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# A CASE OF ACUTE MYOCARDIAL INFARCTION IN A PATIENT WITH ESSENTIAL THROMBOCYTHAEMIA TREATED WITH ANAGRELIDE

Ekrem Yetiskul[1], Aqsa Nisar[1], Salman Khan[1], Faris Qaqish[1], Danyal Khan[2], Alexander Bershadskiy[3]

[1] Department of Internal Medicine, Staten Island University Hospital, Staten Island, USA
[2] Department of Cardiology, Staten Island University Hospital, Staten Island, USA
[3] Department of Hematology and Oncology, Staten Island University Hospital, Staten Island, USA

**Corresponding author:** Ekrem Yetiskul **e-mail:** eyetiskul@northwell.edu

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## ABSTRACT

Anagrelide is a medication primarily used to manage thrombocytosis, an abnormal increase in platelet levels in the blood. It is often prescribed for patients with myeloproliferative disorders, such as essential thrombocythaemia (ET). Given the heightened susceptibility to thromboembolism associated with this condition, the primary emphasis in treatment revolves around reducing the risk of thrombotic events through the administration of cytotoxic agents. While anagrelide is generally effective in reducing platelet counts, it comes with potential side effects, including an increased risk of certain thrombotic events. Anagrelide acts by inhibiting megakaryocyte maturation and platelet release, thereby reducing platelet production. However, this platelet-lowering effect may be accompanied by an increase in platelet activation and reactivity, which could contribute to a prothrombotic state. We present a case of a 60-year-old female with a history of ET, managed with anagrelide and hydroxyurea therapy, who experienced an acute ST-elevation myocardial infarction.

## KEYWORDS

Essential thrombocythaemia, anagrelide, myocardial infarction, thrombosis

## LEARNING POINTS

- The dual role of anagrelide: although anagrelide is effective in lowering platelet levels in essential thrombocythaemia, it can increase platelet activation, raising thrombotic risk. Clinicians need to monitor patients closely for thrombotic events.
- Balancing efficacy and side effects: the risk of severe side effects such as myocardial infarction, as seen in this case report, necessitates a balanced approach in using anagrelide, weighing its benefits against potential risks.

## INTRODUCTION

Essential thrombocythaemia (ET) is a chronic myeloproliferative neoplasm characterised by an increased platelet count in the peripheral blood and excessive megakaryopoiesis in the bone marrow[1]. ET is associated with an elevated risk of haemorrhaging, vasomotor symptoms and thrombosis, especially thrombus in the brain, and peripheral and heart arteries; the incidence of acute coronary events

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is 9.4%[2]. Consequently, the primary goal in treating ET is to prevent vascular complications, as they constitute the leading cause of morbidity and mortality[3]. The primary approach to treating ET involves rapidly reducing the patient's platelet count to within the normal range, aiming to forestall the onset of complications associated with ET[4]. Therapeutic options for ET patients range from the most conservative approach (careful observation) to low-dose aspirin and, in the upper extreme, cytoreductive drugs[5]. For a patient with a high risk of developing thrombotic events, antiplatelet (low-dose aspirin) and cytoreductive therapy are the choices[6]. Anagrelide serves as a second-line cytoreductive option specifically aimed at lowering platelet counts[7]. However, anagrelide has the potential to directly induce vasospasm in the coronary arteries, giving rise to significant cardiovascular complications including congestive heart failure, arrhythmias, and acute coronary syndrome. Although acute coronary syndromes are reported in 1%–5% of individuals undergoing anagrelide treatment, the overall incidence of such syndromes remains rare[4]. In this report, we present a case of a 60-year-old female with a history of ET who developed an acute ST-segment elevation myocardial infarction (STEMI) while on cytoreductive therapy with anagrelide. This patient lacked any cardiovascular risk factors, implying the potential association of anagrelide with the onset of her acute STEMI.

## CASE DESCRIPTION

A 60-year-old female with a past medical history of essential thrombocythaemia, managed with hydroxyurea and anagrelide, presented to the emergency department with substernal chest pain, which began approximately one hour prior to her arrival. The pain was characterised as a crushing sensation in the central chest region and had radiated to her left arm. The patient reported feeling an overwhelming sense of pressure and tightness, and the discomfort was unrelenting, persisting despite attempts at rest. Alongside the chest pain, she experienced notable shortness of breath, diaphoresis, and nausea. Vital signs during triage showed a temperature of 36.5°C, heart rate of 60 beats/min, systolic blood pressure of 139 mmHg, diastolic blood pressure of 76 mmHg, respiratory rate of 20 breaths/min and oxygen saturation of 97% on ambient room air. The patient denied the presence of any cardiovascular risk factors such as diabetes, hyperlipidaemia, smoking, or a family history of cardiovascular diseases.

Given the concern for acute coronary syndrome, an electrocardiogram (ECG) was immediately performed during triage, which was significant for Wellens syndrome, demonstrating inverted T-waves in leads V2 and V3, indicating possible proximal left anterior descending (LAD) stenosis *(Fig. 1)*. Code STEMI was subsequently activated; the patient was given loading doses of aspirin and clopidogrel, started on nitroglycerin and heparin infusion, and was immediately transported to the cardiac interventional suite for cardiac angiogram and revascularisation.

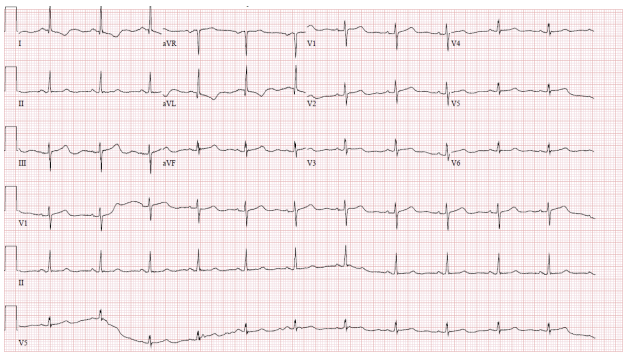


*Figure 1. ECG performed during triage showed inverted T-waves in leads V2 and V3. The patient had a ventricular rate of 69 beats per minute (BPM), an atrial rate of 69 BPM, a P-R interval of 146 milliseconds, a QRS duration of 70 milliseconds, a Q-T interval of 404 milliseconds, a calculated QTc (Bazett) of 432 milliseconds, a P axis of 27 degrees, an R axis of 14 degrees and a T axis of 135 degrees.*

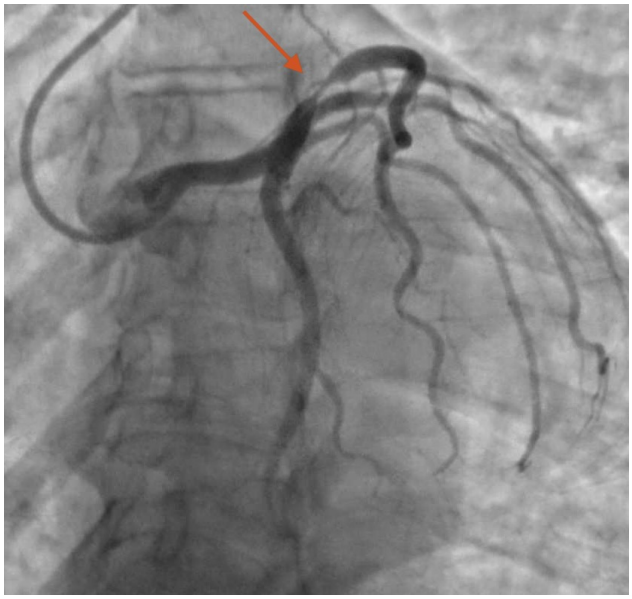

*Figure 2. During cardiac angiography, the patient was found to have one vessel disease with 99% stenosis in the proximal LAD (red arrow).*

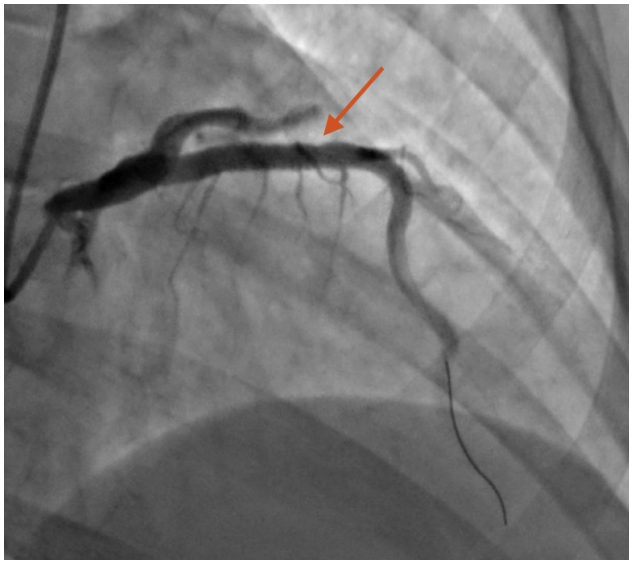

*Figure 3. Percutaneous coronary intervention (PCI) was successfully performed with the placement of one drug-eluting stent (Megatron 4.0 x 16) in the proximal LAD (red arrow).*

Laboratory findings during admission were significant for a haemoglobin (Hgb) of 10.2 g/dl (reference range 12.0–16.0 g/dl), a mean corpuscular volume of 105 fl (reference range 81–99 fl), a platelet count of 301 K/µl (reference range 130 K/µl–400 K/ µl), a cardiac troponin level of 0.8 ng/ml (reference range < 0.01 ng/ml), a total cholesterol level of 252 mg/dl (reference range < 199 mg/dl), a high-density lipoprotein level of 72 mg/dl (reference range > 51 mg/dl), a low-density lipoprotein level of 165 mg/dl (reference range < 99 mg/dl) and haemoglobin A1C of 5.4%.

During cardiac angiography, the patient was found to have one vessel disease with 99% stenosis in the proximal LAD *(Fig. 2)*. Percutaneous coronary intervention (PCI) was successfully performed with the placement of one drug-eluting stent (Megatron 4.0 x 16) in the proximal LAD *(Fig. 3)*. Following PCI, the patient's chest pain and T-wave inversions on ECG disappeared. After PCI, the chest pain and T-wave inversions on ECG resolved *(Fig. 4)*. Anagrelide was discontinued and aspirin, clopidogrel, atorvastatin, metoprolol and isosorbide mononitrate were added. The patient was then discharged without further cardiac symptoms.

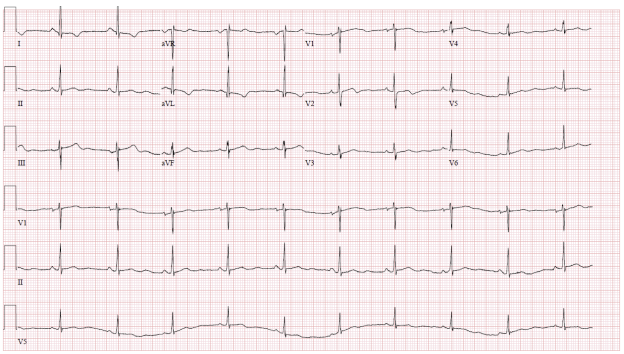


*Figure 4. ECG performed after revascularisation showed resolution of previously inverted T-waves in leads V2 and V3. The patient had a ventricular rate of 62 beats per minute (BPM) and a corresponding atrial rate of 62 BPM. The P-R interval is measured at 144 milliseconds, while the QRS duration is 70 milliseconds. The Q-T interval is observed to be 402 milliseconds, and the QTc calculation using Bazett's formula yields a value of 408 milliseconds. The P axis is determined to be at 30 degrees, the R axis at 12 degrees and the T axis at 118 degrees.*

## DISCUSSION

ET is an acquired myeloproliferative disorder characterised by a sustained elevation of platelet number with a tendency for thrombosis and haemorrhage[8]. Myocardial infarction occurrence in ET patients often stems from in situ thrombosis in the absence of associated coronary atherosclerosis[9]. Vianello et al. illustrated that individuals with ET exhibit endothelial dysfunction and a diminished coronary flow reserve[10]. In two extensive cohorts of ET patients, Rossi et al. and Carobbio et al. found the incidence of myocardial infarction varied from 2% to 9.4%, with the majority having additional notable cardiovascular risk factors; all patients were over the age of 40[11,12]. Without the implementation of a successful cytoreductive treatment, individuals with ET may develop acute coronary syndromes due to the involvement of coronary arteries. Nevertheless, the incidence of myocardial infarctions in well-managed cases of ET is infrequent, and the majority of reported cases involve elderly individuals with diverse cardiovascular risk factors[4]. Apart from her age, our patient did not have cardiovascular risk factors. Her atherosclerotic cardiovascular disease (ASCVD) risk score was calculated from the lipid panel obtained during hospitalisation and was determined to be 3.9%, indicating that her risk of having a cardiovascular event in the next ten years was low.

When our patient was diagnosed with ET, it was determined that her international prognostic score for essential thrombocytosis (IPSET) was 3 due to her age and detection of *JAK2* V617F mutation, deeming her to be at high risk for annual thrombosis with a 3.56% likelihood. The treatment of choice for a high-risk patient is antiplatelet (low-dose aspirin) and cytoreductive therapy[13]. Hydroxyurea stands as the sole cytoreductive agent with established efficacy in diminishing thrombotic events through a randomised controlled trial. It continues to be the favoured initial treatment for most patients in need of therapeutic intervention[14]. Anagrelide is currently used as second-line therapy for patients where hydroxyurea is inadequate or not tolerated[13]. Our patient was initiated on hydroxyurea, and anagrelide was added 6 months later to her regimen by her oncologist as her platelet levels did not show appropriate reduction on combined aspirin and hydroxyurea. With the addition of anagrelide her disease was well controlled, with a reduction of her platelet level after 1.5 months of therapy. Naranjo et al. developed the Naranjo scale as a tool to assess the probability that an observed adverse drug reaction is directly attributable to a specific medication, as opposed to being caused by other variables[15]. Our patient received a score of 7 based on the Naranjo scale, which indicates a probable adverse drug reaction. Given that our patient's only cardiovascular disease risk factor was age, and she had a low ASCVD score, a well-controlled platelet level and a temporal association with starting anagrelide therapy, her STEMI was probably caused by anagrelide therapy.

While well-managed cases of ET are generally associated with a low incidence of myocardial infarctions, this patient's development of acute STEMI after the initiation of anagrelide therapy raises concerns about the potential cardiovascular adverse effects of this cytoreductive agent. The currently established cardiovascular adverse effects of anagrelide include vasospasm of the coronary arteries, congestive heart failure, arrhythmia or acute coronary syndrome, with the majority of the side effects of anagrelide developing within one month of starting therapy; the side effects are dose-dependent[4]. In the event of life-threatening adverse effects, anagrelide should be discontinued[4].

Anagrelide effectively lowers platelet count by inhibiting thrombopoiesis, but its exact mechanism is not fully understood[16]. It is believed to work by suppressing transcription factors involved in thrombopoiesis[17]. Anagrelide also inhibits cyclic adenosine monophosphate

phosphodiesterase III pharmacologically and has inotropic and vasodilator properties; thus, the most common cardiovascular adverse events associated with anagrelide include tachycardia/palpitations[16]. Anagrelide's impact on coronary arteries is debated, with reports of both vasospasm and vasodilation[16]. Its inhibition of phosphodiesterase III is thought to cause vasodilation, but it might also increase the release of sympathetic neurotransmitters, leading to varied vascular responses[16]. A report by Ahluwalia et al. suspected that vasoconstriction and vasodilation can occur depending on the expression patterns of alpha- and beta-adrenergic receptors in particular vessels[17]. 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[16].

## CONCLUSION

The occurrence of acute STEMI in a patient without significant cardiovascular risk factors suggests the need for increased awareness and monitoring of potential adverse effects associated with anagrelide. Further research and clinical studies may be warranted to better understand the underlying mechanisms and identify factors that could predispose certain individuals to such adverse cardiovascular events during ET treatment.

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