JACC: CASE REPORTS VOL. 19, 2023

CASE REPORT

INTERMEDIATE

CLINICAL CASE SERIES

Coronary Artery Vasospasm in Patients With Eosinophilia

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ABSTRACT

Coronary vasospasm is a relatively well-documented cause for ischemia and myocardial infarction in patients with nonobstructive coronary artery disease. Patients with coexisting eosinophilia present with severe manifestations and are often refractory to traditional therapies. There are few reported cases in the literature. We describe 3 cases occurring within 10 months. (**Level of Difficulty: Intermediate.**) (J Am Coll Cardiol Case Rep 2023;19:101932) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Ischemia and myocardial infarction with nonobstructive coronary disease are increasingly being recognized as common presentations in cardiac patients. One cause of these presentations is coronary vasospasm, with a prevalence of ≤40%.[1] Coronary vasospasm generally affects younger patients when compared with myocardial ischemia due to atherosclerosis, and it affects female and male persons equally.[2] Patients typically present with nonexertional chest pain, which is more frequently nocturnal, and symptoms generally respond well to antianginal medication.[3] Rarely, coronary vasospasm can be associated with eosinophilia and other related conditions such as aspirin-exacerbated respiratory disease (AERD).[4,5] It is important to identify this subset of patients for 3 main reasons. The first is the aggressive nature of the condition with a lack of response to typical antianginal agents. Second, this form of coronary vasospasm is responsive to both corticosteroids and interleukin (IL)-5 inhibition. Finally, the condition may be exacerbated by aspirin, which is commonly used in many other ischemic conditions.[6,7] Reports of these cases in the literature are sparse, which suggests that the condition is uncommon; however, here we report 3 cases at our institution within 10 months.

LEARNING OBJECTIVES

- To understand the different causes of coronary vasospasm.
- To consider investigating for eosinophilia or eosinophilia-related conditions in patients presenting with severe and/or refractory forms of coronary vasospasm.
- To consider treatment with corticosteroids and IL-5 inhibitors in patients with coronary vasospasm and either of these conditions: 1) elevated peripheral eosinophil count; or 2) history of eosinophil-related condition (eg, AERD, EoE).

CASE 1

PRESENTATION. A 67-year-old man presented with ischemic chest pain, and an electrocardiogram (ECG)

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received June 4, 2023; accepted June 6, 2023.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2023.101932

ABBREVIATIONS AND ACRONYMS

AERD = aspirin-exacerbated respiratory disease

ECG = electrocardiogram

EoE = eosinophilic esophagitis

GTN = glyceryl trinitrate

IL = interleukin

PDA = posterior descending artery

RCA = right coronary artery

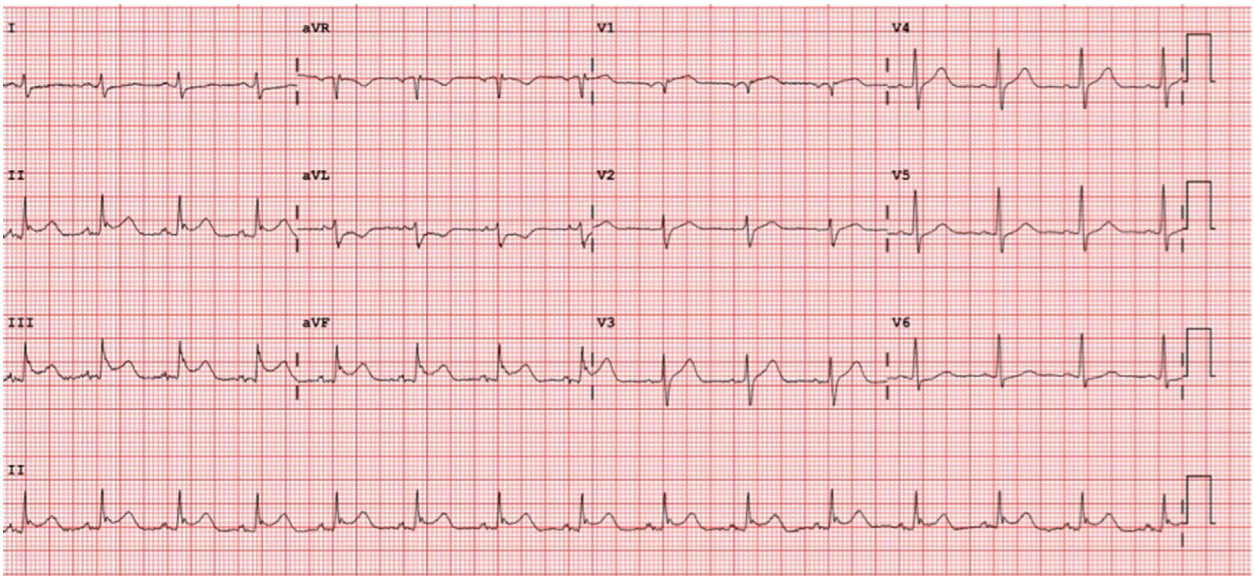
STEMI = ST-segment elevation myocardial infarction

demonstrated inferior ST-segment elevation (Figure 1). He was treated with intravenous unfractionated heparin, aspirin, and sublingual glyceryl trinitrate (GTN) and underwent an emergency coronary angiogram. He became pain free before coronary angiography, with normalization of his ECG. Coronary angiography demonstrated mild nonobstructive disease of his right coronary artery (RCA) (Figure 2).

BACKGROUND. His medical history included a previous inferior ST-segment elevation myocardial infarction (STEMI) treated at another health service. He received thrombolysis because of his remote location at the time, with coronary angiography demonstrating mild stenosis of his RCA. He was subsequently treated with dual antiplatelet therapy, a statin, and angiotensin converting enzyme inhibitor. His other significant medical history included a diagnosis of AERD managed with bronchodilators and corticosteroids as required. Benralizumab, a monoclonal IL-5 inhibitor, was started the day before this presentation.

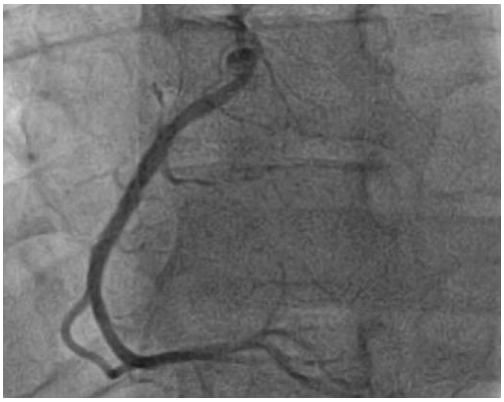
PROGRESS. A high-sensitivity troponin T peaked at 31 ng/L (reference range <15 ng/L), and the result of transthoracic echocardiography was normal. Verapamil was started in view of his reversible obstructive airway disease with a primary diagnosis of coronary vasospasm. After discharge, he presented 10 days later to another hospital with an inferior STEMI and again received thrombolysis because of his remote location, with repeated coronary angiography demonstrating mild RCA stenosis. A fourth presentation occurred 1 month later with a non-STEMI and with knowledge of his previous coronary angiography, this was managed conservatively. At this time, he had experienced a peripheral eosinophilia of 0.60×10^9/L (reference range $0.02\text{-}0.50 \times 10^9$/L). Despite receiving high-dose verapamil and isosorbide mononitrate, he continued to experience frequent, predominantly nocturnal angina, resulting in a fifth admission during which a peripheral eosinophilia was identified with an eosinophil count of 12.94×10^9/L, and troponin T peaked at 337 ng/L. Causes of secondary eosinophilia were investigated, and the results of testing for antineutrophil cytoplasmic antibodies, an infective screen, and cytogenetics were all unremarkable. CMR demonstrated evidence of inferolateral scar consistent with previous infarction. He was commenced on 60 mg of prednisolone, with good clinical and biochemical response, and the prednisolone was tapered down and ceased during outpatient follow-up visits over the next 4 months.

FIGURE 1 12-Lead Electrocardiogram: Patient 1



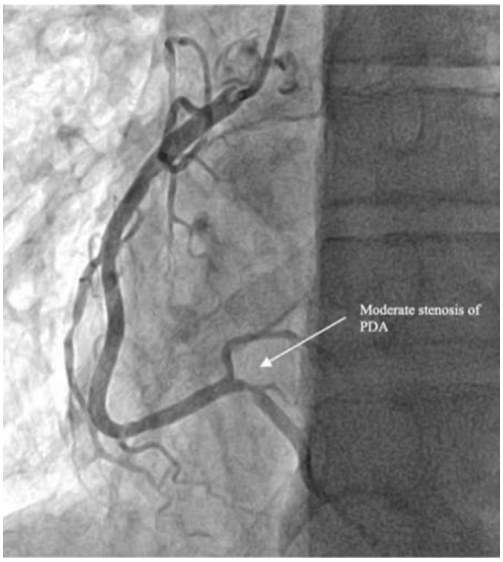
Inferior ST-segment elevation is demonstrated.

FIGURE 2 **Coronary Angiogram: Patient 1**



Mild stenosis of the right coronary artery is demonstrated.

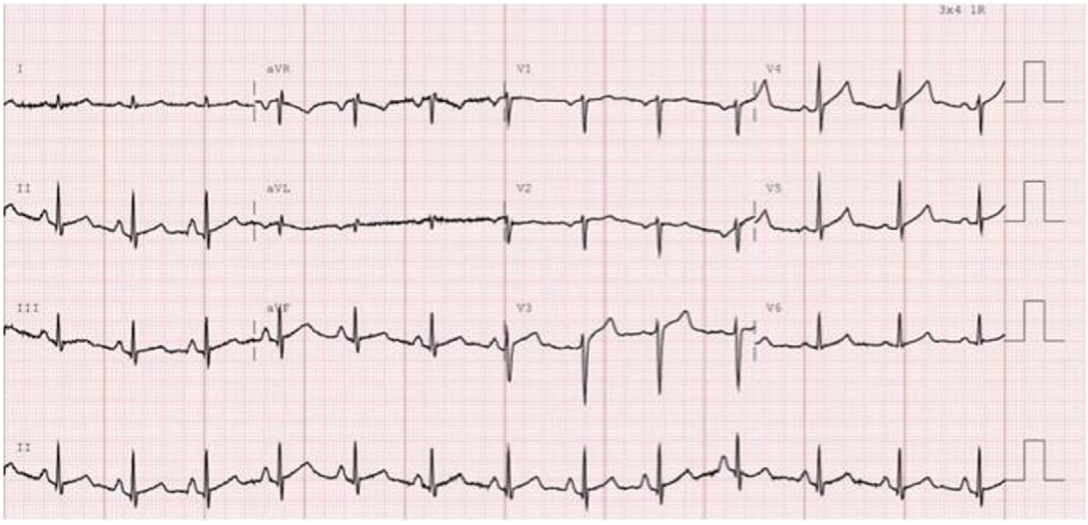
FIGURE 4 **Coronary Angiogram: Patient 2**



Moderate stenosis of the posterior descending artery is shown.

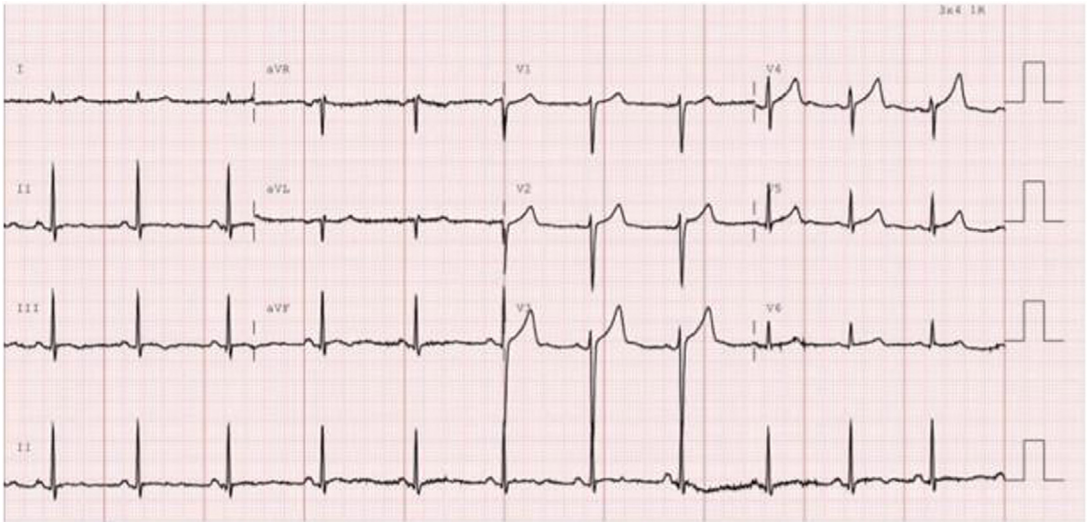
Four months later, he had a further inferior STEMI with a ventricular fibrillation arrest at an external hospital, where he received percutaneous coronary intervention to his proximal RCA and was discharged the following week. He again presented to our hospital 1 week later with a threated inferior STEMI. His eosinophil count had risen to 4.72×10^9/L, and he was again commenced on prednisolone 30 mg and received an implantable cardiac defibrillator. He again achieved a good clinical and biochemical response, was prescribed mepolizumab, an alternative IL-5 inhibitor to benralizumab, and has been asymptomatic since.

FIGURE 3 **12-Lead Electrocardiogram: Patient 2**



Normal sinus rhythm with no ST-segment changes is shown.

FIGURE 5 **12-Lead Electrocardiogram: Patient 2**



New T-wave inversion in the inferior leads III and aVF is demonstrated.

CASE 2

PRESENTATION. A 53-year-old man presented with ischemic chest pain radiating to both arms. His ECG showed normal sinus rhythm with no ST-segment changes (Figure 3). He received sublingual GTN, and his pain resolved. He reported having experienced intermittent, nonexertional central chest pain within the preceding 3 weeks.

BACKGROUND. His medical history included a diagnosis of AERD treated with regular intranasal corticosteroids and, bronchodilator inhalers. He had recently commenced aspirin desensitization with 300 mg of aspirin twice daily 4 months previously.

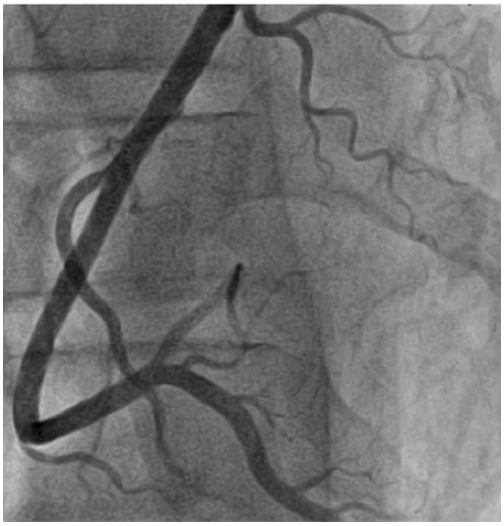
PROGRESS. The high-sensitivity troponin T peaked at 1,289 ng/L, while coronary angiography revealed a 50% stenosis of the right posterior descending artery (PDA) (Figure 4). The result of transthoracic echocardiography was normal, and he was given colchicine and sublingual GTN with the differential diagnoses of myopericarditis or coronary vasospasm. He represented 4 days later with intermittent central chest pain. His ECG demonstrated new inferior T-wave inversion (Figure 5) with a troponin T elevation from 197 to 228 ng/L. Repeated coronary angiography showed resolution of the previously identified stenosis (Figure 6). A diagnosis of coronary vasospasm was made, and he was given isosorbide mononitrate and amlodipine. He subsequently died out of the hospital 3 months later. A retrospective review of his medical record showed eosinophilia of 1.10×10^9/L at his first admission and 3.05×10^9/L during his second admission.

CASE 3

PRESENTATION. A 59-year-old woman presented with central chest pain radiating to the neck with associated dyspnea and presyncope. Her ECG demonstrated inferolateral ST-segment elevation and complete heart block (Figure 7). Urgent coronary angiography demonstrated moderate stenoses of the proximal, mid, and distal RCA that resolved after the administration of intracoronary GTN (Figure 8). The patient's symptoms had resolved and she had reverted to normal sinus rhythm at the conclusion of the procedure.

BACKGROUND. Her medical history included angina and previous coronary angiography demonstrating mild LAD and RCA disease, treated with aspirin, statin, metoprolol, and isosorbide mononitrate. Her

FIGURE 6 **Coronary Angiogram: Patient 2**

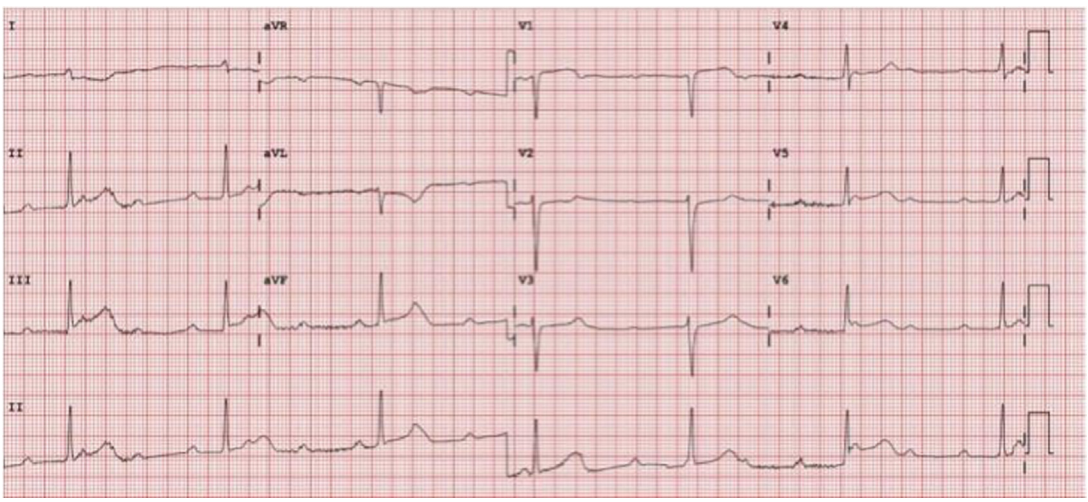


Resolution of previous moderate stenosis of the posterior descending artery is shown.

other history included asthma, gastroesophageal reflux disease, type 2 diabetes mellitus, and prior cigarette smoking.

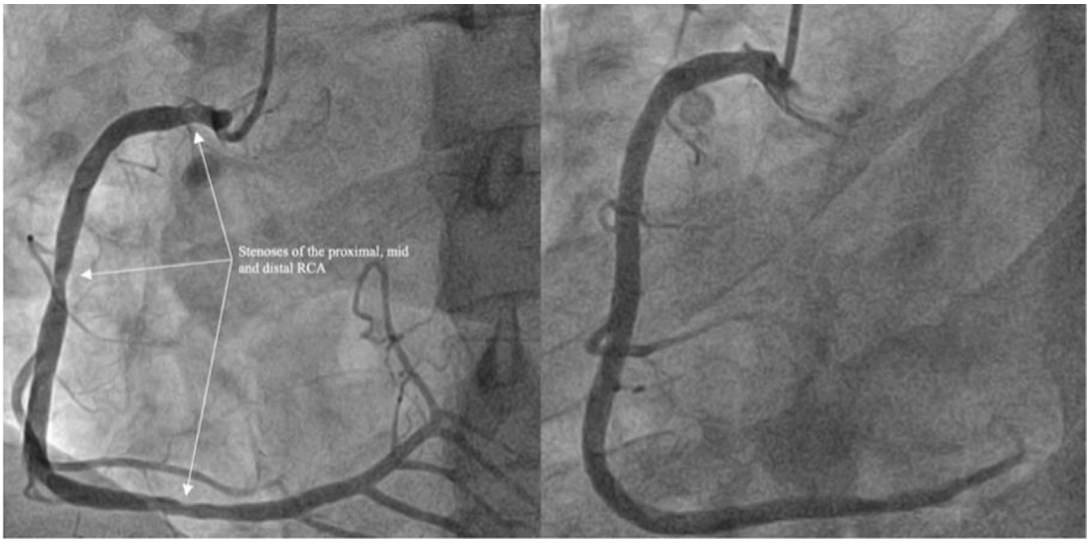
PROGRESS. An intravenous GTN infusion was begun. The patient's troponin T peaked at 32 ng/L. Metoprolol was ceased, and diltiazem was begun. A CT pulmonary angiogram demonstrated no pulmonary embolus but showed incidental diffuse esophageal thickening. Gastroscopy demonstrated gastritis, and biopsy specimens were taken. Histopathologic analysis confirmed a diagnosis of eosinophilic esophagitis (EoE), and she was prescribed a protein pump inhibitor and discharged home. Her peripheral eosinophil count was normal at 0.28 $\times$ 10^9/L. She presented again 1 week later with an inferior STEMI and complete heart block that self-resolved in the ambulance. Urgent coronary angiography again revealed moderate RCA stenoses, resolving with intracoronary GTN administration. Nifedipine was begun, and her diltiazem and isosorbide mononitrate were uptitrated. A peripheral eosinophilia of 2.33 $\times$ 10^9/L was identified, and prednisolone 50 mg daily was begun, with normalization of her eosinophilia the following day; her aspirin was ceased. After discussion with the rheumatology service, prednisolone was ceased until the results of her secondary eosinophilia screen could be reviewed as an outpatient, and she was discharged on day 3. She then represented the following week with intermittent central chest pain and a high-sensitivity troponin T rise to 25 ng/L. Her eosinophils had risen to 2.73 $\times$ 10^9/L, and she was again given prednisolone 20 mg daily, with a good clinical and biochemical response. She was prescribed mepolizumab as an outpatient, and

FIGURE 7 **12-Lead Electrocardiogram: Patient 3**



Complete heart block with inferior ST-segment elevation myocardial infarction is shown.

FIGURE 8 Coronary Angiogram: Patient 3



Resolution of stenoses of the proximal, mid, and distal glyceryl trinitrate **(left)** after administration of intracoronary glyceryl trinitrate **(right)** is demonstrated.

her prednisolone was tapered down and ceased with no recurrence of symptoms.

DISCUSSION

Coronary vasospasm is a common cause of myocardial ischemia in patients with nonobstructive coronary disease. Generally, these patients respond well to standard antianginal medications and have favorable outcomes. However, in 10% to 20% of cases, patients with vasospasm are refractory to both calcium channel blockers and nitrate therapy.[8] A subset of these patients have associated peripheral eosinophilia or eosinophilia-related conditions such as AERD and EoE.

Although the manifestations of typical coronary vasospasm and of eosinophilia-associated vasospasm are similar, the underlying mechanisms and therefore treatment are different. Classic coronary vasospasm is mediated by vascular smooth muscle cell hyperactivity coupled with a decreased production of endogenous nitric oxide by coronary endothelial cells.[8] In comparison, it is thought the mechanism of vasospasm in patients with eosinophilia is related to infiltration of eosinophils and mast cells in the adventitia of the coronary arteries, with the release of histamine and cytokines inducing the vasospasm.[9] This would account for the efficacy of corticosteroids in the treatment of these subsets of patients.

CONCLUSIONS

Although reports of eosinophilia-related coronary vasospasm appear infrequently in the literature, this may be due to under-recognition, as highlighted by the 3 cases pf patients presenting in short succession within our institution.

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KEY WORDS **aspirin-exacerbated respiratory disease, coronary vasospasm, eosinophilia, eosinophilic coronary periarteritis**