

CASE OF THE MONTH

A Young Woman with Someone Else's Heart

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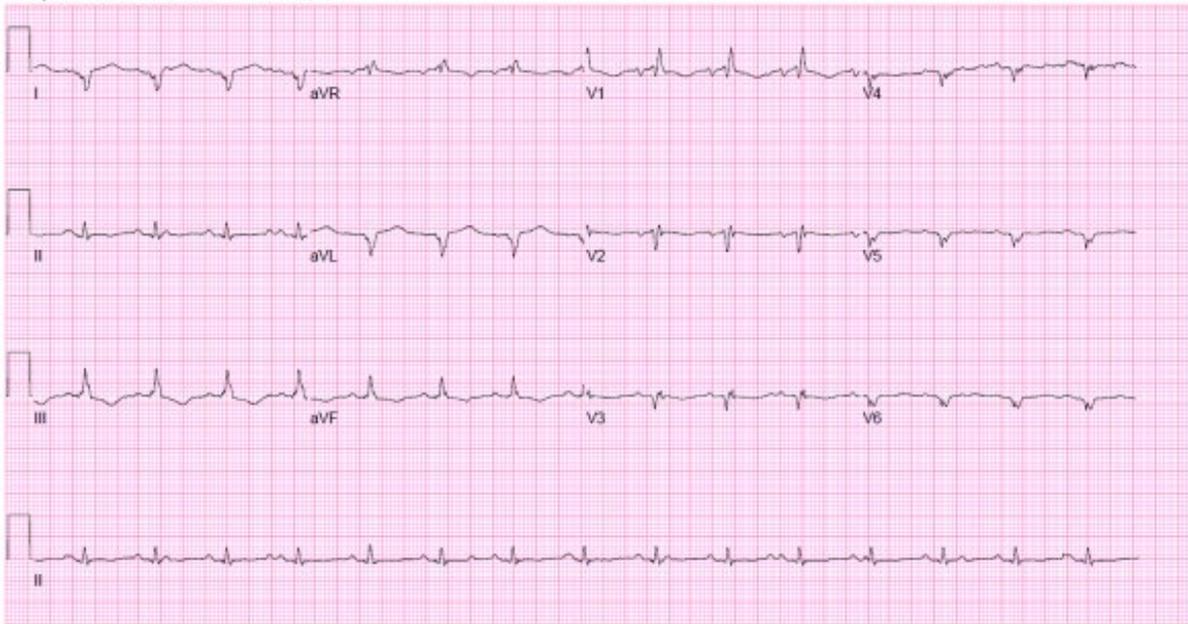
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CASE PRESENTATION

The patient was a 26-year-old woman with a history of two previous heart transplants, the first one performed in 2014 for hypertrophic cardiomyopathy with intractable heart failure and the second one in 2016 for graft failure. She continued to have multiple episodes of rejection despite different antirejection protocols. Serial ejection fractions (EF) by echocardiography over the past 2 years were in the low-to-mid 30% range with anteroseptal and apical akinesis and a layered apical thrombus for which she was given apixaban. Coronary computed tomography angiography in October 2018 showed normal coronary arteries. The same year, she had an implantable cardioverter-defibrillator placed because of the low EF and multiple episodes of nonsustained ventricular tachycardia. A positron emission tomography scan done in 2019 revealed a moderate-size fixed defect in the distal septal and anterior segments and decreased fluorodeoxyglucose uptake in the apex that was consistent with nonviable segments, presumed to have resulted from previous rejection episodes. Resting EF was 31% and her calcium score was zero.

The patient also had steroid-induced diabetes and severe obesity. In 2019, she underwent laparoscopic sleeve gastrectomy. She was in NYHA class II heart failure and stable until 2 weeks before admission, when she developed nausea and intermittent emesis that progressed over 3 days and was accompanied by increasing dyspnea and 6-pound weight gain. Because of these symptoms, she was directly admitted from the transplant clinic for further evaluation. An electrocardiogram (ECG) was performed on admission (Figure 1).

Figure 1: Electrocardiogram on admission



Physical Examination on Admission

VITALS: Temperature 98.4°F, pulse 96 BPM, respirations 17/min, blood pressure 89/53 mm Hg, oxygen saturation 96% on room air

GENERAL: Well-nourished overweight female in mild respiratory distress

HEENT: Normocephalic, atraumatic; no carotid bruits or jugular vein distention.

HEART: Regular rhythm; no murmurs or gallops

LUNGS: Bibasilar crackles present, equal expansion on both lungs

ABDOMEN: Soft, no guarding, hypoactive bowel sounds

EXTREMITIES: Trace bilateral lower extremity edema present, 2+ pulses throughout

SKIN: Cool and clammy extremities; no rashes

NEUROLOGY: No focal abnormalities

Initial Laboratory Findings

Elevated creatinine at 2.16 mg/dL (increased from a baseline of 1.6 mg/dL)

Normal electrolytes

Hb 9.7 g/dL

Mild troponin I elevation at 0.366 ng/mL (unchanged from a month ago)

BNP 2700 pg/mL (increased from 288 pg/ml one month prior)

INR 1.0

PTT 28.1 sec

Normal liver functions tests

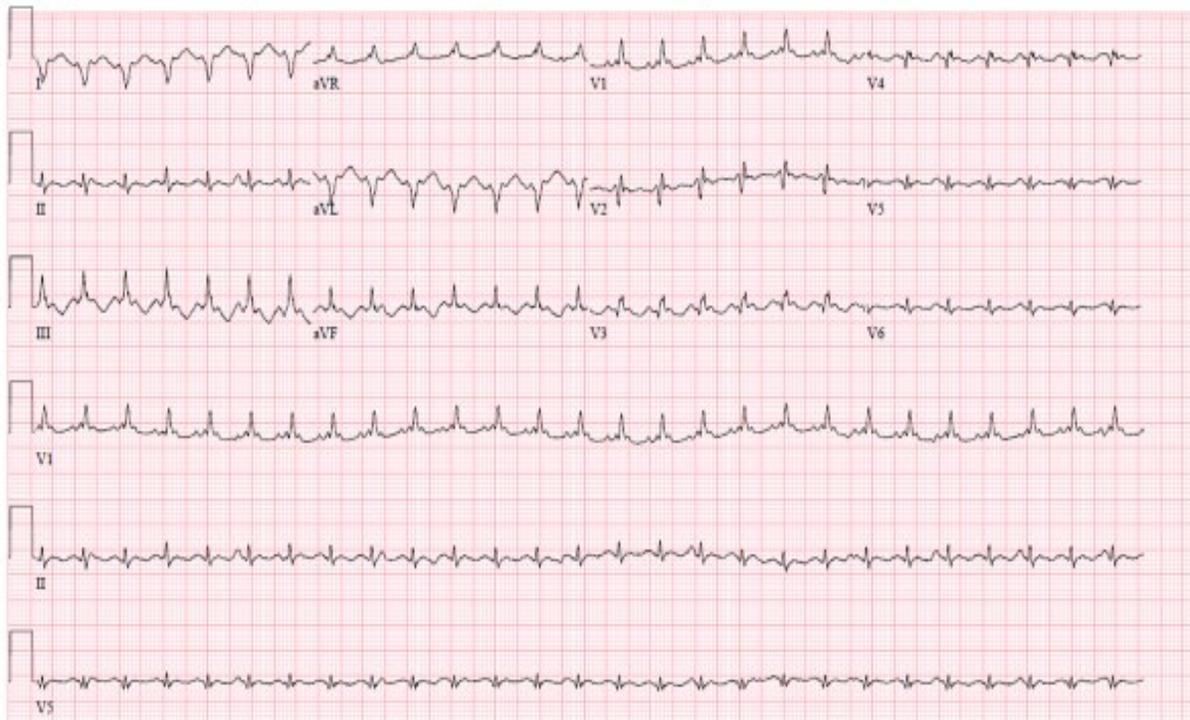
Initially, she was treated for her gastrointestinal symptoms. An echocardiogram demonstrated an EF similar to previous ones (EF in the 30% range) with anteroapical akinesis and an apical thrombus (Video

1). Pulmonary artery systolic pressure was estimated at 32 mm Hg with a right arterial (RA) pressure of 10 mm Hg.

Video 1: Echocardiogram on admission <https://youtu.be/RtVfAs5LbSs>

On the second hospital day, the patient complained of palpitations and worsening dyspnea. An ECG was performed (Figure 2).

Figure 2. Electrocardiogram taken during palpitations



QUESTION 1: The electrical rhythm shown is:

- A. Sinus tachycardia
- B. Supraventricular tachycardia
- C. Atrial flutter
- D. Atrial fibrillation

ANSWER

C: Atrial flutter.

Explanation: Ventricular rate is ~150 BPM, and in leads II, AVF, and V1, one can see two P-waves at a rate of ~300 BPM, consistent with atrial flutter with 2:1 atrioventricular conduction.

QUESTION 2: What would you do next?

- A. Start a diltiazem drip to lower the heart rate
- B. Initiate treatment with amiodarone and intravenous steroids, followed promptly by endomyocardial biopsy

- C. Perform a transesophageal echocardiography-guided cardioversion
- D. Give intravenous labetalol drip to lower the heart rate

ANSWER

B: Initiate treatment with amiodarone and intravenous steroids, followed promptly by endomyocardial biopsy

CASE CONTINUED

The patient was treated with amiodarone 150 mg bolus followed by 1 mg/min for 6 hours, then 0.5 mg/min for 18 hours. She was then taken to the catheterization laboratory for hemodynamics and an endomyocardial biopsy. The following measures were obtained:

Cardiac output	5.7 L/min
RA pressure	14 mm Hg
Pulmonary artery (PA) pressure	34/22 mm Hg
Mean pulmonary capillary wedge (PCW) pressure	20 mm Hg

Endomyocardial biopsy demonstrated no evidence of acute cellular rejection, but the immunohistochemical stain for C4d was positive in 30% of myocardial capillaries in the setting of newly detected donor-specific antibodies. Therefore, the patient was diagnosed with acute antibody-mediated rejection. She converted to sinus rhythm within 1 day of treatment with intravenous amiodarone and was transitioned to PO 200 mg daily continued through discharge. Antirejection therapy was optimized resulting in gradual clinical improvement. The patient was discharged 3 weeks after admission and has remained stable. EF improved to 40% by echocardiography and 38% by cardiac magnetic resonance. The anteroapical wall motion abnormalities and the mural thrombus persisted.

DISCUSSION

The prognosis of heart transplant continues to improve over time as medical management and surgical techniques advance. Median survival after heart transplantation between 2002 and 2009 was 12.5 years.¹ Acute graft failure, infection, and rejection account for the leading causes of death during the first months after transplant; other causes, including malignancy, cardiac allograft vasculopathy, and renal failure, contribute more frequently with time after transplant.¹ Manifestations of allograft rejection are manifold and include cardiac arrhythmias. Early detection of significant arrhythmias as a harbinger of acute allograft rejection is a clinical skill that should be recognized.

Under normal physiology after orthotopic heart transplant (OHT), the absence of parasympathetic innervation results in elevated resting heart rates.² The pathogenesis of arrhythmias after OHT are driven by multiple mechanisms, and the timing of arrhythmia onset relative to transplant time often signals distinctive mechanisms with varying severity. One case series showed that acute rejection often involved the conduction system as much as the myocardium itself.³ Occasionally, acute allograft rejection has been shown to selectively involve the conduction system.⁴ By contrast, early post-operative mechanisms include surgical trauma and ischemia during donor preservation, while later

onset arrhythmias may reflect causes such as accelerated atherosclerosis and chronic obstructive vasculopathy of the sinoatrial artery.³

Bradycardia requiring pacemaker implantation following OHT is not uncommon with pacemaker implantation rates of 10% to 20% reported in several case series.⁵⁻⁸ Initial management may include theophylline, terbutaline, or albuterol for mild to moderate SA nodal disease. Severe bradycardia or bradycardia persisting greater than 2 weeks may require pacemaker placement. The more recent use of the bicaval surgical technique has resulted in a lower requirement for pacemaker implantation.⁹

Right bundle branch block is one of the most common conduction disturbances after OHT, with an incidence of approximately 70%.¹⁰ Prognosis is thought to be benign, and there is no association with increased mortality or sudden cardiac death in an observational study.¹¹

Atrial fibrillation and atrial flutter have been observed in 5% to 11% of case series within the first 2 months following OHT.¹² In a case series of 729 patients, atrial flutter was observed more frequently than atrial fibrillation (9% vs 7%, respectively).¹³ Late presentations (ie, after 1 month post OHT) of atrial fibrillation have been associated with decreased systolic function and increased mortality.¹⁴ Furthermore, sustained atrial flutter and atrial fibrillation can reflect allograft rejection. This should be quickly recognized by the clinician so that prompt action can be taken; possible responses include evaluation of heart function by echocardiography, endomyocardial biopsy, empiric pulse dose steroid administration, and intensification of the immunosuppressive regimen. These actions are usually done in consultation with an advanced heart failure team.

The pharmacologic management of atrial fibrillation and atrial flutter following OHT requires special considerations. In general, experts have cautioned against the use of adenosine for diagnosis or management of atrial flutter due to its potential for significant bradyarrhythmias, although a recent case series involving both pediatric and adult patients has suggested adenosine to be safe.¹⁵

Atrioventricular nodal blockers including nondihydropyridine calcium channel blockers and beta-blockers have traditionally been avoided due to the potential to cause significant bradyarrhythmia. Diltiazem inhibits the CYP3A enzyme that metabolizes tacrolimus and cyclosporine. This drug-drug interaction leads to toxic levels of tacrolimus and cyclosporine.

Patients with atrial fibrillation or flutter after cardiac transplant are often treated with a rate control strategy followed by cardioversion if necessary. One case series described the use of beta-blockers, amiodarone, and sotalol followed by discontinuation of the antiarrhythmic after restoration of normal sinus rhythm to avoid adverse effects. This approach was observed to be associated with low recurrence rates.^{13,16} Patients failing initial antiarrhythmic therapy have undergone successful radiofrequency ablation.¹³ Anticoagulation for stroke prevention is favored in those with late-presenting supraventricular tachycardia because observational studies have shown higher rates of stroke in transplant patients with atrial fibrillation or flutter treated based on CHADS2 score compared to transplant patients in normal sinus rhythm.¹⁷

Our patient had antibody-mediated rejection. She was treated with amiodarone in addition to an intensified immunosuppressive regimen. With these interventions, she returned to normal sinus rhythm and clinically recovered to her baseline function.

TAKE-HOME POINTS

- Atrial fibrillation and atrial flutter may present after orthotopic heart transplant and may signal acute heart failure and graft rejection.
- Prompt recognition is key. Endomyocardial biopsy is the method of choice to diagnose rejection. However, antirejection treatment should be instituted while awaiting biopsy results.
- Amiodarone, beta blockers, or sotalol have been used for initial pharmacologic management in appropriate cases.
- Nondihydropyridine calcium channel blockers and have traditionally been avoided. Diltiazem interacts with the CYP3A enzyme and may lead to toxic levels of tacrolimus and cyclosporine.

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