Anagrelide potentially provokes acute coronary syndrome even in an adolescent affected with essential thrombocythemia concomitant with underlying persistent coronary endothelial dysfunction

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Abstract

Thrombohemorrhagic disorders are the main cause of morbidities and mortalities of essential thrombocythemia (ET), which are typically observed at age 50–60 years and rarely encountered in adolescence or childhood. Recently, anagrelide, a quinazinolone derivative, has been used as a therapeutic agent for ET. Although it is used to reduce platelet count, its cardiotoxicity has been reported. Here, we present an 18-year-old boy with ET who was treated with anagrelide and developed acute myocardial infarction. This was presumed to be an effect of anagrelide administration and, specifically, damage to the coronary arterial endothelial cell exacerbated by ET.

Introduction:

Essential thrombocythemia (ET) is a form of myeloproliferative neoplasms characterized by markedly increased mature megakaryocytes in the bone marrow and sustained thrombocytosis of peripheral blood.[1, 2] Patients with ET, especially those with mutations in the gene encoding Janus kinase 2 (*JAK2*), may experience thrombohemorrhagic complications due to multifactorial etiologies.[3-6] Anagrelide is a non-leukemogenic cytoreductive drug used for the treatment of ET in patients with a long life-expectancy; however, it is associated with the incidence of various cardiovascular side effects (5%–30%).[7-9] Here, we present an 18-year-old boy with ET who developed ST-segment elevation myocardial infarction (STEMI) occurring after anagrelide initiation.

Case description:

An 11-year-old boy was referred to the pediatric hematology/oncology department of our institution for investigation of increased platelet count (1273×10^9/L). ET was diagnosed based on the hematological criteria including abnormal bone marrow findings (Fig. 1A), identification of the *JAK2* V617F mutation, and absence of the *BCR-ABL1* fusion gene.[1, 2] His mother reported that he had intractable headache since age 2. The migraine-like severe headache was determined to be a vasomotor symptom of ET.[10] Low-dose aspirin (100 mg/day) was administered to attenuate the microcirculatory symptom, which successfully ameliorated his headache.[2, 10] However, the platelet count remained high for years, reaching 1250×10^9/L by the age of 18. Eventually, an intramuscular hemorrhage developed in the right buttock. Based on current epidemiological evidence, he was assumed to be at a high-risk of thrombohemorrhagic events. [2, 8, 11]; therefore, cytoreductive therapy was started. Because of the concerns of the leukemogenic potential, we administered anagrelide (1.0 mg/day) instead of hydroxyurea.[12, 13] We confirmed that cardiac function at baseline was normal to initiate drug therapy because of its toxic potential.[7-9] Anagrelide successfully reduced the platelet count (range,

500–700×10^9/L). Clinically, there was no recurrence of thrombohemorrhagic events; however, he periodically complained of palpitations or vague chest sensations.

Five months after the anagrelide initiation, he was transferred to our cardiac center because of progressive worsening of precordial discomfort. On arrival, he was conscious with a body temperature, 36.5°C; heart rate, 87 beats/min; and systolic/diastolic pressure, 133/87 mmHg. The electrocardiogram showed sinus rhythm and prominent ST-T elevation in leads II, III, aVF, and V1-V3 with a reciprocal change (Fig. 1B). Blood tests revealed leukocytosis (white blood cell count of 14.7 × 10^9/L with neutrophils 81.5%), thrombocytosis (platelet count 894 × 10^9/L), and elevated markers for cardiac injury (troponin I 1288 pg/mL, creatine-kinase 9734 IU/L). He had no smoking history. Emergent coronary angiography revealed total middle right coronary artery (RCA) occlusion and spastic stenosis of the distal left anterior descending artery (LAD) (Figs. 1C and 1D). The RCA was recanalized by thrombus aspiration and intra-coronary nitroglycerin infusion, whereas the LAD was dilated with the intra-coronary nitroglycerin infusion alone (Figs. 1E and 1F). ^{99m}Technetium-pyrophosphate scintigraphy was performed 3 days later; cardiac magnetic resonance imaging performed 10 days later demonstrated extensive myocardial infarction in the broad inferior and apical anterior wall (Figs. 2A-C).

Anagrelide was considered as a potential causative agent for the STEMI; thus, its administration was ceased. Instead, hydroxyurea (1000 mg/day) together with low-dose aspirin (100 mg/day) was initiated, which successfully controlled the platelet count (platelet count 500–700×10^9/L) without any recurrence of thrombohemorrhagic events. To date, the patient has been asymptomatic regarding cardiovascular manifestations, with the continuation of a renin-angiotensin-aldosterone-system inhibitor (enalapril, 10 mg/day) and coronary vasodilators (diltiazem, 200 mg/day; isosorbide, 40 mg/day).

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 intra-coronary acetylcholine infusion (Figs. 2D-G). Optical coherence tomography of the RCA (Fig. 2H) suggested intimal fibrotic changes without a remarkable atheromatous plaque; thus, continuous administration of the coronary vasodilators was required to prevent coronary ischemia recurrence.

Discussion

Relatively young patients (age 30–45) with ET who do not exhibit traditional coronary risk factors (i.e., dyslipidemia, hypertension, smoking, diabetes, and older age) have also been reported to have acute myocardial infarction (AMI)[14-17]; however, there is little information on the incidence of AMI among patients younger than 20 years, with few reports on such cases.[18]

The mechanisms underlying acute coronary syndrome are considered to be multifactorial. Increased blood cells numbers and increased blood viscosity in ET promote the formation of platelet–leukocyte aggregates, with concomitant release of proteases from the activated leukocytes into circulation, and consequent intravascular hypercoagulability.[19] Besides the hyperviscosity, chronic endothelial cell damage provoked by activated platelets and chronic high shear stress on the vessel wall are potential causative factors for acute coronary syndrome.[19] Most patients with ET (approximately 60%) harbor the *JAK2* V617F mutation in their hematopoietic cells.[2, 20] This somatic mutation causes constitutive activation of the kinase, resulting in myeloproliferative disorders, and is also known as a significant risk factor for cardiovascular events.[2-6, 16] Pathophysiologically, platelets from patients with ET carrying the *JAK2* V617F mutation increased their capacity to generate thrombin associated with platelet activation.[3] Additionally, megakaryocytes from the *JAK2* V617F knocked-in model mice showed accelerated maturation and increased proplatelet formation,[21] indicating that the *JAK2* V617F mutation alters the intrinsic characters of both megakaryocytes and platelets beyond merely increasing in cell numbers. In our case, coronary endothelial cell dysfunction lasted for a year after STEMI onset and was confirmed by a positive acetylcholine provocation test result. We suggest that the presence of the *JAK2* V617F mutation and hyperviscosity since childhood, may have contributed to the persistent chronic coronary pathology.

Anagrelide is a selective inhibitor of thrombopoiesis and is effective for lowering the platelet count.[9, 22-24]

Although the precise mechanism underlying the attenuation of platelet overproduction remains ambiguous, anagrelide's effect may be based on the repression of transcriptional factors related to the megakaryopoiesis including GATA-1 and FOG-1.[25] Furthermore, anagrelide inhibits cyclic adenosine monophosphate phosphodiesterase III pharmacologically, and has inotropic and vasodilator properties; thus, the most common cardiovascular adverse events associated anagrelide include tachycardia/palpitations.[9, 12] However, acute coronary syndrome including AMI and angina have been reported as adverse events of anagrelide.[23, 25] Typically, patients with ET are middle-aged or older[2] and often have the traditional cardiovascular risk factors. Therefore, observation of AMI pathogenesis in our very young patient without any conventional risk factors, except for ET itself and anagrelide administration, was unusual.[13]

The biological effects of anagrelide on the coronary artery are controversial, and both vasospasm[25] and vasodilation[26] have been reported. Theoretically, the inhibition of phosphodiesterase III by anagrelide should induces vasodilatation, but not vasospasm. However, a mouse model study revealed that phosphodiesterase inhibitors increased the release of sympathetic neurotransmitters.[27] A report speculated that depending on the expression patterns of alpha- and beta- adrenergic receptors in particular vessels cause vasoconstriction and vasodilatation, respectively.[25] In addition to the long-lasting endothelial cell damage caused by ET itself, the complex distribution of adrenergic receptors may induce the deterioration of coronary vessel function, eventually resulting in STEMI. In our case, the negative effects of thrombocytosis due to ET on the maintenance of coronary artery integrity, as shown by abnormal findings, together with the pharmacological effects anagrelide on the artery led to the exacerbation of chest symptoms such as palpitations and vague sensations, which finally led to STEMI.

In conclusion, our patient with ET developed STEMI as a consequence of anagrelide administration and persistent coronary endothelial dysfunction caused by the ET itself.

1200/1200 words

Conflict of interest:

The authors declare that they have no conflict of interest.

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Figure legends:

Figure.1

Representative microscopic image (A) of the bone marrow sample stained with hematoxylin and eosin; (B) electrocardiogram showing sinus rhythm and prominent ST-T elevation in leads II, III, aVF, and V1-V3 (arrowheads) with a reciprocal change; (C, E) coronary angiograms showing occlusion of the right coronary artery which was recanalized through thrombus aspiration and intra-coronary nitroglycerin infusion (arrowheads); (D, F) spastic left anterior descending artery, which was dilated only with the intra-coronary nitroglycerin infusion (arrows). Abbreviations: NTG, nitroglycerin.

Figure 2

Representative images from PYP and CMR; (A) PYP showed significant uptake in the inferior and apical walls including the right ventricle (yellow arrows); T2-weighted CMR image showing (B) high signal intensity in the inferoseptal wall and right ventricle (arrows); delayed enhancement was observed in the area with myocardial infarction (C) (arrow heads).

Representative images from follow-up coronary angiography with acetylcholine provocation test and OCT of the RCA; coronary angiogram (arrow heads indicate the right coronary artery; arrows indicate the left anterior descending artery) showing (D and E) non-occlusive coronary arteries at baseline and (F and G) total occlusion upon intra-coronary acetylcholine infusion; (H) OCT of the RCA showing extensive, homogenous bright intimal thickening (yellow arrows) without prominent attenuation, suggesting fibrotic change.

Abbreviations: Ach, acetylcholine; OCT, optical coherence tomography; RCA, right coronary artery; PYP, ^{99m}Tc-pyophosphate scintigraphy; CMR, cardiac magnetic resonance imaging.

Figure 1

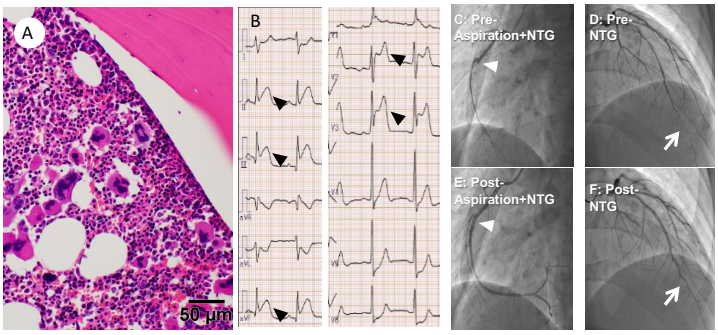

Figure 2