CASE REPORT

Acute Myocardial Infarction in an Adolescent Receiving Anagrelide for Essential Thrombocythemia with Underlying Persistent Coronary Endothelial Dysfunction

Ryuhei Tanaka, MD, Yodo Gatate, MD, Yasumori Suinjo, MD, Maki Todo, MD, Atsuhiko Ohta, MD, Yuki Shimizu, MD, Atsuko Watanabe, MD, Ken Naganuma, MD, Toshihiro Muramatsu, MD, Kenji Fukushima, MD and Shintaro Nakano, MD

Summary

Essential thrombocythemia (ET) is a Philadelphia chromosome-negative myeloproliferative disorder that is characterized by the overproduction of platelets and a marked increase in the numbers of mature megakaryocytes present in the bone marrow. Thrombohemorrhagic disorders are major morbidities of ET, especially those with mutations in the gene encoding Janus kinase 2 (JAK2). In this study, we report the case of an 18-year-old patient with ET carrying JAK2 mutation who developed acute ST-elevation myocardial infarction (STEMI) 5 months after a commencement of anagrelide. Coronary endothelial dysfunction confirmed by positive acetylcholine provocation test lasted a year after the occurrence of STEMI. Furthermore, intracoronary imaging using optical coherence tomography demonstrated non-atheromatous intimal fibrosis possibly due to chronic endothelial damage. The coronary pathologies reflected chronic change potentially associated with properties of ET and JAK2 mutation in addition to hyperviscosity. These observations suggest that the side effect of anagrelide in our patient was considered causative, while underlying chronic endothelial dysfunction and adverse endothelial remodeling may be predisposing factors to his fatal cardiovascular events.

Key words: Oncocardiology, Acute coronary syndrome

Essential thrombocythemia (ET) is a form of myeloproliferative neoplasms. It is a clonal hematopoietic disorder that is characterized by markedly increased clusters ofhyperlobulated mature megakaryocytes in the bone marrow and by sustained thrombocytosis of peripheral blood. Patients with ET, especially those with mutations in the gene encoding Janus kinase 2 (JAK2), may experience cardiovascular complications, such as arterial/venous thrombosis or hemorrhages, due to multifactorial etiologies. Anagrelide is a non-leukemogenic cytoreductive drug used for the treatment of ET in patients with a long life expectancy; however, this drug has been associated with various cardiovascular side effects, such as palpitation, atrial fibrillation, congestive heart failure, coronary artery disease, and arterial hypertension.

In this study, we report the case of an adolescent patient with ET carrying JAK2 mutation who suffered from ST-segment elevation myocardial infarction (STEMI) occurring after the initiation of anagrelide treatment. Persistent nitroglycerin-responsive coronary vasospasm and non-atheromatous intimal fibrosis potentially related to properties of ET and JAK2 were considered as underlying etiologies for his susceptibility to STEMI.

Case Report

An 11-year-old Japanese boy was referred to the pediatric hematology/oncology department of our institution for investigation of increased platelet count (1273 × 10^9/L). The diagnosis of ET was made based on the hematological criteria, such as abnormal bone marrow findings (Supplemental Figure 1), identification of the JAK2 V617F mutation, and absence of the BCR-ABL1 fusion gene. He had suffered from intractable headache; this presumable vasomotor symptom was successfully ameliorated by administration of low-dose aspirin (100 mg daily). However, his platelet count remained high for years, reaching 1250 × 10^9/L by the age of 18 when he presented an intramuscular hemorrhage in the right buttock. As he was assumed to be at high risk for thrombo-hemorrhagic events, non-leukemogenic cytoreductive
therapy with anagrelide (1.0 mg daily) was commenced, after confirming normal cardiac function at baseline (Supplemental Figure 2). Anagrelide successfully reduced the platelet (range, 500-700 × 10⁹/L) and neutrophil count ranged within the normal limit, and aspirin was stopped 2 months after the initiation of anagrelide.

However, the patient began to feel periodic palpitations or vague chest sensations a month after the initiation of anagrelide, although no abnormal 12-lead/24-hour electrocardiographic changes were documented. Five months after the commencement of anagrelide, the patient was transported to our cardiac center due to intermittent but progressively worsening precordial discomfort. Upon arrival, he was conscious with a body temperature of 36.5°C, heart rate of 87 beats/minute, and systolic/diastolic pressure of 133/87 mmHg. Auscultation revealed no rales or abnormal heart sounds except for marginal third sounds. Cardiomegaly and mild pulmonary edema were identified on chest radiography. The electrocardiogram showed sinus rhythm and prominent ST-T elevation in leads II, III, aVF, and V1-V3 with reciprocal change (Figure 1A). Echocardiography showed left ventricular dysfunction with abnormal segmental wall motion (Figure 1B). Blood tests revealed leukocytosis (white blood cell count of 14.7 × 10⁹/L with neutrophils 81.5%, hemoglobin 15.1 g/dL, and hematocrit 45.0%), thrombocytosis (platelet count 894 × 10⁹/L), elevated markers for cardiac injury (serum troponin I 1288 pg/mL [upper limit of normal, 26.2 pg/mL], creatine-kinase 274 IU/L [244 IU/L], and creatine-kinase MB isozyme 16.4 ng/mL [< 5 ng/mL]), almost normal hepatic and renal markers, and negative for thrombophilia markers (see details in Supplemental Table). He had no history of smoking. Emergent coronary angiography revealed total occlusion of the middle right coronary artery (RCA) and spastic stenosis of the distal left anterior descending artery (LAD) (Figure 1C and D). The RCA was successfully recanalized by thrombus aspiration and intracoronary nitroglycerin infusion, whereas the spastic LAD was dilated with the intracoronary nitroglycerin infusion only (Figure 1F and G, maximum serum creatine-kinase 9734 IU/L and creatine-kinase MB isozyme 600 ng/mL, histological findings in Figure 1H and I). ⁹⁹ᵐTc-Technetium-pyrophosphate scintigraphy was performed 3 days later and cardiac magnetic resonance imaging 10 days later, which demonstrated extensive, partially irreversible myocardial infarction in the broad inferior and apical anterior wall (Figure 2).

Anagrelide, a potential causative agent for the observed coronary event, was ceased. Instead, hydroxyurea (1000 mg daily) and low-dose aspirin (100 mg daily)
were initiated, which successfully controlled the platelet count (platelet count 500-700 × 10^9/L). Under the supervision of multidisciplinary Oncocardiology Team, the patient has been asymptomatic up until the present with the continuation of a renin-angiotensin-aldosterone system inhibitor (enalapril, 10 mg daily) and coronary vasodilators (diltiazem, 200 mg daily; isosorbide, 40 mg daily).

Follow-up coronary angiography with the acetylcholine provocation test was performed 12 months later after a 2-day interruption of these vasodilators. Severe multivessel vasospasm was induced by intracoronary acetylcholine infusion (Figure 3A-D). Optical coherence tomography (OCT) of the RCA suggested intimal fibrotic changes without remarkable atheromatous plaque (Figure 3E); thus, administration of the coronary vasodilators was continued to prevent recurrence of coronary ischemia.

**Discussion**

We report the case of an adolescent patient with ET carrying JAK2 V617F mutation who developed acute STEMI after commencing anagrelide treatment. Persistent endothelial dysfunction was confirmed a year after through positive acetylcholine provocation test. Furthermore, intracoronary imaging demonstrated non-atheromatous intimal fibrosis possibly due to chronic endothelial damage. These underlying pathologies related to properties of ET JAK2 V617F mutation may have predisposed the patient to the fatal cardiovascular complication. **Thrombotic complications in ET:** The high risk of developing thrombohemorrhagic is associated with various clinical and biological factors, such as traditional cardiovascular risk factors (dyslipidemia, hypertension, smoking, diabetes, and older age), history of prior thrombosis or hemorrhage, and severe thrombocytosis. Among such complications, coronary artery disease is one of the most devastating manifestations. Although relatively young patients who do not exhibit traditional coronary risk factors have also been reported to suffer from such complications, occurrence of STEMI in patients under 20 years old is uncommon.

The mechanisms underlying acute coronary syndrome are considered to be multifactorial. Increased numbers of blood cells leading to increased blood viscosity in the context of ET promote the formation of platelet-leukocyte aggregates, with concomitant release of proteases from the activated leukocytes into circulation, and consequent intravascular hypercoagulability. Besides the hyperviscosity, chronic endothelial cell damage provoked by activated platelets and chronic high shear stress on the vessel wall are potentially causative factors of acute coronary syndrome. Most patients with ET (approximately 60%) harbor the JAK2 V617F mutation in their hematopoietic cells. This somatic mutation causes constitutive activation of the kinase, resulting in deregulated intracellular signaling that leads to myeloproliferative disorders, and is also known to be a significant risk factor for cardiovascular events potentially by enhancing thrombin generation in relation to platelet activity. In our case, coronary endothelial cell dysfunction demonstrated by positive acetylcholine provocation test was observed a year after the onset of STEMI. We also visualized the non-atheromatous intimal fibrosis in coronary artery using OCT. These findings indicate the presence of endothelial adverse remodeling possibly attributable to chronic endothelial damage and hyperviscosity.
Effect of anagrelide on cardiovascular system: Anagrelide is a selective inhibitor of thrombopoiesis. Although the precise mechanism underlying the attenuation of platelet overproduction remains unclear, it has been postulated that the drug’s effects are based on repression of transcriptional factors related to the megakaryopoiesis including GATA-1 and FOG-1 via a phosphodiesterase III (PDE III)-independent mechanism. Anagrelide also inhibits cyclic adenosine monophosphate PDE III pharmacologically and has inotropic and vasodilating properties; thus, the most common cardiovascular adverse events are nonfatal manifestations, such as tachycardia/palpitations.

However, there have been some reports of acute coronary syndrome as adverse events of anagrelide in patients with ET and traditional cardiovascular risk factors. The biological effects of anagrelide on the coronary artery are controversial; both vasospasm and vasodilation have been proposed.

In our case, multiple mechanisms including sympathetic nerve hyperactivity induced by anagrelide together with underlying endothelial condition may be involved in his coronary pathology. Although the direct association between the presence of JAK2 V617F mutation and the occurrence of AMI cannot be determined, the presence of this mutation is an important cardiovascular risk factor from the epidemiological viewpoint. Therefore, patients with ET and JAK2 V617F mutation, even without traditional cardiovascular risk factors, should be considered at high risk for coronary artery disease especially when treatment with anagrelide is necessary for cytoreduction.

Conclusion

Our adolescent patient with ET carrying JAK2 V617F mutation developed acute STEMI. Anagrelide was considered as a potential trigger, whereas persistent endothelial dysfunction and remodeling, possibly attributable to chronic endothelial damage and hyperviscosity, may be predisposing factors to his fatal cardiovascular events.

Disclosure

Authors’ contributions: YG, YSu, AO, YSh, AW, KN, and TM summarized and interpreted patients’ clinical data and drafted the manuscript. KF performed optimal imaging investigation and analyzed imaging data. SN and RT revised the final version of this manuscript.

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Conflicts of interest: None.

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**Supplemental Files**

Supplemental Table
Supplemental Figures 1, 2

Please see supplemental files; [https://doi.org/10.1536/ihj.20-377](https://doi.org/10.1536/ihj.20-377)