

Recurrent Acute Stent Thrombosis Due to Allergic Reaction Secondary to Clopidogrel Therapy

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Despite significant benefits including mortality advantage demonstrated with antiplatelet therapy in large clinical trials, the occurrence of adverse ischemic events, including stent thrombosis after percutaneous coronary intervention has been the challenging and devastating complication. Clopidogrel as a monotherapy, or more common in combination with aspirin, represents a cornerstone of modern pharmacotherapy in the invasive era. Although vigilance in maintenance of this dual antiplatelet treatment is mandatory, obligatory cessation of one of these agents can be observed in rare circumstances of adverse events. We describe a patient who developed recurrent acute stent thrombosis associated with clopidogrel-induced allergic reaction and discuss our therapeutic considerations.

Keywords: stent thrombosis, allergic reaction, clopidogrel

INTRODUCTION

Stent thrombosis is an infrequent but very severe, and often deadly complication of percutaneous coronary intervention (PCI). Antiplatelet therapies, including aspirin (ASA) and thienopyridines, are key components of pharmacotherapy in acute coronary syndromes (ACS) and PCI. When combined with ASA, clopidogrel (Cp) provides an additional reduction of the risk of ischemic events in patients with ACS and especially those undergoing PCI.¹ Moreover, extended duration of Cp therapy following stent implantation was associated with a lower incidence of death or myocardial infarction (MI), a finding that has immediate implications for clinical practice.^{2–4} Although vigilance in maintenance of this dual antiplatelet treatment is mandatory, obligatory cessation of one

of these agents can be observed in rare circumstances. Herein, we describe a patient who developed recurrent stent thrombosis due to Cp-induced allergic reactions and discuss our therapeutic approach in dealing with this difficult case.

CASE REPORT

A 44-year-old male patient was admitted to our hospital with severe chest pain lasting for 1 hour. He had been smoking for 7 years, and had no previous history of cardiovascular disease. On physical examination, the patient was clammy, hypotensive (85/60 mm Hg), and normal heart sounds were present. His electrocardiogram demonstrated ST segment elevation in leads DII-III, derivation I augmented left leg, and ST segment depression in lead derivation I augmented left arm (Figure 1A). The diagnosis of acute inferior MI was established, and the patient was immediately transferred to cardiac catheterization laboratory for invasive management. At the time of transfer, the patient received 300 mg of ASA, 600-mg loading dose of Cp, and 5000 U of intravenous unfractionated heparin. Coronary angiography (CAG) was performed and showed proximal occlusion of left circumflex (LCX)

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Conflict of Interest: none.

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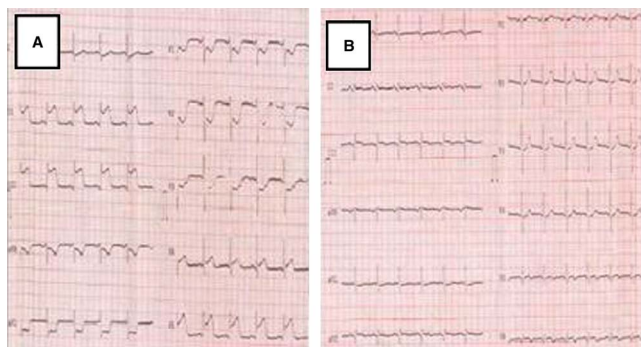


FIGURE 1. A, Pre-PCI electrocardiography showed ST segment elevation in leads II-III, AVF, ST segment depression in leads I, AVL. B, Post-PCI electrocardiography showed resolution of ST segment changes in previously recorded leads.

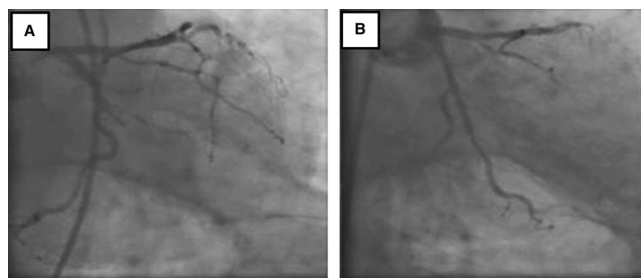


FIGURE 2. A, Pre-PCI CAG (right anterior oblique view) shows occlusion of circumflex coronary artery. B, Final angiographic result following stent implantation. Successful stent deployment at the desired position.

artery with normal left anterior descending artery, a right coronary artery (Figure 2A). We decided to perform a primary emergent PCI on LCX. After passing coronary soft guide wires into the LCX, it was predilated with 2.5×20 -mm balloon inflated at 14 atm. Subsequently, a bare metal 3.0×12 -mm stent was successfully implanted into LCX (Figure 2B). The electrocardiogram taken following 60 minutes of PCI showed resolution of ST segment elevation in previously recorded leads (Figure 1B). However, 6 hours following the coronary intervention, the patient developed severe chest pain concomitant with itching of the whole body especially on the shoulders and on the back followed by an urticarial rash all over his body and enlargement of subcutaneous nodules on the back of the patient's head (Figure 3). Repeat electrocardiogram revealed ST segment elevation in inferior leads and reciprocal changes in lateral leads (Figure 4). Acute stent thrombosis was suspected and CAG was performed immediately, which revealed occlusion of previously stented artery. Targeted stented artery was successfully redilatated (Figure 5A). After patency of the LCX had been confirmed by intravascular ultrasonography, which was performed and showed correct stent apposition and the absence of any abnormal patterns (Figure 5B). Following the PCI, oral antihistamines were added. On the third day after admission the allergic reactions and concomitant chest pain recurred, with the similar electrocardiographic changes revealing second recurrence of stent thrombosis (Figure 6A). The CAG was performed again and



FIGURE 3. A–C, Urticarial rash all over his body especially back, shoulder, and forearm.



FIGURE 4. Reocclusion of stented left circumflex coronary artery.

showed reocclusion of the stented artery (Figure 6B). Cp was stopped and intravenous glycoprotein IIb/IIIa inhibitor, tirofiban, subcutaneous low molecular weight heparin, and oral steroids were added. Neither stent thrombosis nor hemorrhage occurred later, and allergic symptoms were successfully resolved after discontinuation of Cp. Cp was started again in combination with tirofiban and heparin treatment, and patient was closely followed-up during the recovery. Together with Cp treatment subcutaneous low molecular weight heparin and ASA were added to

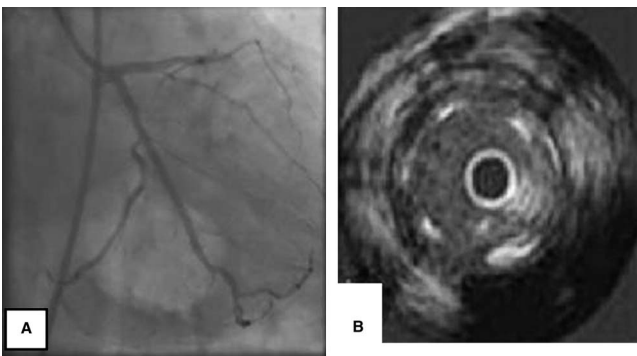


FIGURE 5. A, Successful redilatation of stented artery. B, Intravascular ultrasonography showed the patency of the stent and excluded abnormalities shifting of any plaque or dissection.

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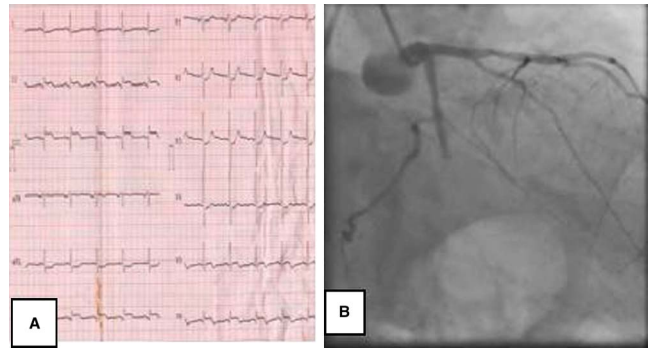


FIGURE 6. A, Relevation of ST segment in lead DII-III, AVF. B, Recurrence of occlusion in circumflex coronary artery.

conventional therapy. Further follow-up was unremarkable, and the patient was free from ischemic events for the next 15 months.

COMMENT

Sufficient and rapid inhibition of platelet activity is an important therapeutic goal for the management of patients with ACS, especially those undergoing primary PCI. Despite significant benefits demonstrated with antiplatelet regimens in large clinical trials, the occurrence of adverse ischemic events, including stent thrombosis after PCI has been the challenging and devastating condition because of its affiliated morbidity and mortality.⁵ Cp is one of the most commonly used and effective inhibitors of platelet activation and aggregation due to its selective and irreversible blockade of the P2Y₁₂ receptor. Although it is mainstay of the treatment and well tolerated by most of the patients, allergic reactions with this novel agent have been rarely documented.^{6,7} Although such reactions were observed in few sporadic reports, and occasionally were successfully resolved by antihistamines, repeated acute stent thrombosis secondary to allergic reaction developing due to the Cp usage has not been previously reported.^{8,9}

However, because the clinical indications for Cp are on the rise, it is more likely that physicians will face more challenges with adverse reactions in the nearest future. On the other hand, the list of risk factors for stent thrombosis is growing too, and now includes patient-, lesion-, procedure-related variables; resistance to, or noncompliance to antiplatelet therapy. Interestingly, allergic reactions induced by metals used in stent design have been anecdotally reported.^{10,11} Although Kounis et al reported the case when MI was associated with allergic reactions to contrast material,¹²

American Journal of Therapeutics (2011) 18(4)

documented stent thrombosis caused by the allergic reaction resulting from the Cp use has never been described. We are pretty confident that the recurrent stent thrombosis in our patient was associated with Cp because it occurred while the patient was under optimal controlled antiplatelet treatment; stent patency was repeatedly demonstrated by imaging; and, finally, allergic rash was observed concomitant with Cp intake and occurrence of stent thrombosis.

There are several reports documenting Cp-induced hypersensitivity reactions, including urticaria, rashes, and angioedema. Moreover, the exact mechanism(s) of such allergy are not entirely obvious, but may be related to direct mast cell activation, T-cell activation, and/or complement activation when Cp is introduced. It seems critical to realize that stent thrombosis caused by allergic reaction secondary to Cp represents a double edged sword in invasive cardiology era because there are obvious vascular risks for abrupt drug discontinuation.

Our knowledge with regard to the optimal therapeutic management of such patients is very limited. Alternative strategies such as substitution of Cp with ticlopidine or cilostazol, adding warfarin as desensitization protocols were reported in previous reports.^{13,14} Although ticlopidine seems to be a potential drug of choice here, when desensitization with ticlopidine has been previously reported,¹⁵ we decided not to use the older thienopyridine due to its deleterious side effects including bone marrow toxicity, and potential cross-reactivity with the Cp. There is an obvious lack of vascular outcome data with cilostazol, so we preferred to avoid this antiplatelet agent as well. Our approach to use intravenous tirofiban acutely, and then switch to Cp on top of protection with oral steroids deserves further considerations.

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