M. Barbandi, M.D.

A CASE SERIES OF REVERSIBLE ACUTE CARDIOMYOPATHY ASSOCIATED WITH H1N1 INFLUENZA INFECTION

Mazen Barbandi, M.D.^a; Andrea Cordero-Reyes, M.D.^b; Carlos M. Orrego, M.D.^b; Guillermo Torre-Amione, M.D., Ph.D.^{b, c}; Harrish Seethamraju, M.D.^d; Jerry Estep, M.D.^b

^aWeill Cornell Medical College, New York, New York/The Methodist Hospital, Houston, Texas; ^bMethodist DeBakey Heart & Vascular Center, The Methodist Hospital, Houston, Texas; ^cInstitutos y Centros Médicos del Tecnológico de Monterrey Hospital San José TEC, Monterrey, Mexico; ^dBaylor College of Medicine, Houston, Texas

Introduction

Cardiomyopathy refers to nonspecific myocardial dysfunction that may be due to a variety of causes. Viral illnesses have long been known to cause cardiomyopathy, and the list of viral causes is extensive.¹ Influenza infection is a rare cause of myocarditis. Recent reports, however, indicate that influenza A (H1N1) can cause acute myocarditis and cardiomyopathy in adults and fulminant myocarditis in children as seen during the 2009 global outbreak of the H1N1 influenza virus.^{2, 3} The following presents a case series of adult patients with acute reversible cardiomyopathy associated with influenza A (H1N1) infection (see Table 1 for patient characteristics).

Table 1. Patient characteristics at time of admission and treatment during hospitalization.

	Case 1	Case 2	Case 3
Age (years)	58	48	66
Gender	Male	Female	Male
Race	Caucasian	Caucasian	Hispanic
Co-morbidities			
Coronary artery disease	+	-	-
Diabetes mellitus	+	+	-
Hypertension	+	-	-
Hyperlipidemia	+	-	-
Chronic kidney disease	-	+	-
Chronic lung disease	-	+ ¶	+ £
Symptoms	productive cough SOB fatigue	productive cough SOB	dry productive cough SOB
Selected Laboratory Values			
Creatine kinase at admission (U/L)	261	260	67
Peak creatine kinase (U/L)	1337	289	144
Troponin I at admission (ng/ml)	0.8	0.16	1.06
Peak troponin I (ng/ml)	1.91	3.43	1.17
BNP at admission (pg/ml)	105	182	1065
Peak BNP (pg/ml)	*	1175	2754
Arrhythmia during course of illness	-	-	+**
Treatment during course of illness			
Diuretics	+	+	+
B-Blockers	-	+	-
Vasopressors/Inotropes	+	-	+
IABP	-	-	+
Oseltamivir	+	+	+
IVIG	-	+	+
Antibiotics	+	+	+

*Single BNP value; **AF: atrial fibrillation; SOB: shortness of breath; BNP: brain natriuretic peptide; IABP: intra-aortic balloon pump; IVIG: intravenous immunoglobulin; ¶: cystic fibrosis; £: idiopathic pulmonary fibrosis post double lung transplant.

Table 2. Echocardiographic parameters of three cases with H1N1 Influenza at time of admission and at time of recovery (8 to 14 days after admission).

	Case 1		Case 2		Case 3	
	Admission	Day 7	Admission	Day 10	Admission	Day 14
Heart rate (bpm)	92	82	106	104	105	96
LVEF (%)	32	57	15	67	25	62
Depressed RV function	-	-	-	-	+	-
Impaired LV relaxation	+	+	+	-	+	-
Regional wall motion abnormalities	-	-	+	-	-	-
Estimated RAP (mmHg)	12	10	5	5	10	5
Estimated systolic PAP (mmHg)	40	24	20	15	-	35
LVEDd (cm)	5.4	5.1	4.0	3.5	4.2	3.9
LVPWd (cm)	1.1	1.1	0.8	0.8	1.0	1.1
Left atrial volume (ml)	46.4	49.0	24.0	30.0	31.9	37.0
VOT TVI (cm)	10.9	21.0	9.0	18.8	9.4	14.0
Cardiac output (L/min)	3.8	7.5	3.0	4.5	3.6	5.0
Cardiac index (L/m/m2)	2.0	3.9	2.0	3.0	2.3	3.2
Early mitral valve inflow, E (cm/s)	93.5	91.6	81.2	8.4	58.8	55.3
Late mitral valve inflow, A (cm/s)	81.1	96	59.6	70.4	-*	46.7
E/A ratio	1.2	1	1.4	1.3	-*	1.2
E/E' ratio	12.5	9.9	8.6		9.2	11.5

* Unable to determine due to the presence of atrial fibrillation; RAP: right atrial pressure; PAP: systolic pulmonary artery pressure; LVEDd: left ventricular end diastolic diameter; LVPWd: left ventricular posterior wall dimension; LVOT TVI: left ventricular outflow tract time velocity integral.

Case 1

A 58-year-old Caucasian man with a past history of coronary artery disease (CAD) status post bypass surgery, hypothyroidism, and type 2 diabetes mellitus presented to his primary care physician complaining of a 10-day history of productive cough, shortness of breath, and general fatigue. He was prescribed a course of oral antibiotics for presumed upper respiratory tract infection and afterwards reported only a mild improvement in his symptoms. He developed worsening shortness of breath and lethargy and was taken to a nearby hospital, where he was intubated for respiratory failure and started on dopamine prior to referral to our institution. On arrival at the Methodist DeBakey Heart & Vascular Center, electrocardiogram (EKG) showed Q-waves consistent with an old inferior infarct but no acute ST segment or T wave changes. Chest radiograph revealed diffuse bilateral patchy infiltrates and pulmonary vascular congestion. Notable 2-dimensional echocardiographic findings included a left ventricular ejection fraction (LVEF) of 30% to 34% with diffuse hypokinetic wall motion abnormalities and impaired left ventricular relaxation (Table 2). A nasopharyngeal swab at admission revealed Influenza H1N1 by real-time polymerase chain reaction (RT-PCR), and it was confirmed with positive viral cultures from bronchoalveolar lavage testing 6 days later. Oseltamivir 75 mg orally twice daily was started within 24 hours after initial results were confirmed, and the patient completed a 5-day course of treatment. No other bacterial or fungal pathogens were isolated, and blood cultures drawn at the time of admission were unremarkable. His clinical condition gradually improved and he was successfully extubated 6 days after admission. Repeat echocardiography 8 days after admission revealed normal wall motion with an LVEF of 55% to 59% (Figure 1). The patient was subsequently discharged home in stable condition on his previous medical regimen. Long-term follow-up is unavailable.

Figure 1. Two-dimensional echocardiography demonstrating (A) left ventricular end diastolic diameter on admission (5.4 cm); (B) left ventricular end systolic diameter on admission (4.2 cm), thus fractional shortening is 22%, which equates to an LVEF of 37%; (C) left ventricular end diastolic diameter at day 7 (5.1 cm); and (D) left ventricular end systolic diameter at day 7 (3.6 cm), which equates to an increase in fractional shortening of 29% and LVEF 50%.

Case 2

A 48-year-old woman with a past history of advanced cystic fibrosis, chronic sinusitis, pancreatic insufficiency, and frequent respiratory infections presented to the hospital with a 2-day history of productive cough, fever up to 102.9° F, and shortness

of breath that was significantly worse from her baseline. Chest radiograph on admission revealed signs of cystic bronchiectasis but without overt consolidations or effusions. A nasopharyngeal swab returned positive for influenza antigen by RT-PCR and the culture was positive for the H1N1 strain. The patient was treated with oral oseltamivir 75 mg twice daily. Her cough and fevers gradually subsided after treatment but the shortness of breath persisted. A CT scan of the thorax and repeat pulmonary function testing showed no changes from prior studies. Echocardiography revealed normal LV and right ventricular (RV) size and severe LV dysfunction with a LVEF less than 20%. Her initial EKG was in sinus tachycardia with a ventricular rate of 100 to 120 bpm but otherwise unremarkable. The patient was started on furosemide, captopril, and digoxin 0.125 mg per day, and she also received a 3-day course of 10 gm of intravenous immunoglobulin (IVIG) daily. Her symptoms gradually improved. Cardiovascular magnetic resonance imaging performed 8 days after admission revealed no late gadolinium uptake. Repeat EKG 10 days after admission showed an LVEF of 65% to 69% and normal ventricular function. The patient was sent home on captopril 6.25 mg orally 3 times daily. At 1-year follow-up, the patient is in good health with no evidence of cardiomyopathy relapse.

Case 3

A 67-year-old man with a past history of idiopathic pulmonary fibrosis (IPF), status post double lung transplant on chronic immune suppression, presented to the hospital complaining of fatigue, sore throat, sinus congestion, subjective fevers, and dry cough for 3 days. Nasal swab testing performed on admission returned positive for H1N1 influenza antigen by RT-PCR. He also had a chest radiograph that revealed diffuse bilateral patchy infiltrates, atelectasis, and pulmonary edema. The patient developed refractory hypoxemia requiring endotracheal intubation and mechanical ventilation. Bronchoscopy and bronchoalveolar lavage were performed and confirmed findings of H1N1 influenza by viral culture. The patient was treated with oral oseltamivir 75 mg twice daily, IVIG 10 gm daily for 3 days, and broad-spectrum antibiotics. Echocardiography performed 2 days after admission revealed normal LV and RV size with severe global hypokinesis and an LVEF of 20% to 24%. Paroxysmal atrial fibrillation with a rapid ventricular response (140 to 160 bpm) was noted on cardiac telemetry that lasted for 4 days into his hospitalization and later converted to sinus rhythm. The patient developed hypotension (systolic blood pressure <80 mmHg) despite intravenous norepinephrine, and a femoral intra-aortic balloon pump (IABP) was placed; this later was converted to the axillary-subclavian position due to extensive peripheral vascular disease. He was supported on the IABP for 10 days. His respiratory function improved after several days of treatment, and he was gradually weaned off the ventilator. A repeat EKG 2 weeks after admission revealed normal wall motion and an LVEF of 60% to 64%. Though his cardiopulmonary function improved, the patient unfortunately developed a small bowel perforation requiring immediate surgical intervention. Despite surgery, the patient succumbed to overwhelming septic shock and expired 2 days later.

Discussion

The cases above describe Influenza A (H1N1) infection complicated by acute myocardial dysfunction in patients with no prior history of heart failure. Though viral infections have been associated with cardiotoxicity, only a few reports have linked the Influenza A (H1N1) subtype to myocarditis or acute myocardial

dysfunction.^{4,5} In our case series, all patients had multiple risk factors for developing complicated influenza infection (2 of the 3 patients had chronic underlying lung disease), but none of them had acute ischemic events or a persistent primary rhythm disturbance detected by EKG or telemetry to explain the acute deterioration in myocardial function. The documented compromise in cardiac systolic function with the acute viral syndrome, and the subsequent recovery of myocardial function after resolution of the viral illness, supports the concept that H1N1 influenza is the cause of acquired myocarditis.

While the clinical course of these patients was variable, the clinical presenting symptoms of shortness of breath and cough were evident in all 3 patients and are consistent with other reports of acquired viral cardiomyopathy.^{5,6} The duration of symptoms prior to presentation ranged from 1 to 10 days, which is also consistent with what is reported in the literature.⁷

The prevalence of myocardial involvement for all influenza virus infections ranges from 0% to 11% depending on which diagnostic criteria are used.⁸ The Guidelines for the Diagnosis and Treatment of Myocarditis have outlined clinical criteria to diagnose acute myocarditis.⁹ Common cardiac clinical features in our case series included the following: (1) global hypokinesis with depressed LV systolic function; (2) normal LV diastolic dimensions; and (3) elevated cardiac biomarkers. Viral cardiomyopathy is thought to occur either via direct cytotoxic effects of the virus itself or via an immune-mediated mechanism.¹⁰ The resulting myocardial inflammation results in disruption of myocardial function at both the cellular and parenchymal levels. Cardiac biomarkers such as troponin I are thus elevated in about 35% of patients with suspected myocarditis and in 31% to 85% of critically ill patients with sepsis.¹¹ In our study, all patients had mildly increased serum levels of troponin I that rapidly normalized.

Echocardiographic findings often seen in viral myocarditis in general and with the 2009 H1N1 pandemic in Japan include ventricular systolic dysfunction and global wall motion hypokinesis.^{1,12} Subclinical cardiac dysfunction as measured by tissue Doppler echocardiography has been reported with the H1N1 influenza infection.¹³ In contrast, patients with fulminant acute myocarditis have higher atrial pressures, depressed LV systolic function, less frequent ventricular dilatation, and more frequent clinical hemodynamic instability.¹⁴ In our case series, all 3 patients had significantly depressed LV systolic function with a low estimated cardiac index (2.0 to 2.3 L/min/m²), and 2 of the 3 had more fulminant illness with hemodynamic compromise requiring IABP or inotropic support. Interestingly, Felker et al. noted that patients with fulminant cardiomyopathy were found to be more likely to recover LV function.¹⁴ All patients in our review had a clinical course that demonstrated recovery of LV function within 2 weeks, though one of the patients did ultimately succumb to comorbid illness.

Other cardiac complications have been described in H1N1 cardiomyopathy. A recent case series of 4 patients who had Influenza A (H1N1) infection showed that ventricular tachycardia and cardiac arrest were among the leading reasons for ICU admission.⁷ Another case series during the 2009 Influenza A pandemic in Japan showed that H1N1 myocarditis was associated with arrhythmias and marked elevations in cardiac enzymes.¹² In addition, some cases of adults with myocardial infarction related to H1N1 infection have been documented.¹⁵ In our case series, paroxysmal atrial fibrillation was seen in 1 patient for a period of 4 days. This patient later converted to sinus rhythm and had noted improvement in LVEF with IABP support at day.¹⁴

The management of viral myocarditis is largely supportive care. Although there is consensus that early detection and treatment with antiviral therapy may be of benefit, no specific treatment recommendations are currently available. All 3 patients in our series received early treatment with oseltamivir, a neuraminidase inhibitor that has been reported to effectively treat Influenza A (H1N1) by blocking the function of the viral neuraminidase protein and preventing virus reproduction.¹⁶ Two of the 3 patients in our series were also treated with IVIG, although this form of treatment for myocarditis is still controversial.¹⁷ Similar to our series, in the 2009 Japan national survey on myocarditis with H1N1, 2 out of 15 patients were treated with high-dose immunoglobulin with noted significant improvement in cardiac function.¹² Clinical data regarding the use of IVIG in acute myocarditis illustrate that although it has shown some benefit in experimental models and uncontrolled case series, it proved no better than placebo in one clinical trial.¹⁸ Its routine use in treating acute myocarditis in adults is therefore not recommended at this time. In our series, a high level of suspicion of cardiac involvement led to early detection and aggressive supportive treatment that may have altered the natural history of the disease and had a significant impact on recovery of ventricular function.

Conclusion

Our case series illustrates that H1N1 influenza A virus infections may be complicated by acute cardiomyopathy and severe left ventricular dysfunction. Echocardiography should be considered as part of the patient evaluation in patients with H1N1 infections if there is otherwise unexplained evidence of persistent clinical deterioration. Early initiation of treatment with concurrent hemodynamic support may have a favorable impact in the resolution of the acquired acute cardiomyopathy.

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