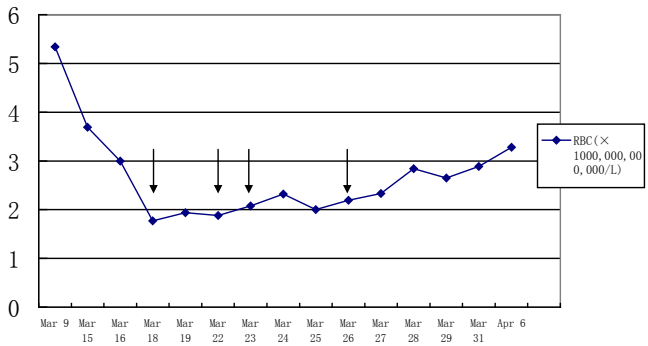


**Figure 2:** The changes of RBC level. In the days (arrow) the patients were infusion. 2011-3-18: Two units of erythrocyte suspension were infused .2011-3-23: Washed erythrocyte suspension 2U was infused. 2011-3-27: Fresh frozen plasma 200ml and washed erythrocyte suspension 2U were infused, 2011-3-28: Fresh frozen plasma 200ml was infused. RBC (4-5.5×$10^{-12}$/L): red blood cell, MCV (120-160g/L): mean cell volume, MCH (80-100fl): mean corpuscular hemoglobin, MCHC (320-360g/L): mean corpuscular hemoglobin concentration, HCT(40-50%): haematocrit, RET (0.4-1.9×$^{-12}$/L): reticulocyte.

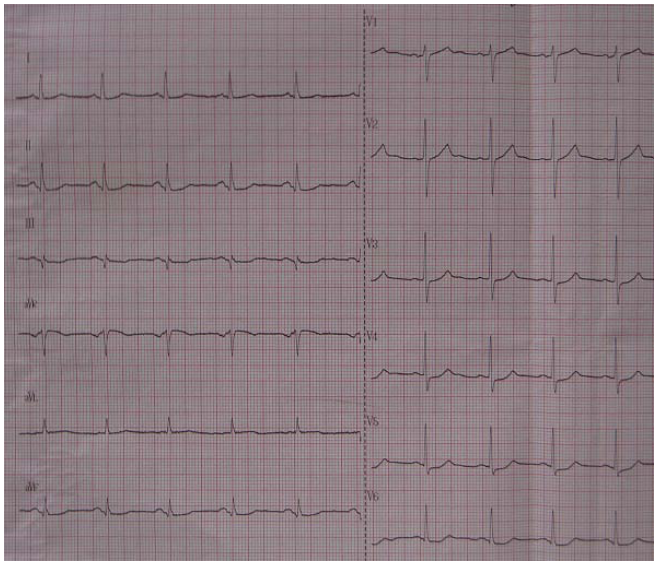

**Figure 3:** ECG (2011-3-9, admitted into the hospital).

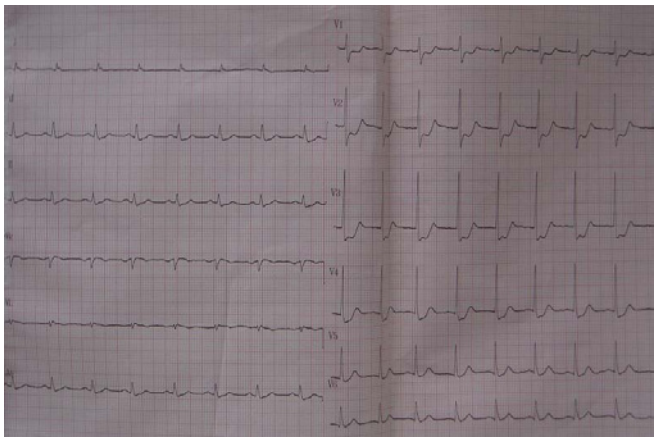

**Figure 4:** ECG (2011-3-22, reattack of angina pectoris).

medications. There was a slim possibility of such antigens as aspirin, clopidogrel and enoxaparin inducing the antigen-antibody reactions. And the patient had taken aspirin and enoxaparin since admission. The decline of hemoglobin occurred at Day 7 post-admission. Thus the possibility of aspirin and clopidogrel causing hemolysis might be ruled out. As of March 14, the patient received the therapy of low-molecular-weight heparin. Since March 16, the level of hemoglobin declined and low-molecular-weight heparin was withdrawn. Later the level of hemoglobin showed no marked change. On March 23, myocardial ischemia re-occurred. The possibility of in-stent thrombosis was considered. And low-molecular-weight heparin was re-started. The level of hemoglobin showed no re-decline. Thus there was a slim possibility of low-molecular-weight heparin causing hemolysis. During hospitalization, the patient even underwent a special therapy of PCI. During the procedure, a drug-eluting stent Endeavor was used. Endeavor stent has a driver platform. Phosphorylcholine coating is applied over a zotarolimus-eluting stent. As one kind of Sirolimus analogue, zotarolimus belongs to the limus family. With strong anti-proliferative capacities, it works through an inhibition of mTOR (mammalian target of Sirolimus). As the target protein of Sirolimus, TOR is a key regulatory kinase of protein translation, cell cycle and cell proliferation. At the carboxyl group terminus, the target protein undergoes phosphorylation to lose its decomposing activity. As a result, a series of subsequent effects are impacted so that the cells during G1 phase fail to enter into S phase and cell migration is simultaneously inhibited. After blood absorption, 95% of Sirolimus is distributed in erythrocytes, its plasma content takes up merely 3% and its un-conjugated form is even smaller. There were evidences of sirolimus is associated with anemia. Zotarolimus is an analogue of Sirolimus. After blood absorption, it is also predominantly distributed in erythrocytes. While conjugated with erythrocyte, zotarolimus may present as one kind of hapten forming a complete antigen jointly with erythrocytes. Autoimmune body reactions are elicited to induce the occurrence of anemia. Within 30 days of Endeavor stent implantation into coronary artery, 90% zotarolimus is released. The timing basically coincides with the declining level of hemoglobin and its gradual rise in this patient. Thus the possibility of anemia caused by zotarolimus can not be ruled out. In addition, all package inserts of Sirolimus and various drug-eluting stents mention the fact that anemia is one of side effects of stent. Therefore the primary cause of anemia should be of hemolytic nature due to the inherent drug of DES.

What lesson can we learn from this patient? If encountering the progressive post-stent decline of hemoglobin, a physician should consider many possibilities and conduct multiple examinations. An initial possibility of hemorrhage comes to mind since hemorrhage is one major etiologic cause for post-stent anemia. But the examinations of hemolysis and bone marrow hematopoiesis should also be conducted. A physician may rule out quickly the possibility of hemorrhagic anemia through a large battery of examinations. For the patients with a heavy load of thrombosis within coronary artery, the anti-platelet and anti-coagulation drugs should not be discontinued since a re-occurrence of cardiovascular event may be lethal.