Internal Medicine
The Japanese Society of Internal Medicine

【 CASE REPORT 】

Efficacy of Corticosteroid Treatment for Refractory Multivessel Vasospastic Coronary Angina with Hypereosinophilia

Toshiki Takano, Kazuyuki Ozaki, Komei Tanaka, Takao Yanagawa,
Takuya Ozawa and Tohru Minamino

Abstract:
   A 43-year-old man was diagnosed with acute myocardial infarction (AMI) due to multivessel coronary vasospasm. Accordingly, two coronary vasodilators were administered, and he was discharged without an angina attack. However, from the following day, he reported frequent chest pain and was re-hospitalized. Despite adding multiple coronary vasodilators, it was difficult to completely suppress the angina attack. He also demonstrated hypereosinophilia from the onset of AMI, and his eosinophil count gradually increased up to 6,238/μL. After corticosteroid administration was started, the vasospasm was completely controlled, and his eosinophil count normalized. He remained free from angina attacks for two years with corticosteroid therapy.

   Key words: corticosteroid therapy, coronary spastic angina, eosinophilia, Rho kinase inhibitor

Introduction

   Despite the good prognosis of coronary spastic angina (CSA), it might cause acute myocardial infarction (AMI) and sudden cardiac death in cases of complications, such as the organic narrowing of coronary arteries and unstable coronary spasm (1, 2). Although coronary vasodilators, such as nitrates and calcium-channel blockers, usually control coronary vasospasm attacks, resistance to these drugs has been reported in rare cases. In addition, studies have demonstrated that hypereosinophilia is associated with refractory CSA, and corticosteroids are useful for treating this condition (3, 4).

   We herein report a case of AMI due to refractory multivessel CSA with hypereosinophilia treated with corticosteroids.

Case Report

   A 43-year-old man visited our hospital on experiencing sudden epigastric pain after lunch. He was treated with in-haled budesonide for bronchial asthma and nasal drop of fluticasone for allergic rhinitis. He had a smoking history of only 6 months when he was 20 years old. Electrocardiogram (ECG) revealed an ST-segment elevation in V3-5, II, III, aVF leads, poor R wave progression in V3-5 leads, complete right bundle branch block, and a heart rate of 110/min with atrial fibrillation (Fig. 1). In addition, transthoracic echocardiography (TTE) revealed the anteroseptal and apical hypokinetic wall motion. Furthermore, his other findings were blood pressure of 91/65 mmHg, pulse rate of 107/min (regular), serum creatine kinase (CK) level of 3,837 IU/L, and CK-MB isozyme (CK-MB) of 337 IU/L. Based on these findings, he was diagnosed with AMI.

   We initiated the intravenous administration of nicorandil because his blood pressure was low, and his symptoms and ST-segment elevation on ECG immediately improved. Thereafter, we performed emergency cardiac catheterization. While left coronary angiography (LCAG) revealed normal findings, right CAG (RCAG) revealed severe stenotic legions in segment 2 and 4PD (Fig. 2A), which were normalized after the intracoronary administration of isosorbide dinitrate (ISDN; Fig. 2B). In addition, left ventriculography
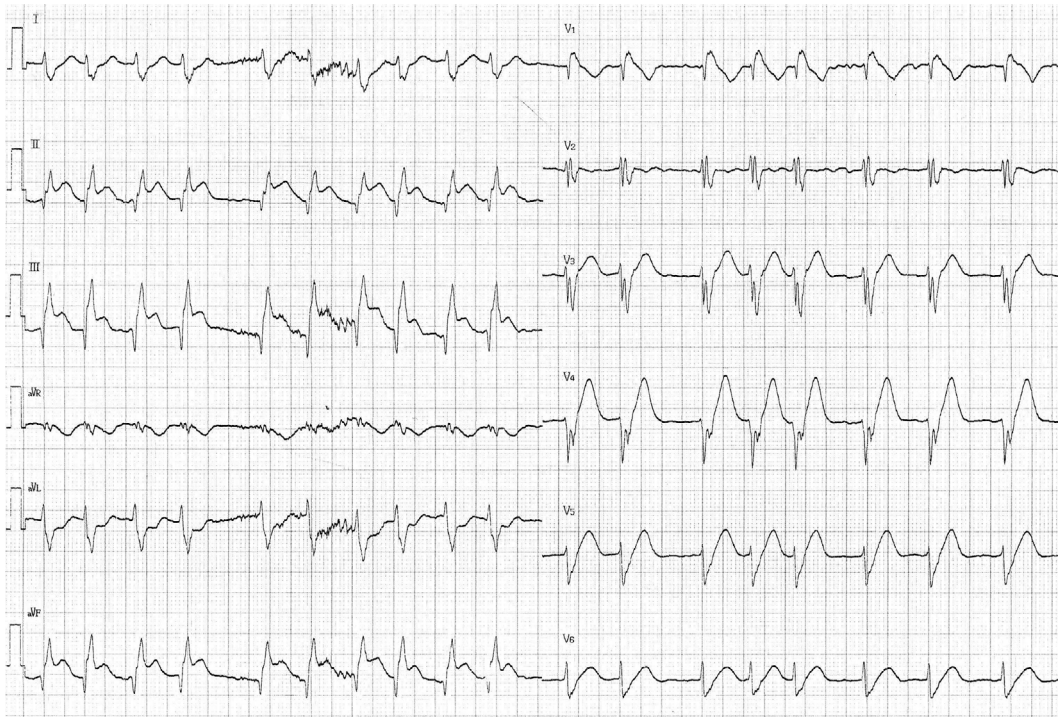
Figure 1. Twelve-lead ECG findings on admission. ECG demonstrated an ST-segment elevation in V3-5, II, III, aVF leads, poor R wave progression in V3-5 leads, complete right bundle branch block, and a heart rate of 110/min with atrial fibrillation.
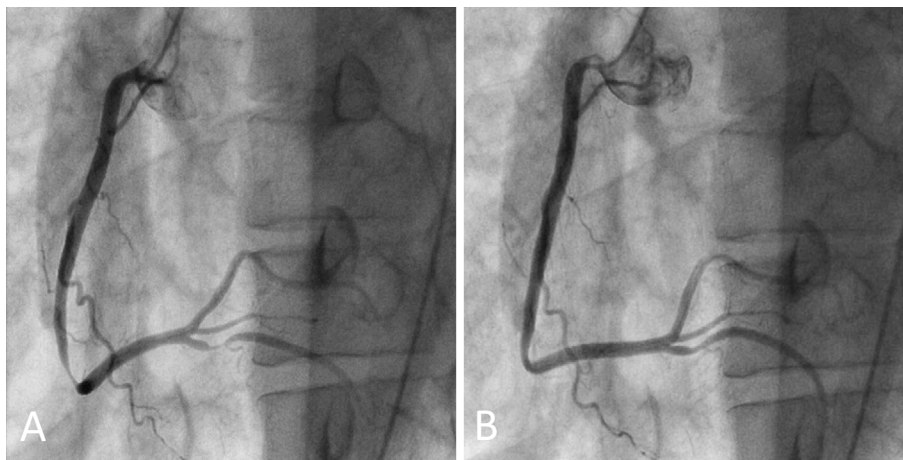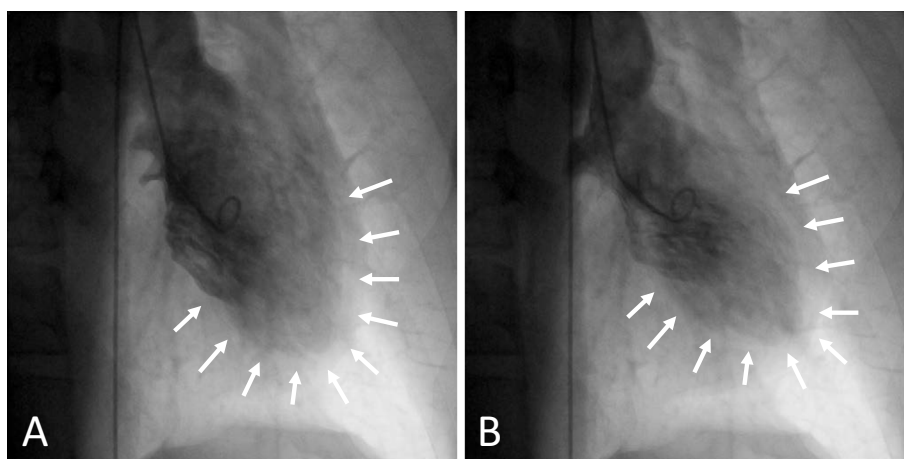

Figure 2. RCAG findings of emergency cardiac catheterization. Initial RCAG revealed severe coronary stenotic lesions in segment 2 and 4PD (A). The stenotic lesions were improved after the intracoronary injection of ISDN (B).

(LVG) exhibited anterolateral, diaphragmatic hypokinesis, and apical, septal, and posterolateral akinesis (Fig. 3). The maximum elevated levels of CK and CK-MB at 4 hours after admission were 8,414 and 749 IU/L, respectively. Based on the findings of cardiac catheterization, he was diagnosed with AMI due to vasospasm. Accordingly, we prescribed oral benidipine, isosorbide mononitrate (ISMN), and enalapril. The patient reported no angina attack during the first hospitalization. We performed the vasospasm provocation test on day 20 of hospitalization. The administration of ergonovine (50 μg) to the left coronary artery provoked va-

sospasm in the proximal left anterior descending artery (LAD; Fig. 4B), suggesting multivessel coronary spasm.

Although the patient was discharged on day 27 of hospitalization, he experienced angina attacks every day from the day after discharge and was admitted against 7 days after the first discharge. We observed no marked changes on ECG or TTE except for the exacerbation of hypereosinophilia (Fig. 5). We therefore dismissed the possibility of secondary hypereosinophilia, such as Churg-Strauss syndrome, parasitic infections, human immunodeficiency virus infection, chronic eosinophilic leukemia, Addison's disease, hyperthyroidism,

Figure 3. LVG findings of emergency cardiac catheterization. (A) Diastole and (B) systole. LVG revealed anterolateral and diaphragmatic hypokinesis as well as apical, septal, and posterolateral akinesis.
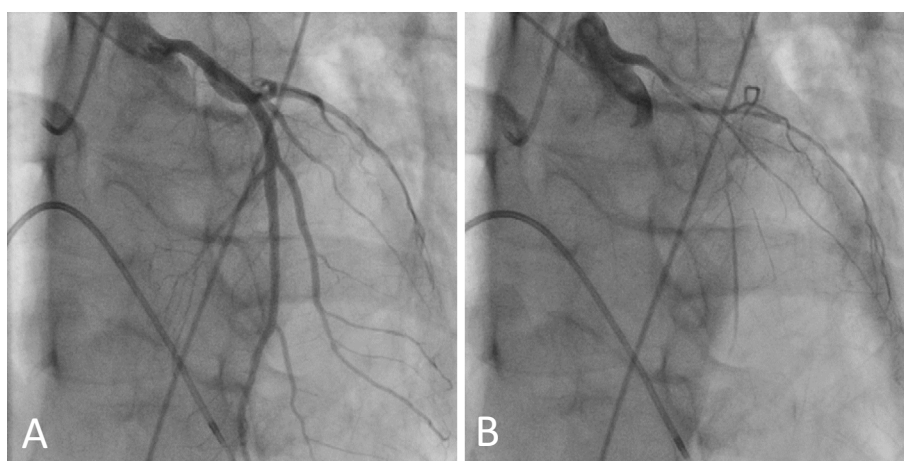
Figure 4. Vasospasm provocation test of the left coronary artery. Control LCAG revealed no organic stenosis (A). After the intracoronary administration of ergonovine (50 µg), vasospasm was provoked in the proximal LAD (B).

and drug-induced hypereosinophilia. Based on the elevation of the IgE level and his medical history of allergic diseases, we suspected the hypereosinophilia might have been related to an allergic disease. However, the patient reported no episodes of changing his home environment after the first hospitalization. Although we first added the continuous infusion of nicorandil followed by the continuous infusion of nitroglycerin to control CSA, an anginal attack could not be controlled with a gradual increase of eosinophilia. The additional intravenous administration of fasudil (a Rho kinase inhibitor) at 30 mg 3 times a day exerted a partial effect on CSA; however, the patient experienced angina attacks nearly every day.

Finally, we started him on 30 mg of prednisolone (PSL). The eosinophil count rapidly decreased to the normal range, and the angina attacks completely disappeared on day 4 after starting PSL, which allowed us to discontinue intravenous fasudil, nitroglycerin, and nicorandil. We gradually decreased the PSL dosage until 20 mg without hypereosinophilia or angina attack (Fig. 5). At 52 days after the second admission, the patient was discharged with no symptoms. At the time of reporting this case, the patient had been free from angina attacks for approximately two years under PSL treatment.

Discussion

CSA causes myocardial infarction at times; a study has reported myocardial infarction in 5% of patients with CSA in the Japanese population (1). Although mechanical stress due to coronary artery spasm can cause plaque rupture (5), the precise mechanism of how coronary artery spasm causes myocardial infarction remains unclear. The clinical predictors of myocardial infarction in patients with CSA were the presence of significant organic coronary artery stenosis, multivessel coronary artery spasm, and diffuse coronary artery
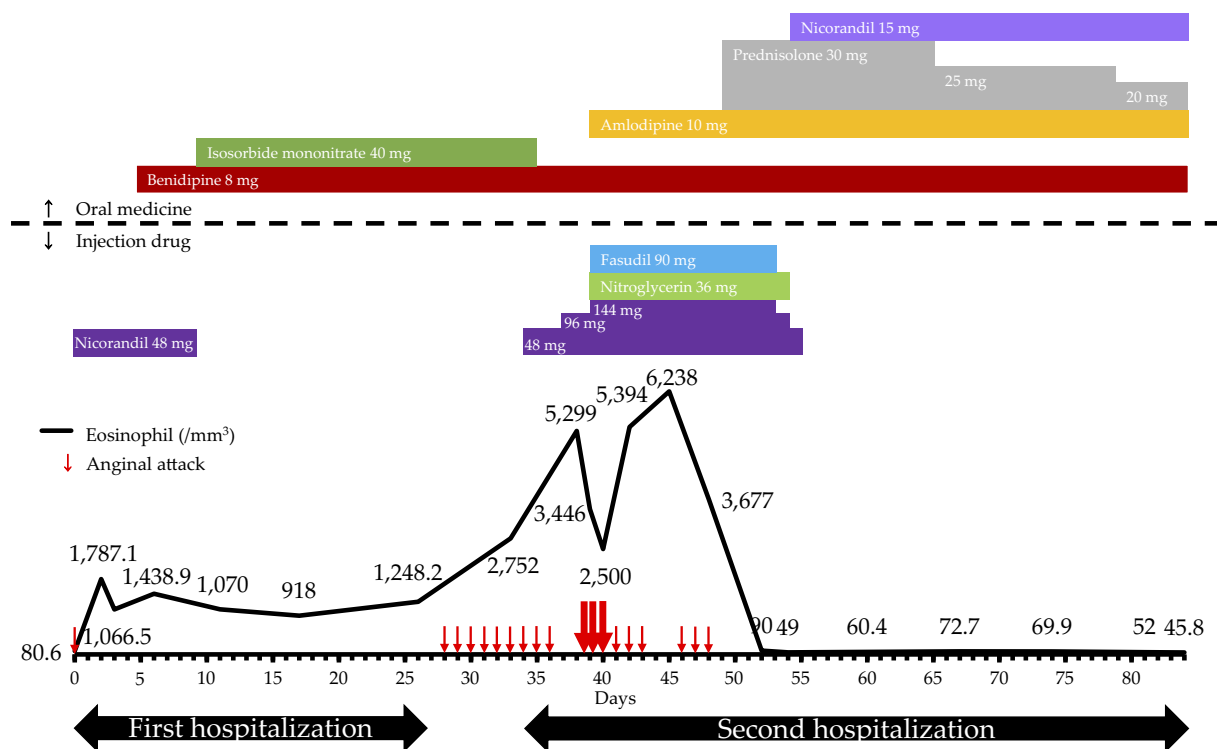
Figure 5. The clinical course of the first and second hospitalizations.

spasm (1, 6). The present case had no organic artery stenosis but did have multivessel and diffuse coronary artery spasm.

In addition, some reports have also highlighted the existence of refractory CSA cases that cannot control coronary spasm by specific vasodilator drugs, such as calcium-channel blocker and nitrates. A study has reported the occurrence of refractory CSA in 13.7% of Japanese patients with CSA (7). In addition, diffuse coronary artery spasm was found to be a clinical predictor of refractory CSA, and patients with refractory CSA reportedly tend to be younger and have a smoking habit and a normal blood pressure compared with those without refractory CSA (7).

A renin-angiotensin system (RAS) inhibitor was used to prevent left ventricular remodeling caused by AMI in the present case. Indeed, adding an RAS inhibitor to antianginal drugs has been reported to control refractory CSA (8). RAS inhibitor may have some preventive effect against CSA.

For patients with refractory CSA resistant to calcium-channel blockers, the administration of an Rho kinase inhibitor, which accelerates calcium sensitization, might be effective. Rho kinase reduces myosin the phosphatase activity by phosphorylating the myosin-biding subunit of the enzyme, thereby augmenting the vascular smooth muscle contraction. Some studies have shown that Rho kinase inhibitors suppress coronary spasm in patients with refractory CSA (9, 10). In the present case, fasudil was used at a standard dose for the treatment of cerebral vasospasm. There was also a case report in which the additional intravenous administration of fasudil (90 mg/day) controlled refractory CSA (9), and the intracoronary administration of fasudil

(300 μg/min for 15 minutes) reportedly suppressed coronary spasm (10). However, the effective dose of Rho kinase inhibitor drugs for CSA with hypereosinophilia has not been determined. Furthermore, our case suggests that suppressing the inflammation of the coronary artery is a more effective therapy than administrating any vasodilators.

Some case reports have described refractory CSA with hypereosinophilia. In our case, hypereosinophilia was not observed before the onset of AMI; as the eosinophil count increased after AMI, it accordingly increased the risk of CSA attacks. From the clinical perspective, we deduced a correlation between the patient's eosinophilia and CSA attacks. Wong et al. observed multivessel spasms in 54%, repeated angina attack in 53%, and elevated myocardial enzymes at the first-time admission in 79% of CSA patients with hypereosinophilia (3). In addition, they reported that Churg-Strauss and idiopathic eosinophilia syndromes are the leading causes of eosinophilia. Notably, we observed all of these clinical characteristics in our case. An autopsy case reported that eosinophils and mast cells had infiltrated the coronary spasm artery (11, 12). We assumed that the coronary spasm in the present case was caused by a vascular overreaction due to the inflammation of the local vessel wall.

Several studies have reported the efficacy of corticosteroid treatment for refractory CSA with hypereosinophilia. PSL was found to significantly inhibit coronary spasm recurrence events (3), and corticosteroid suppressed the arterial hyperactivity by relieving inflammation and inhibiting spasm (13). In our opinion, refractory CSA with hypereosinophilia should be treated with combined corticosteroid therapy. Fur-

thermore, a study reported that CSA attacks recur during the process of decreasing the corticosteroid dosage (14). Therefore, while corticosteroid therapy is imperative for prolonging the survival of patients with CSA, the maintenance dose must be examined carefully on a case-by-case basis.

The authors state that they have no Conflict of Interest (COI).

References

1. Nakamura M, Takeshita A, Nose Y. Clinical characteristics associated with myocardial infarction, arrhythmias, and sudden death in patients with vasospastic angina. Circulation **75**: 1110-1116, 1987.
2. Yasue H, Takizawa A, Nagao M, et al. Long-term prognosis for patients with variant angina and influential factors. Circulation **78**: 1-9, 1988.
3. Wong CW, Luis S, Zeng I, Stewart RA. Eosinophilia and coronary artery vasospasm. Heart Lung Circ **17**: 488-496, 2008.
4. Nomura T, Keira N, Taminishi S, et al. Corticosteroid therapy was effective in controlling refractory coronary vasospasms complicated by hypereosinophilia. Intern Med **53**: 735-738, 2014.
5. Lin CS, Penha PD, Zak FG, et al. Morphodynamic interpretation of acute coronary thrombosis, with special reference to volcano-like eruption of atheromatous plaque caused by coronary artery spasm. Angiology **39**: 535-547, 1988.
6. Kim PJ, Seung KB, Kim DB, et al. Clinical and angiographic characteristics of acute myocardial infarction caused by vasospastic angina without organic coronary heart disease. Circ J **71**: 1383-1386, 2007.
7. JCS Joint Working Group. Guidelines for diagnosis and treatment of patients with vasospastic angina (Coronary Spastic Angina) (JCS 2013). Circ J **78**: 2779-2801, 2014.
8. Sakamoto T, Shintomi Y, Yoshimura M, Ogawa H. Successful treatment of refractory angina pectoris due to multivessel coronary spasm with valsartan. Intern Med **46**: 1425-1429, 2007.
9. Nakamura A, Gotoh A, Hoshi N. Refractory vasospastic angina controlled by additional administration of a selective Rho-kinase inhibitor: a case report. Shinzo **40**: 631-635, 2008 (in Japanese).
10. Masumoto A, Mohri M, Shimokawa H, Urakami L, Usui M, Takeshita A. Suppression of coronary artery spasm by the Rho-kinase inhibitor fasudil in patients with vasospastic angina. Circulation **105**: 1545-1547, 2002.
11. Forman MB, Oates JA, Robertson D, et al. Increased adventitial mast cells in a patient with coronary spasm. N Eng J Med **313**: 1138-1141, 1985.
12. Kajihara H, Kato Y, Takanashi A, et al. Periarteritis of coronary arteries with severe eosinophilic infiltration. A new pathologic entity (eosinophilic periarteritis). Pathol Res Pract **184**: 46-52, 1988.
13. Takagi S, Goto Y, Hirose E, et al. Successful treatment of refractory vasospastic angina with corticosteroids: coronary arterial hyperactivity caused by local infamation? Circ J **68**: 17-22, 2004.
14. Okubo T, Yano T, Tsuchida K, et al. Successful corticosteroid treatment for refractory mutivessel coronary spastic angina accompanied by bronchial asthma and allergic rhinitis: case report. Shinzo **46**: 1114-1118, 2014 (in Japanese).