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CASE REPORT

Fulminant myocarditis as a primary manifestation of H1N1 infection: A first reported case from Serbia

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Abstract A 19-year-old male was admitted to our clinic with a diagnosis of suspected acute pericarditis and acute coronary syndrome. The initial diagnostics at our clinic revealed fulminant myocarditis. Twenty-four hours after admission, the patient's condition deteriorated, and he required mechanical ventilation and cardiopulmonary resuscitation. Unfortunately, the patient died. Clinical course, postmortem pathohistological findings and virus serology indicated that an H1N1 viral caused fulminant myocarditis and was the primary manifestation.

1. Brief Introduction

Fulminant myocarditis is one of the major causes of acute-onset heart failure and is responsible for approximately 10%-20% of cases sudden death among young patients and 6%-10% of cases of recent-onset dilative cardiomyopathy.[1] Myocardial involvement in seasonal influenza infection has been reported in up to 10% of cases,[2] although the frequency of myocarditis in H1N1 influenza remains unclear. The presentation of influenza myocarditis varies from asymptomatic infection to early fulminant myocarditis, cardiogenic shock and eventually death, whereas complications ranges from arrhythmias, atrioventricular (AV) blocks, congestive heart failure, cardiac tamponade, disseminated intravascular coagulation, septic shock, renal failure, alveolar hemorrhage, viral pneumonia and multisystem organ failure[3].

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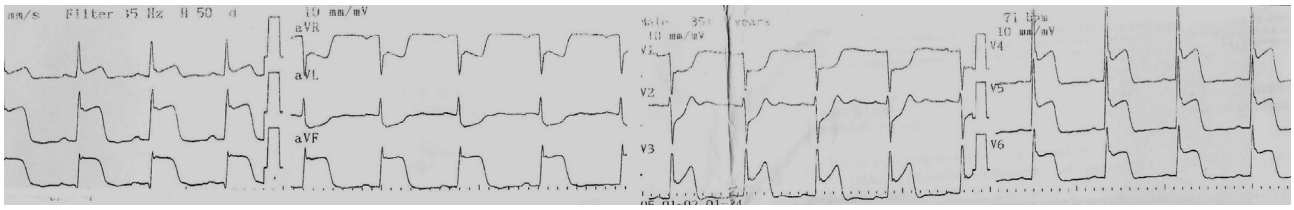

Figure 1 ECG at admission: ST elevations in the anterolateral and inferior leads.

2. Case Presentation

A 19-year-old male was admitted to our clinic from a hospital in Čačak with a diagnosis of acute pericarditis and suspected acute coronary syndrome. He was hospitalized the previous day due to constant chest pain that had begun during the night. Two days before admission, the patient had been chopping wood after which he felt sweaty and chill. Laboratory analyses from the Čačak hospital showed elevated cardiac specific enzymes (CK-MB 112 U/L and troponin I 1.1 μg/mL) but no elevations in markers of inflammation (CRP 3 mg/L, WBC 8.6 ×109 /L).

The initial ECG in our clinic (Figure 1) showed ST elevation in the anterolateral and inferior leads with single PVCs, whereas echocardiography showed small circumferential pericardial effusion, measuring 2-3 mm, without any abnormalities (ejection fraction 50%, left ventricular end-systolic diameter 32 mm, left ventricular end-diastolic diameter 49.3 mm, and thickness of ventricular septum 11 mm). Laboratory investigations revealed elevated inflammatory markers (CRP 13 mg/L, WBC 13.3 x10^9/L and fibrinogen 3.519 g/L) and elevated cardiac specific enzymes (CK-MB 335 U/L and troponin I 35.34 μg/mL), followed by coronary angiography indicating normal findings in the coronary arteries, except a small muscle bridge in the LAD with TIMI III flow. Because the ECG elevation persisted, the patient was transferred to the Coronary Unit with non-steroid antirheumatic and gastroprotective therapy in addition to anticoagulant, antiarrhythmic and antibiotic therapy.

Several hours after admission, patient's condition worsened with increased chest pain and cough with expectoration of bloodstained sputum. His blood pressure lowered to 90/60 mmHg with increased heart rate, and the ECG showed incomplete right bundle branch blockage with previously described ST elevations. Laboratory results indicated further elevation of cardiac specific enzymes (CK-MB 1049 U/L and troponin I 74 μg/mL) along with increased transaminases and positive inflammation markers (AST 1239 CRP 13 mg/L). Chest X-ray showed bilateral stain, parahilar shadows and pronounced lung interstitium. Low oxygen saturation was corrected with oxygen and administration of diuretics, after which blood gas analysis showed normal oxygen saturation and pO2.

Later during the day, the patient's condition deteriorated further. He was subfebrile with 62% oxygen saturation and arterial blood pO2 of 4.8 KPa. He remained resistant to treatment with diuretics and oxygen and had to be intubated and connected to mechanical ventilation. Repeated chest X-ray showed progression, of non-cardiogenic pulmonary edema compared with previous X-rays and mild signs of acute respiratory distress syndrome (Figure 2). Blood pressure was maintained at 100/60 mmHg with inotropic support. The patient was unstable in the next few hours with mixed acidosis and low pO2. We immediately started intensive resuscitation measures and the use of antibiotics, bronchodilators, cardiotonic, anticoagulants, antacids, antiarrhythmic drugs, inotropes, analgesics and vitamins. Despite intensive therapy and reanimation measures, significant hemodynamic instability with bradycardia and asystole occurred.

Histopathological findings from representative regions of the left ventricle (anterior, lateral and posterior walls), apex, septum and right ventricle (Figure 3) indicated extensive zones of necrosis along with degenerative myocardiocytes and inflammatory infiltrate. The inflammatory infiltrate was dominated by neutrophilic leukocytes interspersed with areas of degenerated cardiomyocytes (Figure 3A). The inflammatory infiltrate was much scarcer and generally consisted of lymphocytes alone or clustered in groups of two to six cells distributed along the sarcolemma and often achieving close contact with this region (Figure 3B). The left ventricle showed a necrotic zone with leukocytes and a degenerative zone with lymphocytic infiltrate (Figure 3C). Additionally, the right ventricle was infiltrated with massive lymphocyte and leukocyte inflammation (Figure 3D). The lungs showed abundant edemic liquid that filled the interstitium and intraalveolar spaces, with lymphocytes, erythrocytes, alveolar epithelial cells and rare neutrophils, macrophages and hemosiderophages. The blood vessels were dilated and filled with blood and

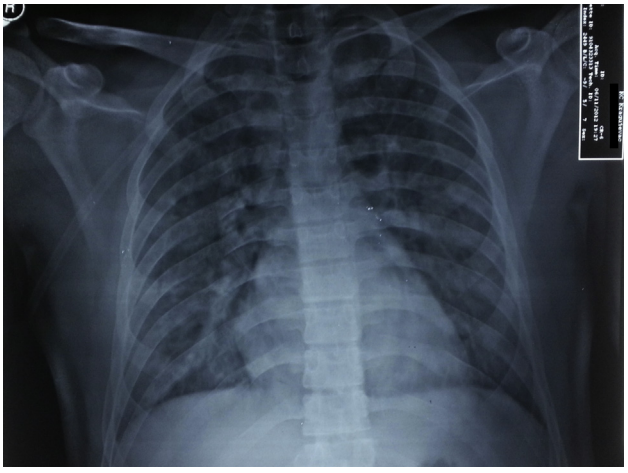

Figure 2 Chest X-ray of patient: bilateral, parahilar shadows with pronounced lung interstitium.

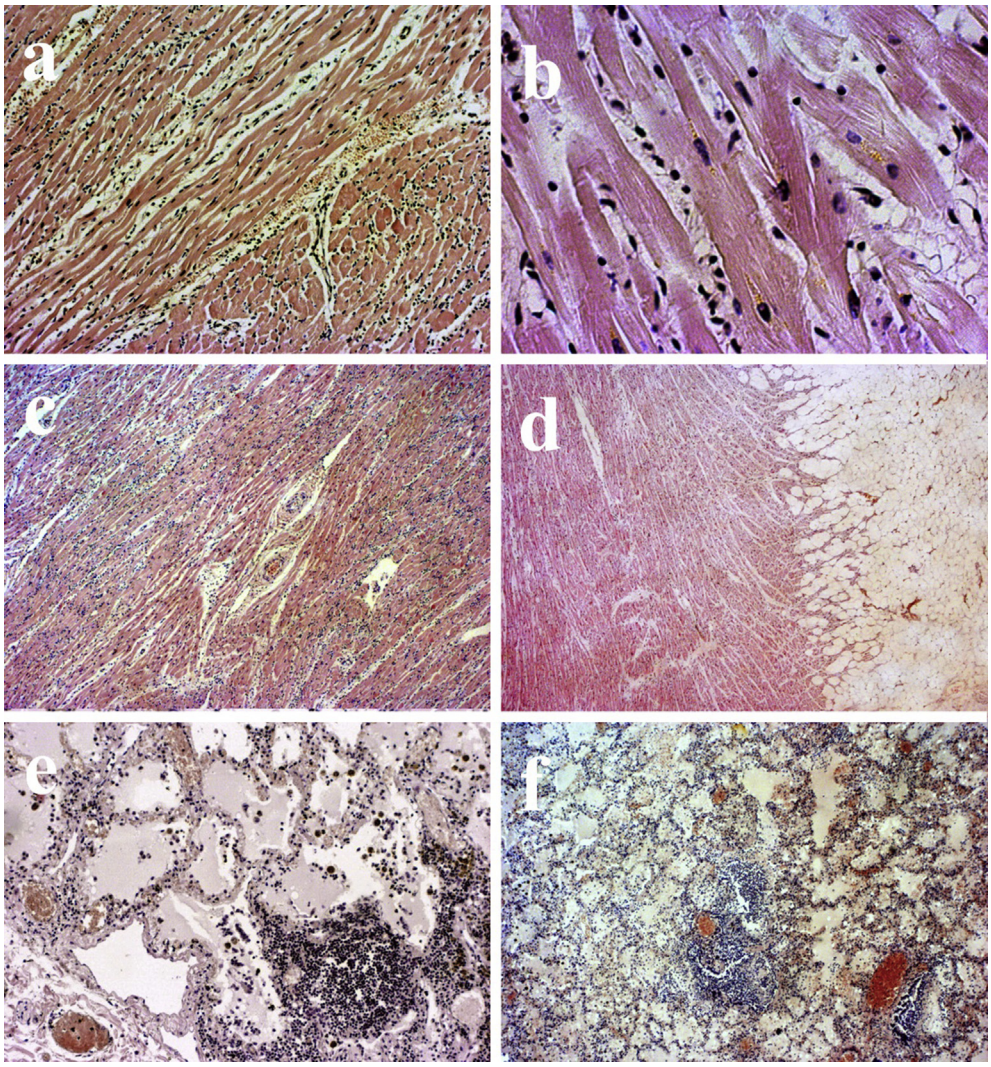

Figure 3 Histopathological findings (H&E stained, original magnification, ×100 (Figure 3c, 3d, 3f), ×200 (Figure 3a, 3e) and ×400 (Figure 3b): Figure 3a — Left ventricle — Inflammatory infiltrate dominated by neutrophilic leukocytes. Figure 3b — Lymphocytes in contact with sarcolemma, degenerative altered cardiomyocytes with granular, brown pigments indicating lipofuscin. Figure 3c — Left ventricle showed necrotic zone with leukocytes and degenerative zone with lymphocytic infiltrate. Figure 3d — Right ventricle infiltrated with massive lymphocyte and leukocyte inflammation. Figure 3e — Lungs — lung edema and focus of inflammation (lymphocytes, erythrocytes, alveolar epithelial cells and rare neutrophils, macrophages and hemosiderophages) with thrombosis of a blood vessel. Figure 3f — Lung edema, bronchial lumen filled with inflammatory exudate and inflammatory infiltrate forming small bronchopneumonia foci.

agglutinated erythrocytes (Figure 3E). The bronchial lumen was filled with inflammatory exudate and inflammatory infiltrate that permeated the wall and form small bronchopneumonia foci (Figure 3F).

Postmortem hemoculture was negative, whereas ELISA virus serology showed elevated IgM antibodies only for H1N1 virus and negative for other viruses.

3. Discussion

In most cases, fulminant myocarditis is caused by coxsackie B virus, whereas the incidence of H1N1-associated myocarditis is the subject of debate. Ukimura et al. reported 29 patients with H1N1 myocarditis within a 2-year observation period in Japan, and 17 of these patients had fulminant myocarditis with fatal arrhythmias or varying degrees of cardiogenic shock[4] among 20.62 million patients infected with influenza A H1N1 in 2009.[5] However, the prevalence of H1N1 influenza, as well as fulminant myocarditis as a complication of H1N1 infection, in Serbia is unknown. At the time of this report, no cases of fulminant myocarditis as a complication of H1N1 infection have been reported in Serbia.

The pathogenesis of H1N1 myocarditis differs from other forms of myocarditis. Significant mechanisms of cardiac injury, such as cytokine storm, with a massive release of proinflammatory cytokines into the circulation, oxidative stress and endothelial dysfunction, could play a major role in disease pathogenesis.[3] The clinical presentation of H1N1

myocarditis varies greatly; cardiac dysfunction has progressed rapidly in 12 out of 15 patients (as we also observed in our patient), whereas 10 patients had fatal arrhythmias and/or cardiogenic shock. Cardiopulmonary arrest was the first cardiac symptom described in only two out of 15 patients.[3]

The development of viral myocarditis requires direct myocardial injury with the release of intracellular antigens, followed by an immune response directed against the pathogens.[6] On cardiac biopsy, lymphocyte infiltration and myocyte damage are typically present. Ultimately, the body can clear the virus, leading to recovery, or the infection can become chronic, leading to cardiomyopathy.[6] The myocardium of our patient was completely involved with a severe form of inflammation and inflammatory infiltrate dominated by lymphocytes that were in close contact with the sarcolemma, indicated that he had already developed lymphocytic, viral, myocarditis.

H1N1 infection is a respiratory infection with primary changes affecting the lung tissue. Progressive pneumonia, acute respiratory distress syndrome, multiorgan failure are major but not so rare forms of this infection. Inflammation in the lungs leads to the development of acute respiratory distress syndrome and impaired gas exchange with systemic release of inflammatory mediators, causing inflammation, hypoxemia and metabolic acidosis. Acute respiratory distress syndrome is associated with the highest mortality rate and clinical presentation of dyspnea, cyanosis, tachypnea, diaphoresis, use of accessory muscles of respiration, cough, and chest pain. Our post-mortem, pathohistological findings from the lungs of our patient document pulmonary edema and pneumonitis rather than a picture of diffuse alveolar damage, which is the usual morphologic correlate of acute respiratory distress syndrome.[7]

The course of disease in our patient demonstrated that fulminant myocarditis was the primary manifestation of H1N1 infection. Our assumption is based on the initial symptoms and signs of myocarditis that developed, including chest pain, ECG changes and elevated cardiac specific enzymes but no evidence of elevated inflammatory markers. After two days of his illness, he developed signs of pulmonary infection and pneumonitis and was admitted to the hospital. Using an advanced literature search, we could not find any similar case reports, as well as no proven pathophysiological mechanisms that could explain the primary manifestation of H1N1 infection as fulminant myocarditis.

4. Conclusions

By analyzing and summarizing the entire clinical course and histopathological findings, we conclude that this fulminant myocarditis was the primary manifestation of H1N1 virus infection and that this report is the first described case report of such H1N1 infection. Additionally, to the best of our knowledge, this report describes the only case of H1N1 fulminant myocarditis from Serbia.

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