Acute Coronary Syndrome in a 52-Year-Old Woman With Scleroderma

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Foreword

Information about a real patient is presented in stages (boldface type) to expert clinicians (Drs Mauri and Dr MacRae), who respond to the information, sharing their reasoning with the reader (regular type). A discussion by the authors follows.

Patient presentation: A 52-year-old woman with a medical history of an acute coronary syndrome (ACS) managed with percutaneous coronary intervention (PCI) and scleroderma presented to outpatient cardiology clinic with chest discomfort. She was in her usual state of health until 1 week before presentation, when she developed fatigue and malaise that persisted throughout the week. On the evening before presentation, she awoke with substernal chest pressure that worsened over the next several hours and prevented her from falling back asleep. She presented to her primary cardiologist the following morning with ongoing chest discomfort.

Her medical history was notable for a prior circumflex PCI, diffuse cutaneous systemic sclerosis, mononeuritis multiplex, thrombocytopenia, hypertension, hyperlipidemia, hypothyroidism, and gastroesophageal reflux disease. Her PCI occurred 1 year earlier, when she presented with atypical chest pain in the setting of a scleroderma flare and was found to have lateral ST depressions on her ECG and an elevated troponin T level of 0.12 ng/mL. Coronary angiography was performed and revealed 99% occlusion of the left circumflex artery (LCx; Figure 1). The lesion was successfully treated with a everolimus-eluting stent.

Her scleroderma was first diagnosed at 29 years of age, when she presented with Raynaud syndrome, sclerodactyly, telangiectasias, and esophagitis and was found to have a positive anticentromere antibody, leading to a diagnosis of limited cutaneous systemic sclerosis. At 34 years of age, she developed widespread skin thickening and subcutaneous calcinoses, leading to a subsequent diagnosis of diffuse cutaneous systemic sclerosis. At 42 years of age, she developed multiple mononeuropathies with electromyographic evidence of mononeuritis multiplex, for which she was treated with a limited course of cyclophosphamide and prednisone with subsequent clinical improvement.

Her thrombocytopenia was chronic and without a clear origin. Prior workup revealed positive anti–cardiolipin IgM and anti–β2-glycoprotein 1 antibodies that were thought to be nonspecific. She had no prior thromboembolic events.

Her home medications included aspirin 81 mg daily, clopidogrel 75 mg daily, lisinopril 40 mg daily, levothyroxine 50 μg daily, and pantoprazole 40 mg daily. Her scleroderma and mononeuritis multiplex flares were managed with intermittent mycophenolate mofetil and prednisone, which last occurred ≈6 months before presentation. She was married and worked as a nurse educator. She rarely consumed alcohol and had never used tobacco products or illicit substances. Her mother suffered a myocardial infarction in her 50s and later died of heart failure. Her father died at a young age in a motor vehicle accident.

On presentation to her cardiologist's office, she was found to appear ill and to be in moderate discomfort. Physical examination was notable for bilaterally symmetrical and normal blood pressures, nonelevated jugular venous pressure, regular heart rate and rhythm, normal S1 and S2 in addition to an S4, and the absence of any murmurs. ECG was obtained and revealed 1- to 2-mm ST-segment depressions in leads I, aVL, and V_3 through V_6. She was given sublingual nitroglycerin, with improvement in her chest discomfort, and she was taken to the emergency department for further evaluation. Basic laboratories were checked and notable for an elevated troponin T level of 0.04 ng/mL. She was given aspirin 325 mg, atorvastatin 80 mg, and intravenous unfractionated heparin and was taken to the cardiac catheterization laboratory.

Dr MacRae: The differential diagnosis of severe chest pain in this setting is quickly circumscribed by a history and physical examination. Given the prior coronary lesion, there is certainly concern for more extensive coronary disease, and with her known systemic sclerosis, an inflammatory myocardial or pericardial process is also a possibility. In this context, there is also an increased risk of thromboembolism and aortic aneurysmal disease, each of which might present with similar symptoms. Other common causes of chest pain are less likely but also should be entertained on direct inquiry,

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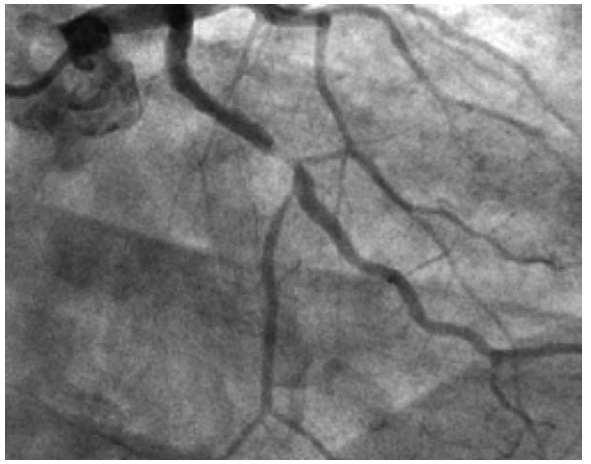

Figure 1. Coronary angiogram in the right anterior oblique view showing 99% occlusion of the middle segment of the left circumflex artery.

including the esophageal syndromes encountered in systemic sclerosis. Physical examination may help condition the differential through positive or negative findings. Symmetrical blood pressures, the absence of jugular venous distension, a pericardial rub, and an aortic regurgitant murmur were all helpful. The S4 had been present since her previous event.

During the original presentation with ACS-like symptoms, the possibility of a coronary arteritis was considered, but given the critical flow-limiting nature of the lesion and the thrombus burden, it was decided to proceed to PCI and drug-eluting stent implantation. The adjunctive use of intravascular ultrasound was also discussed, but it was thought unlikely to change the management of the lesion and was considered high risk. The occurrence of this new episode in the setting of another possible flare in her systemic sclerosis raised the suspicion for vasculitis with possibly a new lesion or an atypical complication of the prior PCI.

Patient presentation (continued): **Coronary angiography was performed. The right coronary artery contained a 40% proximal focal stenosis that was unchanged from her angiogram 1 year previously. There was no evidence of obstructive coronary disease in the left main and left anterior descending coronary arteries. Angiography of the LCx revealed a patent prior stent immediately distal to 3 serial 90% stenoses with an overall appearance suggestive of "beads on a string" (Figure 2, top left). There was a detailed discussion among the interventional cardiology, outpatient cardiology, and rheumatology teams, who agreed that the differential diagnosis included coronary vasculitis; coronary thrombosis, possibly secondary to antiphospholipid syndrome; fibromuscular dysplasia (FMD) with or without spontaneous coronary artery dissection (SCAD); and ACS secondary to atherosclerotic plaque rupture. The risks and benefits of coronary stenting versus medical therapy were weighed in detail. Given that she was now without chest pain and hemodynamically stable with an angiogram suggestive of vasculitis, intervention was deferred at that time in favor of medical therapy.**

Dr Mauri: Coronary angiography showed a normal appearance of the drug-eluting stent placed in the LCx artery the previous year without restenosis or aneurysm. However, proximal to this stent, where the vessel had appeared to be without evidence of atherosclerotic plaque 1 year previously, there were now 3 tandem, severe focal lesions without angiographic evidence of plaque rupture or thrombus. Although the absence of thrombus and ulceration is nonspecific, the appearance of beads on a string was suggestive of a nonatherosclerotic process. Coronary vasculitis, SCAD, and FMD were considered possible diagnoses at this time; of these, vasculitis was most likely on the basis of the patient's rheumatologic history, clinical presentation, and angiographic findings. Because of the lack of immediate urgency for revascularization and the uncertain time course of the development of this stenosis, a trial of immunosuppressive therapy to target an inflammatory cause was planned as guided by rheumatology while antiplatelet and anticoagulation were continued to avoid thrombosis, with consideration for coronary stenting should signs or symptoms of ischemia progress.

Patient presentation (continued): **She was admitted to the inpatient cardiology service, where she was treated with heparin, aspirin, clopidogrel, atorvastatin, mycophenolate mofetil, and methylprednisolone. The rarity of association between scleroderma and coronary vasculitis prompted suspicion for either an undiagnosed systemic vasculitis with coronary involvement or an overlap mixed connective tissue disease syndrome with features of rheumatoid arthritis or systemic lupus erythematous that are more commonly associated with coronary vasculitis. Further evaluation to delineate these possibilities included a broad laboratory workup. Antinuclear, anti–cardiolipin IgM, and anti–β2-glycoprotein 1 antibodies were positive, as they had been in the past, and several other rheumatologic laboratory tests were negative (Table 1).**

Dr MacRae: Another factor in the management of the initial presentation was the perceived low likelihood of a vasculitis in classic systemic sclerosis. Nevertheless, the history of mononeuritis multiplex already suggested that this might be an overlap syndrome, and the angiographic features now evident were consistent with this diagnosis. These contentions only serve to emphasize how rudimentary our current assessment of vascular biology is in individual patients with coronary syndromes, highlighting how powerful studies that are more mechanistic might be in elucidating individual clinical presentations.

Given the extant data on stenting in the setting of active coronary vasculitis and after discussion with the rheumatology team, it was elected to pursue an initial trial of medical therapy. The mechanism of flow limitation was not obvious from the angiogram, which did not reveal clear evidence of intraluminal thrombus, but we elected to treat the presumed primary inflammatory process, vasospasm, and both platelet- and fibrin-based thrombus. The planned duration of our initial trial of purely medical therapy was arbitrary but based on consensus inference from other acute inflammatory manifestations of systemic sclerosis. The immunosuppressive regimen was based on earlier case reports of responses.

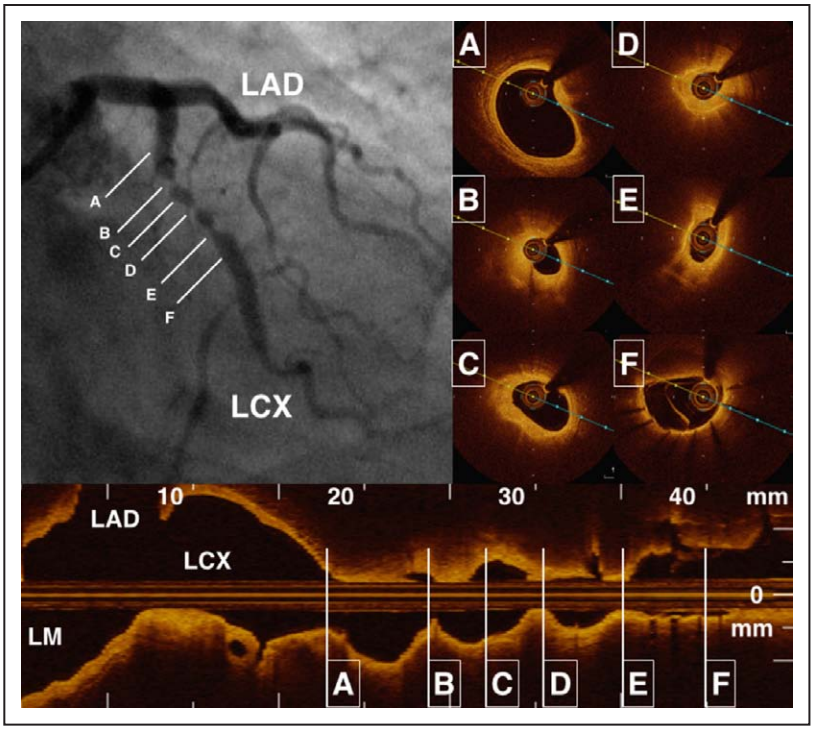

Figure 2. Top Left, Coronary angiogram in the right anterior oblique caudal view showing 3 sequential stenoses with an unchanged overall appearance of "beads on a string." **A**, Optical coherence tomography (OCT) of the proximal left circumflex artery (LCX) with fibroatheroma at 12 and 5 o'clock. **B** through **E**, OCT of the proximal LCX stenoses showing multiple homogeneous concentric stenoses with hyperreflective, thickened intima and isolated areas of hypoattenuation. **F**, OCT of the proximal edge of the prior stent showing moderate eccentric in-stent restenosis without any inflammatory changes. LAD indicates left anterior descending artery; and LM, left main artery.

Patient presentation (continued): **Cardiac magnetic resonance imaging was obtained and revealed a resting perfusion defect in the basal to mid inferior and inferolateral walls, matching regions of hypokinesis, without evidence of late gadolinium enhancement to suggest prior infarct, inflammation, or infiltration. These findings were thought to be consistent with hibernating myocardium in the LCx territory without evidence of coexisting myocarditis or pericarditis. Whole-body fluorodeoxyglucose positron emission tomography–computed tomography was then pursued and did not reveal any evidence of large-vessel vasculitis.**

After several days of high-dose immunosuppression with mycophenolate mofetil and methylprednisolone, anticoagulation, and dual antiplatelet therapy, she had persistent chest pain and ECG evidence of ischemia with minimal exertion. Her heparin infusion was weaned on multiple occasions, each time leading to worsening chest pain within several hours of discontinuation. Medical therapy was continued for a total of 10 days but was ultimately ineffective at improving her symptoms and ischemia. The decision was made to perform repeat coronary angiography with intracoronary imaging.

Dr MacRae: The magnetic resonance imaging was obtained to assess possible associated myocardial or pericardial inflammation and to evaluate pericardial physiology. Notably, at no stage in the current or previous admission were general inflammatory indexes (erythrocyte sedimentation rate or C-reactive protein) elevated. In addition, it was hoped that magnetic resonance imaging might reveal baseline features that could be followed up as indexes of response for the arteritic process. Similarly, fluorodeoxyglucose positron emission tomography was undertaken to define the extent of any extracardiac vasculitis in medium or large vessels that might influence prognosis and management. The documentation of hibernating myocardium in the LCx territory in the absence of any evidence of active inflammation in myocardium or elsewhere focused our attention on the clinical features of the ACS as end points. Despite initial improvement in the patient's systemic symptoms, with ambulation on maximal medical therapy, it was obvious that there were still significant coronary flow abnormalities that would prevent early discharge and might be progressing in severity. It was elected to return to the catheterization laboratory to assess any changes (in either direction) in the LCx lesions, to undertake optical coherence tomography (OCT) or intravascular ultrasound to characterize the biological nature of the underlying coronary process, and to proceed with percutaneous intervention if indicated.

Patient presentation (continued): **Repeat coronary angiography revealed an unchanged appearance of the proximal LCx stenoses (Figure 2). OCT was performed and revealed multiple homogeneous concentric stenoses in the proximal LCx with hyperreflective, thickened intima and isolated areas of hypoattenuation, consistent with a predominantly fibroproliferative and primary inflammatory process (Figure 2). There was no evidence of dissection, thrombosis, or atherosclerosis within these segments on OCT, although the ostial LCx had evidence of nonobstructive atherosclerotic plaque, separate from the new proximal LCx lesions. These findings, including the absence of evidence for a typical ACS or SCAD, were essential at arriving at the diagnosis of coronary vasculitis. A everolimus-eluting stent was placed to treat the severe lesion with excellent angiographic result (Figure 3). She had no recurrent symptoms after stenting and was discharged 2 days later.**

Dr Mauri: The OCT findings illustrate 2 possible concomitant disease processes: nonobstructive coronary artery disease and inflammatory infiltration consistent with vasculitis. Because of a lack of regression of the angiographic stenosis

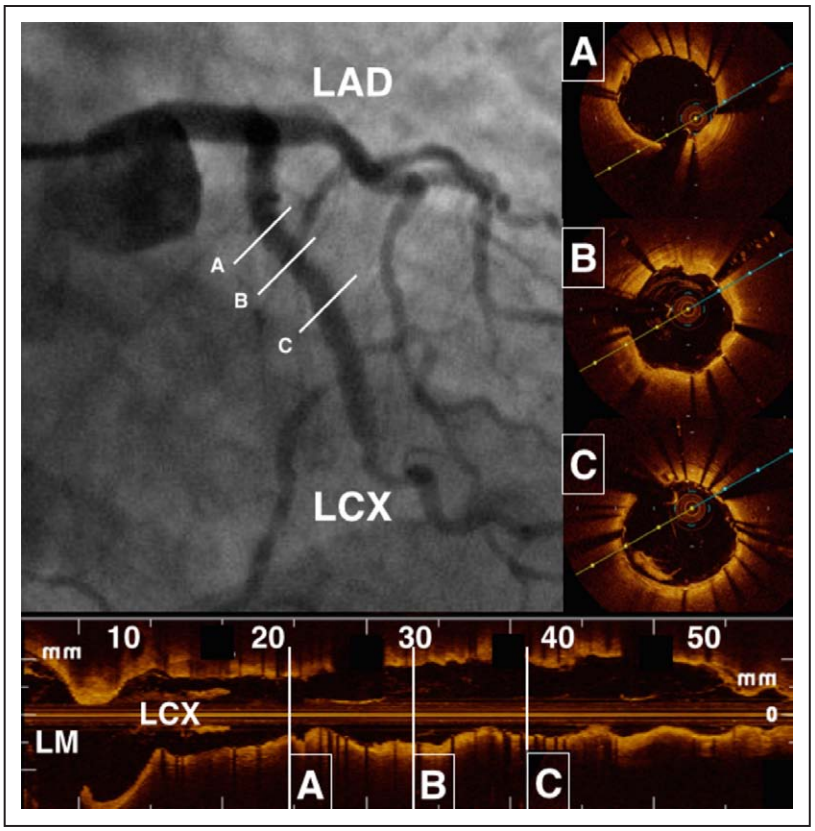

Figure 3. Top Left, Coronary angiogram in the right anterior oblique view caudal immediately after placement of a 3.5×29-mm everolimus-eluting stent. **A** and **B**, Optical coherence tomography (OCT) images of the proximal and middle stent segments revealing a well-expanded and well-apposed stent. **C**, OCT image of the overlapping old and new stents. LAD indicates left anterior descending artery; LCX, left circumflex; and LM, left main artery.

with immunosuppressive therapy and remaining viable LCx myocardium in the presence of persistent symptoms of exertional chest pain, the severe stenosis were treated with a drug-eluting stent. Although there are few data on the effectiveness of drug-eluting stents in the setting of chronic vasculitis, the patient's prior local response to such treatment was excellent. It is notable that everolimus itself has previously been used as an immunosuppressant. After PCI, attention to the prevention of both pathologies that could influence regional disease progression elsewhere in the coronary tree would be necessary, including conventional therapies (dual antiplatelet therapy and statin), although how best to avoid recurrent vasculitis was uncertain.

Patient presentation (continued): **She did well after discharge with recurrent ischemia or scleroderma flare on a medical regimen of aspirin, clopidogrel, atorvastatin, lisinopril, and mycophenolate. Repeat coronary angiography was obtained 6 months after discharge to reassess her disease burden and to inform decisions to titrate her mycophenolate dosing. This revealed patent LCx stents without evidence of restenosis or new inflammatory disease (Figure 4). The 40% proximal right coronary artery stenosis was again present and unchanged. OCT was used to further investigate the right coronary stenosis and revealed typical atherosclerotic plaque without evidence of inflammatory disease. To this date, 9 months after her initial PCI, she has remained free of recurrent symptoms or signs of ischemia.**

Discussion

We present a patient with ACS secondary to coronary artery vasculitis and refractory to medical therapy that ultimately was treated with PCI. This case challenged our differential diagnosis for ACS and highlighted our limited understanding of the causes of, diagnostic testing for, and optimal treatment for coronary artery vasculitis.

Coronary artery vasculitis can occur secondary to a variety of systemic inflammatory, infectious, and metabolic diseases (Table 1).[1,2] Coronary disease is the leading cause of morbidity and mortality in systemic vasculitis.[2] Coronary artery

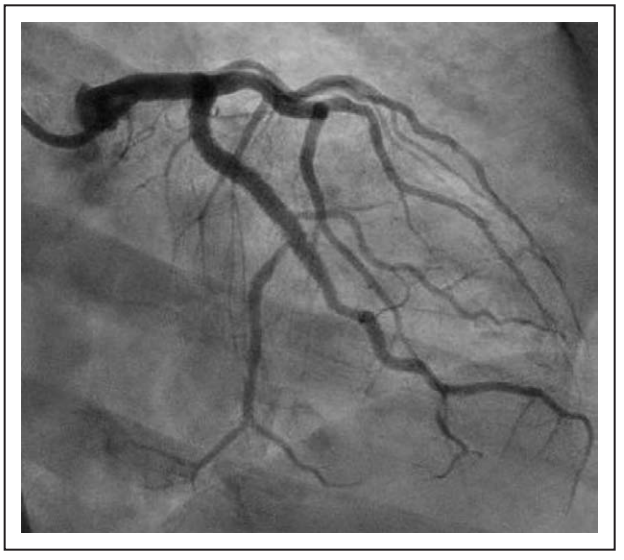

Figure 4. Coronary angiogram in the right anterior oblique caudal view showing patent stents in the proximal and mid left circumflex artery without evidence of in-stent restenosis or new coronary lesions compared with the earlier angiogram.

Table 1. Serum Rheumatologic Laboratory Results

Test	Value	Units	Reference Range
Antinuclear antibodies	Positive at 1:640	N/A	Negative
Pattern of antinuclear antibodies	Speckled	N/A	Negative
Anti–cardiolipin IgM	16	MPL units	0–15
Anti–cardiolipin IgG	16	MPL units	0–15
Anti–β2-glycoprotein 1 IgM	>150	Units	0–20
Anti–β2-glycoprotein 1 IgG	4	Units	0–20
Erythrocyte sedimentation rate	3	mm/h	0–18
C-reactive protein	0.7	mg/L	0–3
Anti-neutrophil cytoplasmic antibodies	Negative	N/A	Negative
Anti-Smith antibodies	0	EU/mL	0–20
Anti–U1-ribonucleic protein antibodies	2	EU/mL	0–20
Anti-Ro antibodies	2	EU/mL	0–20
Anti-La antibodies	0	EU/mL	0–20
Anti–double-stranded DNA antibodies	3	EU/mL	0–25
Complement 3	140	mg/dL	90–180
Complement 4	24	mg/dL	10–40

Ig indicates immunoglobulin; and MPL, immunoglobulin M phospholipid units.

vasculitis has been most frequently reported with Takayasu arteritis and polyarteritis nodosa, but it has been associated with many other large-, medium-, and small-vessel vasculitides such as giant-cell arteritis, Kawasaki disease, eosinophilic granulomatosis with polyangiitis, and Behçet disease.[3] Coronary vasculitis has also been described as a manifestation of autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis, infectious diseases, including tuberculosis and syphilis, and a variety of other conditions, including lysosomal storage and metabolic diseases.[1]

The pathophysiology of coronary involvement is a function of the underlying systemic process. In systemic vasculitis, perivascular inflammatory infiltrates invade the coronary arterial walls, causing concentric intimal thickening, often further complicated by coronary aneurysm formation and intramural thrombosis.[3] Rheumatologic diseases are also associated with inflammatory intimal thickening, often exacerbated by fibrosis, fibrinoid necrosis, and immune complex deposition. Some infectious diseases can directly invade or seed the coronary arteries, and certain metabolic diseases can cause metabolic substances to deposit in the coronary arterial walls.[1]

Coronary artery vasculitis is rarely discovered until luminal stenosis becomes severe enough to cause ischemia. The signs and symptoms on presentation are secondary to myocardial ischemia and can include stable angina, ACS, heart failure, and arrhythmias. Physicians are challenged to distinguish coronary vasculitis from atherosclerotic disease, necessitating a high-level suspicion in patients with atypical substrate for atherosclerotic disease and underlying predisposing conditions for coronary vasculitis.

Coronary angiography is the gold standard for diagnosis, and various findings have been described in association with different underlying disease processes (Table 2).[2,3] The diagnostic accuracy is limited by nonspecific findings that can be difficult to distinguish from typical atherosclerotic disease. When coronary angiography findings are nonspecific, the use of intracoronary imaging with intravascular ultrasound and OCT has been reported.[4] Findings on OCT include homogeneous concentric stenosis with hyperreflective, thickened intima and high tissue backscatter.[4] The absence of obvious atherosclerotic disease is also important in establishing the diagnosis. Intracoronary nitroglycerin, which often improves coronary stenosis secondary to vasospasm, also can be used to help differentiate vasospasm from vasculitis, which is usually unaffected by nitroglycerin. In addition to invasive techniques, noninvasive imaging with cardiac multidetector computed tomography has been described for coronary vasculitis[3] The utility of noninvasive imaging compared with angiography and intracoronary imaging for the diagnosis of coronary vasculitis has not been studied.

In the present case, the differential diagnosis for the patient's coronary angiographic findings initially included both FMD and SCAD. FMD is a noninflammatory condition that can rarely involve the coronary arteries and is strongly associated with SCAD.[5] Patients with FMD with coronary involvement usually have tortuous coronary arteries and multiple, smooth, irregular stenoses, sometimes accompanied by segmental dilatation and ectasia.[5] SCAD traditionally appears on angiography as multiple radiolucent lumen with a "tram track" appearance; however, it can also present with diffuse coronary stenoses or with tubular stenoses mimicking typical atherosclerotic disease.[6] Although the angiogram in this case could also be consistent with FMD and SCAD, the combination of the clinical context, the dynamic nature of the patient's coronary anatomy, and the OCT findings supported a diagnosis of segmental vasculitis.

Table 2. Coronary Findings Associated With Various Vasculitides and Conditions That Can Mimic the Findings of Coronary Vasculitis[1–3,5,6]

Disease	Coronary Findings
Takayasu arteritis	Type 1: stenosis or occlusion of the coronary ostia and proximal segments of the coronary arteries
	Type 2: diffuse or focal coronary arteritis
	Type 3: coronary aneurysms
Kawasaki disease	Acute, multifocal ectatic and stenotic changes with or without mural thrombus
	Chronic, giant coronary aneurysms and thrombotic occlusion
Giant-cell arteritis	Diffuse coronary arteritis with intimal wall fibrosis or thrombosis
Polyarteritis nodosa	Diffuse coronary arteritis
	Serial focal coronary stenoses with characteristic "beads on a string" appearance
	Luminal narrowing, superimposed thrombosis, dissection, or aneurysmal dilatations
Behçet disease	Coronary artery aneurysm with thrombus formation resulting in distal stenosis
IgG4-related periarteritis	Soft tissue encasement at the coronary artery with or without luminal narrowing
Eosinophilic granulomatosis with polyangiitis	Coronary artery aneurysm with concentric wall thickening
Moyamoya	Coronary artery wall thickening caused by fibrous or fibrofatty tissue
Fibromuscular dysplasia	Tortuous coronary arteries with irregular, smooth stenoses sometimes associated with segmental dilatation and ectasia.
Coronary dissection	Multiple radiolucent lumen with "tram track" appearance
	Diffuse coronary stenoses with abrupt changes in arterial caliber
	Long tubular segments of luminal narrowing
Cocaine use	Single or multiple focal coronary stenoses

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The OCT findings, in particular the homogeneous, hyperreflective, thickened intima suggestive of local edema, are consistent with coronary vasculitis and are nearly identical to an earlier case report of OCT in vasculitis.[4] These findings are less consistent with the OCT features of FMD or SCAD. The OCT findings in FMD include intimal, medial, and adventitial thickening with a heterogeneous mixture of high- and low-reflectivity areas corresponding to areas of fibrosis and infiltrates, respectively, as well as loss of elastic lamina and vessel wall cavitation.[6] OCT in SCAD will show separation of the intima and media and will often display an intimal tear or intramural hematoma, none of which was present in our patient.[7] In this case, OCT showed areas of homogeneous, hyperreflective, thickened intima without patchy low-reflectivity areas or vessel wall cavitation suggestive of FMD and more consistent with previous descriptions of the OCT findings in coronary vasculitis.[4] These observations, combined with the patient's clinical history and presentation, were essential to making the diagnosis of coronary vasculitis.

The role of revascularization in the treatment of coronary artery vasculitis is unclear. There are no prospective studies evaluating treatment options. Medical therapy usually includes anti-inflammatory, immunosuppressive, and disease-modifying agents directed at the underlying disease process. There are several case reports of patients with coronary vasculitis presenting with myocardial infarction who achieved angiographic and clinical improvement with immunosuppressive therapy alone without undergoing coronary intervention.[7–10] Revascularization is usually reserved for cases of high-risk ACS associated with hemodynamic instability and ischemia refractory to medical therapy.[2] Multiple cases of revascularization via percutaneous and surgical methods have been reported, the majority of which were performed in patients with underlying systemic vasculitis who failed medical therapy.[11–17] The outcomes of coronary stenting have been mixed, with some patients showing sustained clinical improvement and others experiencing early restenosis and recurrent inflammatory lesions.[11–17] Although it is difficult to generalize these findings given the limited number of cases, complications of percutaneous revascularization similar to vasculitic lesions in noncoronary vessels resulting from large-vessel vasculitides such as Takayasu and giant-cell arteritis have been described more commonly, with high associated rates of restenosis and adverse vessel remodeling.[18–21]

Although there is no clear consensus for the timing and role of revascularization in coronary vasculitis, the reported success with medical therapy and immunosuppression, in addition to the established complications of stenting other noncoronary vasculitic lesions, should prompt clinicians to consider an initial trial of medical therapy whenever clinically feasible. Long-term follow-up of patients with coronary vasculitis should include monitoring of disease activity and a low threshold to repeat coronary investigation for signs or symptoms concerning for myocardial ischemia.

This case illustrates the multitude of challenges associated with managing coronary artery vasculitis. The cause of the patient's presentation was initially unclear, with a history of ACS presumed secondary to atherosclerotic plaque rupture and several traditional coronary artery disease risk factors but in the setting of an active scleroderma flare with angiographic findings concerning for vasculitis. The cause of the coronary vasculitis was perplexing without clear evidence of a systemic vasculitis or overlapping rheumatologic disorder that has been associated with coronary involvement. Finally, the treatment was challenging with refractory ischemia despite maximal medical therapy for 10 days that ultimately required coronary stenting. Moving forward, her follow-up will likely continue to challenge her physicians, and the absence of clear laboratory or noninvasive methods

to trend disease activity may warrant periodic coronary angiography and intracoronary imaging.

Conclusions

This case challenged our traditional differential diagnosis for an acute coronary process, highlighted our limited understanding of the disease states associated with coronary artery vasculitis, and revealed the utility of careful selection of diagnostic studies to navigate a complex case. Furthermore, it required careful consideration of the history, presentation, and response to therapy in the management of an unusual disorder in which there are few if any rigorous data. Current algorithms for the management of typical ACSs must be balanced with the need for circumspect navigation of rare disease biology using first principles, the tools of modern cardiology, and collaborative clinical engagement on the risks and benefits for specific therapies.

Disclosures

Dr Mauri has received consulting fees from AstraZeneca, Biotronik, Boeringher Ingleheim, Corvia, Daiichi Sankyo, Recor, Sanofi, and St. Jude Medical. The other authors report no conflicts.

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