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CLINICAL VIGNETTE

Coronary Vasculitis: A Multidisciplinary Diagnostic and Management Challenge

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Case Report

A 42-year-old man with Sjogren's disease presented to the emergency department (ED) for a 3-week history of cough, dyspnea on exertion, chest discomfort, and generalized malaise. In the ED, he was found to have an abnormal electrocardiograph (ECG) with borderline ST elevations in the inferior and anterior leads concerning for myocardial infarction (MI). In addition to Sjogren's he has microscopic polyangiitis (myeloperoxidase (MPO) positive anti-neutrophil cytoplasmic antibody (ANCA) positive) treated with rituximab, methotrexate and prednisone. Laboratory testing was significant for troponin elevation to 0.16 (baseline < 0.1), ESR >130, CRP 3.8, and MPO antibody > 740.

The patient underwent urgent cardiac catheterization and found to have 80-90% ostial stenosis of left main (LM). His cardiac catheterization did not reveal atherosclerotic disease, and he underwent further imaging to evaluate for vasculitis as a cause for his obstructive coronary artery disease (CAD). Trans-thoracic echocardiogram (TTE) was unremarkable with mild concentric left ventricular hypertrophy and normal systolic function. Coronary CT angiography (CTA) demonstrated an irregularly thickened LM wall with distal luminal compression and edematous fascia suggestive of vasculitis. Magnetic resonance angiography (MRA) of the chest did not demonstrate any vasculitis in extra-cardiac vessels. A multidisciplinary recommendation involving Cardiology, CT surgery, and Rheumatology, recommended a trial of inpatient medical therapy. The patient was treated with heparin drip, nitroglycerine drip, metoprolol, aspirin, and atorvastatin. In addition, a 5-day course of pulse dose methylprednisolone was administered. Repeat coronary CTA showed persistent wall thickening of the left main coronary artery with resultant high-grade stenosis, which remained unchanged compared to the earlier coronary CTA. Given persistent severe left main disease and his symptomatology, the patient underwent coronary artery bypass graft (CABG). Intraoperatively, he was found to have dense pericarditis with adhesions as well as a fibrotic mammary artery that was biopsied and showed active vasculitis. He underwent 2-vessel CABG with saphenous vein grafts to his LAD and obtuse marginal branch and lysis of pericardial adhesion. He was discharged on high dose prednisone with cardiology and rheumatology follow ups. Given cardiac involvement from MPA, he was also treated with oral cyclophosphamide for 6 months and then transitioned to rituximab infusions.

Coronary CTA was repeated 7 months after CABG, and it showed unchanged high-grade LM stenosis, patent grafts, and a calcium score of 0. He has done well after CABG and is without cardiac complaints.

Background and Etiology

ANCA-associated vasculitis (AAV) are a group of systemic, small vessel vasculitides that are pauci-immune and characterized by the presence of ANCA.¹ AAV includes granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA).²⁻⁴ AAV typically affects small vessels including capillaries, venules, arterioles, and small arteries, but can rarely affect larger arteries leading to overlapping clinical signs with other autoimmune vasculitides.⁴⁻⁶ Overall worldwide prevalence is approximately 42/100,000 persons.⁶ Annual incidence varies depending on geographic location, but has been reported as 3/100,000 persons in one US population-based study.^{6,7}

Clinical manifestations are nonspecific and include but are not limited to constitutional symptoms, malaise, weight loss, arthralgia, myalgia, rash, sinusitis, but serious organ manifestations with pulmonary-renal syndrome, neurologic involvement, gastrointestinal involvement and cardiac involvement may also occur.^{2,5} The overall relative risk of coronary heart disease (CHD) in patients with AAV is increased 2-4 fold compared to controls despite similar prevalence of risk factors such as obesity, hyperlipidemia, and diabetes mellitus.^{8,9} One meta-analysis reported a 65% increase in cardiovascular events including ischemic heart disease, cerebrovascular accidents, and peripheral artery disease.¹⁰ The frequency of coronary arteritis, defined as thromboses, stenoses, aneurysms, or dissections, has been reported between 9-50%, and pericarditis between 10-27%.¹¹ Cardiac involvement significantly worsens prognosis, with one study reporting approximately 14% of patients will have a major cardiovascular event within 5 years of diagnosis.^{11,12}

Pathophysiology

Loss of tolerance to autoantigen targets such as MPO and proteinase 3 (PR3), two neutrophil primary granule proteins that become exposed to the cell surface once primed by pro-inflammatory cytokines, is thought to play a role in the pathogenesis of AAV.^{2,4} A histologic perinuclear staining

pattern seen in p-ANCA is associated with MPO while a cytoplasmic staining pattern seen in c-ANCA is associated with PR3.² Multiple environmental, genetic, drug-mediated, and infectious factors can induce the development of effector cell-mediated MPO and PR3-ANCAs which then activate primed neutrophils.²⁻⁴ Activated neutrophils produce endothelial damage via reactive oxygen species, degranulation, and promote further pro-inflammatory cascades to produce tissue injury.^{3,4}

Multiple mechanisms may play a role in coronary involvement in AAV including premature atherosclerosis from inflammation, active vasculitis affecting small vessels, endothelial cell dysfunction, and arterial stiffness as measured by pulse wave velocity.^{9,11,13,14} One study postulated direct involvement of autoantibodies or a regulatory T cell deficiency, both of which may directly promote atherosclerosis by further activating endothelial cells.¹⁰ In *in vitro* studies, MPO has been linked to atherosclerotic plaque instability via pathways that induce platelet aggregation, release tissue factor, and promote apoptosis.¹⁵ Data comparing acute coronary syndrome prevalence between MPO and PR3-ANCAs are lacking, but patients with MPO-ANCA have higher risk for overall cardiovascular disease (CVD).^{12,16} In addition, serum MPO levels are significantly elevated in patients with coronary artery disease (CAD) and after an acute MI.¹⁷⁻²⁰ There have been few studies on LM involvement in AAV, and large prospective trials are lacking.

Physical Exam

Physical exam features are nonspecific, but some that should prompt suspicion for cardiac involvement in AAV include visceral infarcts without embolic etiology, subclavian or aortic bruits, asymmetric or absent radial pulses, signs of acute or chronic pericarditis, paresthesias, arrhythmias, murmurs, and vasculitic rashes.^{5,11} One case report in a middle-aged male documented distal LAD spontaneous coronary artery dissection (SCAD) and intermittent vision loss as presenting features of AAV.²¹ Patients with a known history of AAV presenting with cardiopulmonary complaints warrant close monitoring and further evaluation.

Diagnosis

A definitive diagnosis of coronary vasculitis requires biopsy.¹¹ However, biopsies are invasive and often shows nonspecific inflammatory patterns.¹¹ As such, a combination of clinical findings suggestive of CAD, increased serum inflammatory markers, and radiographic evidence of vasculitis can aid in diagnosis.¹¹ Additionally, some patients may present with an acute coronary syndrome and require emergent cardiac catheterization.⁵ While catheterization can assess luminal narrowing, it does not fully evaluate inflammation. Angiographic features can include tapered narrowing of vessels, ostial or proximal stenosis, skip lesions, and coronary aneurysms, but are not specific to AAV.⁵

Elevated inflammatory biomarkers such as ESR and CRP may be helpful to aid diagnosis of flare, but are not specific for cardiac involvement. Serum MPO levels have been shown to be elevated in patients with angiographically proven CAD, and also increase with severity of CAD.¹⁷ MPO levels are also useful to predict risk for subsequent cardiovascular events.¹⁷ Coronary CT can detect chronic inflammatory changes such as aneurysms, stenoses, wall thickening, and thromboses.²² Cardiac MRA with contrast can provide information on pericarditis, active myocardial inflammation, and nonviable tissue.^{5,22} Positron emission tomography (PET) has been used to predict cardiac wall motion abnormalities in a subset of AAV, but cannot differentiate between vasculitic or atherosclerotic causes of perfusion reduction.^{5,23,24}

Management

Treatment of AAV with cardiac involvement often requires a multidisciplinary approach that includes cardiology, rheumatology, and cardiothoracic surgery. Rituximab and cyclophosphamide are commonly used agents for induction and treatment of AAV, and patients should be closely monitored for response to therapy.²⁵ CVD is the most common cause of death in patients with ANCA-associated AAV, and risk stratification using cardiac imaging or cardiovascular event prediction models is recommended for prognostication and prevention.^{12,26,27} Patients with confirmed AAV should undergo ECG and transthoracic echocardiography (TTE) to detect arrhythmias and structural cardiac abnormalities.^{11,23} While management depends on which cardiac structures are affected, coronary vasculitis frequently requires high-dose steroids.²⁸ It is important to periodically assess and control traditional cardiovascular risk factors such as dyslipidemia, hypertension, obesity, and smoking.²⁷⁻²⁹ Current guidelines for medical management should be followed. Data are limited to determine if patients qualify for lower cutoffs to initiate medications.²⁸

To date, there are no prospective randomized controlled trials comparing revascularizations methods or timing in patients with AAV who present with acute coronary syndrome.⁵ Clinical judgment, laboratory data, and a multidisciplinary approach are helpful to weigh the risks and benefits of percutaneous coronary intervention versus CABG.⁵ Given significant LM disease in our patient, the decision was made to control inflammation with high dose steroids and proceed with CABG.

Serial assessment with inflammatory markers and imaging is suggested for disease monitoring, without data regarding to the frequency and specific imaging modality.^{5,26} TTE can be used for serial assessment of structural function. Cardiac multi-detector CT and MRA are options to evaluate for coronary vasculitis involvement and active inflammation.^{22,28} While PET can be used to follow therapy efficacy in large vessel vasculitis and detect extra-coronary inflammation, it has poor sensitivity for small to medium vessel disease.^{5,24,30} Our patient is closely followed by rheumatology to trend inflammatory markers including ESR, CRP, and MPO ANCA. After treatment with cyclophosphamide, he was started on rituximab at regular

intervals to maintain remission and continued on prednisone 5 mg daily. TTE and coronary CTA have been repeated to follow disease progression, and the patient has been medically optimized after his CABG.

Conclusion

Coronary vasculitis is an important cause of morbidity and mortality in patients with systemic vasculitis. Diagnosis requires clinical suspicion and is aided by increased inflammatory markers including MPO ANCA. TTE, coronary CTA, and cardiac MRA can provide information about structural defects and inflammatory patterns. Traditional cardiovascular risk factors should be appropriately managed. To date, there are no guidelines on the use of a specific imaging modality or timing for follow-up. Further research is needed to determine long-term management strategies in patients with AAV.

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