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Case Report

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Triple Therapy When Thrombotic Risk Exceeds Bleeding Risk: Polycythemia Vera in a Patient With Atrial Fibrillation and Subacute Stent Thrombosis

Elif Aksoy[a, b, c], Isaac Akkad[a], Giorgio Medranda[a], Anoop Titus[a], Ramesh Daggubati[a]

Abstract

Currently, there is no approved guideline regarding management of patients with polycythemia vera (PCV) undergoing percutaneous coronary intervention (PCI) given the low prevalence. Standard maintenance therapy may be inadequate in cases where patients' response to standard treatment show heterogeneity. Approximately 5-10% of patients undergoing PCI are reported to have an additional indication for triple antiplatelet therapy consisting of aspirin, an adenosine diphosphate (ADP)-receptor antagonist and oral anticoagulant. However, considering the higher bleeding risk that arises with triple antiplatelet therapy, physicians act reluctantly in prescribing the regimen. Here, we present a case of subacute stent thrombosis in a patient with PCV prompting the consideration of triple antiplatelet therapy given increased thrombotic risk.

Keywords: Triple therapy; Polycythemia vera; Stent thrombosis; Atrial fibrillation; Acute myocardial infarction

Introduction

Polycythemia vera (PCV) is a chronic myeloproliferative disease characterized by erythrocytosis which predisposes to stasis, endothelial damage and thrombosis. Patients with PCV presenting with acute myocardial infarction (AMI) despite appropriate antiplatelet therapy have been reported in the literature [1]. Here we present a case of subacute stent thrombosis (ST) in a patient with PCV prompting the consideration of triple antiplatelet therapy (TT) given increased thrombotic risk and failure to dual antiplatelet therapy (DAPT) consisting of aspirin and clopidogrel. We hope to illustrate the need to evaluate duration and choice of TT when adequate and compare between regimens to maximize outcomes while decreasing bleeding complications.

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[a]Cardiology Department, NYU Langone Long Island Hospital, 259 1st St, Mineola, NY 11501, USA
[b]Baglarbasi mah. Akil Muhtar sk. No:17/8 Tosunlar apt, Maltepe, Istanbul, Turkey
[c]Corresponding Author: Elif Aksoy, Baglarbasi mah. Akil Muhtar sk. No:17/8 Tosunlar apt. Maltepe, Istanbul, Turkey. Email: elifaksoy1996@gmail.com

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Case Report

An 80-year-old Caucasian woman with a past medical history of PCV, paroxysmal atrial fibrillation, hypertension, hyperlipidemia, left ventricle thrombus on warfarin, coronary artery disease status post remote PCI to left anterior descending artery (LAD) and recent PCI to right coronary artery (RCA) 2 days prior to her admission presented with ST-segment elevation myocardial infarction (STEMI). She had been taking clopidogrel and warfarin alone without aspirin with a therapeutic international normalized ratio. On arrival, she was found to be in cardiogenic shock secondary to inferior wall MI with ST elevations on leads II, III, and aVF and complete heart block at a rate of about 40 bpm. Patient received aspirin 325 mg and was loaded with 180 mg of ticagrelor and 4,000 units of heparin as a bolus. A dopamine infusion was initiated and transcutaneous pacing pads were placed as the patient was transported to the catheterization laboratory. On arrival to the cathetherization lab, patient was in cardiogenic shock, so a transvenous pacemaker was placed alongside mechanical support with intra-aortic balloon counterpulsation (IABP).

Coronary angiography revealed chronically occluded distal LAD, 70% mid LAD, mild diffuse disease of the left circumflex artery and subtotal occluded RCA at the ostium by a large thrombus burden.

Records were obtained from recent angiogram from the outside hospital which reported two drug-eluting stents at RCA 2 days prior to her admission. The proximal stent appeared to be approximately 4 mm extended into the aorta from the RCA ostium. The patient had successful PCI to the proximal and mid RCA with post balloon dilation. Patient developed rapid atrial fibrillation with reperfusion to RCA. The patient was supported with intravenous (IV) fluids, IABP and dopamine while admitted to the coronary care unit (CCU). Bedside transthoracic echocardiography revealed approximately 40% left ventricular ejection fraction and inferior wall motion hypokinesis. Ultimately IABP, dopamine and transvenous pacemaker were weaned off and patient was stable for discharge 5 days

after admission. The choice was made to continue indefinitely warfarin, ticagrelor and aspirin.

Discussion

The general incidence of ST has been reported to be 0.5-2% [2, 3]. ST has major clinical outcome implications as it confers a significantly higher incidence of sudden death, STEMI complicated by cardiogenic shock, arrhythmias, or acute decompensated heart failure [4]. In-hospital mortality is reportedly greater in patients with early ST compared with late and very late ST (7.9% vs. 3.8% and 3.6%; $P < 0.01$) in a study that was carried out on 7,315 ST events [5]. Many patient-related, lesion-related, procedural, post-procedural, technical and clinical factors were noted to be associated with the pathogenesis of ST.

Stenting in aorta-ostial lesions remains a practical challenge due to ambiguous landmarks and common presentation of unique three-dimensional funnel-shaped morphology with a variable angle of takeoff of the coronary artery from the aorta [6]. As a consequence, exact positioning can be difficult and thus, various maneuvers are used in the management of aorta-ostial lesions [7]. Especially, stenting in RCA is associated with high restenosis rates due to excessive elastic recoil after dilatation. Frequently, ostial stent is mildly protruded into the aorta to obtain a better coverage of the ostium during the procedure [8]. Stent misplacement was found in 54% of cases with 52% of them being placed too proximally (> 1 mm proximal to the angiographically determined ostium) in a retrospective study that was carried on 100 consecutive coronary aorta-ostial lesions [9]. Misplaced stents generally cause no clinical symptoms, yet they are a potential source of thrombus or emboli [10]. Unfortunately, fully deployed coronary stents cannot be extracted or repositioned after deployment given the significant risk of endothelial injury, dissection or perforation [6, 11].

Nonmechanical causes (e.g. hypercoagulable state, thrombocytosis, or aspirin/clopidogrel resistance) should be considered in a small number of cases. In our case, an important factor predisposing to ST is PCV. PCV is a rare disorder which is a type of chronic myeloproliferative neoplasm [1]. Several studies show a prevalence of approximately 22 cases per 100,000 population. PCV is more prevalent among men than women regardless of race or ethnicity [12]. The total incidence of acute coronary disease in patients with PCV was 11.4% [4]. Estimated median survival is 14 years for PCV. The diagnosis is based on the World Health Organization criteria, requiring all three majors or the first major and one minor criterion. Major criteria include hemoglobin > 16.5 g/dL in men or > 16.0 g/dL in women or hematocrit > 49% in men and > 48% in women or increased red cell mass, hypercellular bone marrow with trilineage growth, and presence of a JAK2 mutation, while minor criteria include hypercellular bone marrow with trilineage growth, low serum erythropoietin levels and endogenous erythroid colony formation. Most commonly seen clinical symptoms include pruritus after a hot shower, splenomegaly, vasomotor symptoms, arterial and venous thrombosis [13]. Erythrocytosis, the hallmark of PCV, is the main reason behind the most common serious complications of PCV.

Uncontrolled erythrocytosis can predispose to thrombogenicity, systemic and pulmonary hypertension, impaired renal and cerebral blood flow through hyperviscosity of the blood results from an increased red blood cell mass, can lead to leukemia and overall has been found to shorten life expectancy [12, 14]. Although hyperviscosity is crucial, there are alternative suggested mechanisms such as overactive JAK/STAT pathway [15]. Current risk stratification model in PCV consists of two risk categories: high-risk (age > 60 years or thrombosis history) and low-risk (absence of both risk factors) which is used as an estimation tool for the likelihood of recurrent thrombosis [13].

Emergent PCI is the first-line treatment of ST especially if presented as AMI [16]. The current post-procedural treatment after drug-eluting stent and bare-metal stent (BMS) placement is to continue DAPT for 1 year (some argue 3 - 6 months) and at least 1 month respectively for BMS. Previous studies have shown that DAPT was conclusively more effective in prevention of complications than anticoagulation treatment after BMS [17]. Maintenance therapy may be modified in cases where patients' response to standard treatment shows heterogeneity [18].

Currently, there is no approved guideline regarding management of patients with PCV undergoing PCI given the low prevalence. AMI presentation in patients with PCV is due to underlying hyperviscosity and is related to acute aortic occlusion and recurrent ST regardless of standard maintenance therapy. Greatest benefit in mortality reduction and minimizing the bleeding risk was provided by cytoreductive therapy along with aspirin in patients with PCV presenting with acute coronary syndrome. Hematocrit levels should be lowered to less than 45% by pre-procedure phlebotomy whenever possible in order to prevent ST. Additional myelosuppressive agents such as hydroxyurea or more recent drug ruxolitinib, a JAK1/2 inhibitor are used to treat high-risk cases. Additionally, coronary reperfusion is used to treat PCV patients; however, it is not clear that which procedure patients most benefit from [1]. Arterial catheterization with stent placement may predispose thrombosis in an uncontrolled PCV patient [19].

Our patient was prescribed aspirin 81 mg once daily and ticagrelor 90 mg twice daily and warfarin as triple therapy and no problem has occurred in the last 3 months since the current regimen was started. Approximately 5-10% of patients undergoing PCI are reported to have an additional indication for TT consisting of aspirin, an ADP-receptor antagonist and oral anticoagulant. However, TT has a higher risk of bleeding than DAPT and bleeding risk increases even further with prolonged use [20]. Some studies demonstrated a three- to five-fold rise in bleeding rates associated with TT in comparison to various combinations of DAPT. But in a meta-analysis, TT was shown to be more efficacious than DAPT in the prevention of major adverse cardiovascular events and led to significant reduction in all-cause mortality [21]. In addition, risk of ST is reported to be lower in a study conducted in patients treated with TT containing cilaztazol which showed similar efficacy as warfarin in another study [22]. The use of anticoagulants such as warfarin along with antiplatelet agents is also suggested in few studies to prevent recurrent thrombosis in patients with

PCV [1]. Insufficient guidance on prescribing TT challenges clinicians to prescribe the regimen and for those who prescribe it then for how long. We believe TT should be investigated further as an alternative approach in ST in patients with PCV or other hypercoagulable states. Even though 3 - 6 months is the proposed time period for triple therapy, we decided to continue indefinitely warfarin, ticagrelor and aspirin considering the high thrombotic risk [20]. Further studies are required to assess optimal regimen and optimal duration of triple therapy adjusted according to each patient's need individually.

Conclusion

Currently, there is no approved guideline regarding the management of patients with PCV after PCI. We present a case of high-risk PCV patient with a past medical history of recurrent thrombosis developing subacute ST after undergoing PCI. Patient has had no complaints since the triple therapy started 3 months ago. Thus far hematocrit has been stable and there are no reported bleeding events. Insufficient guidance on when triple therapy should be started, what agents to use and for how long remains to be determined. Even though 3 - 6 months is the suggested time period for triple therapy, dose and time adjustments may be required depending on patients' circumstances. Given the low incidence and prevalence of ST in patients with hypercoagulable states in general and PCV in particular, we hope that this case report will add to the literature and eventually help physicians determine therapy for this selected group of patients.

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Conflict of Interest

None to declare.

Informed Consent

Not applicable.

Author Contributions

Elif Aksoy collected data and drafted the manuscript. Isaac Akkad made critical revisions and participated in the design of the manuscript. Giorgio Medranda helped in language editing, made revisions and participated in the design of the manuscript. Anoop Titus reviewed the literature, collected data and helped in drafting the manuscript. Ramesh Daggubati found the case, participated in coordination and made critical revisions during the process. All authors made substantial contributions to the content, read and approved the final version of the manuscript.

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