Myocardial Catastrophe
A Case of Sudden, Severe Myocardial Dysfunction

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Forward
Information about a real patient is presented in stages (boldface type) to expert clinicians (Dr James M. Kirshenbaum and Dr Gayle L. Winters), who respond to the information, sharing their reasoning with the reader (regular type). A discussion by the authors follows.

A 44-year-old woman presented to her local emergency room with a 1-day history of nausea, fatigue, and fever of 101°F. At that time, she denied chest pain, dyspnea, cough, orthopnea, or lower-extremity edema. An ECG was reportedly normal, and she was treated with antiemetics and fluids and discharged home. The next day, she developed persistent, aching pain in her chest and jaw and presented to her primary care physician. Her medical history included obesity, depression, hyperlipidemia, and antiphospholipid antibody syndrome (APLAS) initially diagnosed in 1989 when she was 20 years of age complicated by 4 miscarriages, pulmonary emboli, and deep vein thrombosis for which she underwent inferior vena cava filter placement in 1997. She had experienced no thromboembolic events over the next 15 years. Her home medications were rivaroxaban 20 mg daily, aspirin 81 mg daily, furosemide 20 mg daily, simvastatin 20 mg daily, escitalopram 20 mg daily, and omeprazole 20 mg daily. She worked as a nurse and lived with her husband and 4 adopted children. She never smoked. Her mother carried the diagnosis of factor V Leiden. She was scheduled for an elective gastric bypass surgery in 2 days and had been instructed to hold her rivaroxaban for 4 days before surgery; therefore, she stopped anticoagulation 2 days before presentation.

Dr Kirshenbaum: Her initial symptoms are quite nonspecific, with nausea and a low fever suggesting a viral process. However, the subsequent development of chest and jaw pain also raises the possibility of cardiac causes such as an acute coronary syndrome. Myocarditis also often presents with chest pain that can mimic an acute coronary syndrome and can be preceded by a viral prodrome. In addition, the recent discontinuation of rivaroxaban in a patient with a history of severe thrombophilia and APLAS is worrisome. Rivaroxaban carries a boxed warning that anticoagulant if clinically warranted.1 This patient had no bridging anticoagulation prescribed. Therefore, a new thrombotic event such as mesenteric ischemia or coronary thrombosis (epicardial or microvascular occlusion) must also be considered.

Patient presentation (continued): Her chest pain led to a repeat evaluation in the same emergency room where she had presented the day before. At this point, her ECG had ST-segment elevations in the inferior and apical leads (Figure 1) that were new compared with her ECG 24 hours earlier. Her laboratory work at that time was notable for a troponin I level of 19 ng/mL. She was given aspirin, clopidogrel, and atorvastatin, started on unfractionated heparin; and transferred to a percutaneous coronary intervention–capable facility for cardiac catheterization.

On arrival at the closest percutaneous coronary intervention–capable facility, she was afibrile and had a heart rate of 107 bpm, blood pressure of 105/74 mm Hg, respiratory rate of 24 breaths per minute, and oxygen saturation of 97% on 2 L oxygen. On physical examination, she appeared mildly dyspneic, complaining of positional chest pain. She was flushed and mildly diaphoretic. Her jugular venous pressure was 12 cm H2O; her lungs revealed bibasilar rales; and her cardiac examination was notable for tachycardia with a normal S1, narrowly split S2, and I/VI systolic murmur radiating from the apex to the base with no rub present. The abdomen was obese without ascites, hepatomegaly, or bruit. Distal lower extremities were slightly cool with 1+ symmetrical pulses and trace bipedal edema. Chest radiograph at that time was reported as mild pulmonary edema. Her complete blood count revealed a white blood cell count of 12.2×109 cells/L, a hematocrit of 34.7%, and a platelet count of 150×109 cells/L. Her electrolytes and renal function were normal. Her international normalized ratio (INR) was 1.45 and partial thromboplastin time (PTT) was >150 seconds on unfractionated heparin. Liver function tests showed the following: aspartate aminotransferase, 194 U/L; alanine aminotransferase, 66 U/L; alkaline phosphatase, 92 U/L; total bilirubin, 0.2 mg/dL; and direct bilirubin, less than assay.

Catheterization performed via the left radial artery revealed normal epicardial coronary arteries (Figure 2) with Thrombolysis in Myocardial Infarction (TIMI) grade

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2 flow throughout. A left ventriculogram demonstrated moderate systolic dysfunction and a left ventricular (LV) ejection fraction of 40% with midanterior wall and apical wall hypokinesis and inferior wall akinesis (Figure 3 and Movies I and II in the online-only Data Supplement).

Dr Kirshenbaum: At this point, an acute coronary syndrome resulting from epicardial thrombosis has been ruled out, yet the patient has evidence of systolic dysfunction and myocardial necrosis. TIMI grade 2 flow noted by catheterization may be due to elevated interstitial pressures in the myocardium secondary to myocardial edema or possibly to microvascular dysfunction or thrombosis. Her left ventriculogram demonstrates evidence of systolic dysfunction. Clinically, she has signs of biventricular failure with an elevated jugular venous pressure, trace lower-extremity edema, rales, and cool extremities. In this setting, myocarditis seems to be the most likely diagnosis.

A viral pathogen or the subsequent immune response is the most common cause of acute myocarditis; however, other causes must be considered. Giant-cell myocarditis can present with severe, acute systolic dysfunction that can improve with immunosuppression; therefore, timely diagnosis is crucial. Necrotizing eosinophilic myocarditis can also cause dramatic systolic dysfunction. In this patient with a history of APLAS, lupus myocarditis is also possible because ≈40% of APLAS patients have concomitant systemic lupus erythematous and patients with primary APLAS can progress to APLAS with systemic lupus erythematous. Lupus myocarditis can affect ≈10% of patients with lupus, typically presents with an indolent course, but can present acutely as well. In addition, her history of APLAS and recent cessation of rivaroxaban raise the possibility of a thrombotic process causing her symptoms. The absence of epicardial thrombosis on her coronary catheterization does not preclude microcirculatory thrombosis,
which often occurs in APLAS and may be reflected by the TIMI grade 2 flow that was noted by catheterization.

Diagnostically, transthoracic echocardiography will provide a more detailed assessment of her systolic function, but it will not distinguish between the entities currently entertained in the differential diagnosis. Cardiac magnetic resonance imaging (MRI) provides a wealth of information about the myocardium itself and therefore has become an increasingly common component of the evaluation for myocarditis and for other causes of myocardial necrosis. Parameters such as LV dysfunction with or without regional wall motion abnormalities, pericardial effusion, edema, hyperemia and capillary leak, necrosis, and fibrosis can all be evaluated with cardiac MRI and may establish the diagnosis of myocarditis versus a thrombotic process. Myocardial biopsy may also need to be considered, depending on her clinical course.

**Patient presentation (continued):** After catheterization, she continued to have chest pain with nausea, and her troponin I climbed to 26 ng/mL. Transthoracic echocardiogram demonstrated an ejection fraction of 30% with multiple wall motion abnormalities, most notable inferiorly. Because of her history of APLAS, she was continued on unfractionated heparin, and a computed tomography scan of her chest/abdomen/pelvis with contrast was negative for a pulmonary emboli or any arterial filling defects. The night after catheterization, she experienced ≥30 minutes of transient left-sided monocular blindness that completely resolved. She remained tachycardic and became increasingly dyspneic despite treatment with furosemide. Her worsening clinical status prompted transfer to a tertiary care center.

**Dr Kirshenbaum:** This patient has a rapidly progressive process causing a precipitous clinical decline and warrants urgent transfer to a tertiary care facility. The occurrence of amaurosis fugax after catheterization is worrisome for an embolic complication of the catheterization. Alternatively, this may be a thrombotic event secondary to her baseline APLAS. Although thrombosis on heparin with a therapeutic PTT is unlikely, lupus anticoagulants are common in APLAS, the presence of which can falsely elevate the PTT; thus, she could be subtherapeutically anticoagulated despite the appearance of a therapeutic PTT. Heparin-induced thrombocytopenia (HIT) is another possibility in a patient who develops thrombosis while on heparin. A careful history to obtain prior heparin exposures is necessary while her platelet count is closely monitored.

Patient presentation (continued): When she arrived at the tertiary care facility, she remained afebrile and had a heart rate of 105 bpm and regular, blood pressure of 100/70 mm Hg, respiratory rate of 22 breaths per minute, and an oxygen saturation of 95% on 4 L oxygen by nasal cannula. Her examination was similar to that described previously except for a notably cyanotic left distal index finger and mild cyanosis of the third through fifth fingers. The left radial catheterization site had a palpable pulse without hematoma. Her neurological examination was normal. Pertinent laboratory values included the following: creatinine, 0.92 mg/dL; troponin T, 4.39 ng/mL; C-reactive protein, 291 mg/L (normal < 3 mg/L); erythrocyte sedimentation rate, 115 mm/h (normal < 18 mm/h); PTT, 85 seconds (while on heparin); INR, 1.5; white blood cell count, 14×10⁹/L (differential with 90% neutrophils, 7% lymphocytes, no eosinophils); hematocrit, 34%; and platelet count, 77×10⁹/L (150×10⁹/L previously). ECG on transfer revealed persistent inferior and apical ST-segment elevations similar to those in Figure 1. A transthoracic echocardiogram was repeated, demonstrating severe systolic dysfunction (LV ejection fraction, 15%–20%), global hypokinesis affecting mostly the apex, and vague echodensities in the akinetic apex, raising the possibility of an intraventricular thrombus (Figure 4 and Movie III in the online-only Data Supplement).

**Dr Kirshenbaum:** Before transfer, myocarditis had seemed to be the most likely diagnosis. However, she now has had clinical evidence of digital thromboses in her left hand, an echocardiogram with a possible LV thrombus, an episode of amaurosis fugax, and thrombocytopenia, all of which raise the possibility that multiple thromboembolic or in situ thrombotic events are occurring. Amaurosis and the cyanotic fingers could be attributed to an embolus from an LV thrombus, a complication from catheterization, or a diffuse thrombotic process. Progressive thrombocytopenia and multiple prior exposures to heparin raise concern for HIT; however, thrombocytopenia can be seen in APLAS also. Catastrophic APLAS (C-APLAS) is a unifying diagnosis that would explain multiple thrombotic events and progressive systolic dysfunction resulting from microvascular occlusion. Therefore, the next diagnostic study must differentiate myocarditis from a thrombotic process.

The gold standard for diagnosis of myocarditis is an endomyocardial biopsy; however, cardiac MRI is now used routinely in the diagnosis of myocarditis because of its safety compared

![Figure 3. Left ventriculography in the long-](Image) and short-axis view revealed that the left ventricular cavity had a normal size with severely impaired systolic function, as well as anterior and apical wall hypokinesis and inferior wall akinesia (Movies I and II in the online-only Data Supplement). There was mildly increased thickness of the left ventricular wall, seen best in the short-axis view (B).
with biopsy. This particular patient has a Class I indication for myocardial biopsy with progressive systolic dysfunction over a short period of time (Table 1); however, the risk of a myocardial biopsy is relatively high in this situation. A native heart biopsy carries the risk of perforation with tamponade. Therefore, the risks of bleeding and tamponade are elevated, whereas cardiac MRI is noninvasive and has a high likelihood to distinguish between myocarditis and a more diffuse thrombotic process.

Key management decisions for the patient at this point include whether immunosuppression should be empirically started out of concern for giant-cell myocarditis and for anticoagulation management. Immunosuppression is not routinely recommended in suspected cases of myocarditis; however, early immunosuppression is beneficial in giant-cell myocarditis. After careful consideration of immunosuppression, this line of therapy was not pursued empirically because of concern that it may worsen her clinical situation if she had a viral myocarditis. Hematologic consultation is necessary at this point for expert guidance in anticoagulation while the diagnosis of C-APLAS and HIT are both entertained. In addition, empirical therapy of C-APLAS may need to be considered while further diagnostic testing proceeds.

**Patient presentation (continued):** The patient’s heparin was stopped and bivalirudin was started out of concern for HIT. Platelet factor 4 (PF-4) antibodies were sent, as well as antiphospholipid antibody testing. Right heart catheterization with pulmonary artery catheter placement was performed to guide management with the following results: right atrium, 12 mm Hg; right ventricle, 45/12 mm Hg; pulmonary artery, 46/30/37 mm Hg; pulmonary capillary wedge pressure, 27 mm Hg; cardiac output, 2.9 L/min; and cardiac index, 1.4 L·min⁻¹·m⁻². Cardiac MRI revealed a mildly dilated LV, severe biventricular systolic dysfunction (LV ejection fraction, 20%; right ventricular ejection fraction, 19%), without an LV thrombus (Movies IV and V in the online-only Data Supplement). There was diffuse myocardial edema with patchy subendocardial perfusion defects (Movie VI in the online-only Data Supplement) and diffuse late gadolinium enhancement consistent with myocarditis, microvascular obstruction, or vasculitis (Figure 5).

Per the evaluation by hematology, HIT was deemed unlikely as a result of the timing of the decrease in her platelet count. Thrombocytopenia caused by HIT typically occurs after several days of treatment with heparin, whereas her platelet count dropped on the same day as exposure to heparin, and she had no heparin exposures in the prior 6 months. The initial assessment was that myocarditis was the most likely explanation of her symptoms and that C-APLAS was unlikely because her primary manifestations were predominantly cardiac.

**Dr Kirshenbaum:** The results of the cardiac MRI are consistent with a diffuse necrotic process involving the entire myocardium. There was no LV thrombus, making it less likely that the episode of amaurosis fugax or the cyanotic fingers were due to embolization originating from the heart. Unfortunately, the cardiac MRI was not able to distinguish between myocarditis or a diffuse microvascular ischemic process. The cardiac MRI also raised the possibility of a third entity, namely a vasculitis that had not been considered previously.

At this point in her clinical course, she has rapidly worsening heart failure with hemodynamic compromise evidenced by elevated filling pressures and low cardiac output. Each evaluation of her systolic function demonstrates progressive decline. Her biomarkers have continued to rise, and unfortunately, her diagnostic workup thus far has not distinguished between myocarditis and a thrombotic process. Therefore, a biopsy should be performed as the next diagnostic test with careful management of her anticoagulation and hemodynamics around the time of biopsy (Table 1).

**Patient presentation (continued):** A serological evaluation for vasculitis, including ANA, double-stranded DNA, HIV, and hepatitis serologies, was ultimately negative. Bivalirudin was stopped and heparin was reinitiated with monitoring of factor Xa levels. Initial attempts at diuresis were successful; however, she subsequently developed atrial fibrillation with a rapid ventricular response, causing significant hemodynamic instability that required initiation of inotropes and intubation. As a result of progressive hemodynamic collapse, a percutaneous LV assist device (LVAD; TandemHeart) was inserted on hospital day 2. When the patient was stabilized...
Table 1. Current Guidelines on the Use of Endomyocardial Biopsy Presented as 14 Distinct Clinical Scenarios

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Clinical Scenario</th>
<th>Class of Recommendation (I, IIa, IIb, III)</th>
<th>Level of Evidence (A, B, C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>New-onset heart failure of &lt;2-wk duration associated with a normal-sized or dilated left ventricle and hemodynamic compromise</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>2</td>
<td>New-onset heart failure of 2-wk to 3-mo duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1–2 wk</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>3</td>
<td>Heart failure of &gt;3-mo duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1–2 wk</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>4</td>
<td>Heart failure associated with a DCM of any duration associated with suspected allergic reaction or eosinophilia</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>5</td>
<td>Heart failure associated with suspected anthracycline cardiomyopathy</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>6</td>
<td>Heart failure associated with unexplained restrictive cardiomyopathy</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>7</td>
<td>Suspected cardiac tumors</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>8</td>
<td>Unexplained cardiomyopathy in children</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>9</td>
<td>New-onset heart failure of 2-wk to 3-mo duration associated with a dilated left ventricle, without new ventricular arrhythmias or second- or third-degree heart block, that responds to usual care within 1–2 wk</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>10</td>
<td>Heart failure &gt;3-mo duration associated with a dilated left ventricle, without new ventricular arrhythmias or second- or third-degree heart block, that responds to usual care within 1–2 wk</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>11</td>
<td>Heart failure associated with unexplained HCM</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>12</td>
<td>Suspected ARVD/C</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>13</td>
<td>Unexplained ventricular arrhythmias</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>14</td>
<td>Unexplained atrial fibrillation</td>
<td>III</td>
<td>C</td>
</tr>
</tbody>
</table>

ARVD/C indicates arrhythmogenic right ventricular dysplasia cardiomyopathy; DCM, dilated cardiomyopathy; and HCM, hypertrophic cardiomyopathy. Reproduced from Cooper et al.9

Management of C-APLAS consists of persistent anticoagulation, strategies to reduce inflammation, and reducing the titer and pathogenicity of the antiphospholipid antibodies present (Table 2).12 Intravenous corticosteroids have been used to reduce inflammation and the systemic inflammatory response syndrome that occurs during C-APLAS. Intravenous immunoglobulin has been used to block the antiphospholipid antibodies and to increase their clearance,11 but it would constitute a large volume load for a patient in cardiogenic shock. Plasma exchange has emerged as one of the most effective treatments of C-APLAS because it removes the pathological antibodies and inflammatory cytokines and replaces anticoagulant proteins such as proteins C and S, which become depleted during C-APLAS.11,13 Rituximab, a monoclonal antibody for CD20-positive B cells, has also been used in the treatment of C-APLAS in an effort to reduce the production of the antiphospholipid antibodies.14

In addition to the management of the C-APLAS itself, her tenuous hemodynamics must be addressed. Support with a percutaneous LVAD is temporary, and she will need to be transitioned to more definitive long-term therapy. Consideration of an LVAD is reasonable; however, the possibility of an LVAD thrombosis is very real. In addition, the diffuse nature of her myocardial injury may necessitate biventricular support rather than an LVAD alone. Surgery is a common trigger for C-APLAS because of the associated systemic inflammatory response syndrome.11 Therefore, placing an LVAD via a sternotomy would likely increase the risk of an LVAD thrombus in the perioperative period. If LVAD or biventricular support is pursued, one must also consider if she would receive such support as a bridge to transplantation or recovery or as destination therapy. Cardiac transplantation will carry similar...
thrombotic risks around the time of surgery. However, it is certainly reasonable to begin an evaluation for cardiac transplantation should this be deemed an option.

Patient presentation (continued): Fortunately, our patient stabilized on the percutaneous LVAD, and discussions focused on the possibility of VAD implantation and concern about thrombosis. In consultation with the hematology service, it was decided to proceed with VAD placement. To reduce the likelihood of thrombosis, she was treated with heparin, steroids, rituximab, and plasmapheresis using a replacement fluid of fresh-frozen plasma on the day before surgery. On the day of surgery, she underwent plasmapheresis during the operation, and her titer of antibodies to β-2 glycoprotein-1 decreased to 12 U by postoperative day (POD) 1. Biventricular Thoratec paracorporeal VADs were implanted as a bridge to recovery or transplantation. Her chest was left open because of edema. She again underwent plasmapheresis on PODs 1 and 2. Heparin was reinitiated on POD 1. She returned to the operating room on POD 4 for attempted chest closure but was still too edematous. Her chest was ultimately closed on POD 8. She underwent plasmapheresis around the time of each surgery. She continued weekly rituximab infusions for a total of 5 doses. Her heparin was transitioned to warfarin with a goal INR of 3 to 4.5. She suffered a small stroke causing mild right arm weakness in the perioperative period. She was discharged 64 days after presentation to home with services. Eleven months after implantation, no clotting events have occurred. She has had recurrent gastrointestinal bleeding while anticoagulated. Follow-up evaluations of her cardiac function have shown some mild improvement in her LV function but continued VAD dependence on the right. She is currently listed for heart transplantation.

Discussion

Management of Novel Anticoagulants

There are now many choices for oral anticoagulation, and the use of novel oral anticoagulants (NOACs) has spread to several indications. The majority of data supporting the clinical use of NOACs are in the setting of venous thromboembolism and nonvalvular atrial fibrillation. To date, there has not been a completed randomized trial of NOACs in the setting of APLAS; however, a randomized trial comparing rivaroxaban with warfarin in this setting is currently underway. In the absence of data supporting the use of NOACs in APLAS, current recommendations for the treatment of APLAS suggest the continued use of warfarin.

The Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) trial compared the use of rivaroxaban and warfarin in patients with nonvalvular atrial fibrillation and demonstrated that rivaroxaban was noninferior to warfarin in that setting. At the end of the trial, patients were transitioned from the study drug to warfarin. There was an observed increase in stroke and non–central nervous system embolism in patients...
randomized to rivaroxaban as they transitioned back to warfarin within the first 30 days after the trial ended compared with patients who had been on warfarin during the trial (22 versus 6 events; \( P=0.004 \)). On the basis of these data, there was concern that the cessation of rivaroxaban may lead to a rebound effect and the generation of a prothrombotic state, which led to a boxed warning in the packaging of rivaroxaban. The warning indicated that discontinuation of rivaroxaban increases the risk of thrombotic events and suggested transition to another anticoagulant when clinically feasible. Similar to the end of the ROCKET AF trial, an increase in stroke and systemic embolization was observed at the end of the Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation (ARISTOTLE) trial when patients were randomized to apixaban as they transitioned back to warfarin. This phenomenon led to a similar boxed warning for apixaban.

Subsequent analysis of the ROCKET AF patients demonstrated that during the trial, thrombotic events were similar between the rivaroxaban group and the warfarin group when either anticoagulant was stopped temporarily or permanently, and only during the transition to warfarin did the increase in thrombotic events occur. The excess thrombotic risk during this time was attributed to a prolonged period during which the INR was not therapeutic in the patients transitioned from apixaban to warfarin. This phenomenon led to a similar boxed warning for apixaban.

In general, these data underscore that discontinuation of NOACs is clinically distinct from cessation of warfarin, and bridging with another anticoagulant should be pursued if clinically appropriate. Further guidelines need to be developed to guide clinicians through the nuances of treatment with NOACs. In the meantime, however, bridging anticoagulation should be strongly considered in patients like ours with a significant history of thrombophilia.

**Evaluation of Suspected Myocarditis**

Establishing the diagnosis of myocarditis is often quite challenging. Its presentation can range from asymptomatic to cardiogenic shock. Symptoms of chest pain, heart failure, and arrhythmias are common; thus, it cannot be reliably diagnosed by clinical criteria alone. Viral myocarditis is the most common cause, but identifying the virus responsible can be quite challenging. Often, serological evidence of a viral infection is interpreted as evidence of viral myocarditis. However, a recent study comparing viral serologies with viral DNA and RNA isolated from myocardial biopsies showed no correlation. Therefore, serologies alone cannot be relied on to make the diagnosis of viral myocarditis. Eosinophilic myocarditis must be considered early and is typically seen in conjunction with a prior history of allergies, atopy, or asthma, as well as peripheral eosinophilia. As mentioned, giant-cell myocarditis must also be considered early in the course of a patient with rapidly progressive systolic dysfunction because early treatment with immunosuppression may alter the dismal prognosis of this entity.

Typically, the diagnosis is inferred on the basis of clinical presentation, biomarkers, and imaging studies such as cardiac MRI. However, the gold standard for diagnosis remains the myocardial biopsy. Although biopsy carries inherent risk, when it is performed in experienced centers, the complication rate is low, with a published rate of serious complications of \( \approx 1\% \) in native heart biopsies. Patients with elevated right-sided pressures, recent treatment with heparin, and right ventricular enlargement may be at a higher risk. Although the false-negative rate of biopsy is near 50\% owing to sampling error, this may be improved through guidance from the MRIs, and in a patient with a global process that affects the entire myocardium, the false-negative rate may be less. In a patient like ours whose presentation is consistent with fulminant myocarditis, the risk of biopsy is likely outweighed by the diagnostic information gained through biopsy and should be pursued if possible (Table 1).

**Diagnosis and Management of C-APLAS**

C-APLAS is a disorder of thrombotic events or obstetric complications such as repeated miscarriages in the presence of sustained high titters of antiphospholipid antibodies. C-APLAS is a rare subset of APLAS characterized by clotting in multiple vascular beds over a short period of time, often leading to multiorgan failure and carrying a very high mortality rate. Diagnostic criteria of this entity include involvement of \( \geq 3 \) organ systems with manifestations in \( <1 \) week, evidence of small-vessel occlusion by biopsy, and presence of antiphospholipid antibodies. C-APLAS must be suspected early in the disease course to initiate multidisciplinary treatment of the disease itself and its end-organ effects. Our patient’s presentation was slightly atypical in that she had predominant involvement of 1 organ system; however, she clearly had thrombotic events that affected her central nervous system (amaurosis fugax) and her hand distal to her radial catheterization site. In general, arterial catheterization should be used judiciously in patients suspected of having C-APLAS because intravascular instrumentation can lead to new clot formation.

Mechanisms leading to C-APLAS are incompletely understood but likely initially involve activation of the endothelium from infection, oxidative stress, or injury. Activated endothelium can then be bound by immune complexes of \( \beta-2 \) glycoprotein-1, which promotes thrombosis through a number of mechanisms, resulting in vessel injury, cytokine release, the...
systemic inflammatory response syndrome, and then further activation of endothelium, which triggers the formation of more microthrombi. Microvascular thrombosis itself may also lead to a thrombotic cascade in APLAS patients as a result of tissue necrosis, generation of thrombin, and consumption of natural anticoagulant proteins such as proteins C and S.

Standard initial testing for antiphospholipid antibodies will include an ELISA for the IgG and IgM forms of both cardiolipin and β-2 glycoprotein-1 antibodies. In addition, coagulation studies will be performed to detect the presence of a lupus anticoagulant. The presence of a lupus anticoagulant will often falsely elevate the PTT and is suspected when there is prolongation of in vitro clotting assays such as the PTT that does not correct with a mixing study. Therefore, the presence of a lupus anticoagulant makes dosing of heparin more problematic as a result of the artificial prolongation of the PTT. To ensure that appropriate anticoagulation is achieved, one must follow anti-factor Xa levels in the presence of a lupus anticoagulant. Multiple antibodies can possess lupus anticoagulant activity, including antibodies to prothrombin, cardiolipin, β-2 glycoprotein-1, or annexin V.

Risk of thrombosis in APLAS patients is dependent on their antiphospholipid antibody profile. Having a lupus anticoagulant present confers an odds ratio of 11 for thrombosis compared with control subjects versus 1.6 in the presence of antcardiolipin antibodies alone. Patients who are positive for a lupus anticoagulant, antcardiolipin antibody, and anti-β-2 glycoprotein-1 antibodies (so-called triple-positive patients) are at particularly high risk for rethrombosis. Unfortunately, our patient was triple positive. The most common clinical risk factors for thrombosis are infection, surgery, and stopping anticoagulation, as happened in this case.

Because C-APLAS is a rare clinical entity, data and guidelines pertaining to therapy are derived mostly from registries of patients rather than randomized studies of treatment strategies. The mainstay of treatment in C-APLAS include anticoagulation, immunomodulation, and reduction of pathogenic antibody titers through plasma exchange or intravenous immunoglobulin (Table 2). An analysis of 280 patients with C-APLAS indicated that the greatest marginal benefit was achieved with anticoagulation, followed by the addition of corticosteroids and either plasma exchange or intravenous immunoglobulin therapy. Treatment with anticoagulation, steroids, and plasma exchange had the highest rate of recovery at 77.8%, whereas a small number of patients who had rituximab added to this regimen (in most cases because of an aggressive clinical course) had a survival rate of 75%. Cyclophosphamide has also been used, but its use has not demonstrated any benefit over anticoagulation, steroids, and plasma exchange.

Use of Mechanical Support in C-APLAS

The use of mechanical support in a patient with APLAS or C-APLAS is fraught with concern about VAD thrombosis. VAD thrombosis is a dreaded complication of mechanical support that may lead to stroke, distal arterial embolism, or hemodynamic collapse and is often treated with pump exchange. Therefore, anticoagulation management must be precisely planned around the time of VAD implantation in a patient with C-APLAS. There are 5 cases in the literature in which a VAD has been used to treat patients with APLAS. At least 3 patients survived until transplantation, proving that APLAS patients can survive a transplantation with careful anticoagulation management around the time of surgery. However, none of these patients were noted to have C-APLAS. The diagnosis of APLAS was not known at the time of LVAD implantation in 4 of these cases. In the other case, the patient was managed with plasmapheresis and rituximab before LVAD implantation. In our patient, we followed a similar approach with steroids, rituximab, and plasma exchange performed before VAD implantation, allowing anticoagulation to be stopped in the perioperative period without thrombosis. Of the reported cases, 1 LVAD thrombosis occurred in a patient who was diagnosed with APLAS postmortem. To the best of our knowledge, this case represents the first reported case in which biventricular VAD support was used in the treatment of C-APLAS.

Summary

This case underscores the need to apply a wide differential diagnosis in a patient with an atypical and dramatic presentation of acute heart failure progressing to cardiogenic shock. Cardiac MRI and myocardial biopsy played a central role in the timely diagnosis of her disease and should be considered early in the diagnostic workup of a fulminant presentation. Only with a multidisciplinary approach involving several subspecialties of cardiology, hematology, pathology, radiology, and cardiac surgery was this patient rescued from a nearly fatal event; she now awaits transplantation.

Disclosures

None.

References


20. US Food and Drug Administration. Safety information: Eliquis (apixaban)


Key Words: anticoagulants ■ antiphospholipid syndrome ■ heart-assist devices ■ shock, cardiogenic