Case Report

Myocarditis complicating H1N1 pneumonia:

Case report and literature review

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ABSTRACT

Influenza infection most commonly affects the upper and lower respiratory tracts, but can involve also extrapulmonary sites, including the myocardium. We report a case of a previously healthy adult diagnosed with pneumonia complicated with myocarditis caused by H1N1 influenza virus, and we review the literature on influenza myocarditis. The patient was male, 37 years old, and presented in the emergency department on January this year, with fever, pleuritic chest pain and shortness of breath of ten days duration. Chest X-ray and CT-scan findings depicted bilateral infiltrates compatible with severe pneumonia and the test for H1N1 in nasopharyngeal secretions was positive for H1N1. Because of elevated cardiac enzymes and abnormal electrocardiograph (ECG), myocarditis was suspected and finally confirmed by Cardiac Magnetic Resonance (CMR). We concluded that myocarditis of various severity is an unusual and potentially fatal complication of H1N1 infection and high level of clinical suspicion is essential for timely diagnosis and treatment.
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INTRODUCTION

Influenza is highly contagious and constitutes a significant public health problem due to its rapid transmission and the high associated morbidity and mortality. It is commonly associated with pulmonary complications, but may involve a number of other organ systems, including the myocardium[1]. The prevalence of myocardial involvement in influenza infection ranges from 0% to 10% depending on the diagnostic criteria used to define myocarditis. The diagnosis is based on clinical and laboratory data, such as ECG, imaging tests (echocardiography, CMR) and endomyocardial biopsy for histopathological confirmation[2]. The clinical expression varies from asymptomatic to fulminant myocarditis, which can result in severe hemodynamic dysfunction, necessitating mechanical circulatory support. Myocarditis is treated in three ways: (1) intervention to eliminate the cause, (2) intervention to improve hemodynamic compromise, and (3) intervention for cardiac dysfunction[3].

We report on a case of a previously healthy adult with pneumonia caused by documented H1NI influenza A virus complicated with myocarditis and we review the literature on influenza myocarditis.

CASE PRESENTATION

A 37 year old previously healthy male smoker, overweight (BMI 28) presented to the emergency department on January this year due to fever and productive cough with mucoid sputum, pleuritic chest pain and shortness of breath, progressively worsening during the past ten days (0-->III according to modified Medical Research Council scale for the assessment of dyspnea, mMRC). He had received antimicrobial treatment (cefuroxime) at home without improvement. He was admitted in poor general condition, febrile (38,5°C), with acute hypoxemic respiratory failure (arterial blood gases: pH: 7.50, PO_2: 51mmHg, PCO_2: 41 mmHg, FiO_2: 21%) with tachypnea (respiratory rate 32), haemodynamically unstable (systolic blood pressure: 90mmHg), and diffuse inspiratory crackles in lower lung fields bilaterally during the auscultation. Chest radiography (CxR) revealed diffuse bilateral alveolar infiltrates (Figure 1). The Electrocardiograph (ECG) on admission showed sinus rhythm with ST segment elevation in the lateral leads (I and aVL) and ST segment depression in the inferior leads (III and aVF), followed by normalization of the ST segment and inverted T-waves in III lead in the next few days (Figure 2a, b). Laboratory findings included normal values of white blood cells: 6.500/μL (60% neutrophils, 30% lymphocytes), normal C- reactive protein (CRP) and procalcitonin (CRP: 0,86 mg/dl, PCT: 0,25 μg/l), elevated hepatic function tests and cardiac enzymes [troponin I (TNI): 0.250 ng/ml (0-0,056 ng/ml), creatine kinase (CK): 1775 U/L (39-308 U/L), MB isoenzyme (CK-MB): 6,7 ng/ml (0-3,6 ng/ml), serum glutamic oxaloacetic transaminase (SGOT): 336 U/L (15-37 U/L), lactate dehydrogenase (LDH): 1247 U/L (85-227 U/L)]. A Computed Tomography Pulmonary Angiography (CTPA) was perfomed which was negative for pulmonary embolism but revealed extensive ground glass opacities at the upper lobes and diffuse patchy ground glass opacities, mainly with subpleural distribution, bilaterally (Figure 3). Blood and sputum cultures and urine antigens for *Legionella pneumophila* and *Streptococcus pneumoniae* were negative. The reverse transcriptase polymerase chain reaction assay (PCR) from nasopharyngeal swab was positive for H1N1. Treatment included oseltamivir 75mg b.i.d., intravenous levofloxacin 750mg once daily, hydration and oxygen therapy. The patient underwent heart ultrasound which demonstrated normal left ventricular function (ejection fraction 66%), without pericardial effusion, and the 24-hour ECG monitoring showed sinus rhythm with average heart rate 98 bpm (52-156 bpm), a few ventricular and supraventricular extrasystoles and inverted T-waves in inferior leads (II, III and aVF). Serology blood tests for *Mycoplasma pneumoniae*, *Legionella pneumophila*, *Chlamydia pneumonia & psittaci*, *Rickettsia*, *Coxsackie, Coxiella burnetii, Adenovirus*, *Echo, Herpes virus I, II, III, EBV, CMV, HIV*, and autoantibodies tests were negative. An angiotensin-converting-enzyme inhibitor and a beta-blocker was added in patient's treatment. A cardiac magnetic resonance (CMR) study was performed in the 18th day of his hospitalization and the images on the T2-weighted sequence showed high signal intensity indicative of myocardial edema in the apical intraventricular septum and the apical lateral wall of the left ventricle, while the delayed enhancement images showed sub epicardial high signal intensity indicative of myocarditis in the lateral wall of the left ventricle (Figure 4a, b). These findings were associated with resolved acute myocarditis without indications of fibrosis or scar at that time. As the patient was hemodynamically stable and showed significant improvement in clinical and laboratory markers, with normalization of myocardial enzymes and ECG findings and improvement of respiratory failure and CxR infiltrates, a further hemodynamic control and endomyocardial biopsy was not performed. He was discharged in a very good condition after a twenty-day hospitalization with the diagnosis of pneumonia due to H1N1 influenza A virus complicated with myocarditis.

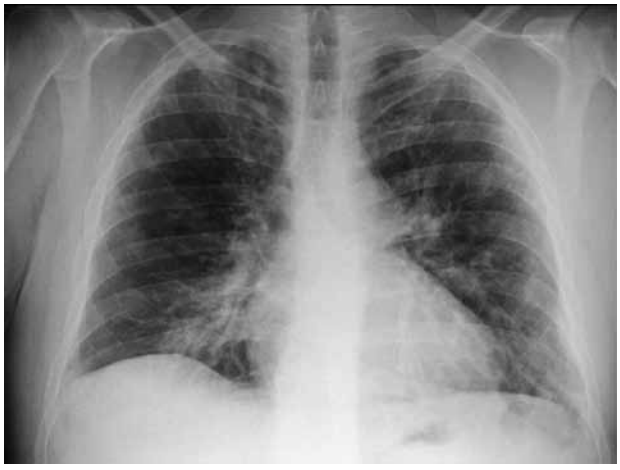

FIGURE 1. Chest X-ray at the time of admission. Diffuse pulmonary infiltrates bilaterally, mainly at the lower fields..

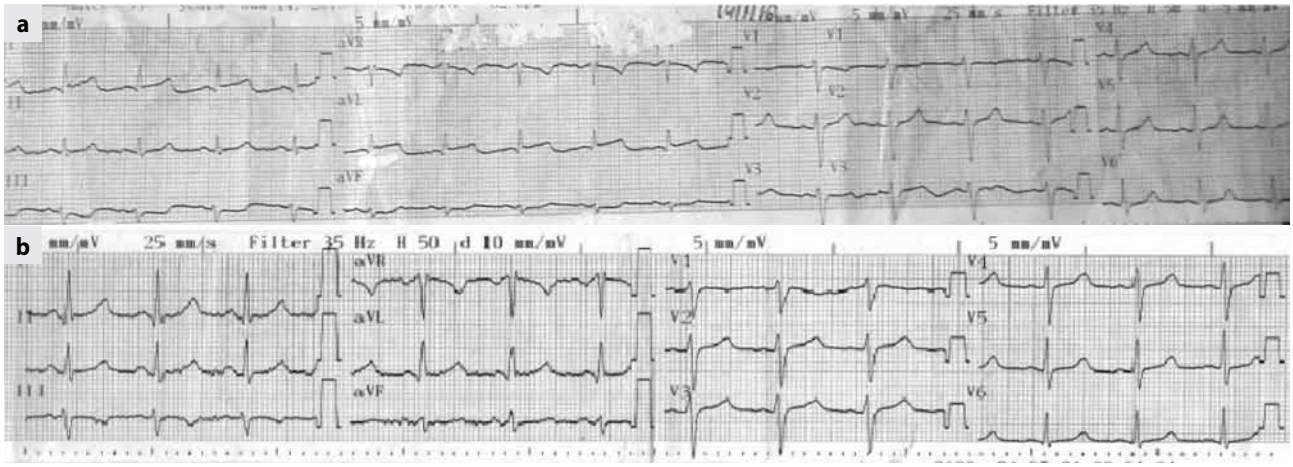

FIGURE 2. ECG. **a)** on admission which showed sinus rhythm with ST segment elevation in the lateral leads (I and aVL) and ST segment depression in the inferior leads (III and aVF), whereas, **b)** the next days showed normalization of the ST segment and inverted T-waves in III lead.

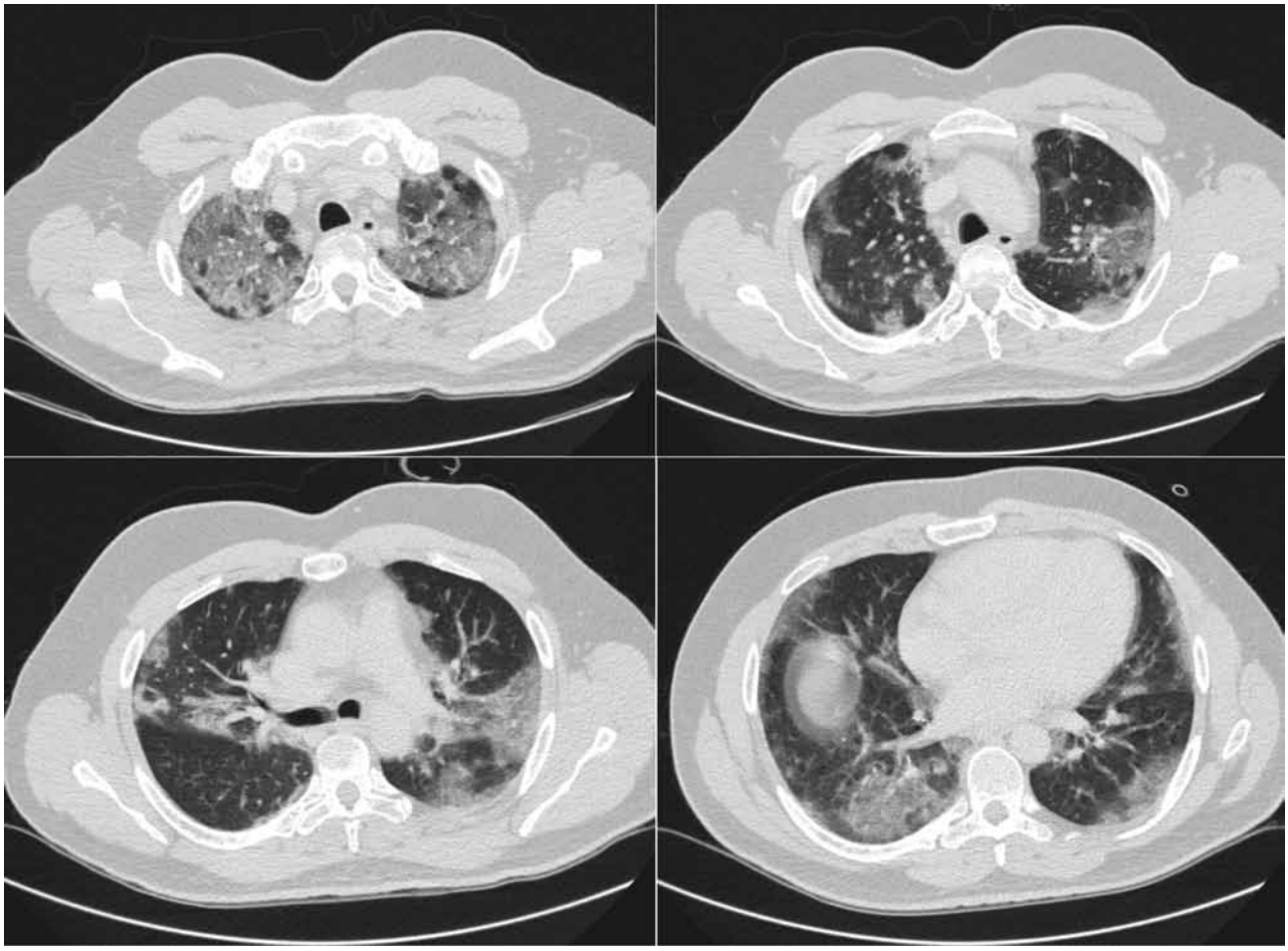

FIGURE 3. Chest CT. Extensive ground glass opacities at the upper lobes and diffuse patchy ground glass opacities, mainly with subpleural distribution, bilaterally.

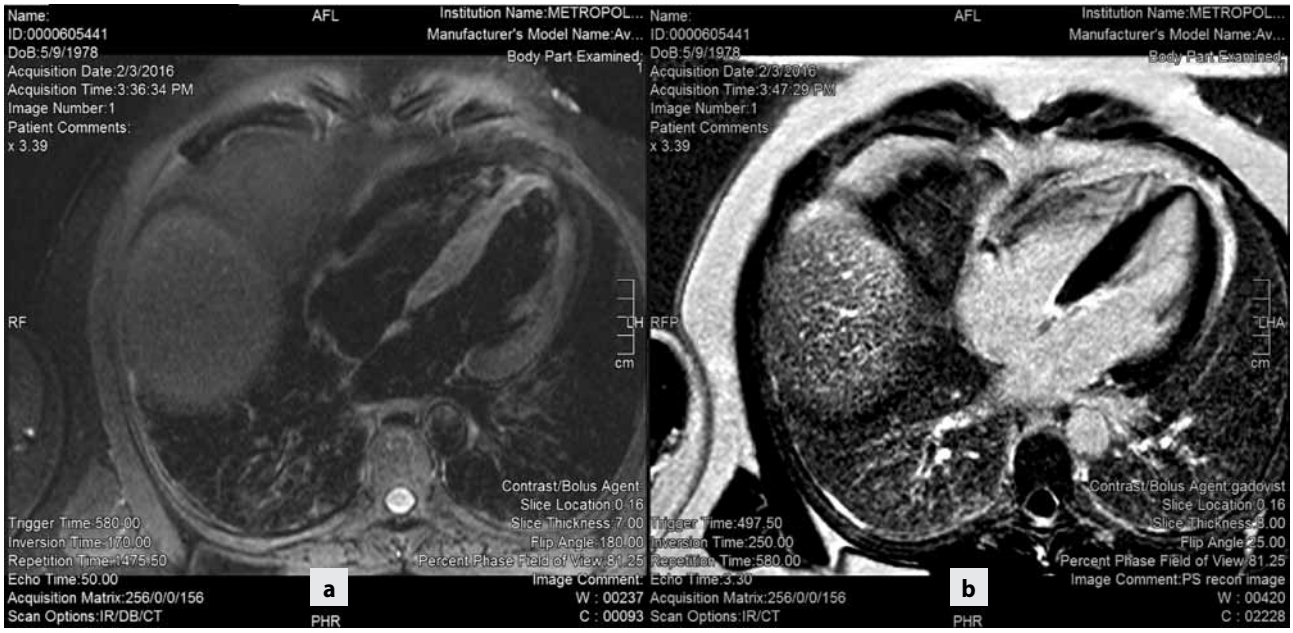

FIGURE 4. Cardiac magnetic resonance (CMR) **a)** T2 weighted fat suppression images. Four chamber view. High signal intensity indicative of myocardial edema is seen in the apical intraventricular septum and the apical lateral wall of the left ventricle, **b)** Delayed enhancement images. Four chamber view. Sub epicardial high signal intensity indicative of myocarditis is seen in the lateral wall of the left ventricle.

DISCUSSION

In the present study we report on a young patient with H1N1 pneumonia complicated with myocarditis diagnosed and treated successfully through timely clinical suspicion, microbiologic documentation and prompt cardiac function evaluation and management.

Influenza virus kills hundreds of thousands of people worldwide each year. According to WHO estimates, 450 million cases of pneumonia are recorded every year; about 4 million people die from this illness[4,5]. In most cases, influenza infection is self-limited, mild illnesses lasting 4 to 5 days with predominantly upper airway symptoms. It is commonly associated with pulmonary complications, such as primary influenza viral pneumonia, secondary bacterial pneumonia and mixed viral and bacterial pneumonia. Primary influenza viral pneumonia may be the least common of the pneumonic complications but it is also the most severe[1].

Risk factors associated with severe disease include age <5 and >65 years old, comorbidities (e.g. chronic lung disease, neurologic disease, hemato-oncologic disease, cardiac disease), pregnancy and immunosuppressed patients.[1] It is remarkable that a younger age of patients with critical illness is seen during pandemics, including the 2009 H1N1. While many people are affected by seasonal influenza every year, complications in non-respiratory tissues (e.g., encephalopathy, myocarditis, and myopathy) occur only occasionally.[1] The frequency of myocardial involvement in influenza infection varies (0-10%) depending on the diagnostic criteria and is likely elevated with influenza H1N1 compared to seasonal influenza.[3,6] The Japanese pandemic influenza registry reported 15 patients with H1N1 associated myocarditis, ranging from a child to a man over 70 years old.[7] Bratincsák et al, in a retrospective review of children admitted with H1N1 to a children's hospital for a single month in the fall of 2009, reported that 4 out of 80 patients were found to have acute myocarditis based on T1 release or abnormal heart ultrasound and emphasized the relevance of H1N1 influenza A virus in severe myocarditis[8]. There are some individual case reports of fulminant myocarditis from the USA and Europe, and a few fatal cases in Europe and Japan[9-16].

The clinical presentation of myocarditis of viral etiology varies from asymptomatic to fulminant myocarditis. It is characterized by the presence of flu-like symptoms (chills, fever, headache, muscle aches, general malaise) or gastrointestinal symptoms such as decreased appetite, nausea, vomiting, and diarrhea. Cardiac manifestations

appear a few hours to a few days after the initial signs and symptoms and they consist of those of heart failure, chest pain due to pericardial irritation and symptoms associated with heart block and arrhythmia[17].

The ECG is a sensitive and convenient tool for diagnosis of myocarditis and the findings such as ST segment elevation, T inversion and conduction block are frequently observed. Continuous ECG monitoring is also useful to detect potentially fatal arrhythmias. The heart ultrasound contributes in diagnosis and classical findings include transient wall thickening, reduced wall motion and reduced cardiac chamber size in addition to pericardial effusion, but the absence of these findings do not exclude the diagnosis. The ECG and the heart ultrasound must be repeated in every patient with suspected myocarditis.[16-18] Erden *et al* and Sahin *et al* reported acute myocarditis mimicking acute myocardial infarction associated with H1N1 infection, with chest pain and ST elevation, suggesting that coronary artery disease should be excluded in cases with severe chest pain by cardiac catheterization.[19,20] Mavrogeni and Manoussakis described the cardiac involvement of patients with documented infection due to H1N1 influenza[21]. In their study, a considerable number of patients with documented H1N1 influenza infection had mild cardiac symptoms. They documented by CMR the presence of myocarditis in a minority of them, who also had abnormal ECG, elevated cardiac enzymes (TNI, CK-MB) and normal heart ultrasound. These findings should make clinicians aware of possible myocardial involvement during H1N1 infection and support the application of CMR as a tool for cardiac assessment in these patients, especially if the echocardiographic evaluation is negative[21].

Myocarditis is confirmed by the findings of elevation of CPK, CK-MB, AST, LDH and cardiac troponin I in blood[17]. The diagnosis of viral infection can be confirmed with the detection of the H1N1 influenza virus by a rapid diagnostic test and an RT-PCR assay from a nasal swab.

Endomyocardial biopsy (EMB) is considered as the "gold standard" for diagnosis of viral myocarditis. However, it is an invasive examination whose safety remains to be evaluated, which limits its clinical application. The inconsistencies in sampling time, region error and diagnosis standard, limit the accuracy of the diagnosis, so, even if the results of cardiac biopsy are negative, the presence of myocarditis cannot be excluded[22].

Empirical antiviral treatment must be started immediately in patients who are at higher risk for developing complications (including those younger than six years, morbidly obese, asthmatic, immunocompromised or pregnant subjects), in patients requiring hospitalization and in progressive, severe, or complicated illness, regardless of previous health status.[23,24] There are compelling indications for the use of beta blockers and/or angiotensin-converting enzyme inhibitors for the treatment of a subacute phase of the illness; additional supportive intervention is essential as first-line therapy for myocarditis patients with heart failure. In severe cases with rapidly progressive hypoxemia and high ventilatory demands, evolving in acute respiratory distress syndrome (ARDS), mechanical support could be required.

In conclusion and in view of the high mortality rate associated with acute myocarditis, this case emphasizes the importance of a high index of clinical suspicion in healthcare providers, to diagnose this complication of influenza infection and treat it appropriately.

COMPETING INTERESTS

All the authors declare that they do not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

REFERENCES

1. Ruuskanen O, Lahti E, Jennings LC, et al. Viral pneumonia. Lancet 2011;377:1264-75.
2. CS Joint Working Group. Guidelines for diagnosis and treatment of myocarditis (JCS, 2009). Circ J 2011;75:734-43.
3. Mamas MA, Fraser D, Neyses L. Cardiovascular manifestations associated with influenza virus infection. Int J Cardiol 2008;130:304-9.
4. The World Health Organization. The global burden of disease: 2004 update. Switzerland: Work Health Organization; 2008. Available at: http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf. Accessed April 8, 2016.
5. Tsiodras S. Influenza pandemic: Is there a real threat? Pneumon 2009;22:211-2.
6. Onitsuka H, Imamura T, Miyamoto N, et al. Clinical manifestations of influenza a myocarditis during the influenza epidemic of winter 1998-1999. J Cardiol 2001;37:315-23.
7. Ukimura A, Izumi T, Matsumori A; Clinical Research Committee on Myocarditis Associated with the 2009 Influenza A (H1N1) Pandemic in Japan organized by the Japanese Circulation Society. A National Survey on Myocarditis Associated with the 2009 Influenza A (H1N1) Pandemic in Japan. Circ J 2010;74:2193-9.
8. Bratincsák A, El-Said HG, Bradley JS, et al. Fulminant myocarditis associated with pandemic H1N1 influenza A virus in children. JACC 2010;55:926-33.
9. Cunha B, Syed U, Mickail N. Fulminant fatal swine influenza (H1N1): myocarditis, myocardial infarction, or severe influenza pneumonia? Heart Lung 2010;39:453-8.

10. Khouzam R, Parizianu C, Hafiz A, et al. Fulminant myocarditis associated with novel H1N1 influenza A. Heart Lung 2011;40:566-8.
11. Weiss T, Knut H, Stensaeth K, et al. Myocarditis in a juvenile patient with influenza A virus infection. Eur Heart J 2010;31:277.
12. Penela D, Regueiro-Cueva A, Ortiz-Pırez JT, et al. Myocarditis due to pandemic influenza A (H1N1). Rev Esp Cardiol 2010;63:1386-7.
13. Al-Ammodi M, Rao K, Rao S, et al. Fulminant myocarditis due to H1N1 influenza. Circ Heart Fail 2010;3:7-9.
14. Vila de Muga M, Torre Monmany N, Asensio Carretero S, et al. Caracteristicas clinicas de la gripe A H1N1 2009: estudio multicentrico. An Pediatr 2011;75:6-12.
15. Cabral M, Brito MJ, Conde M, et al. Fulminant myocarditis associated with pandemic H1N1 influenza A virus. Rev Port Cardiol 2012;31:517-20.
16. Komai T, Nakazawa G, Asai S, et al. Fatal fulminant myocarditis associated with novel influenza A (H1N1) infection. Eur Heart J 2011;32:283.
17. CS JointWorking Group. Guidelines for diagnosis and treatment of myocarditis (JCS, 2009): digest version. Circ J 2011;75:734-43.
18. Hiramitsu S, Morimoto SI, Kato S, et al. Transient ventricular wall thickening in acute myocarditis: a serial echocardiographic and histopathologic study. Jpn Circ J 2001;65:863-6.
19. Erden I, Erden EC, Ozhan H, et al. Acute myocarditis mimicking acute myocardial infarction associated with pandemic 2009 (H1N1) influenza A virus. Cardiol J 2011;18:552-5.
20. Sahin DY, Demir M, Kurtaran B, et al. A case of myocarditis mimicking acute coronary syndrome associated with H1N1 influenza A virus infection. Turk Kardiyol Dern Ars 2010;38:572-5.
21. Mavrogeni S, Manoussakis MN. Myocarditis as a complication of influenza A (H1N1): Evaluation using cardiovascular magnetic resonance imaging. Hellenic J Cardiol 2010;51:379-380.
22. Lv S, Rong J, Ren S, et al. Epidemiology and Diagnosis of Viral Myocarditis. Hellenic J Cardiol 2013;54:382-91.
23. HA Central Committee on Infectious Disease and Emergency Responses (CCIDER). Interim guideline on antiviral treatment, chemoprophylaxis and pneumococcal vaccination for human swine influenza/influenza A (H1N1) Infection. 21 Oct 2009. Available at:http://www.ha.org.hk/haho/ho/hsflu/Interim_Treatment_091021.pdf.
24. CDC. Updated Interim Recommendations for the Use of Antiviral Medications in the Treatment and Prevention of Influenza for the 2009-2010 Season. Available at: http://www.cdc.gov/h1n1flu/recommendations.htm. Accessed April 8, 2016.