

Mepolizumab for the treatment of aspirin-exacerbated respiratory disease associated with coronary spasm

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Clinical Implications

- Mepolizumab may be an effective intervention for the treatment and prevention of aspirin-exacerbated respiratory disease–related coronary spasm. Rapid response to mepolizumab treatment suggests that eosinophilic inflammation could be the underlying mechanism.

TO THE EDITOR:

Aspirin-exacerbated respiratory disease (AERD) is defined as a triad of bronchial asthma, chronic rhinosinusitis with polyposis, and respiratory sensitivity reaction to aspirin.¹

We describe a 35-year-old woman with a long history of severe asthma and several intensive care unit admissions for acute asthma exacerbations triggered by nonsteroidal anti-inflammatory drugs. In addition, the patient suffered severe chronic rhinosinusitis with polyposis and was awaiting surgical intervention. She was on chronic high-dose inhaled and intranasal corticosteroid treatment and failed a trial of omalizumab several years earlier.

As for other symptoms, the patient suffered a year-long history of episodic dull upper back pain that lasted between several minutes to several hours and was relieved by rest and applied pressure. She did not have significant cardiac risk factors.

After a couple of weeks during which the patient suffered more severe episodes of upper back pain, she presented to the emergency room in cardiogenic shock assumed to be secondary to an acute myocardial infarction. Admission echocardiogram showed ST-segment elevation in leads I and AVL, with ST depression in leads II, III, and AVF (Figure 1, A). Her troponin I level was greater than 146,000 ng/L (N < 50). The patient was intubated and underwent urgent primary percutaneous coronary intervention, which showed critical lesion (95% stenosis) in the proximal left circumflex (LCx) artery and a second moderate lesion (70% stenosis) in the mid-left anterior descending (LAD) artery. However, following successful direct stenting of the LCx lesion, a second LCx narrowing appeared immediately distal to the placed stent. This narrowing, together with the mid-LAD lesion, was rapidly reversed by intracoronary nitrate infusion (Figure 1, B). Based on this finding, a diagnosis of an acute coronary spasm was established. However, because a drug-eluting stent was already placed, the patient required an ongoing aspirin treatment and aspirin desensitization was considered.²

Given history suggestive of AERD in the presence of the recent life-threatening events, a modified Scripps-Clinic desensitization protocol³ was used to confirm the diagnosis of AERD and to allow continuous aspirin treatment. For this purpose, the patient was started on montelukast (10 mg/d) and high-dose

prednisone treatment (1 mg/kg/d) and a 3-day desensitization protocol was initiated the following day (Table 1). Although a minimal aspirin dose of 100 mg is required to prevent in-stent thrombosis, we aimed for a daily dose of 300 mg, the minimal dose suggested to be effective in AERD.⁴ Following a successful desensitization protocol, the patient was discharged on 300 mg aspirin, montelukast, and rapid prednisone tapering, in addition to a conventional secondary prevention treatment with ticagrelor (90 mg twice a day), ramipril (1.25 mg/d), amlodipine (5 mg/d), and atorvastatin (80 mg/d).

The association between AERD and coronary spasm has been described in a large cohort of patients with AERD⁵ and was associated with higher peripheral absolute eosinophil count (AEC) and eosinophil activity.^{5,6} In addition, it was suggested that aspirin desensitization by itself can lead to an increase in peripheral AEC.^{5,7} In accordance, the AEC of our patient was 1200/μL upon admission, dropped to 0/μL with systemic corticosteroids but gradually increased upon prednisone tapering to a maximum of 2600/μL.

Despite the initial tolerance to aspirin, a couple of months into treatment the patient complained of worsening nasal symptoms requiring treatment with systemic steroids. Because of the increase in her AEC together with worsening nasal symptoms, aspirin dose was reduced first to 100 mg/d and later to 50 mg/d, without improvement. In addition, the patient described recurrence of occasional mild upper back pain, assumed to represent ongoing coronary spasm.

Based on published data, it is difficult to conclude whether aspirin desensitization causes coronary spasm or leads to more severe coronary spasm symptoms.⁵ However, the increase in her the AEC together with worsening nasal symptoms and recurrence of upper back pain led us to consider an alternative treatment approach. Since it was suggested that eosinophils might play a role in AERD-associated coronary spasm, since anti-IL-5 treatment was shown to be effective in patients with nasal polyposis,^{8,9} and since the patient had a history of severe asthma with peripheral blood eosinophilia, subcutaneous mepolizumab treatment at a conventional dose of 100 mg/mo was initiated.

Within a week of the first dose the patient reported significant improvement. Her nasal symptoms improved dramatically, her sense of smell recovered, and she did not require either systemic or nasal steroids. Objectively, nasal polyps that were visible on physical examination pretreatment disappeared after the second mepolizumab dose. In addition, her peak expiratory flow improved from a baseline of approximately 250 L/min to 360 L/min and she was able to discontinue inhaled corticosteroids. Most importantly, the patient reported total complete resolution of her back pains, all while still on low dose of daily aspirin (50 mg/d).

The presented case suggests that anti-IL-5 treatment may be an effective treatment for AERD and AERD-related nasal polyposis. In addition, the favorable rapid response to standard mepolizumab dose of 100 mg/mo may suggest that AERD-related nasal polyposis represents a distinct polyposis endotype, highly sensitive to anti-IL-5 treatment. As for the coronary spasm, Shah NH et al⁵ reported that AERD-associated coronary spasm does not respond to typical antianginal treatments but instead responds to systemic corticosteroids; therefore, a trial of prednisone treatment should be considered. The life-threatening

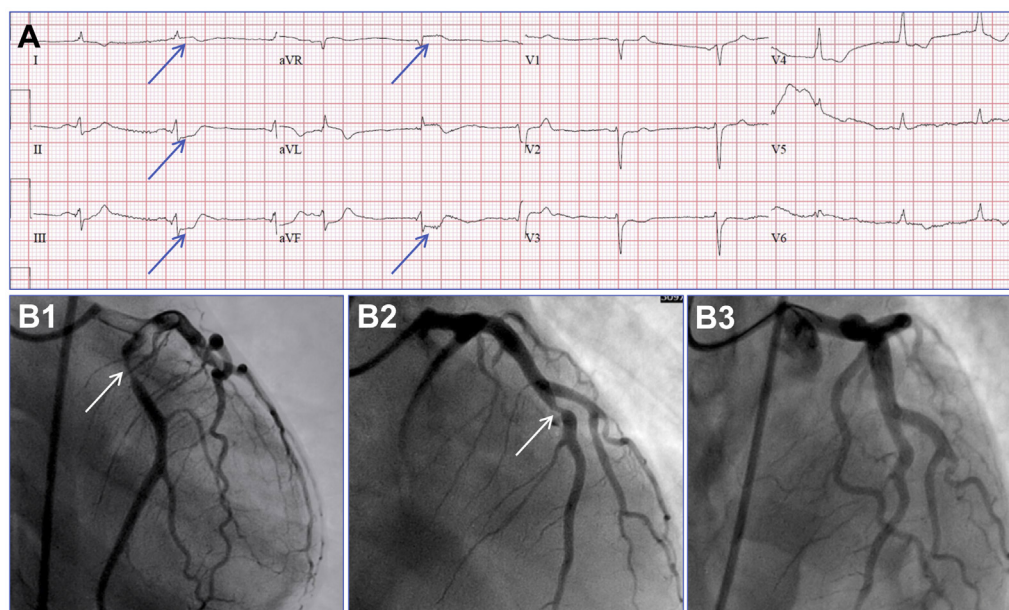


FIGURE 1. A, Admission electrocardiogram showed ST-segment elevation in leads I and AVL, with ST depression in leads II, III, and AVF. B, Coronary angiography demonstrating significant narrowing of the proximal LCx (B1) and mid-LAD (B2) coronary arteries. Intracoronary nitrates application resulted in complete reversal of narrowing in both coronary arteries (B3).

TABLE I. Aspirin challenge and desensitization protocol

Day	Aspirin dose (mg)	Peak expiratory flow (L/min)	Response
Day 1			
08:00 am	10	200	None
10:00 am	20	250	None
12:00 pm	40	250	None
14:00 pm	60	270	None
Day 2			
08:00 am	60	260	None
11:00 am*	80	210*	Significant rhinorrhea and sneezing*
15:00 pm	80	240	None
Day 3			
08:00 am	80	240	None
11:00 am	160	270	None
15:00 pm	300	250	None

*Positive challenge test as defined by significant nasal symptoms and drop of 20% in peak expiratory flow relative to the previous dose. Challenge continued following treatment and resolution of symptoms.

event our patient suffered suggests that the approach of “as-needed” or chronic systemic steroid treatment could be replaced by an efficient prophylactic anti-IL-5 treatment that addresses both respiratory and cardiac symptoms.

Finally, the presented efficacy of anti-IL-5 treatment supports eosinophilic inflammation as the underlying mechanism causing AERD-related coronary spasm.

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Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

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