

Tacrolimus-Induced Diffuse Coronary Artery Spasm

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Abadil Samer¹, Fahad Almeahmadi¹, Ahmed Krimly², Abdullah Alrajhi³

1. Medicine, King Saud Bin Abdulaziz University for Health Sciences, Jeddah, SAU 2. Cardiology, King Abdulaziz Medical City, Jeddah, SAU 3. Cardiology, King Faisal Cardiac Center, King Abdulaziz Medical City, Jeddah, SAU

Corresponding author: Abadil Samer, 3badil.s.3s@gmail.com

Abstract

Prinzmetal angina, also known as vasospastic angina, is defined as an intermittent focal or diffuse coronary artery narrowing, which is often associated with transient ST-segment elevation on an electrocardiogram. Also, it could be associated with an atherosclerotic lesion at the site of the spasm. Vasospastic angina might be induced by medications, most commonly with cocaine and other examples which include catecholamines such as epinephrine, norepinephrine, isoproterenol, dopamine, and dobutamine. Parasympathomimetic agents include acetylcholine, methacholine, and pilocarpine. It is rarely caused by tacrolimus. The clinical evaluation includes an electrocardiogram and echocardiogram. The confirmed diagnosis is done by coronary angiography. Cardiac catheterization is indicated in such cases to rule out coronary artery disease.

Categories: Cardiology, Internal Medicine, Nephrology

Keywords: coronary artery spasm, renal failure, solid organ transplant, tacrolimus, immunosuppressant

Introduction

Tacrolimus is a cornerstone immunosuppressant for most solid organ transplant recipients [1]. It functions through calcineurin inhibition that subsequently reduces T-lymphocyte proliferation. Vasoconstrictive properties of tacrolimus contribute to its commonly encountered nephrotoxicity. Cardiovascular toxicity manifests in the form of hypertension, but diffuse multi-vessel coronary spasms are rarely encountered [2]. Here, we report a case of presumed tacrolimus-induced multi-vessel coronary artery spasm.

Case Presentation

A 35-year-old male with a known history of hypertension, end-stage renal disease (ESRD), and a non-smoker male, received a living donor renal transplant that was done in another country. Subsequently, his graft progressively failed, and the patient ended up back on dialysis for the last five years. To prevent graft-antibody-mediated rejection, the patient was kept on oral tacrolimus and prednisolone. The patient presented to the emergency room with severe respiratory distress and cardiogenic shock. On initial evaluation, the patient's vitals showed a temperature of 97.2°F, blood pressure of 152/87 mmHg, heart rate of 107 beats per minute, respiratory rate of 30 breaths per minute, and oxygen saturation of 98% on room air. Lab work was done at that time without significant results.

His presenting electrocardiogram (ECG) showed diffuse ST-segment elevation along with significant elevation of high sensitivity troponin (hs-Trop) at >180,000 units (Figure 1). With prolonged vasospasm, elevated high sensitivity troponin might be seen. Catheterization lab was immediately activated for an emergency. His tacrolimus level at that time was within acceptable at 5.10 ng/mL. The normal tacrolimus serum range is (3-7 ng/mL).

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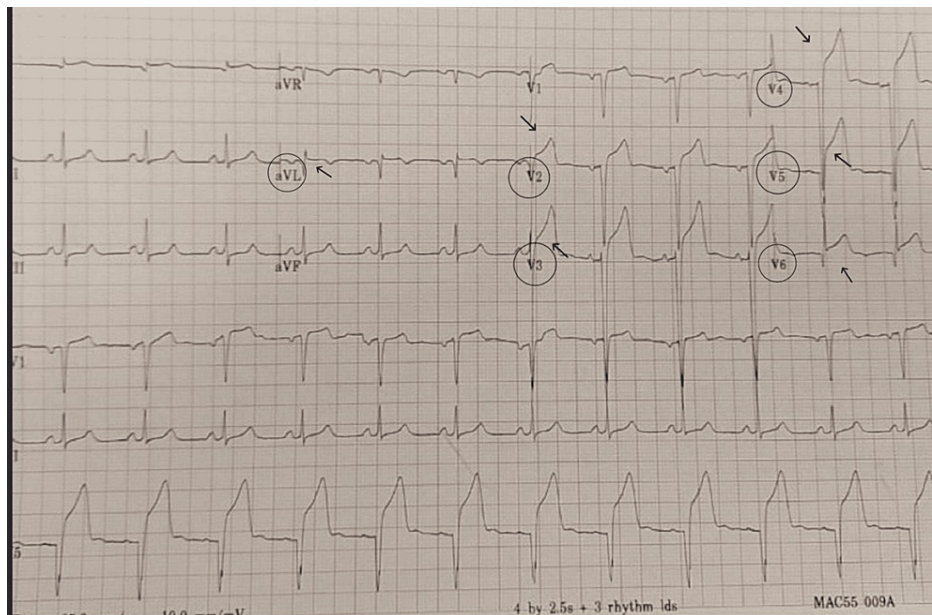


FIGURE 1: Electrocardiogram (ECG) showing ST-elevation in V2-6 and aVL

The coronary angiogram showed severe left anterior descending (LAD) artery spasm, ostial-mid 99.9% diffuse spasm followed by a normal artery with no clear coronary artery disease (Figure 2). Suddenly, the LAD artery showed no flow distally and the patient had a severe drop in blood pressure and loss of pulse. Cardiopulmonary resuscitation (CPR) was immediately started for six minutes, and intra-coronary nitroglycerin 200 µg was injected without significant improvement in coronary flow. The patient continued to be hypotensive, and the decision was to place an intra-aortic balloon pump (IABP) for support.

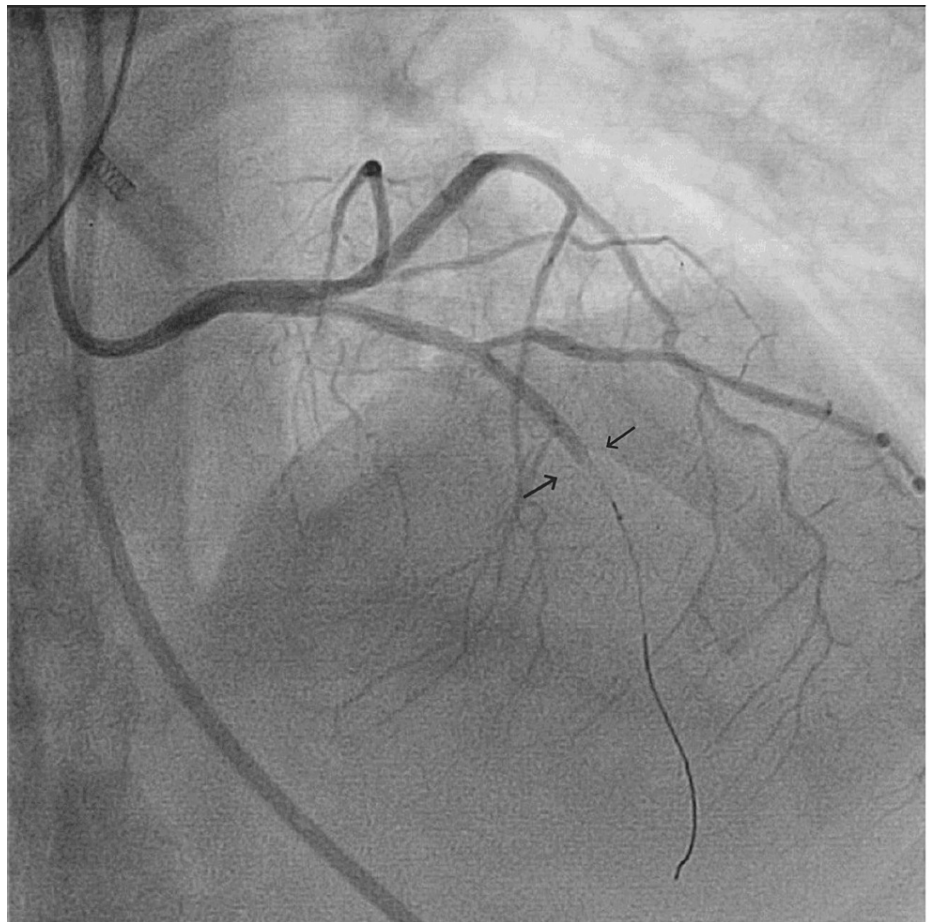


FIGURE 2: Severe left anterior descending (LAD) artery spasm

Intravascular ultrasound was done and showed no evidence of underlying coronary disease, dissection, or thrombus. The distal-mid-proximal left anterior descending artery shows no significant coronary artery disease (Video 1). Attempted percutaneous coronary intervention (PCI) failed to restore coronary flow. The decision was to opt for a conservative strategy and redo the coronary angiogram in 24-48 hours. Consulting critical care and transplant nephrology, the decision was to hold tacrolimus, meanwhile, as the culprit for the patient's presentation. The patient was transferred to the critical care unit. Laboratory analysis was done and showed glucose levels of 10 mg/dL (reference range: 0-15 mg/dL). Other significant results were neutrophils of 81.7% (reference range: 34-67.9%), potassium of 3.3 mEq/L (reference range: 3.5-5.3 mEq/L), creatinine of 1.5 mg/dL (reference range: 0.6-1.2 mg/dL), and magnesium of 0.7 mEq/L (reference range: 1.3-2.1 mEq/L). The calcium level was 1.25 mg/dL (reference range: 8.6-10.3 mg/dL) and phosphorus was 2.11 mg/dL (reference range: 2.8-4.5 mg/dL). The patient's blood glucose was 88 mg/dL (70-99 mg/dL). Coagulation studies and liver function tests were within the normal limit.



VIDEO 1: Intravascular ultrasound was done and showed no evidence of underlying coronary disease

View video here: <https://www.youtube.com/watch?v=ajsARvI0oEI>

During the admission, (IABP) protocol was followed. The patient was treated daily with a magnesium oxide of 400 mg orally. Clopidogrel 75 mg, prednisolone 5 mg, and atorvastatin 40 mg were given orally in the morning.

heparin 5000 U/ml injection was given every 12 hours along with acetaminophen injection of 750 mg every eight hours. Clonidine 0.1 mg was given orally to keep him hemodynamically stable.

A relook coronary angiogram two days later showed complete resolution of the coronary spasm (Figure 3). An echocardiogram was done four days later and showed left ventricular hypertrophy. Also, apical echoes consistent with trabeculae were noted (Video 2). Left ventricular ejection fraction dramatically improved from 20% with multi-territory wall motion abnormalities to 36%.

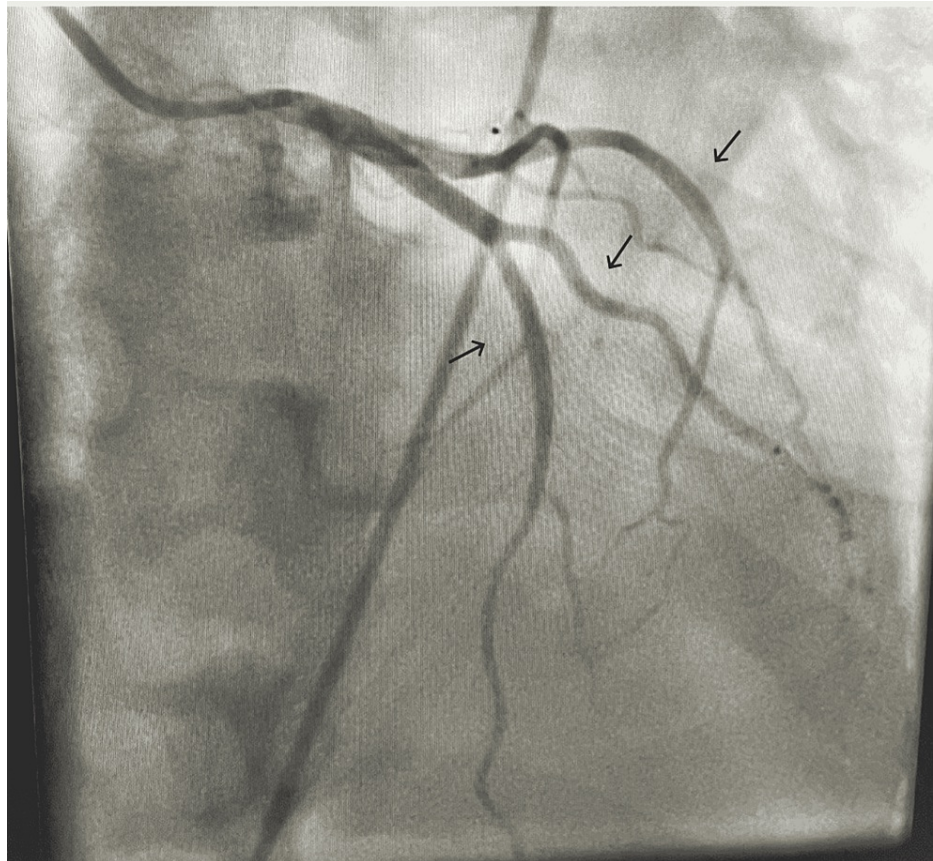


FIGURE 3: Coronary angiogram two days later showed complete resolution of the coronary spasm



VIDEO 2: An echocardiogram was done four days later and showed left ventricular hypertrophy

View video here: <https://www.youtube.com/watch?v=aDNvodJcvXU>

Discussion

The coronary spasm can be induced by medication, most common with cocaine. Other examples include

catecholamines (epinephrine, norepinephrine, isoproterenol, dopamine, dobutamine), parasympathomimetic agents (acetylcholine, methacholine, pilocarpine), and rarely tacrolimus [3].

The coronary spasm induced by tacrolimus is usually seen in patients with a high concentration level of the drug. The mechanisms underlying vasoconstriction induced by tacrolimus have different theories. First, tacrolimus binds FK-binding protein (FKBP) and forms a complex which then inhibits calcineurin, a Ca^{2+} -dependent phosphatase. Thus, it increases intracellular calcium concentration, a known spasm trigger [4]. Second, calcium channel blockers (CCB) are often used to control hypertension in kidney transplant patients [5], and both drugs, tacrolimus and CCB, are metabolized by the CYP3A system, which decreases the clearance of tacrolimus and increases the drug blood level to reach a toxic level [6].

Nitrates sublingually or intravenously should be used to decrease the risk of cardiac ischemic attacks, and they remain the mainstay of treatment to relieve the attacks of spasms [7]. The role of cardiac catheterization in such cases is to rule out coronary artery disease as the underlying cause. For patients with no evidence of coronary artery disease, further investigations should be done to exclude any other causes and to prevent episodes from reoccurring [8].

Coronary spasms are treated acutely by CCB. They relieve vasoconstriction and promote vasodilation in coronary circulation. Complete or near reduction of coronary artery spasm events is observed with non-dihydropyridine CCBs more than dihydropyridine CCBs. Although coronary spasms might lead to fatal arrhythmias, the implantable cardioverter-defibrillator (ICD) indication is not clear. It depends on the case. There is no clear indication of ICD as primary prevention in coronary artery spasms [9].

The nifedipine was held in our case to prevent any possible vasoconstriction. We can prevent this side effect by doing a dose adjustment or switching to a mammalian target of rapamycin (mTOR) inhibitor, i.e., sirolimus or everolimus, to prevent any further cardiovascular adverse events [10].

Conclusions

Physicians, especially in emergency department settings at transplant centers, should be aware of this rare but serious cardiac complication of commonly used immunosuppressants among transplant patients. Furthermore, it is important to highlight that the management of coronary spasms in the setting of tacrolimus is different.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

1. Staatz CE, Tett SE: Clinical pharmacokinetics of once-daily tacrolimus in solid-organ transplant patients. *Clin Pharmacokinet*. 2015, 54:993-1025. [10.1007/s40262-015-0282-2](https://doi.org/10.1007/s40262-015-0282-2)
2. Vanhove T, Annaert P, Kuypers DR: Clinical determinants of calcineurin inhibitor disposition: a mechanistic review. *Drug Metab Rev*. 2016, 48:88-112. [10.3109/03602532.2016.1151037](https://doi.org/10.3109/03602532.2016.1151037)
3. Yasue H, Nakagawa H, Itoh T, Harada E, Mizuno Y: Coronary artery spasm--clinical features, diagnosis, pathogenesis, and treatment. *J Cardiol*. 2008, 51:2-17. [10.1016/j.jjcc.2008.01.001](https://doi.org/10.1016/j.jjcc.2008.01.001)
4. Chiasson VL, Quinn MA, Young KJ, Mitchell BM: Protein kinase C β II-mediated phosphorylation of endothelial nitric oxide synthase threonine 495 mediates the endothelial dysfunction induced by FK506 (tacrolimus). *J Pharmacol Exp Ther*. 2011, 337:718-23. [10.1124/jpet.110.178095](https://doi.org/10.1124/jpet.110.178095)
5. Seeman T, Feber J: Should ACE inhibitors or calcium channel blockers be used for post-transplant hypertension?. *Pediatr Nephrol*. 2021, 36:539-49. [10.1007/s00467-020-04485-8](https://doi.org/10.1007/s00467-020-04485-8)
6. Leroy S, Isapof A, Fargue S, et al.: Tacrolimus nephrotoxicity: beware of the association of diarrhea, drug interaction and pharmacogenetics. *Pediatr Nephrol*. 2010, 25:965-9. [10.1007/s00467-009-1402-8](https://doi.org/10.1007/s00467-009-1402-8)
7. Guidelines for diagnosis and treatment of patients with vasospastic angina (coronary spastic angina) (JCS 2013). *Circ J*. 2014, 78:2779-801. [10.1253/circj.cj-66-0098](https://doi.org/10.1253/circj.cj-66-0098)
8. Kleyman R, Goyal R, Patel N, Joseph J, Akel R: Vasospastic angina and role of cardiac catheterization. *Cureus*. 2019, 11:[10.7759/cureus.5588](https://doi.org/10.7759/cureus.5588)
9. Rodríguez-Mañero M, Oloriz T, le Polain de Waroux JB, et al.: Long-term prognosis of patients with life-threatening ventricular arrhythmias induced by coronary artery spasm. *Europace*. 2018, 20:851-8. [10.1093/europace/eux052](https://doi.org/10.1093/europace/eux052)
10. Malvezzi P, Rostaing L: The safety of calcineurin inhibitors for kidney-transplant patients. *Expert Opin Drug Saf*. 2015, 14:1531-46. [10.1517/14740338.2015.1083974](https://doi.org/10.1517/14740338.2015.1083974)