Original Article

Eosinophilia-Associated Coronary Artery Vasospasm in Patients with Aspirin-Exacerbated Respiratory Disease

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What is already known about this topic? Coronary artery vasospasm has been associated with peripheral eosinophilia, but few reports have characterized this event in the setting of aspirin-exacerbated respiratory disease (AERD).

What does this article add to our knowledge? Coronary artery vasospasm can cause angina-type chest pain in patients with AERD and eosinophilia. Patients who have been desensitized to aspirin and are on high-dose aspirin therapy may be especially prone to developing eosinophilia and subsequent chest pain. This pain is often refractory to conventional antianginal medications.

How does this study impact current management guidelines? Clinicians should be aware that the most appropriate course of treatment for patients with AERD who develop angina-type chest pain in the absence of traditional cardiac risk factors or atherosclerotic lesions may be eosinophil-suppressing treatment such as corticosteroids.

BACKGROUND: Some patients with aspirin-exacerbated respiratory disease (AERD) and eosinophilia report angina-type chest pain that occurs at rest and responds to corticosteroid therapy. The frequency of eosinophilia-associated coronary artery vasospasm in patients with AERD, a disease characterized by blood and respiratory tissue eosinophilia, however, is unknown.
OBJECTIVE: The objective of this study was to understand the cause of the chest pain described above and determine the most appropriate treatment for it.
METHODS: A chart review of 153 patients with AERD who are followed at Brigham and Women's Hospital was performed. Patients who reported any type of chest pain were assessed for the presence of cardiac risk factors, eosinophilia, and response of chest pain to a variety of treatments. Two patients with AERD and eosinophilia who had recurrent chest pain due to suspected vasospasm are described in detail, and 8 other cases are also summarized.
RESULTS: Of the 153 patients reviewed, 10 had a history of chest pain concerning for ischemia. Of the 10 patients with chest pain, 8 had undergone aspirin desensitization and initiated high-dose aspirin therapy; of these, 6 reported an increase in the frequency or severity of chest pain while on high-dose aspirin with improvement after aspirin discontinuation or dose reduction. Many patients had traditional cardiac risk factors, but none had any evidence of coronary atherosclerosis; almost all had significant eosinophilia. Their chest pain did not improve with typical antianginal treatments but did respond to corticosteroid therapy.
CONCLUSIONS: Although uncommon, patients with AERD can develop eosinophilia-associated coronary artery vasospasm, which is occasionally worsened by high-dose aspirin. Patients with AERD who present with symptoms of ischemic chest pain should be screened for eosinophilia, as early treatment with corticosteroids can be life-saving. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;4:1215-9)

Key words: *Eosinophilia; Vasospasm; Aspirin-exacerbated respiratory disease; AERD; Steroid; Chest pain*

Eosinophilia is known to be associated with coronary artery vasoconstriction that responds to eosinophil-suppressing treatments.[1-7] Such vasospasm can be severe enough to cause a patient with mild or no coronary atherosclerosis to have a complete coronary occlusion with subsequent acute coronary syndrome such as a myocardial infarction[3,5] or even fulminant heart failure.[2]

Aspirin-exacerbated respiratory disease (AERD) is characterized by asthma, eosinophilic nasal polyposis, and pathognomonic

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Abbreviations used
ACE- Angiotensin-converting enzyme
AERD- Aspirin-exacerbated respiratory disease
CTA- Computed tomography angiogram
EKG- Electrocardiogram

respiratory reactions to the ingestion of cyclooxygenase-1 inhibitors; mild-to-moderate peripheral eosinophilia is also common in patients with AERD who are not taking systemic steroids. Patients with AERD whose symptoms are refractory to standard medical therapies often benefit from aspirin desensitization to begin high-dose aspirin. Through a mechanism that has not yet been elucidated, high-dose aspirin can result in a reduction in the rate of polyp regrowth as well as an improvement in respiratory symptoms. However, daily aspirin therapy can also induce peripheral eosinophilia in patients with AERD.[8] Brigham and Women's Hospital is a referral center for AERD. We observed that some patients with AERD reported ischemia-type chest pain that, similar to the cases of eosinophilia-associated coronary vasospasm reported in the literature, did not respond to conventional antianginal treatment but did respond to eosinophil-suppressing corticosteroid therapy.[9] We sought to understand the frequency and cause of such chest pain as well as to determine the most appropriate treatment for it. Two patients with AERD and eosinophilia who developed suspected recurrent coronary vasospasm are described in detail, and a retrospective review of 8 additional patients from our AERD registry is also presented.

CASE 1

Case 1 is a 42-year-old woman with a history of gastroesophageal reflux disease and AERD. She had been treated with 6 nasal polypectomies and eventual aspirin desensitization, after which she remained on high-dose aspirin (650 mg twice per day). Three months after initiation of high-dose aspirin, she developed substernal chest pain refractory to both proton-pump inhibitor therapy and histamine-2 receptor blocker therapy. Episodes of chest pain occurred several times per week, frequently at rest, and lasted from a few minutes to several hours. There was no identifiable trigger or association with food. Pain radiated to her neck and arms and was associated with tingling, diaphoresis, and nausea. Pulmonary function tests and a full gastrointestinal workup including upper endoscopy were unrevealing. A cardiac evaluation including cardiac examination, electrocardiography (EKG), and cardiac computed tomography angiography (CTA) was also unrevealing. Acetaminophen, simethicone, and lorazepam were all trialed; none led to a significant reduction in pain. Considering her negative cardiac workup, etiologies other than coronary atherosclerosis were considered. Incidentally, during the 5-month period of ongoing chest pain, she developed a sinus infection and was treated with a short course of prednisone, after which she noted complete resolution of chest pain. A retrospective review of her chart revealed eosinophilia of 930/mm^3. Eosinophilia-induced coronary artery vasospasm was suspected. The patient continued her daily aspirin regimen without further episodes of chest pain (for 3.5 years of follow-up at the time of manuscript preparation), but she was prescribed 20 mg of daily prednisone to take as needed for recurrent symptoms. To date, she has not yet needed to take this.

CASE 2

Case 2 is a 41-year-old woman with AERD treated with 4 nasal polypectomies and subsequent aspirin desensitization to initiate high-dose aspirin therapy. Within 2 months of starting 650 mg aspirin twice per day, she developed gastrointestinal side effects as well as left-sided chest pain with radiation to her arm and back that occurred at rest with no identifiable trigger. A full gastrointestinal workup including upper endoscopy was unremarkable; nonetheless, her pain was attributed to gastritis, and her aspirin dose was reduced to 325 mg twice per day. Despite this, she continued to have ongoing chest pain and presented to her primary care provider 3 months later during an episode of burning chest pain. She was found to be hypertensive with an abnormal EKG and elevated troponin levels. She was diagnosed with a non-ST elevation myocardial infarction with resultant cardiomyopathy and was subsequently hospitalized for evaluation and treatment. Coronary angiography performed during her hospital admission showed no significant blockages in her coronary arteries but was notable for ongoing coronary artery vasospasm. She was begun on atorvastatin, diltiazem, lisinopril, and isosorbide mononitrate for treatment of her cardiomyopathy, but her chest pain continued at the same severity for several weeks on this regimen. She mentioned this chest pain to her allergist who found her absolute eosinophil count to be 600/mm^3 and suspected eosinophilia-induced coronary artery vasospasm. Aspirin was discontinued at this time, and she was treated with a burst of prednisone followed by daily maintenance prednisone therapy. With this treatment, both her EKG and her ejection fraction normalized, and her chest pain resolved. She remains on low-dose maintenance prednisone (5 mg every other day), diltiazem, and atorvastatin with no further chest pain (for 8.5 months of follow-up at the time of manuscript preparation).

METHODS

We performed a retrospective chart review of 153 patients who were referred to Brigham and Women's Hospital for evaluation of possible AERD and who agreed to participate in our AERD registry between September 2013 and July 2015. We identified patients who had reported any type of chest pain and analyzed their charts for the presence or absence of traditional cardiac risk factors (family history, hyperlipidemia, hypertension, diabetes, smoking), any cardiac workup (EKG, echocardiography, any form of stress testing, coronary angiography, cardiac CTA), eosinophilia, and response of chest pain to conventional treatments (statins, calcium channel blockers, angiotensin-converting enzyme [ACE] inhibitors/angiotensin receptor blockers, nitrates, selective beta blockers) and unconventional treatments (corticosteroid therapy, cytotoxic therapy). When complete data were not readily available from our medical records, patients were contacted for further information and/or permission to contact their other health care providers for additional documentation. Unless otherwise noted, lab values for absolute eosinophil count were collected within 6 months of onset of chest pain or, when chest pain had been ongoing before presentation to health care, within 6 months of initial presentation with chest pain. The Partners Human Research Committee approved the study, and all subjects provided written consent to participate in the AERD registry.

RESULTS

One hundred and fifty-three patient charts were reviewed (Figure 1). Ten patients had a history of chest pain concerning

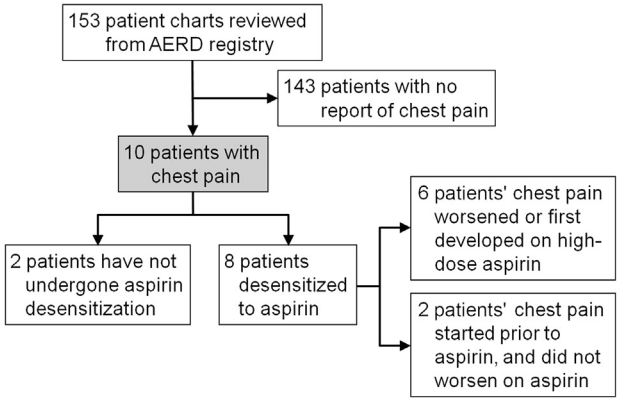

FIGURE 1. Flow diagram of study population. Diagram detailing the breakdown of subject characteristics and treatment trajectory in reference to chest pain and aspirin desensitization/dosing is shown. *AERD,* Aspirin-exacerbated respiratory disease.

for ischemia (left-sided or substernal, pressure or squeezing sensation with radiation to left or both arms, jaws, back, or neck; associated with lightheadedness, dizziness, nausea, diaphoresis, pallor, or cardiac symptoms such as palpitations; Table I). Of the 10 patients, 8 (80%) were female, compared with our entire registry of patients with AERD in which 57% were female. The average age at the onset of chest pain was 47.2 years. Chest pain always occurred at rest and did not worsen with exercise or other forms of exertion for the 6 patients for whom this information was documented. Seven patients had a cardiac workup, defined as evaluation by cardiac CTA (2 patients), coronary angiography (3 patients), or an exercise stress test (2 patients). Of these 7 patients, none were determined to have evidence of coronary atherosclerosis. Of 10 patients, 9 (90%) had eosinophilia noted at the time of chest pain, and the patient with an absolute eosinophil count of 0/mm^3 was on prednisone at the time of her laboratory testing. The average eosinophil count of the 10 study patients was 822/mm^3 (n = 10, standard deviation 761, range 0-2400), compared with an average count of 544/mm^3 (n = 79 as not all patients in registry have a documented eosinophil count, standard deviation 367, range 6-1760) for the rest of our AERD cohort. The 2-sided *P* value was .055; notably, if the patient on prednisone for all of her eosinophil testing was excluded, the 2-sided *P* value became .014. Of the 10 patients with chest pain, 8 had undergone aspirin desensitization and initiated high-dose aspirin; of those, 6 reported an increase in the frequency or severity of chest pain while on high-dose aspirin with improvement after aspirin discontinuation or dose reduction. Four patients remained on aspirin therapy at the time of manuscript preparation, though notably 1 patient's dose was reduced to 162 mg twice daily; 4 patients had discontinued aspirin (Figure 1).

DISCUSSION

This case series demonstrates that the eosinophilia that accompanies AERD can be associated with coronary vasospasm, both in patients being treated with high-dose aspirin and those not on aspirin. Such spasm seems to be related to the eosinophilia itself rather than the underlying AERD. Petrakopoulou et al[6] published a case study of a 50-year-old woman with Churg-Strauss syndrome and recurrent chest pain with eosinophilia and negative coronary CTA whose pain was refractory to calcium channel blockers, ACE inhibitors, and vasodilators but ultimately resolved with low-dose corticosteroid use. Similarly, Wong et al published a summary of the 17 case reports available in the literature as of 2008 as well as 2 new patient case reports that demonstrated that, despite the absence of conventional cardiovascular risk factors, patients with significant eosinophilia due to a variety of underlying causes were prone to angina-type chest pain. Coronary angiography showed no signs of coronary atherosclerosis in these patients but did demonstrate coronary artery vasospasm. Symptoms did not improve with conventional cardiac ischemia regimens such as nitrates and calcium channel blockers but responded to prednisone with subsequent recurrence after discontinuation or tapering of corticosteroid therapy.[1] In the published cases discussed above and in the introduction, cardiac symptoms resolved with reduction in eosinophilia, whether that was through corticosteroid treatment,[2] treatment of the underlying cause of eosinophilia, such as parasitemia,[3] or cytotoxic treatment such as cyclophosphamide.[4,7]

Although the exact mechanism by which eosinophils cause coronary artery vasospasm is unknown, it is hypothesized that eosinophils may release vasospastic mediators on activation.[10] One study in swine showed that cysteinyl leukotrienes, which can be produced by eosinophils, cause coronary artery vasospasm and subsequent myocardial ischemia if infused into a coronary artery.[11] It is therefore noteworthy that patients with AERD tend to have dramatically higher systemic levels of cysteinyl leukotrienes than do aspirin-tolerant asthmatics. A case report on the Kounis-Zavras syndrome suggests that an allergic insult can cause coronary vasospasm via release of inflammatory mediators such as histamine, tryptase, and cytokines; notably, however, the aspirin sensitivity in AERD is not felt to be allergic.[12,13] Mast cells are the dominant producers of histamine and tryptase and also produce large quantities of cysteinyl leukotrienes; therefore, mast cells are another plausible source of mediators leading to vasospastic episodes. Activated eosinophils and mast cells are both found in the respiratory and cardiac tissues of patients with AERD. Increased infiltration of mast cells into the adventitia of the involved artery has been implicated in a case of coronary spasm that resulted in sudden cardiac death.[14] Identification of activated mast cells in or eosinophilic infiltration into the coronary arteries of patients with AERD would help understand the underlying mechanism of the chest pain; however, in the absence of biopsied cardiac tissue, any direct or local involvement of specific effector cells can only be proposed and not confirmed.

Case reports in the literature have shown an association between eosinophilia and both low- and high-dose aspirin. One of these reports describes a patient with AERD who developed eosinophilia with Prinzmetal's angina after aspirin desensitization, which subsequently resolved after aspirin discontinuation.[8,15,16] As our series demonstrates, however, even patients with AERD who are not taking aspirin can have peripheral eosinophilia and chest pain. Furthermore, although the average eosinophil count for the 10 study patients who had chest pain was greater than the average eosinophil count for the rest of the patients in the registry, the degree of peripheral eosinophilia in our series was not predictive of the severity of chest pain. Notably, the majority of patients in our AERD registry have had peripheral eosinophilia without development of chest pain. Many patients with AERD are not at high risk for an acute coronary

TABLE I. Patient characteristics

Subject	Age (y)†	Sex	Absolute eosinophil count (per mm^3)‡	Cardiac risk factors¶	Cardiac workup	Nature of CP
1*	41	F	930	None	CTA normal	CP ↑ with asa, ↓ with prednisone; currently on asa; 3.5 y CP-free
2*	42	F	600	+FH	CA with no atherosclerosis, active vasospasm	CP ↑ with asa, ↓ with prednisone + stopping asa; 8.5 mo CP-free
3	67	F	2400	+FH	No advanced cardiac workup	CP started on asa; ↓with prednisone + asa dose reduction; 7.5 mo CP-free
4	48	M	1640	30 PY smoking history	No advanced cardiac workup	CP ↓ with prednisone and high-dose asa; asa stopped for GI reasons; 19 mo CP-free on mycophenolate (started for eczema)
5	62	F	430	+FH	CA with no atherosclerosis	CP ↑ with asa, ↓ asa cessation; 18 mo CP-free
6	41	F	0§	+FH	CTA with no atherosclerosis	CP ↑ with asa, ↓ with asa cessation; 17 mo CP-free
7	43	F	1360	None	No advanced cardiac workup	CP ↑ with asa, ↓ with daily prednisone; 19 mo CP-free
8	38	F	310	+FH	Exercise stress test negative for ischemia by EKG	CP before desensitization; not worse on high-dose asa; remains on asa; 14 mo CP-free
9	35	M	340	+FH	Normal exercise stress test	CP before desensitization, ↓ with prednisone; has not yet been desensitized
10	55	F	210||	40 PY smoking history	CA with no atherosclerosis	CP before desensitization, ↓ with prednisone; has not yet been desensitized

asa, Aspirin; CA, coronary angiography; CP, chest pain; CTA, computed tomography angiogram; EKG, electrocardiogram; F, female; FH, family history; GI, gastrointestinal; M, male; PY, pack year.

*Subjects 1 and 2 are presented in greater detail as Case 1 and Case 2 in the introduction of this paper.

†Age at the time of the first experience of chest pain or, if pain ongoing before presentation to medical care, at the time of the first presentation to medical care with chest pain.

‡Normal absolute eosinophil count 0-350/mm^3.

§Patient on prednisone when all recent eosinophil counts measured, but was as high as 500/mm^3 in the years before her frequent use of prednisone.

||Absolute eosinophil count from 19 months after chest pain onset.

¶Includes positive cardiac history including, when available, personal history of hyperlipidemia, diabetes, smoking, and family history of hyperlipidemia, hypertension, arrhythmia, myocardial infarction, cerebrovascular accident, sudden cardiac death, and coronary artery disease.

syndrome due to plaque rupture; therefore, when they present to medical care for chest pain, their chest pain may be falsely attributed to a noncardiac etiology such as a gastrointestinal, respiratory, or even musculoskeletal focus. However, despite the absence of traditional cardiac risk factors, these patients can develop an acute coronary syndrome that can lead to significant complications and even death. Moreover, some of these patients may also have existing coronary artery disease that has been previously treated with a stent or coronary artery bypass graft and develop true plaque rupture or in-stent restenosis in the setting of aspirin intake or eosinophilia.[17,18] Although it is difficult to confirm the etiology in all patients, it is suspected that, in patients with AERD and no pre-existing coronary artery disease, the etiology of these cardiac complications is coronary vasospasm rather than atherosclerotic plaque. Therefore, because the etiology is different, the treatment must also be different; prompt identification is crucial and requires a high level of suspicion on the part of health care providers.

For allergists and clinicians caring for patients with AERD or other hypereosinophilic conditions, it is prudent to know that eosinophilia-induced coronary artery vasospasm exists and, as demonstrated by many of the outcomes described in the case reports above, can be dangerous. However, not all chest pain is cardiac in etiology, and not all cardiac chest pain is vasospastic in etiology. Although eosinophilia-induced coronary artery vasospasm remains on the differential for the 10 patients in our case series, we cannot prove that this is the mechanism of all of these patients' chest pain, and further studies are necessary to determine causality. Ultimately, although this entity exists and should be considered in patients with eosinophilia and chest pain, it is still rare and should not discourage providers from offering aspirin desensitization and subsequent high-dose aspirin therapy to patients with AERD who warrant it. Rather, in patients with AERD whose treatment plan includes aspirin desensitization and high-dose aspirin, clinicians should obtain a detailed cardiac and chest pain history and have a low threshold to suspect coronary vasospasm as a cause of ischemic-type chest pain in these patients. Baseline blood eosinophil levels may be helpful to detect eosinophilia, though the degree of eosinophilia may not necessarily correlate with the presence or severity of chest pain. Providers in all specialties who may encounter these patients should be educated about this diagnosis so that they know to consider it and look for it, particularly in patients with eosinophilia. When patients present with chest pain refractory to conventional therapy, providers should consider a trial of treatment with prednisone. Lastly, patients should be adequately counseled so that they know to seek immediate medical attention if symptoms of chest pain develop. They should feel empowered to advocate for themselves by discussing eosinophilia-associated vasospasm, particularly if their treating providers are unaware of this phenomenon, as this may be the only way to ensure that these patients are promptly and appropriately evaluated and treated.

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