

78666\_Auto\_Edited.docx

2

**Name of Journal:** *World Journal of Clinical Cases*

**Manuscript NO:** 78666

**Manuscript Type:** CASE REPORT

**What is responsible for acute myocardial infarction in combination with aplastic anemia? A case report and literature review**

Zhao YN *et al.* AMI in combination with AA

Ya-Nan Zhao, Wei-Wei Chen, Xiao-Yu Yan, Kun Liu, Guo-Hui Liu, Ping Yang

## **Abstract**

### **BACKGROUND**

Aplastic anemia (AA) complicated with myocardial infarction (MI) is rare and associated with poor prognosis. Here, we present a case of AA with recurrent acute MI (AMI) in a patient treated with cyclosporine A (CsA) and stanozolol. In this patient, we suspect the long-term use of medication linked to platelets hyperfunction.

### **CASE SUMMARY**

In 2017, a 45-year-old man was rushed to the emergency department of China-Japan Union Hospital due to precordial pain for 5 h. Based on his symptoms, medical history, blood tests, and findings from coronary angiography (CAG), the patient was diagnosed with acute anterior wall, ST-segment elevated MI (STEMI), Killip II grade, AA, and dyslipidemia. In 2021, the patient was readmitted to the hospital for 2 h due to chest pain. Because the patient's platelet count was  $30 \times 10^9/L$  and he had severe thrombocytopenia, we performed CAG following platelet transfusion. Optical coherence tomography (OCT) revealed lipid plaque and thrombus mass in his right coronary artery. The antithrombotic approach was adjusted to employ only anticoagulants (factor Xa inhibitors) and adenosine diphosphate inhibitors (clopidogrel) after assessing the risk of bleeding/thrombotic events. Long-term follow-up revealed that the patient had made a good recovery.

### **CONCLUSION**

Patients with AA should be closely monitored for the risk of thrombosis and cardiovascular events, particularly when taking stanozolol or CsA for an extended period of time.

**Key Words:** Aplastic Anemia (AA), Myocardial Infarction (MI), Cyclosporine A (CsA), Stanozolol, Percutaneous Coronary Intervention (PCI), Case Report

Zhao Y, Chen W, Yan X, Liu K, Liu G, Yang P. What is responsible for acute myocardial infarction in combination with aplastic anemia? <sup>1</sup> A case report and literature review. *World J Clin Cases* 2022; In press

**Core Tip:** Acute myocardial infarction (AMI) combined with aplastic anemia (AA) has been reported but not well studied. The medicine used to treat AA in this patient may have caused coronary artery and left ventricular thrombosis. <sup>1</sup> Coronary intervention, particularly stenting, is still controversial in this rare clinical scenario. Thus far, no specific management regarding this disease, especially for intracoronary findings, has been reported. Early revascularization may be the most important factor in improving patient prognosis.

## **INTRODUCTION**

Aplastic anemia (AA) is a kind of bone marrow hematopoietic failure syndrome defined by the decreased proliferation of bone marrow hematopoietic cells and peripheral blood cytopenia, which can be caused by a variety of factors<sup>[1]</sup>. The most prevalent clinical manifestations are anemia, hemorrhage, and infection. AA is treated with immunosuppressive agents such as cyclosporine A (CsA) and anabolic steroids such as stanozolol, with the purpose of stimulating bone marrow hematopoiesis<sup>[2]</sup>. However, long-term use of these medicines may increase the risk of abnormal blood lipid metabolism and atherosclerosis<sup>[3, 4]</sup>. AA complicated by myocardial infarction (MI) is considered uncommon in the clinic. Herein, we present a case of recurrent acute MI (AMI) in a patient with AA who was receiving long-term CsA and stanozolol treatment. We suspect that this occurrence is linked to platelet hyperfunction and long-term medication usage.

## <sup>1</sup> **CASE PRESENTATION**

### ***Chief complaints***

A 45-year-old man was admitted to the hospital with chest pain.

### ***History of present illness***

The patient's chest pain started 5 h prior to presentation while at work; he was transferred to the hospital *via* ambulance. He described a crushing pain located posterior to the interruption of the sternum, which radiated to the back of the shoulder. The pain was not relieved by sublingual nitroglycerin. The patient complained of persistent pain even after arriving at the hospital.

### ***History of past illness***

Four years before this admission, AA was diagnosed based on the patient's bone marrow biopsy pathology report. CsA 75 mg and stanozolol (Conlone) 2 mg (t.i.d.) were prescribed for AA. The patient had no history of smoking, hypertension, or type 2 diabetes.

### ***Personal and family history***

His family had no early onset history of cardiovascular diseases.

### ***Physical examination***

Physical examinations showed normal blood pressure (120/70 mmHg), and chest auscultation revealed lung rales.

### ***Laboratory examinations***

Table 1 shows the blood test result, including blood count, liver function, renal function, and markers of myocardial injury, *et al* Table 1. Column 1 presents the results of blood tests at the first admission.

### ***Imaging examinations***

Electrocardiogram (ECG) showed that ST-segment in the V1–V6 Leads was elevated, and the T wave was high and sharp (Figure 1A). According to the ECG data, the motion

amplitude of the left ventricular anterior wall and anterior septum was reduced, and the ejection fraction was 60.6% (Figure 1B). An emergency coronary angiography (CAG) revealed that the proximal segment of the anterior descending coronary artery was completely occluded (Figure 1C).

### **FINAL DIAGNOSIS**

Based on his symptoms, medical history, blood tests, and CAG findings, the patient was diagnosed with acute anterior wall ST-segment elevated MI (STEMI), Killip II grade, AA, and dyslipidemia.

### **TREATMENT**

Based on the CAG findings, one stent was implanted in the Left descending coronary (LAD) to revascularize the artery (Figure 1D). Following the thromboelastography (TEG) results (Table 1) and the risk of bleeding and thrombus, the patient was prescribed clopidogrel 75 mg and rosuvastatin 10 mg, once a day.

### **OUTCOME AND FOLLOW-UP**

In 2021, the patient was readmitted to the hospital for chest pain for 2 h. The ECG result revealed left posterior branch block and Q-wave formation in the anterior wall lead (Figure 2A). Table 1, Column 2 displays the results of the blood test. The results of coronary artery computed tomographic angiography (CTA) revealed that the thrombus had occluded the proximal segment of the right coronary artery, resulting in moderate-to-severe stenosis of the corresponding lumen (Figure 2B). Meanwhile, thrombosis of the left ventricle was discovered (Figure 2C). Based on his symptoms, medical history, blood test results, and CTA findings, the patient was diagnosed as acute non-STEMI, Killip II grade, AA, and dyslipidemia. Following several guidelines and expert consensus's directions<sup>[5]</sup>, we performed CAG after platelet transfusion because the patient had severe thrombocytopenia (TP). CAG revealed total occlusion of the proximal segment of the right coronary artery (Figure 2D). After percutaneous coronary intervention (PCI) and

thrombus aspiration, the coronary blood flow recovered to Thrombolysis In Myocardial Infarction (TIMI) 3. (Figure 2E). We further performed optical coherence tomography (OCT) to determine the cause of coronary artery occlusion. According to the OCT results, the proximal segment of the right coronary artery displayed a significant attenuation zone with a blurred edge and high dorsal reflection. The OCT revealed a fibrous cap at the surface of the atherosclerotic plaque area, as well as a homogenous high-signal area with minimal attenuation (Figure 2F), and a low-signal zone with diffuse boundaries in the lipid-rich core. Meanwhile, the thrombus mass attached to the surface of the lumen was visible (Figure 2G). The minimum lumen area was 2.6 mm<sup>2</sup>. The rate of area stenosis was 65%. TEG was utilized to detect platelet function. The result showed that the adenosine diphosphate (ADP) channel inhibition rate was 28.3%, while the arachidonic acid channel inhibition rate was 75.1%. Although the patient's platelet count was low (30×10<sup>9</sup>/L), thrombus could still develop in his coronary artery and left ventricle, which indicated that the platelet count and function likely play independent roles in thrombosis<sup>[6, 7]</sup>. After the risk of bleeding and thrombotic events was evaluated, the antithrombotic strategy was modified to include only anticoagulants (factor Xa inhibitors) and ADP inhibitors (clopidogrel). Long-term follow-up showed that the patient had made a good recovery.

## **DISCUSSION**

The first documented case of AMI complicating AA was in 1994. Such cases have remained relatively uncommon<sup>[8]</sup>. Table 2<sup>[8] [9] [10] [11] [12]</sup> shows the cases of AA associated with MI that have been published in PubMed. During the treatment of AA with steroids and CsA, there is an increased risk of AMI<sup>[9]</sup>. AA complicated by AMI has a poor prognosis in the majority of patients. This could also be worsened by pulmonary fungal infection as a result of the drop in white blood cell count in most individuals<sup>[11]</sup>. Literature<sup>[10]</sup> suggested that revascularization early in the course of these individuals' treatment improves their prognosis. Taken together, these case reports indicate that using anabolic steroids and immunosuppressive drugs may be one of the risk factors for AMI.

### **Anabolic steroid hormone (stanozolol) and cardiovascular disease**

The side effects of anabolic steroids may have an influence on the cardiovascular system. Stanozolol is a non-aromatic steroid synthesized from dihydrotestosterone<sup>[13]</sup>, which is one of the most extensively used steroids worldwide<sup>[14, 15]</sup>. Stanozolol can induce MI, atrial fibrillation<sup>[3]</sup>, and ventricular arrhythmias in those who take a large dose or use it for long periods. Table 3<sup>[16] [17] [18] [19] [20] [21] [22] [23] [24]</sup> lists case reports of cardiovascular adverse events caused by stanozolol. The following cardiovascular risk factors may be linked to the use of stanozolol:

**1. Influence on blood lipid metabolism.** Stanozolol can increase <sup>3</sup> low-density lipoprotein cholesterol (LDL-c) while reducing high-density lipoprotein cholesterol (HDL-c) and serum lipoprotein (a) levels<sup>[25]</sup>. These changes are reversible with the withdrawal of medication<sup>[19]</sup>. LDL-c is an independent risk factor for the diagnosis and prognostication of arteriosclerotic cardiovascular disease (ASCVD)<sup>[26-28]</sup>.

**2. Influence on blood pressure.** Stanozolol can cause sodium and water retention as well as vasospasm, which may further increase in systolic and diastolic blood pressure<sup>[29, 30]</sup>.

**3. Influence on platelet aggregation.** Stanozolol has been demonstrated to enhance platelet aggregation by increasing thromboxane A<sub>2</sub> synthesis while lowering prostacyclin levels<sup>[31-34]</sup>.

**4. Endothelial dysfunction.** Endothelial dysfunction is the initial step in atherosclerosis and is significantly related to cardiovascular disease<sup>[35]</sup>. Endothelial dysfunction is caused by an imbalance between vasoconstrictors and vasodilators, which is disrupted by oxidative stress<sup>[36]</sup>. Stanozolol inhibits guanylate cyclase, which may increase the aorta's response to vasoconstrictors while reducing the response to vasodilators, resulting in less nitric oxide-mediated arterial relaxation<sup>[37, 38]</sup>. Furthermore, stanozolol has been shown to promote endothelial dysfunction by enhancing oxidative stress *via* catalase (CAT), Super Oxide Dismutase 1 (SOD1), and Glutathione peroxidase 4(GPX4), as well as activating the hemostatic system and increasing fibrinolytic activity<sup>[39-41]</sup>.

**5. Myocardial injury.** Left ventricular hypertrophy is the most prevalent pathological sign in postmortem hearts of long-term stanozolol users<sup>[42]</sup>, which might be the



consequence of direct action on cardiac androgen receptors<sup>[43]</sup>. Animal studies have also shown that stanozolol stimulates the immune system and enhances oxidative stress<sup>[44-46]</sup>. In an *in-vitro* investigation, stanozolol was shown to promote cardiac cell apoptosis<sup>[47]</sup>. All these factors play a critical role in the development of atherosclerosis and cardiovascular disease<sup>[48]</sup>.

### **CsA and cardiovascular disease**

CsA is a common T lymphocyte immunosuppressant that has been utilized extensively in the treatment of allograft rejection and kidney disease. CsA can inhibit the opening of mitochondrial permeability transition (MPT) pores. The opening of the MPT pore causes a breakdown of membrane, uncoupling of the respiratory chain, and the outflow of cytochrome C and other pro-apoptotic molecules, which can lead to cell apoptosis or necrosis<sup>[49]</sup>. Whether the usage of CsA prior to myocardial ischemia in animal experiments can reduce the infarction area remains ambiguous<sup>[50-53]</sup>. According to clinical research, CsA injection prior to PCI did not improve clinical outcomes in terms of left ventricular ejection fraction (LVEF), mortality, recurrent MI, re-hospitalization, and heart failure<sup>[54, 55]</sup>. Long-term CsA medication has been shown to have adverse effects on the cardiovascular system, including pericarditis<sup>[56, 57]</sup>, hyperlipidemia, and increased risk of atherosclerosis. The following cardiovascular risk factors may be linked to the usage of CsA:

**1. Dyslipidemia and arteriosclerosis.** CsA lowers the rate of catabolism and the generation of LDL-c <sup>[4]</sup>, reduces liver X receptor ligand synthesis and 27-hydroxycholesterol efflux, which may lead to foam cell macrophage formation and the development of atherosclerotic plaques. Thus, CsA's ability to suppress lipolysis may contribute to plasma triglyceride accumulation. CsA reduces the levels of lipoprotein lipase (LPL) in adipose tissue and skeletal muscle in rats<sup>[58]</sup>. LPL activity was consistently observed to be reduced in the plasma of dyslipidemia patients treated with CsA<sup>[59]</sup>.

**2. Endothelial dysfunction.** CsA, like stanozolol, can promote endothelial dysfunction by increasing superoxide generation<sup>[60]</sup>.

### **Possible causes of MI in our patient**

The patient in this case used stanozolol and CsA for approximately 5 years before suffering an AMI. He did not smoke and had no family history of cardiovascular disease; therefore, he did not have traditional risk factors for atherosclerosis or thrombosis. However, the OCT revealed lipid plaque and thrombus mass in the right coronary artery. Meanwhile, his LDL-c levels were high (6.82 mmol/L) and his HDL-c levels were low (0.74 mmol/L). CTA revealed a ventricular thrombus, indicating abnormal platelet function and coagulation. We cannot be sure as to what caused the ventricular thrombosis; however, a previously published case report showed that long-term, high-dose stanozolol usage was linked to ventricular thrombosis<sup>[61]</sup>. Based on the available facts from this case report and the literature, we suspected that combined long-term use of stanozolol and CsA are responsible for the risk of atherosclerosis and thrombosis.

#### **PCI treatment for patients with low platelet count**

AA is characterized by decreased bone marrow hematopoietic cell proliferation and peripheral blood pancytopenia, with bleeding and infection as the most prevalent clinical symptoms. Morphological and functional changes in platelets <sup>5</sup> play an important role in the occurrence and development of coronary heart disease. TP is a rare complication of coronary heart disease that affects around 5.4% patients (platelet count:  $<150 \times 10^9/L$ )<sup>[62]</sup>. Thompson *et al*<sup>[63]</sup> found that large platelets have a greater coagulation capability than small platelets. Ulu *et al*<sup>[64]</sup> found that mean platelet volume (MPV) is associated with left ventricular thrombosis. In this instance, the MPV increased, which suggests platelet hyperfunction and necessitates further research on platelet activation status. There were several challenges in balancing antiplatelet therapy with bleeding control in this patient. The European Society of Cardiology (ESC) has issued a guideline for the management of individuals with acute coronary syndrome (ACS) and TP. There are three levels of severity based on platelet count <sup>4</sup>: (1) Mild: platelet count,  $100\text{--}150 \times 10^9/L$ ; (2) Moderate: platelet count,  $50\text{--}100 \times 10^9/L$ ; (3) Severe: platelet count,  $<50 \times 10^9/L$ . Mild TP has no effect on antiplatelet therapeutic regimens. For patients with moderate TP, PCI is a viable option. After PCI, patients are given dual antiplatelet therapy (DAPT) for a month before switching to clopidogrel monotherapy. It is also recommended that a proton pump

inhibitor (PPI) be used in combination with any treatment. In patients with severe TP, all antiplatelet medications should be discontinued, and PCI should be avoided<sup>[5]</sup>. It is important to note that while assessing the risk of antiplatelet therapy for TP patients, platelet function should take precedence over platelet count<sup>[65]</sup>.

### **Choice of treatment strategy**

The platelet count in our patient was  $85 \times 10^9/L$  during his initial MI, indicating a modest reduction in platelets. His cardiac function was damaged at the time of onset, primarily evidenced by persistent and intense chest pain and rales in both lungs. As a result, immediate PCI and revascularization were required. Simultaneously, clopidogrel was given as an antiplatelet therapy based on the TEG result and relevant guidelines. His platelets further decreased to  $30 \times 10^9/L$  during his second MI in the right coronary artery. Following the recommendations of several guidelines and expert consensus<sup>[5]</sup>, we performed CAG post platelets transfusion. This time, we used OCT to examine the intravascular atherosclerotic plaques in more detail. After weighing the risks of bleeding and thrombosis, the anti-thrombotic strategy was changed to focus on anticoagulants (factor Xa inhibitors) and ADP inhibitors (clopidogrel). Follow-up evaluation of the patient showed that the antithrombotic treatment had been fairly successful, since there had been no bleeding and the patient had recovered.

### **CONCLUSION**

Here, we reported a case of AA combined with AMI. Coronary artery and left ventricular thrombosis may be linked to medicines used to treat AA in this patient. Doctors should be aware of the risk of thrombosis and cardiovascular problems in patients with AA, especially if using stanozolol with CsA for a prolonged duration. Antiplatelet therapy for patients with coronary artery disease and low platelet counts must also strike a balance between the risks of thrombosis and hemorrhage. Furthermore, in contrast to past examples, timely revascularization may be the most important factor in improving the patient's prognosis.

5%

SIMILARITY INDEX

PRIMARY SOURCES

1	<a href="http://www.wjgnet.com">www.wjgnet.com</a> Internet	87 words — 3%
2	<a href="http://f6publishing.blob.core.windows.net">f6publishing.blob.core.windows.net</a> Internet	15 words — 1%
3	<a href="http://www.jstage.jst.go.jp">www.jstage.jst.go.jp</a> Internet	15 words — 1%
4	<a href="#">Cremer, Malte, Hannes Sallmon, Pamela J. Kling, Christoph Bühner, and Christof Dame. "Thrombocytopenia and platelet transfusion in the neonate", Seminars in Fetal and Neonatal Medicine, 2016.</a> Crossref	14 words — < 1%
5	<a href="http://pesquisa.bvsalud.org">pesquisa.bvsalud.org</a> Internet	13 words — < 1%

EXCLUDE QUOTES ON  
EXCLUDE BIBLIOGRAPHY ON

EXCLUDE SOURCES < 12 WORDS  
EXCLUDE MATCHES < 12 WORDS