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Erika Jones, Nava Greenfield, Puja K. Mehta, Chrisandra Shufelt, Louise Thomson, C. Noel Bairey Merz

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Introduction: Signs and symptoms of myocardial ischemia in the setting of no obstructive coronary artery disease (CAD) is often found in women. One of the mechanisms thought to contribute is coronary vascular dysfunction (CVaD). Coronary reactivity testing (CRT) is used to assess endothelial and non-endothelial dependent CVaD, but is not routinely performed.

Case Report: We report a case of a healthy 26-year-old male with persistent chest pain after ST elevation myocardial infarction with normal coronary arteries. Stress cardiac magnetic resonance imaging showed normal rest and stress first pass perfusion, with an incidental finding of an enlarged spleen. He underwent CRT and was found to have slow flow and coronary endothelial dysfunction. Due to his enlarged spleen and an elevated hematocrit at 50% he was referred to a hematologist and diagnosed with polycythemia vera (PV). Although the risk of thrombosis and myocardial infarction is known in PV, the pathophysiology is not well understood. In our patient no thrombus was visualized on angiogram.

Conclusion: The findings of his CRT in the setting of PV offer an interesting link between hematological disorders, endothelial dysfunction, and persistent chest pain with no obstructive CAD.

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CASE REPORT

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Keywords: Chest pain, Coronary endothelial dysfunction, Coronary reactivity testing, Microvascular dysfunction, Polycythemia vera

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INTRODUCTION

Polycythemia vera (PV) is a myeloproliferative disorder, associated with an increased risk of myocardial infarction (MI) and stroke. The mechanism for developing these adverse cardiovascular (CV) events has been attributed to the development of thrombosis, either in the micro or macro vasculature, however, recent reports have suggested that there may be more to the pathophysiology, especially for young patients with this disease who present with signs and symptoms of myocardial ischemia [1].

There is a growing body of evidence showing that one cause of myocardial ischemia and persistent chest pain in patients with no obstructive coronary artery disease (CAD) is coronary microvascular dysfunction (CMD) and endothelial dysfunction [2]. CMD refers to impaired hyperemic response of the myocardial resistant vessels in response to exercise or vasodilator stimuli. CMD can

be due to endothelial or non-endothelial dysfunction. Endothelial dysfunction is a proposed mechanism of chest pain, ischemia, and even infarction in at least some cases of patients with PV [3]. We present a case of an otherwise healthy 26-year-old male who developed a MI as his initial presentation of PV and was found to have endothelial dysfunction on invasive coronary reactivity testing (CRT).

CASE REPORT

A 26-year-old male with a past medical history significant for eosinophilic esophagitis and acid reflux presented to the emergency department with a three month history of atypical, progressively worsening substernal chest pain. The chest pain began suddenly and was not associated with exertion or emotion. Given his lack of cardiac risk factors and history of GERD, the chest pain was previously attributed to esophageal spasms for which he was prescribed sublingual nitroglycerin, omeprazole, dextansoprazole, calcium channel blockers and amitriptyline, none of which relieved his pain. On the day of his emergency department visit his substernal chest pain worsened to 10/10. His EKG had ST elevations in leads I, II and avF, labs showed an elevated troponin level that peaked at 1.55, elevated hematocrit (50%), an elevated white blood cell count (15.37 K/uL) and no splenomegaly appreciated on exam. Echo showed normal left ventricular systolic function with no wall motion abnormalities. A cardiac catheterization demonstrated no obstructive CAD, no thrombus was visualized, but slow flow was evident in his left anterior descending artery (LAD). Given lack of evidence of any obstructive CAD his symptoms were thought to be secondary to pericarditis. His pain persisted and with no clear etiology of his chest pain, the patient sought further investigations.

The patient was referred to our facility for further workup where he received a regadenoson stress cardiac magnetic resonance imaging (CMRI) myocardial perfusion study which showed normal rest and stress first pass perfusion, normal biventricular systolic function, no evidence of scar by delayed enhancement. Incidental note was made of splenomegaly with liver length, 16 cm on scout images (Figure 1). Given persistent chest pain and a history of an ST elevation MI, he underwent CRT to clarify diagnosis and to assess endothelial and non-endothelial dependent micro and macro vascular function. CRT was performed by placing a Doppler FloWire (Volcano Inc., San Diego, USA) in the left anterior descending (LAD) artery. Vasoactive substances were infused through a guiding catheter placed in the left main, and changes in LAD diameter and blood flow velocity in response to adenosine, acetylcholine and nitroglycerin were measured. We confirmed slow flow with a thrombolysis in myocardial infarction (TIMI) 2 flow and a TIMI frame count of 42 with a corrected TIMI frame count of 25. His CRT findings are outlined in Table 1.

Figure 1: Coronal scout image done at the time of cardiac magnetic resonance imaging incidentally found increased craniocaudal dimension of the spleen (*) 16 cm.

Table 1: Coronary Reactivity Testing Results

	Patient Results	Normal Reference	Pathway
Adenosine-Coronary Flow Reserve (CFR)	5.5	≥ 2.32	Microvascular-non endothelial dependent
Acetylcholine Coronary blood flow response	160% increase	$\geq 130\%$	Microvascular-endothelial dependent
Acetylcholine LAD diameter response	4.4% constriction	Any dilation	Macrovascular-endothelial dependent
Nitroglycerin LAD diameter response	3% dilation	$\geq 15\%$	Macrovascular-non endothelial dependent

The patient was seen by a hematologist who confirmed a Jak2 mutation and an elevated hematocrit (Hct), consistent with a diagnosis of PV. He was started on aspirin, pegylated interferon, and phlebotomies to keep his Hct below 45%, which improved his symptoms. He continues to experience occasional chest pain, dizziness and fatigue although generally feels drastically improved from his initial presentation.

DISCUSSION

Chest pain is a common chief complaint with a wide differential diagnosis. Problems with diagnosis and treatments arise when patients present with atypical symptoms and/or have little to no risk factors for heart disease. We describe an unusual case of a previously healthy young man with no known cardiac risk factors, in whom an ST elevation MI with no obstructive CAD was the first presentation of PV. There is a growing body of evidence that one of the causes of ischemia with no obstructive CAD is coronary vascular dysfunction (CvD) [2]. Endothelial and non-endothelial dependent vascular function can be abnormal in those with no obstructive CAD who have signs and symptoms of ischemia, and should be considered as an etiology in those with unexplained chest pain. If a coronary angiogram is performed and no thrombosis is visualized then perhaps CRT may add further diagnostic information. In this case the patient demonstrated slow flow which is considered a marker for increased microvascular resistance and endothelial dysfunction [4].

Patients with PV are predisposed to vascular complications such as venous and arterial thrombosis⁵. Prior thrombotic event and age >65 are the two risk factors that increase risk of further CV events in patients with PV [5]. The pathogenesis of coronary thrombosis seen in PV is not fully understood, however it is likely that multiple factors play a part such as hyperviscosity with decreased blood flow, platelet activation and functional abnormalities, leukocyte and platelet aggregation [6]. Increased platelet activation through interaction between abnormal hematocrit, activated white cells, turbulent flow can provoke endothelial activation and injury [6]. Nienteufl et al. [3] investigated endothelium-dependent flow mediated vasodilation (FMD) and endothelium-independent nitroglycerin-induced vasodilation (NMD) in patients with PV versus controls and found that FMD but not NMD was significantly impaired in patients with PV leading to the thought that endothelial dysfunction may play a role in thromboembolic complications.

Acute coronary syndrome (ACS) in patients with PV is thought to be due to coronary thrombosis in large coronary arteries which can be seen on coronary angiography but microthrombi in the coronary microcirculation are not visualized on catheterization. There are case reports of PV presenting as an ST elevation MI with visualized coronary lesions and distal thrombosis [7]; however there are other case reports where an angiogram was performed showing normal coronary arteries in both patient with PV and essential thrombocytosis (ET) [1]. Rossi et al. compared characteristics in patient with PV versus ET and found that ACS was more common in PV, 11.4% versus 9.4%, raising the question of whether ACS is indeed caused by platelet rich thrombi [8]. Studies have shown that thrombi are more common in PV versus ET and therefore thrombocytosis alone is not sufficient to explain coronary thrombi and other mechanisms

such as slow flow, hyperviscosity, microvascular and endothelial dysfunction as a cause of ACS may need to be further investigated. Leukocytosis, which was present in our patient, has been shown to be a risk factor for developing thrombosis [9]. Falanga et al. [10] showed that activated leukocyte markers were simultaneously elevated with markers of endothelial damage including thrombomodulin and von Willebrand factor antigen in both patients with PV and ET compared to controls.

CONCLUSION

We report a young male patient whose first presentation of polycythemia vera (PV) was an ST elevation MI, followed by persistent chest pain, who had an abnormal coronary vascular reactivity test. Coronary slow flow and endothelial dysfunction should be considered in patients with persistent chest pain and no obstructive coronary artery disease (CAD) as in this case. The findings of his abnormal coronary reactivity testing (CRT) in the setting of PV offer an interesting link between hematological disorders, endothelial dysfunction and persistent chest pain with no obstructive CAD.

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Author Contributions

Erika Jones – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Nava Greenfield – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Puja K. Mehta – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Chrisandra Shufelt – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Louise Thomson – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

C. Noel Bairey Merz – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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