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Myocardial infarction as initial presentation of polycythemia vera and its treatment challenges, a case report

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ABSTRACT

Polycythemia vera (PV) is one of Myeloproliferative neoplasm which has common and uncommon mode of presentations. Myocardial infarction (MI) is rare at initial presentation. Here we report 55-year-old women presented with MI and found to have PV in whom, coronary intervention was delayed as there is no evidence based literature guidance in cases of acute MI and PV.

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Introduction:

Myeloproliferative neoplasms [MPN], classically described as BCR /ABL Positive [Chronic myeloid leukemia] [1] and BCR / ABL negative including {polycythemia vera [PV], Essential Thrombocytosis [ET] and Primary Myelofibrosis[MF]} [2]. Myeloproliferative neoplasms usually sporadic however familial cases were described in different parts of the world [3].

Polycythemia vera is a chronic myeloproliferative neoplasm characterized by erythrocytosis and thrombocytosis, other characteristics includes leukocytosis and splenomegaly. It is usually diagnosed incidentally, minority of patients present with disease related signs and symptoms including headache, blurred vision, thrombosis, and bleeding [4].

PV is diagnosed based on the 2016 revised WHO diagnostic criteria of for PV [4] and requires; either all of the 3 major criteria or the first 2 major and the only minor criterion [*low serum erythropoietin level] , the 3 major criteria* are the following :

“1-Hemoglobin >16.5 g/dL in men or > 16 g/dL in women; or hematocrit >49% in men or > 48% in women or increased red blood cell mass.

2-Bone marrow tri-lineage proliferation with Pleomorphic mature megakaryocytes.

3-Presence of *JAK2* mutation”.

Thromboembolic disease is common in PV cases, reported in more than 40% of cases in some studies and can affect both arteries and veins [5].

Although MI is known to be associated with PV, initial presentation as MI like our case is uncommon and mainly reported as case reports.

Different treatment modalities are available for PV, selection depends on what is best for the patient and his/her quality of life [6] . Management depends on risk stratification of PV , patients who low-risk PV often treated with Phlebotomy to maintain the haematocrit <45 percent in addition to Low-dose aspirin . Cytoreduction is added to high risk patients.

Case Report:

A 55-year old woman, whose diabetic, hypertensive and dyslipidemic, lifetime non-smoker, presented in February 2015 through emergency department with epigastric pain, nausea and repeated vomiting and found to have ST elevation myocardial infarction [STEMI] complicated with acute pulmonary oedema. Her coronary angiogram was delayed as the patient was in failure, not able to lie flat and because of her haemoglobin value of 20.3 g/dl, so PV were suspected, and PCI was deferred until after stabilization. She was treated with aspirin, clopidogrel loading and then maintenance doses and was started on heparin, furosemide and nitrates infusions for heart failure. For MI, she was started on carvedilol, lisinopril and atorvastatin.

Her blood test was showed high HB 20.3 g/dl and haematocrit 62.4 % with leucocytosis of 17.2 x10^3/uL with mild thrombocytosis of 413 x10^3/uL confirmed by peripheral smear. Other

blood tests revealed normal electrolytes, LFT, urea and creatinine with a high troponin T HS and pro-PNB [see table 1] denoting acute MI.

Her ECG on initial presentation [Figure 1].

Chest X ray showed evidence of bilateral congested lung field [Figure 2]. Her echocardiography showed moderate LV systolic dysfunction with an EF of 35%, grade III diastolic dysfunction and akinetic apex, anterior and anteroseptal walls with evidence of mild mitral regurgitation and pulmonary hypertension.

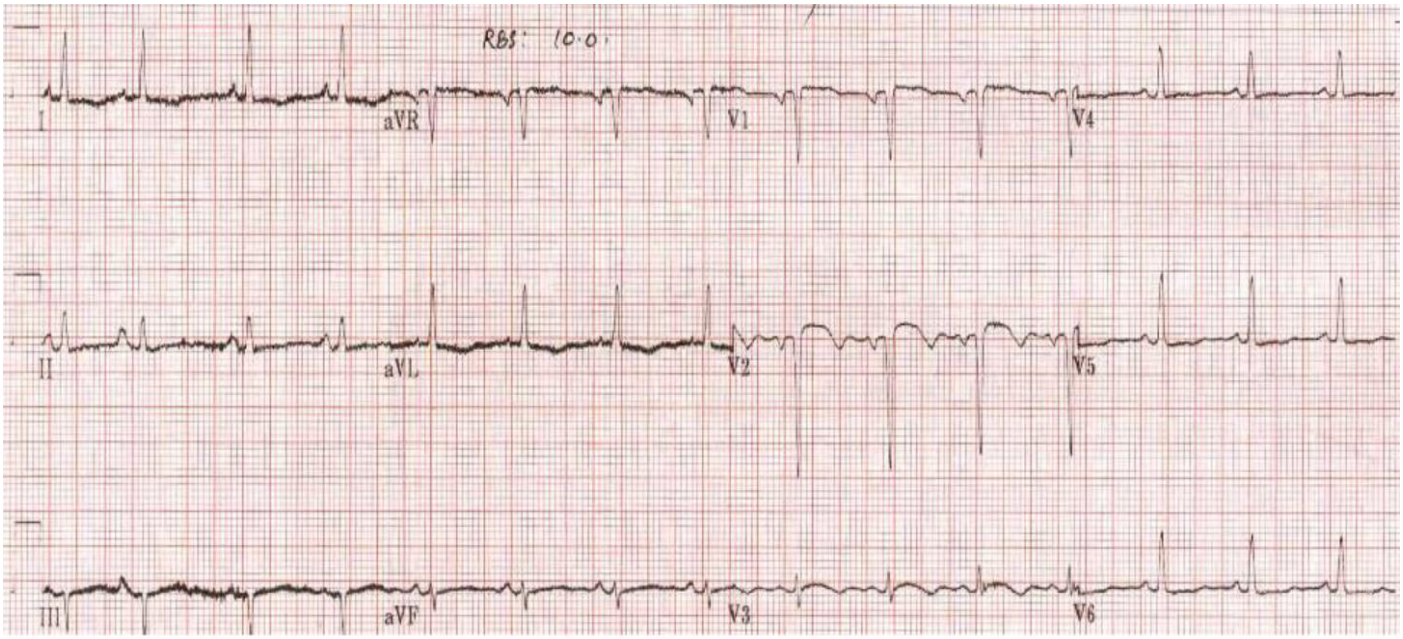
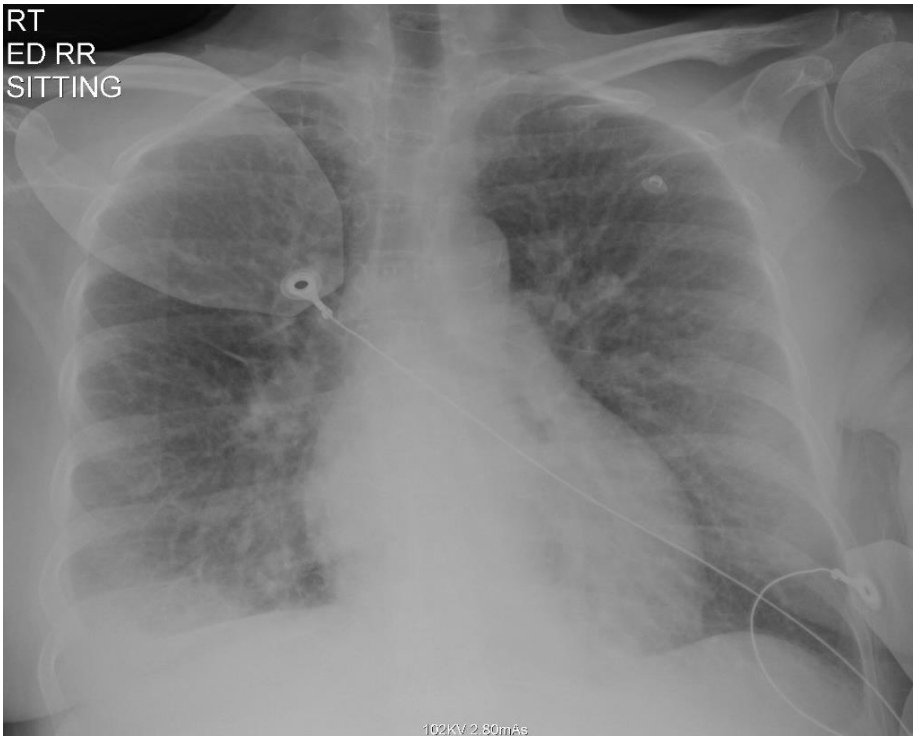


Figure 1 ECG upon presentation : Anteroseptal myocardial infarction

Table [1]: Blood tests upon admission

Detail	Value w/Units	Normal Range
Platelet	413 x10^3/uL	150-400
WBC	17.2 x10^3/uL	4.0-10.0
Hgb	20.3 gm/dL	13.0-17.0
Hematocrit [Hct]	62.4 %	36-46
Creatinine	73 umol/L	62-106
NT pro-BNP	3,034 pg/mL	0-287
CRP		0.0-5.0
D-Dimer	<0.3	0.00-0.49
pH		7.320-7.420
Troponin-T HS [upon admission]	160 ng/L	3-15
Troponin-T HS [after 10 hours]	392 ng/L	3-15
Troponin-T HS [after 16 hours]	641 ng/L	3-15
HbA1C %	10.2 %	
Cholesterol	4.93 mmol/L	
Triglyceride	2.1 mmol/L	
HDL	0.56 mmol/L	
LDL	3.41 mmol/L	
Erythropoietin [EPO]	2.2 mIU/ml	4.3-29.0



Chest X ray showed evidence of bilateral congested lung field

Her repeated blood tests showed high Haemoglobin level of 19.9 g/dl and haematocrit 61.4%. Patient was investigated for the polycythaemia vera, her JAK 2 mutation was positive, JAK2 V617F was detected and erythropoietin level was low 2.2 mIU/ml [normal range 4.3-29.0 mIU/ml] confirming the diagnosis of PV. After this diagnosis the cardiology team was reluctant to send her for angiogram, as there is risk of future stent thrombosis so decided to risk stratify her with adenosine myocardial perfusion scan which showed evidence of severe MI involving the left anterior descending artery [LAD] distribution affecting the anterior wall, apex, and septum. Left circumflex [LCX] and right coronary artery [RCA] demonstrated relatively normal perfusion with no evidence of stress induced ischemia. Case was again discussed with interventional cardiologist and she underwent coronary angiogram which showed single vessel disease with severe proximal LAD stenosis, fixed using a DES stent.

The patient was discharged on full ant ischemic therapy. For PV, she was started on Hydroxyurea 500 mg BID. Upon discharge from hospital she was started on phlebotomy to keep haematocrit level around 42%. She was followed closely in the haematology clinic over the past 5 years with proper response on medical management with no further coronary event.

Discussion:

PV is a myeloproliferative neoplasm [MPN] which is characterized by clonal proliferation of myeloid cells associated with variable morphologic maturity and hematopoietic efficiency. Bleeding, thrombotic, and vascular complications are the major causes of morbidity and mortality in PV, occurring in 40 to 60% of the patients [5], [7], [8] .

Typically, risk of thrombosis is increased with advanced age and a prior history of thrombosis. However, the presence of cardiovascular comorbidities like diabetes, hypertension, dyslipidaemia and smoking are considered predictors' for thrombosis development [9]

The pathogenesis of increased thromboembolic events is not well established but many theories have been implicated. In addition to increased blood viscosity , the axial migration of red cells occurs with displacement of platelets to the mural plasmatic zone, exposing them to maximal vessel wall shearing forces; erythrocytosis enhances platelet-vascular interactions, especially at the high shear rates found in arterioles and capillaries [10] .

structural and functional abnormalities of platelets have been reported in patients with myeloproliferative diseases, including abnormal expression of platelet membrane glycoproteins, spontaneous platelet aggregation and circulating platelet aggregates; increased platelet microparticles; acquired storage pool disease and other structural and biochemical abnormalities [8] [11] .

Few studies have explored the prevalence of MI in cases of MPNs and PV and found to occur in 5.3 & 11% of the cases, respectively [12, 13]. The management of PV/ MPNs cases presenting as MI can be challenging as still there is no definite guidelines about what the best treatment strategy is. Also, no sufficient evidence about types of stents used or effect of newer antiplatelet medications or drug eluting stents. It remains uncertain whether to be managed with per cutaneous intervention [PCI], coronary artery bypass grafting [CABG], thrombolytic therapy or case by case approach. This can create a lot of confusion for cardiologists managing those patients as stents placement can predispose them to future thrombosis and those patients carry the risk of both thrombosis and bleeding.

Our patient was not an exception, so presented initially with MI and then discovered to have PV with high haemoglobin value of 20.3 g/dl, it was opted to defer her PCI initially owing to her expected hyper viscosity which carries increased risk of stent thrombosis and considered later after discussion in multi-disciplinary team involving both cardiologist and haematologist. We also initiated cytoreductive therapy soon after confirming the diagnosis of PV, then, after stabilization she underwent PCI and had a good outcome with no post stenting complications.

Apart from aspirin, which is a cornerstone of treatment in PV [14], the use of other antiplatelet in MPNs in not well explored. In one reported case , Ticagrelor showed a superior benefit to clopidogril in decreaseing PV induced repeated MI and acute stent thrombosis [15], another patient showed a better responce on ticagrelor and aspirin dual therapy after he had six episodes of cerebral infarctions and one MI on clopidogrel monotherapy [16]. Moreover, no clear guidance about the use of GP IIIa/IIb inhibitors in cases of PV, it was used in some reported cases with advanced thrombosis and

cardiogenic shock [17] and led to life threating haemorrhage in another patient [18]

Phlebotomy is a mainstay of treatment for erythrocythaemia and cytoreduction for thrombocytosis, PV managed aggressively with cytoreduction along with phlebotomy is reported to decrease post MI stent and grafts thrombosis [19, 20].

Our patient advised continue aspirin indefinitely, with regular phlebotomy and cytoreduction therapy, he has taken clopidogrel for one year Close follow up is warranted to assess treatment response, and to observe for possible haematological transformation. All cardiovascular risk factors should be controlled.

Further studies are needed to examine the effectiveness of newer antiplatelet therapies like ticagrelor and prasugrel for the treatment of arterial thrombosis in PV patients, especially in a high risk subset of patients with recurrent thrombosis or stent thrombosis, as well as newer generation drug eluting stents. Moreover, exploration of the underlying biological processes may contribute to a better understanding of the pathophysiology of thrombotic events and encourage development of new strategies for preventive methods for PV patients.

Our group is studying the unmet clinical needs in Myeloproliferative neoplasms and CML like cost effective analysis for second generations TKIs when used as upfront [21], the association of tuberclosis with CML [22], the reactivation of hepatitis B with CML [23], ophthalmic manifestations as initial presentation in patients with CML [24], Effects of intermittent fasting on CML [25], autoimmune hemolytic anemia and its association with different therapies in CML [26], priapism [27, 28] and male fertility [29] obesity and obesity related surgeries in patients with CML [30] as well as environmental life style effects in MPNs [31].

Conclusion:

Polycythaemia vera accelerates Cardiovascular complications in all affected patients especially those with other comorbid conditions. Myocardial infarction is prevalent association with polycythaemia vera cases, yet there is no clear guidance for treatment strategies, further studies is recommended for this regard. Newer generations stents and antiplatelet other than aspirin need to be explored in MPNs populations in larger studies.

MPNs patients need risk factor control and close follow up in the clinic.

Declarations:

i. **Funding:** Open Access funding provided by Qatar National Library for funding of manuscript publication.

ii. **Conflicts of interest/Competing interests:** All authors declare no conflicts of interest.

iii. **Ethics approval:** Ethical approval by Medical Research Center – Hamad Medical corporation in Qatar with protocol ID**.**

iv. **Consent to participate:** The patient was consented for the case report.

v. **Consent for publication:** a written consent was obtained from the patient for publication of this case report

vi. **Availability of data and material:** All data are available if required.

vii. **Code availability:** Not applicable.

viii. **Authors' contributions:**

Hadeel Alfar[1], Ahmed A. Elyas[2] -drafting the manuscript, approved final draft.

Mohamed A. Yassin[3]- case report concept, mentoring, approved final draft.

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External Resources

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