

Influenza A positive but H1N1 negative myocarditis in a patient coming from a high outbreak region of new influenza

Frank Himmel¹, Peter Hunold², Heribert Schunkert¹, Frank Bode¹

¹Medizinische Klinik II, Universitätsklinikum Schleswig-Holstein, Campus Lübeck, Germany

²Klinik für Radiologie und Nuklearmedizin, Universitätsklinikum Schleswig-Holstein, Campus Lübeck, Germany

Abstract

We present the case of a 21 year-old man holidaying on the Spanish island of Mallorca, a region of high outbreak of infections with a new influenza A/H1N1 virus. Symptomatic influenza A infection, but not H1N1 positive, led to myocarditis after intimate contact with a woman with positive H1N1 titer. The electrocardiogram showed T-wave inversions in II, III, aVF and V5, V6. Serum chemistry showed elevated levels of troponin T, increased creatine kinase (CK) and CK myocardial band. Cardiac magnetic resonance imaging revealed mid-myocardial and subepicardial hyperintensities in the lateral wall, and subepicardial and mid-myocardial areas of gadolinium enhancement in the inferior wall. Despite intimate contact with an H1N1 positive patient, the analyses on H1N1 (H1 A/Brisbane/59/07, H1 A/California/7/09swine) were negative, but were positive for common influenza (H3 A/Brisbane/10/07). Myocarditis is a rare clinical manifestation of influenza A infection. (Cardiol J 2011; 18, 4: 441–445)

Key words: influenza A, H1N1, myocarditis

Introduction

Myocarditis, an inflammation leading to myocardial cell necrosis, can be caused by various infectious agents such as viruses, bacteria, rickettsia and spirochaeta, but also drugs, toxins and systemic diseases. Of the causes, viral myocarditis is the commonest [1]. Frequent pathogens are coxsackievirus and adenovirus, whereas others like influenza A virus are uncommon and rare causes of myocarditis. The literature describes only a few cases of influenza A associated myocarditis [2–4].

Influenza A is subdivided into 16 hemagglutinin (H1 to H16) and 9 neuraminidase (N1 to N9) subtypes. In contrast to seasonal influenza, the

swine-derived subtype H1N1 is highly contagious and can lead to an outbreak of pandemic H1N1 virus infection [5]. Until now, H1N1 associated myocarditis has not been described. However, because of the pandemic spread, H1N1 infection must be considered in the differential diagnosis of influenza A myocarditis.

The diagnosis of myocarditis is an integrated synopsis including history, clinical evaluation, electrocardiogram (ECG) pattern, biomarkers and cardiac magnetic resonance imaging (MRI). MRI is the primary tool for non-invasive assessment of myocarditis, showing subepicardial late enhancement pattern, thereby visualizing myocarditis-related necrosis [6].

Address for correspondence: Dr. Frank Himmel, Universitätsklinikum Schleswig-Holstein, Campus Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany, tel: +49 451 500 2421, fax: +49 451 500 4951, e-mail: frank.himmel@uk-sh.de

Received: 27.04.2010

Accepted: 15.05.2010



Figure 1. Electrocardiography showing T-wave inversions in II, III, aVF and V5, V6.

Case report

A 21-year old man suffered from an influenza-like illness associated with high fever, cephalgia, dizziness and upper respiratory tract illness while spending his holidays on the Spanish island of Mallorca, a high outbreak region of infections with a new influenza A (H1N1) virus. He complained of intermittent chills and body aches. The history revealed that the patient had had intimate contact with a woman suffering from H1N1 virus infection. One week after the influenza-like symptoms, the patient presented with dyspnea (NYHA-class II), fatigue and ECG changes in our hospital. Typical angina-like chest pain was denied. Clinical examination was normal for age and chest X-ray was unremarkable. The ECG showed T-wave inversions in II, III, aVF and V5, V6 (Fig. 1). Serum chemistry showed elevated C-reactive protein [20.1 mg/L (ref. < 5 mg/L)] and elevated levels of troponin T [1.33 µg/L (ref. < 0.1 µg/L)] and increased lactate dehydrogenase [419 U/L (ref. 80–248 U/L)]. White blood cell count, creatine kinase (CK) and CK myocardial band were normal (Table 1). Transthoracic echocardiography displayed a slightly reduced left ventricular function (50%) without pericardial effusion. Microbiological analyses of blood cultures and serologies were negative for anti-streptolysin, borrelia burgdorferi, brucella species, yersinia species, coxsackie virus, Epstein-Barr virus, echovirus, cytomegalovirus, adenovirus, enterovirus and influenza B. Rheumatological parameters were also normal. Serum influenza A testing and polymerase chain reaction (PCR) for H3 A/Brisbane/10/07 were positive. De-

Table 1. Blood analysis at admission.

		Ref.
Troponin T [µg/L]	1.33	< 0.1
Creatinine kinase (CK) [U/L]	136	15–174
CK myocardial band [U/L]	12	0–23
Lactate dehydrogenase [U/L]	419	80–248
White blood cell [µL]	8080	4000–9000
C-reactive protein [mg/L]	20.1	< 5.0
Creatinine [µmol/L]	95	45–104

Table 2. Influenza serologies and polymerase chain reaction (PCR).

	HHT-Titer	PCR
H1 A/Brisbane/59/07	< 10	Negative
H1 A/California/7/09swine	< 10	Negative
H3 A/Brisbane/10/07	180	Positive
B/Florida/4/06	< 10	Negative
B/Malaysia/2506/04	< 10	Negative

spite contact with a positive-tested and highly contagious H1N1 virus patient, no H1N1 virus infection could be proved. PCR and serologies on H1 A/Brisbane/59/07, H1 A/California/7/09swine were negative (Table 2).

The MRI diagnostic showed typical signs of myocarditis with slightly reduced left ventricular ejection fraction (LVEF 49%) and small pericardial effusion. As correlates for myocardial edema, mid-myocardial and subepicardial hyperintensities, as well

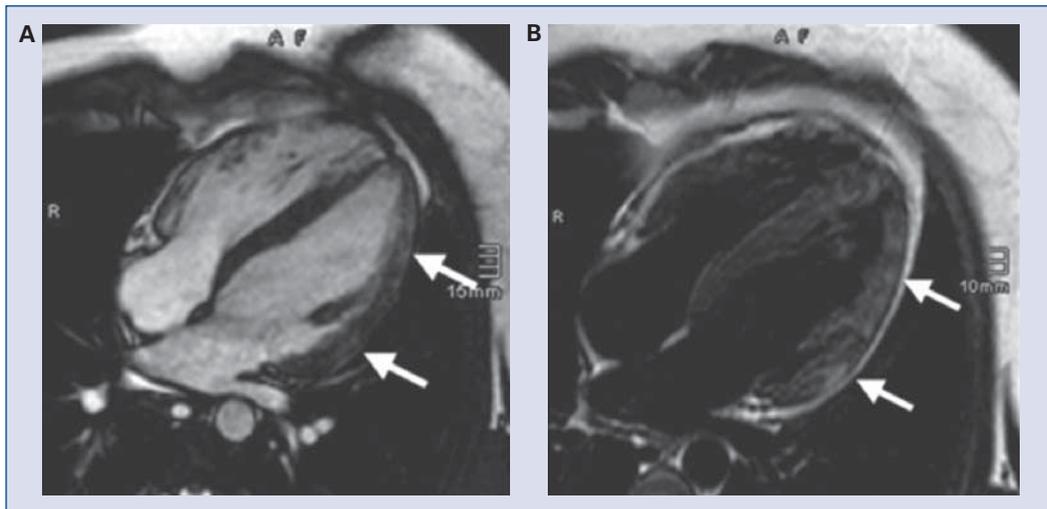


Figure 2. A. Cine steady-state free precession image in four-chamber view acquired during end-diastole. Normal left ventricular volume. Arrows show patchy, mid-myocardial hyperintensities in the lateral wall. Due to the T2 features of the utilized sequence, these suggest myocardial edema. There was no regional wall motion abnormality in the cine loop; **B.** T2-weighted black-blood prepared turbo spin-echo image in four-chamber view. Arrows show patchy, clearly distinguishable mid-myocardial and subepicardial hyperintensities in the lateral wall as a correlate of myocardial edema.

as late gadolinium enhancement, were found in the inferolateral wall (Figs. 2, 3) in mid-myocardial or subepicardial location. The patient was treated with angiotensin converting enzyme inhibitors and anti-inflammatory non-steroidal anti-rheumatic drugs. He was discharged symptom-free after 12 days.

Discussion

Myocarditis is defined as myocardial inflammation caused by viral, bacterial, protozoal, toxic or immune reactions and is accompanied by myocellular necrosis. In Europe and the United States, viral infection is the leading cause of myocarditis. Among all pathogens, influenza A is uncommon. Only a few case reports can be found in literature [2–4]. Currently the swine-derived influenza A subtype H1N1 is causing a worldwide pandemic [7]. Until now, H1N1 associated myocarditis has not been described. Yet, due to its rapid global spread, the H1N1 myocarditis must now be considered in the differential diagnosis of acute myocarditis. The diagnosis may be difficult to obtain in the early stages of the disease. In the present case, typical influenza-like symptoms occurred after intimate contact with an H1N1 positive patient. One week after symptom onset, myocarditis was diagnosed by MRI, typical ECG changes and elevated serum biomarkers. Echocardiographic changes such as left ventri-

cular dysfunction or pericardial effusion are common abnormalities during myocarditis, but are not specific. The ‘gold standard’ for diagnosing myocarditis is endomyocardial biopsy combined with histopathology, immunohistology and molecular techniques to identify viral genomes. There are some limitations to be considered, as the sensitivity is limited by potential sampling error and severe complications such as perforation of the ventricle or tamponade may occur [8, 9].

Therefore, recommendations restrict endomyocardial biopsy to patients with severe heart failure [8, 9]. In acute viral myocarditis, the treatment of myocarditis remains supportive. Treatments with antiviral agents like oseltamivir have not been tested in influenza A related myocarditis, and immunosuppression has not been shown to be effective in myocarditis [10]. In the present case, angiotensin converting enzyme inhibitors and anti-inflammatory non-steroidal anti-rheumatic drugs were administered, leading to an improvement of clinical parameters.

The MRI has become the primary tool for non-invasive assessment of myocardial inflammation in patients with suspected myocarditis [6]. As illustrated in Figures 1 and 2, typical myocarditis findings in MRI are myocardial edema, myocardial early and late gadolinium enhancement, pericardial effusion and left ventricular dysfunction [11].

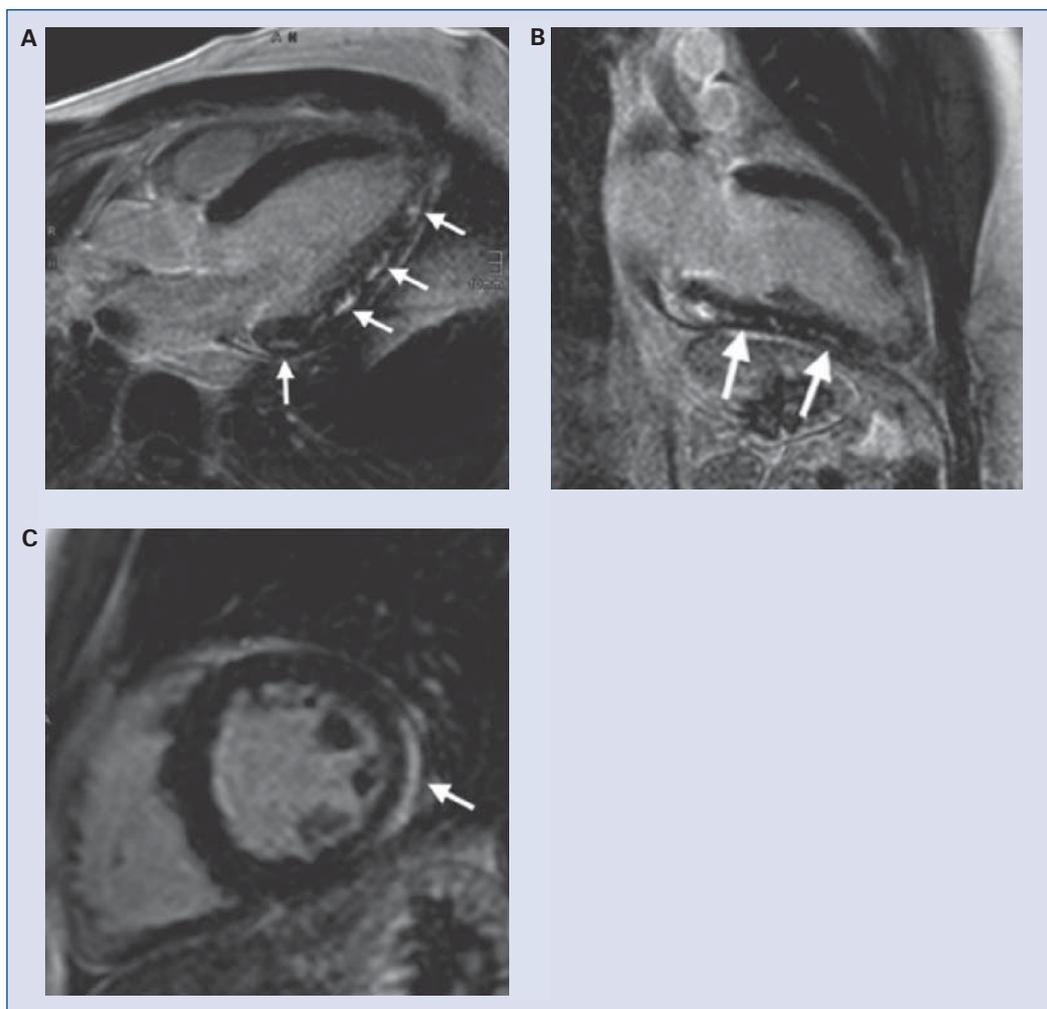


Figure 3. **A.** Three-dimensional inversion-recovery gradient-echo image in three-chamber view acquired ten minutes after administration of gadolinium contrast (0.2 mmol/kg). Arrows show multiple typical areas of well-delineated enhancement ('late Gd enhancement') of the inferolateral wall in mid-myocardial or subepicardial location as a correlate of myocardial edema and/or cell necrosis; **B.** Three-dimensional inversion-recovery late Gd enhancement image in two-chamber view ten minutes after gadolinium. Subepicardial and mid-myocardial areas of Gd enhancement in the inferior wall; **C.** Three-dimensional inversion-recovery late Gd enhancement image of a mid-ventricular short axis ten minutes after gadolinium. Typical subepicardial rim (arrow) of Gd enhancement in the inferolateral wall.

In our patient, PCR and serologies revealed an infection with influenza A without evidence for the highly contagious H1 A/Brisbane/59/07 or H1 A/California/7/09swine viruses. The duration of viral excretion is likely to be similar to seasonal influenza in the pandemic influenza A/H1N1. In seasonal influenza, it lasts generally 3–5 days from onset of symptoms but may persist for up to seven days and in rare cases even longer [12]. A recent study found that children were twice as susceptible to infection with the new pandemic influenza A/H1N1 virus than were adults (19–50 years) [13]. Another reason for the lack of H1N1 virus transmission could be a pre-existing pandemic H1N1 immune response as de-

scribed in serological analyses of the influenza A/H1N1 from the Centers for Disease Control and Prevention [14].

Conclusions

Influenza A infection is an uncommon cause of myocarditis. In contrast to seasonal influenza, the swine-derived subtype H1N1 is highly contagious, leading to the outbreak of a global pandemic. H1N1 myocarditis must be considered in the differential diagnostic analyses of influenza A myocarditis. The incidence of influenza-associated myocarditis might therefore increase. Yet, to date, H1N1 specific

myocarditis has not been reported. Whether the H1N1 subtype is even less cardiotropic than common types of influenza is not known. Therefore, signs of myocarditis must be evaluated in clinically apparent influenza infections. MRI can be useful in detecting myocardial inflammation.

Acknowledgements

The authors do not report any conflict of interest regarding this work.

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