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

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Abstract

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—To understand the cause of and determine the most appropriate treatment for the chest pain described above.

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 eight other cases are also summarized.

Results—Ten of the 153 patients reviewed had a history of chest pain concerning for ischemia. Eight of the ten patients with chest pain had undergone aspirin desensitization and initiated high-dose aspirin therapy; of these, six 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

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atherosclerosis; almost all had significant eosinophilia. Their chest pain did not improve with typical anti-anginal treatments but did respond to corticosteroid therapy.

Conclusions—Though 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.

Keywords

Eosinophilia; Vasospasm; Aspirin-Exacerbated Respiratory Disease; AERD; Steroid; Chest pain

Introduction

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 respiratory reactions to the ingestion of cyclooxygenase-1 (COX-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 anti-anginal 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 eight additional patients from our AERD registry is also presented.

Case 1

Case #1 is a 42-year-old female with a history of gastroesophageal reflux disease and AERD. She had been treated with six 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 work-up 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 work-up, etiologies other than coronary atherosclerosis were considered. Incidentally, during the five-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 $930/\text{mm}^3$. 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 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 female with AERD treated with four nasal polypectomies and subsequent aspirin desensitization to initiate high-dose aspirin therapy. Within two 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 work-up 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 three 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 $600/\text{mm}^3$ 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 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 presence or absence of

traditional cardiac risk factors (family history, hyperlipidemia, hypertension, diabetes, smoking), any cardiac work-up (electrocardiography, echocardiography, any form of stress testing, coronary angiography, cardiac computed tomography angiography), 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 healthcare providers for additional documentation. Unless otherwise noted, lab values for absolute eosinophil count were collected within six months of onset of chest pain or, when chest pain had been ongoing prior to presentation to healthcare, within six 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 fifty three patient charts were reviewed (Figure 1). Ten patients had a history of chest pain concerning 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 1**). Eight of the ten (80%) patients were female, compared to our entire registry of AERD patients in which 57% were female. The average age at 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 six patients for whom this information was documented. Seven patients had a cardiac work-up, defined as evaluation by cardiac computed tomography angiography (two patients), coronary angiography (three patients), or an exercise stress test (two patients). Of these seven patients, none was determined to have evidence of coronary atherosclerosis. Nine of ten (90%) patients had eosinophilia noted at the time of chest pain, and the patient with an absolute eosinophil count of $0/\text{mm}^3$ was on prednisone at the time of her laboratory testing. The average eosinophil count of the ten study patients was $822/\text{mm}^3$ ($n = 10$, standard deviation 761, range 0–2400), compared to an average count of $544/\text{mm}^3$ ($n = 79$ 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 0.055; notably, if the patient on prednisone for all of her eosinophil testing was excluded, the 2-sided p-value became 0.014. Of the ten patients with chest pain, eight had undergone aspirin desensitization and initiated high-dose aspirin; of those, six 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 one patient's dose was reduced to 162 mg twice daily; four 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. 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.⁶ Similarly, Wong et al. published a summary of the 17 case reports available in the literature as of 2008 as well as two 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 following 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}

While the exact mechanism by which eosinophils cause coronary artery vasospasm is unknown, it is hypothesized that eosinophils may release vasospastic mediators upon 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 AERD patients 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 following aspirin desensitization, which subsequently resolved following aspirin discontinuation.^{8,15,16} As our series demonstrates, however, even AERD patients who are not taking aspirin can have peripheral eosinophilia and chest pain. Furthermore, although the average eosinophil count for the ten 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 AERD patients are not at high risk for an acute coronary syndrome due to plaque rupture; therefore, when they present to medical care for chest pain, their chest pain may be falsely attributed to a non-cardiac 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} Though 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 healthcare 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. While eosinophilia-induced coronary artery vasospasm remains on the differential for the ten 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, while 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.

Abbreviations

ACE	angiotensin-converting enzyme
AERD	aspirin-exacerbated respiratory disease

COX-1	cyclooxygenase-1
CTA	computed tomography angiogram
EKG	electrocardiogram
mg	milligrams

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Highlights

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 anti-anginal medications.

How does this study impact current management guidelines?

Clinicians should be aware that the most appropriate course of treatment for AERD patients 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.

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.

Table 1

Patient Characteristics

Subject	Age (y) ^a	Sex	Absolute Eosinophil Count (per mm ³) ^b	Cardiac Risk Factors ^c	Cardiac Work-Up	Nature of CP
#1 [*]	41	F	930	None	CTA normal	CP ↑ with asa, ↓ with prednisone; currently on asa; 3.5 years CP-free
#2 [*]	42	F	600	+FH	CA with no atherosclerosis, active vasospasm	CP ↑ with asa, ↓ with prednisone + stopping asa; 8.5 months CP-free
#3	67	F	2400	+FH	No advanced cardiac work-up	CP started on asa; ↓ with prednisone + asa dose reduction; 7.5 months CP-free
#4	48	M	1640	30 PY smoking history	No advanced cardiac work-up	CP ↓ with prednisone and high dose asa; asa stopped for GI reasons; 19 months CP-free on mycophenolate (started for eczema)
#5	62	F	430	+FH	CA with no atherosclerosis	CP ↑ with asa, ↓ asa cessation; 18 months CP-free
#6	41	F	0 ^d	+FH	CTA with no atherosclerosis	CP ↑ with asa, ↓ with asa cessation; 17 months CP-free
#7	43	F	1360	None	No advanced cardiac work-up	CP ↑ with asa, ↓ with daily prednisone; 19 months CP-free
#8	38	F	310	+FH	Exercise stress test negative for ischemia by EKG	CP prior to desensitization; not worse on high dose asa; remains on asa; 14 months CP-free
#9	35	M	340	+FH	Normal exercise stress test	CP prior to desensitization, ↓ with prednisone; has not yet been desensitized
#10	55	F	210 ^e	40 PY smoking	CA with no atherosclerosis history	CP prior to 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

^a Age at time of first experience of chest pain or, if pain ongoing prior to presentation to medical care, at time of first presentation to medical care with chest pain

^b Normal absolute eosinophil count 0–350/mm³

^c 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

^d Patient on prednisone when all recent eosinophil counts measured, but was as high as 500/mm³ in the years prior to her frequent use of prednisone

^e Absolute eosinophil count from 19 months after chest pain onset