CLINICAL PROBLEM-SOLVING

Caren G. Solomon, M.D., M.P.H., *Editor*

A Shocking Development

Joshua E. Levenson, M.D., Daniel R. Kaul, M.D., Sanjay Saint, M.D., M.P.H., Brahmajee K. Nallamothu, M.D., M.P.H., and Hitinder S. Gurm, M.D.

In this Journal *feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information, sharing his or her reasoning with the reader (regular type). The authors' commentary follows.*

From the Department of Internal Medicine (J.E.L., S.S.) and the Divisions of Infectious Disease (D.R.K.) and Cardiology (B.K.N., H.S.G.), University of Michigan; the Ann Arbor Veterans Affairs (VA) Hospital Outcomes Program of Excellence (HOPE) (S.S.); and the Ann Arbor VA Center for Clinical Management and Research (B.K.N.) — all in Ann Arbor. Address reprint requests to Dr. Levenson at 3116G Taubman Ctr., SPC 5368, Ann Arbor MI 48109-0368, or at levenson@med.umich.edu.

N Engl J Med 2013;369:2253-8.
DOI: 10.1056/NEJMcps1301587

A 20-year-old female college student presented with a 2-week history of fatigue, cough, sinus congestion, and rhinorrhea, followed by 2 days of vomiting, diarrhea, and abdominal pain. The patient's initial symptoms began during her end-of-semester winter examination period; she knew many people who had been ill with similar symptoms, including fatigue and upper respiratory symptoms. The patient was recovering when she began to have nonbilious, nonbloody emesis and frequent, loose, nonbloody bowel movements.

Upper respiratory tract symptoms, particularly when they occur in the winter and involve a number of contacts, are suggestive of a community-acquired respiratory virus, such as influenza. The presence of fever can help differentiate influenza from more typical cold viruses. The most common complications of influenza include viral pneumonia or a secondary bacterial pneumonia. Neither complication is suggested here. The duration of the upper respiratory symptoms and the nature of the gastrointestinal symptoms are not typical of community-acquired respiratory viruses. Other possible infections include acute Epstein–Barr virus infection, cytomegalovirus infection, and human immunodeficiency virus (HIV) infection, all of which may have prolonged symptoms and may include involvement of the gastrointestinal tract. It is also possible that the patient has two separate viral infections (e.g., a viral upper respiratory tract infection followed by a norovirus infection), but this scenario is less likely.

The patient was brought to an urgent care center for evaluation. At that time, she reported abdominal pain related to emesis but said she had no dyspnea, chest pain, fever, or chills. Her medical history was noteworthy for Kawasaki's disease, which she had had at 2 years of age; it was treated with intravenous immune globulin and aspirin. The patient underwent serial echocardiographic evaluations until she was 10 years of age, at which time it was thought that no further follow-up was needed. Currently, she exercised 45 minutes daily and ran in medium-distance races. Her family history was notable for hypertension in both parents. She was sexually active with one male partner. Her only medication was a combined oral contraceptive pill. She attended a college in the Midwest and had never traveled internationally. She had an average of two alcoholic drinks per week and reported no history of smoking or use of illicit drugs.

The primary long-term complication of Kawasaki's disease is the development of stenosis at the site of the earlier coronary-artery aneurysm, which may lead to ischemic heart disease. However, the patient's clinical presentation does not suggest ischemia. In rare instances, visceral arterial aneurysms develop and lead to

ischemic disease in adulthood. Such an occurrence could account for her abdominal pain and emesis but would not explain the symptoms of upper respiratory infection. She appears to be at low risk for acute HIV infection, and her symptoms are not suggestive of pelvic inflammatory disease.

The pulse was 130 beats per minute, and systolic blood pressure ranged from 60 to 70 mm Hg. Emergency medical services were called, and 2 liters of normal saline were administered while the patient was being transported to the emergency department of a local hospital. On arrival, the oral temperature was 34.7°C, pulse 126 beats per minute, blood pressure 99/52 mm Hg, respiratory rate 18 breaths per minute, and oxygen saturation 100% while she was breathing ambient air. She appeared ill but was alert and oriented to person, place, and time. The mucous membranes were dry. Cardiac examination revealed a regular tachycardia without extra heart sounds. There was no jugular venous distention. The lungs, abdomen, and skin were normal.

Although the patient's initial symptoms appear to have been benign, the hypotension and tachycardia raise the possibility of a more serious process, such as septic shock. Given her history of emesis and the finding of dry mucous membranes on examination, dehydration may be contributing to her rapid pulse and low blood pressure, but it would not explain her hypothermia, which also raises the possibility of sepsis. Fluid resuscitation should be started immediately. The examination findings do not suggest a pulmonary or abdominal source of the symptoms and findings.

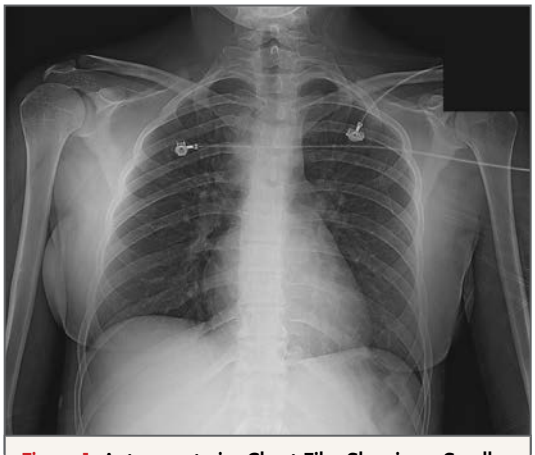

Figure 1. Anteroposterior Chest Film Showing a Small, Ill-Defined Fullness along the Right Mediastinum, Possibly Attributable to the Prominence of the Great Vessels.

The serum sodium level was 139 mmol per liter, potassium 3.8 mmol per liter, chloride 112 mmol per liter, bicarbonate 19 mmol per liter, blood urea nitrogen 9 mg per deciliter (3.2 mmol per liter), creatinine 0.75 mg per deciliter (66 μmol per liter), and calcium 5.5 mg per deciliter (1.4 mmol per liter; reference range, 8.5 to 10.1 mg per deciliter [2.1 to 2.5 mmol per liter]). The white-cell count was 7300 per cubic millimeter, with 66% neutrophils, 21% lymphocytes, 11% monocytes, and 2% eosinophils; the hemoglobin level was 9.7 g per deciliter, and the platelet count 73,000 per cubic millimeter. The level of aspartate aminotransferase was 22 U per liter, alanine aminotransferase 11 U per liter, and alkaline phosphatase 14 U per liter. The level of total bilirubin was 0.1 mg per deciliter (1.7 μmol per liter; reference range, 0.2 to 1.2 mg per deciliter [3.5 to 20.5 μmol per liter]), albumin 1.4 g per deciliter (reference range, 3.5 to 4.9), and total protein 2.8 g per deciliter (reference range, 6.0 to 8.4). The prothrombin time was 13.4 seconds (reference range, 8.0 to 12.5), the international normalized ratio 1.25, and the partial-thromboplastin time 45.0 seconds (reference range, 25.1 to 36.4). The venous lactic acid level was 5.5 mmol per liter (reference range, 0.5 to 2.2). The troponin level was 0.36 ng per milliliter (reference range, 0.0 to 0.06), B-type natriuretic peptide (BNP) 271 pg per milliliter (reference range, 0 to 100), and myoglobin 58.9 U per liter (reference range, 0 to 85).

A chest radiograph revealed no air-space disease or cardiac enlargement; a small, ill-defined fullness was observed along the right mediastinum, possibly attributable to the prominence of the great vessels (Fig. 1). An electrocardiogram (ECG) showed sinus tachycardia, low-voltage, low-anterior forces, flattened T waves, and a mildly prolonged QT interval (Fig. 2).

Myocarditis appears to be the likely diagnosis, especially given the patient's recent upper respiratory tract infection. Most cases are due to common viruses, such as coxsackievirus, which are difficult to identify; nonetheless, nucleic acid tests for community-acquired respiratory viruses, such as influenza virus, should be performed, primarily because such tests may remain positive for a prolonged period. Molecular and serologic assays for cytomegalovirus, Epstein–Barr virus,

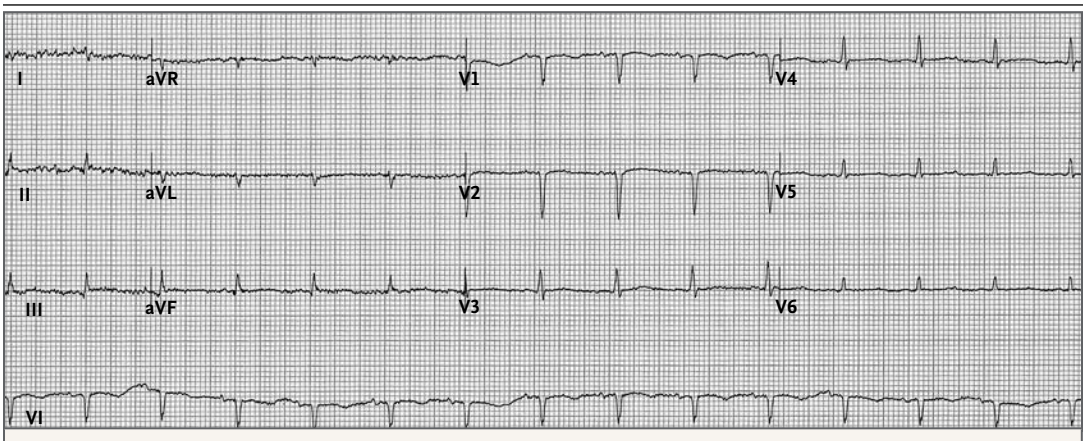

Figure 2. Electrocardiogram Showing Sinus Tachycardia, Low-Voltage, Low-Anterior Forces, Flattened T Waves, and a Mildly Prolonged QT Interval.

parvovirus, and HIV should also be performed. Less common infectious causes of myocarditis include Chagas' disease, toxoplasmosis, trichinosis, and Lyme disease, but there is no history to suggest exposure to their causative agents. The changes on ECG and the elevated levels of troponin and BNP support the diagnosis of myocarditis, but with such a fulminant case, I would expect other signs of heart failure. Even after correction for the low albumin level, the calcium level remains low; this finding may be related to acidosis or sepsis. Whereas low albumin levels can signify prolonged malnutrition, a dramatic decrease in serum albumin levels may accompany sepsis or critical illness. The low platelet count and anemia may also be related to a viral infection. At this point, an echocardiogram is indicated to evaluate the patient for myocarditis or pericardial effusion. I would also screen for drugs that can cause cardiovascular events, especially cocaine.

The patient's presentation was initially attributed to a viral syndrome leading to volume depletion and shock. Blood, urine, and induced-sputum cultures were obtained, and polymerase-chain-reaction (PCR) assays were performed for cytomegalovirus, Epstein–Barr virus, herpes simplex virus, influenza A and B viruses, adenovirus, and rhinovirus. In the emergency department, the patient had a brief period of hypotension and confusion that resolved after the administration of intravenous fluid boluses.

A transthoracic echocardiogram was obtained (see Video 1, available with the full text of this article at NEJM.org). The systolic ejection fraction was 52%, and inferolateral and inferior hypokinesis was detected. Both ventricles appeared unusually thickened and edematous. A small pericardial effusion was seen. The patient was admitted to the intensive care unit. Norepinephrine was infused, and 6 liters of fluid were administered for the treatment of sustained hypotension. Treatment with Indomethacin and colchicine was started to address the possibility of pericarditis.

The echocardiogram reveals abnormalities of the myocardium. Even though most patients with fulminant or acute myocarditis have a global decrease in the ejection fraction, I am still concerned that this patient has an infectious or postinfectious process involving the myocardium, the pericardium, or both. Noninfectious infiltrative diseases of the heart, including amyloidosis and sarcoidosis, rarely develop as rapidly as the illness in this patient, but autoimmune diseases, such as lupus erythematosus or granulomatosis with polyangiitis, should be considered. Pending the results of testing, I would administer a neuraminidase inhibitor empirically for influenza, in addition to broad-spectrum antibiotics.

The next morning, the patient continued to require norepinephrine for hypotension. Intravenous cefepime and vancomycin were administered empirically. A repeat echocardiogram showed deterioration, with severe, global systolic dysfunction of the left ventricle and an ejection fraction of 24% (see Videos 1, 2, and 3). There was also evidence of severe diastolic dysfunction and restrictive filling. The inferior vena cava was dilated without respiratory variation. The patient had sustained confusion and was intubated for airway protection.

Videos showing electrocardiograms are available at NEJM.org

Intravenous dobutamine was started to control the persistent hypotension.

The patient was transferred to a tertiary care center. On arrival, the heart rate was 144 beats per minute, and the blood pressure 77/49 mm Hg. Her arms and legs were cold, with weak pulses. There were no changes in her skin or mucosa. Her lungs were clear and mechanically ventilated. She had tachycardia, with normal S_1 and S_2 sounds and an S_3 gallop. The remainder of her examination was unchanged.

Measurement of arterial blood gas revealed that the pH was 7.24, the partial pressure of carbon dioxide 27 mm Hg, the partial pressure of oxygen 140 mm Hg, and the fraction of inspired oxygen 0.5. The arterial lactate level was 12.8 mmol per liter (reference range, 0.5 to 2.2). The white-cell count was 10,100 per cubic millimeter, with 75% neutrophils, 14% lymphocytes, and 11% monocytes. The hemoglobin level was 10.6 g per deciliter, and the platelet count 70,000 per cubic millimeter. The blood urea nitrogen level was 18 mg per deciliter (6.4 mmol per liter), creatinine 1.0 mg per deciliter (88 μmol per liter), and ionized calcium 1.06 mmol per liter (reference range, 1.12 to 1.30). The level of aspartate aminotransferase was 1217 U per liter (reference range, 8 to 30), and alanine aminotransferase 983 U per liter (reference range, 7 to 35). The troponin I level was 4.3 ng per milliliter (reference range, 0 to 0.3), and the total creatine kinase level was 5883 U per liter (reference range, 26 to 180).

The patient is in cardiogenic shock, with an acute onset of cardiomyopathy. Given her young age and recent illness, a fulminant myocarditis resulting from a viral infection is the most likely diagnosis. Nonetheless, other forms of cardiomyopathy are also possible, including giant-cell cardiomyopathy characterized by granulomatous inflammation. If the tests for infectious pathogens that have been ordered thus far are unrevealing, an endomyocardial biopsy may be necessary.

The patient was immediately referred for extracorporeal membrane oxygenation (ECMO). During cannulation for the administration of ECMO, a transesophageal echocardiogram revealed a large pericardial effusion; a pericardial window was created, without hemodynamic improvement. Continuous renal-replacement therapy was initiated soon afterward to address acute tubular necrosis. Treatment with intravenous inotropes, vasopressors, and antibiotics was continued.

On the day after the patient was transferred to the tertiary care center, test results for a nasopharyngeal swab showed positivity for influenza A RNA; that same morning, a swab collected at the initial hospital also showed positive results for influenza A RNA. Treatment with oseltamivir, at a dose of 150 mg administered orally twice a day, was started. One blood culture grew coagulase-negative staphylococcus, but this result was suspected to be due to a contaminant. Other blood cultures and urine and sputum cultures showed no growth. A PCR assay of a nasopharyngeal specimen was negative for influenza B virus, respiratory syncytial virus, and human metapneumovirus. Serum tests for HIV, coxsackievirus, parvovirus, adenovirus, rhinovirus, Epstein–Barr virus, cytomegalovirus, human herpes virus 6, herpes simplex virus, and hepatitis A, B, and C viruses were negative. The thyrotropin level was normal. Infection with seasonal 2012–2013 influenza A, subtype H3N2, was later confirmed.

After 5 days of ECMO support, a repeat echocardiogram showed recovery of left ventricular systolic function, with no signs of myocardial edema or hypokinesis (see Video 4). The patient was subsequently weaned from ECMO. Intravenous inotropes and vasopressors were tapered and then discontinued over the next several days. She was extubated, and her kidney function normalized. On the 23rd hospital day, the patient was discharged home. At a 4-month follow-up visit, she remained well, with no cardiopulmonary symptoms.

Patients with fulminant myocarditis who survive the initial illness have an excellent long-term prognosis. The benefit of treating influenza with oseltamivir more than 48 hours after the onset of symptoms has not been proved, but the treatment was appropriate for this critically ill patient.

COMMENTARY

Our patient contracted an acute, influenza-like illness, along with members of her family, and while the others recovered, her condition rapidly deteriorated. In a young person with a febrile illness and severe hypotension, the differential diagnosis is broad and must be addressed quickly, given the potentially catastrophic consequences. Any diagnostic evaluation must proceed in tan-

dem with appropriate life-saving measures that include hemodynamic support.

Influenza was initially considered but was not diagnosed until the patient's third hospital day. Clinically, influenza remains very difficult to distinguish from "influenza-like illnesses,"[1] but the distinction is important. Among hospitalized patients, mortality from seasonal influenza and pandemic H1N1 influenza has been estimated to be as high as 8% and 14%,[1,2] respectively, rates of death that are much higher than those from other respiratory viral infections. Complications from influenza must be considered when fever or respiratory symptoms persist, or if they recur soon after the initial syndrome resolves.

Myocarditis is an uncommon complication of influenza, with an overall incidence of up to 11%,[3,4] although it is unknown whether the incidence varies according to the viral strain. Initially, symptoms can be subtle, but presentations with syncope, arrhythmia, and sudden death have been reported.[3-5] In our patient, an elevation in the serum troponin level and low voltage on ECG were two abnormalities that raised concern about myocarditis.

Myocarditis is diagnosed on the basis of clinical, serologic, pathological, and imaging findings. The clinical hallmark of fulminant influenza-associated myocarditis is rapid hemodynamic decompensation within 2 weeks after the onset of influenza symptoms. Our patient's echocardiogram revealed the classic elements of fulminant myocarditis: a thickened, hypocontractile left ventricle without ventricular dilatation.[5,6] The sequence of initially preserved systolic function, rapid decline, and rapid recovery also supports a fulminant, rather than acute or chronic, course.[6]

Electrocardiography remains a sensitive test for most cardiac diseases, including myocarditis. Although almost any ECG abnormality can be found in myocarditis, including the QT prolongation and low voltage observed in our patient, some findings have prognostic significance. For example, a pseudoinfarction pattern — a Q wave with ST-segment elevation — has been correlated with a fulminant course.[7] Cardiovascular magnetic resonance imaging has recently been suggested as a potential diagnostic test for fulminant myocarditis due to influenza.[8] Myocarditis can be diagnosed with the use of endomyocardial biopsy, but false negative results are common. Since in most human cases and animal models of influenza-associated myocarditis, influenza viral replication has not been confirmed in myocardial tissue, biopsy will rarely prove that influenza is the cause of myocarditis.[5,9]

Patients with fulminant influenza-associated myocarditis usually require circulatory support. Intraaortic balloon pumps, percutaneous cardiopulmonary support, surgical left ventricular assist devices, and arteriovenous ECMO have all been used as bridges to myocardial recovery. Even with circulatory support, however, the short-term risk of death remains high; a recent review of 2009 cases of H1N1 influenza-associated myocarditis worldwide reported an in-hospital mortality of 24%.[4] Patients who require prolonged mechanical support should be evaluated for cardiac transplantation.[10]

Patients with fulminant viral myocarditis who survive tend to recover completely within a few weeks[10,11] and to have excellent long-term outcomes, with 1-year and 11-year survival rates estimated at 95% and 93%, respectively.[11]

It is unclear whether antiviral therapy helped our patient. The use of a neuraminidase inhibitor within 48 hours after the onset of symptoms shortens their duration,[12] but the benefit of this treatment with respect to other outcomes remains controversial.[13] Nevertheless, hospitalized patients with suspected or confirmed influenza, such as our patient, frequently receive neuraminidase inhibitors more than 48 hours after symptom onset to reduce the risk of complications. With 2009–2010 influenza A (H1N1), 80 to 90% of critically ill patients were treated with neuraminidase inhibitors, as were 85% of patients with influenza-associated myocarditis.[4] On the basis of observational data, improved outcomes are correlated with early — but not late — use of antiviral therapy in hospitalized patients.[14] Whereas antiviral treatment is reasonable when the diagnosis of complicated influenza is delayed, early empirical antiviral therapy remains the standard of care for all suspected cases.

A finding of direct cardiac involvement as the cause of cardiovascular collapse is rare in young, previously healthy patients and may be overlooked. Early recognition of fulminant myocarditis and rapid escalation of care with mechanical circulatory support probably contributed to our patient's recovery.

Dr. Saint reports receiving fees for board membership from Doximity and Jvion. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

1. Call SA, Vollenweider MA, Hornung CA, Simel DL, McKinney WP. Does this patient have influenza? JAMA 2005;293:987-97.
2. Lee N, Ison MG. Diagnosis, management and outcomes of adults hospitalized with influenza. Antivir Ther 2012;17:143-57.
3. Mamas MA, Fraser D, Neyses L. Cardiovascular manifestations associated with influenza virus infection. Int J Cardiol 2008;130:304-9.
4. Ukimura A, Satomi H, Ooi Y, Kanzaki Y. Myocarditis associated with influenza A H1N1pdm2009. Influenza Res Treat 2012;2012:351979.
5. Ukimura A, Izumi T, Matsumori A. A national survey on myocarditis associated with the 2009 influenza A (H1N1) pandemic in Japan. Circ J 2010;74:2193-9.
6. Felker GM, Boehmer P, Hruban RH, et al. Echocardiographic findings in fulminant and acute myocarditis. J Am Coll Cardiol 2000;36:227-32.
7. Morgera T, Di Lenarda A, Dreas L, et al. Electrocardiography of myocarditis revisited: clinical and prognostic significance of electrocardiographic changes. Am Heart J 1992;124:455-67.
8. Takeuchi I, Imaki R, Inomata T, Soma K, Izumi T. MRI is useful for diagnosis of H1N1 fulminant myocarditis. Circ J 2010;74:2758-9.
9. Pankuweit S, Klingel K. Viral myocarditis: from experimental models to molecular diagnosis in patients. Heart Fail Rev 2012 October 16 (Epub ahead of print).
10. Atluri P, Ullery BW, MacArthur JW, et al. Rapid onset of fulminant myocarditis portends a favourable prognosis and the ability to bridge mechanical circulatory support to recovery. Eur J Cardiothorac Surg 2013;43:379-82.
11. McCarthy RE III, Boehmer JP, Hruban RH, et al. Long-term outcome of fulminant myocarditis as compared with acute (nonfulminant) myocarditis. N Engl J Med 2000;342:690-5.
12. Jefferson T, Jones MA, Doshi P, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. Cochrane Database Syst Rev 2012;1:CD008965.
13. Krumholz HM, Jackevicius CA, Ross JS. Tamiflu: 14 flu seasons and still questions. BMJ 2013;346:f547.
14. Muthuri SG, Myles PR, Venkatesan S, Leonardi-Bee J, Nguyen-Van-Tam JS. Impact of neuraminidase inhibitor treatment on outcomes of public health importance during the 2009-2010 influenza A(H1N1) pandemic: a systematic review and meta-analysis in hospitalized patients. J Infect Dis 2013;207:553-63.

CLINICAL PROBLEM-SOLVING SERIES

The *Journal* welcomes submissions of manuscripts for the Clinical Problem-Solving series. This regular feature considers the step-by-step process of clinical decision making. For more information, please see authors.NEJM.org.