

## Case Report

# Enterovirus Causing Progression of Heart Failure in a Patient with a History of Myocardial Infarction

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## Key words:

**Myocarditis, virus, coronary artery disease, treatment.**

Human enteroviruses (HEV) are an important cause of myocarditis and are associated with the pathogenesis of dilated cardiomyopathy (DCM). Current polymerase chain reaction studies in human myocardium have provided evidence that HEV are present in acute and chronic myocarditis as well as in DCM. To our knowledge, the presence of the HEV genome in the myocardium of human patients with heart failure (HF) after myocardial infarction (MI) has not been reported, nor have HEV been implicated as a factor affecting HF progression in patients after MI. Information about the presence of HEV in the heart tissue seems to be clinically important, since HEV infection is a frequent cause of HF and increased mortality. We present the case of a 54-year-old woman with a history of MI and HF progression. Our investigations suggested HEV as a possible cause of HF progression. Successful treatment with interferon- $\beta$  improved the patient's clinical status, apparently confirming our hypothesis.

## Manuscript received:

November 7, 2014;

## Accepted:

May 5, 2015.

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**H**eat failure (HF) is a common disease that affects 0.4-2% of the European population and is associated with a high mortality rate, ranging from 10% to 50%.<sup>1,2</sup> Coronary artery disease (CAD) is the most frequent reason for HF. Currently, viral aetiology is also considered as an important factor in both myocarditis and HF.<sup>3</sup> One of the most frequent viral aetiological agents is the group of human enteroviruses (HEV).<sup>3</sup> An association between the presence of HEV in the heart tissue and HF progression in patients after myocardial infarction (MI) has not yet been reported. It has been widely documented that HEV infection is a frequent cause of HF and incurs a risk of increased mortality in patients without CAD.<sup>4</sup> Coincidence of the presence of HEV in the heart tissue and CAD

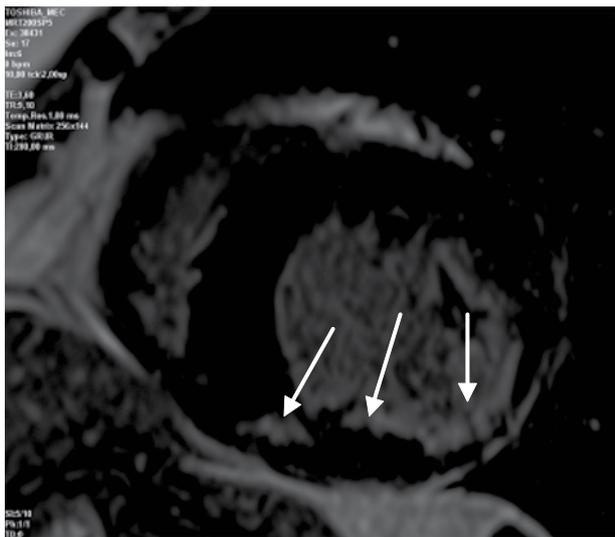
has still not been identified. A Medline search revealed only a few reported cases of HEV infection mimicking acute MI or ischaemia, but there has been no evidence of a patient with viral presence in the heart tissue after MI and HF progression.

## Case presentation

A 54-year-old female was admitted to our hospital for the diagnosis and treatment of HF. Her medical history began three years earlier with acute MI confirmed by coronary angiography (total occlusion of the right coronary artery with collateral circulation from the left descending coronary artery). The patient had not undergone any coronary intervention. During hospitalisation, when MI was diagnosed,

the patient was classified as Class III according to the New York Heart Association (NYHA) classification. Further examination revealed an elevated level of N-terminal-pro-brain natriuretic peptide (NT-proBNP, 10581 pg/mL), cardiac enlargement with an increased left ventricular end-diastolic diameter (LVEDD, 81 mm), low left ventricular ejection fraction (LVEF, 25%) with akinesis of the inferior, inferoseptal and inferolateral walls, and severe global hypokinesis of other walls of the left ventricle. Since then, the patient had been treated for CAD, as well as for arterial hypertension, hypercholesterolaemia, ventricular arrhythmia (carvedilol, ramipril, spironolactone, furosemide, atorvastatin, trimetazidine, aspirin).

Two months later, during her admission to our hospital, all parameters had improved (NYHA class II, NT-proBNP 1869 pg/mL, LVEDD 73 mm, LVEF 35% with inferior and inferolateral wall akinesis and moderate hypokinesis of other walls). Cardiovascular magnetic resonance (CMR) performed in our department showed late gadolinium enhancement (LGE) in the inferoseptal (mid-wall), inferior (sub-endocardial) and inferolateral (transmural) walls (Figure 1). There was no history of recent infection or fever, but we observed LV dilatation, a characteristic pattern of LGE for myocarditis in the inferoseptal and inferior walls, as well as persistence of a slightly elevated concentration of troponin I (0.014 ng/mL). Echocardiography revealed a low correlation between the coro-

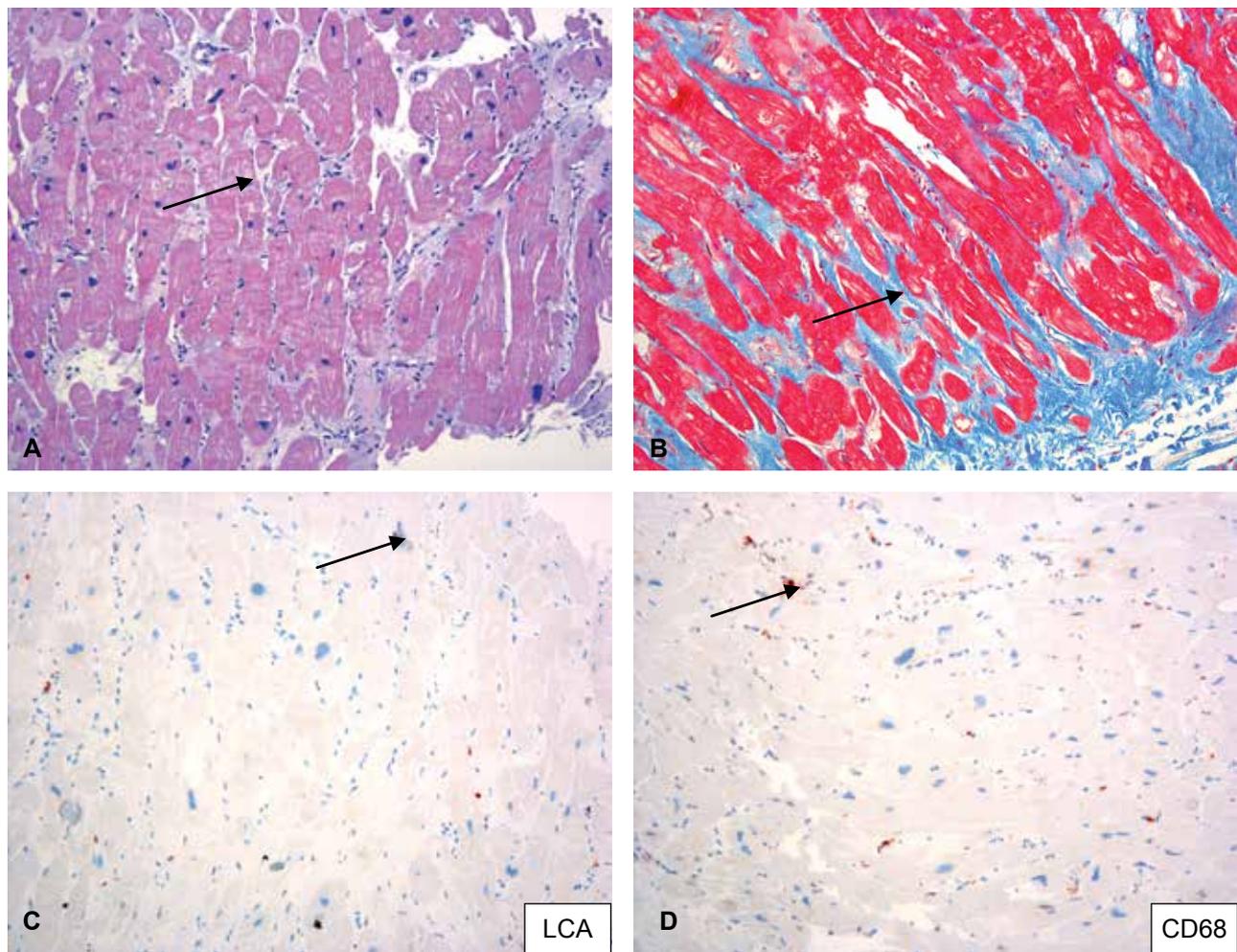


**Figure 1.** Mid-chamber short-axis view from late gadolinium enhancement on cardiac MRI. Arrows show transmural scar with an ischaemic pattern in the inferolateral wall, with mid-wall and sub-endocardial late gadolinium enhancement in the inferoseptal and inferior walls, respectively, exhibiting a myocarditis pattern.

nary artery changes and cardiac contractility. All of the above-mentioned factors raised the suspicion of myocarditis and triggered a decision to perform an endomyocardial biopsy (EMB). However, the EMB did not confirm the suspicion in keeping with the Dallas (presence of myocytolysis and myocardial fibrosis only) and immunohistochemical criteria (no CD3, CD4, CD8-positive cells, single LCA, CD68-positive cells) (Figure 2). Electron microscopy of EMB samples revealed ultrastructural changes in all elements of the heart tissue (myofibrils, nucleus, mitochondrion, endoplasmic reticulum, intercellular connection, blood vessels), but no virus was detected (Figure 3). HF and CAD treatment was administered according to the guidelines of the European Society of Cardiology. However, three months later the patient was rehospitalised because of HF exacerbation (NYHA Class III, NT-proBNP 1980 pg/dL, troponin 3 ng/mL, LVEDD 77 mm, LVEF 30%, 8048 ventricular extrasystoles [ExV] without complex forms on 24-hour Holter ECG monitoring). The results of coronary angiography resembled those observed in the previous examination. Because we were unable to determine the reason for the exacerbation, a real-time polymerase chain reaction examination (qPCR) was performed to detect viral nucleic acids in the samples collected during the previous EMB. Examination of frozen specimens with qPCR revealed the presence of HEV RNA, and viral cardiomyopathy was diagnosed (Figure 4). Based on these new findings, treatment with interferon- $\beta$  was introduced according to the following scheme: 62.5  $\mu$ g (0.25 mL) in the first week, 125  $\mu$ g (0.5 mL) in the second and third weeks, and 187.5  $\mu$ g (0.75 mL) subcutaneously every other day from the fourth to the twenty-fourth week.<sup>5</sup> In the fourth month of the treatment, EMB was performed and no HEV RNA was detected in the heart tissue samples. After six months of treatment with interferon- $\beta$ , the patient had improved significantly: NYHA class I, NT-proBNP 512 pg/mL, LVEDD 68 mm, LVEF 45%. A decrease in the number of ExV in 24-hour Holter recording was also observed (1889 ExV, without complex forms). No adverse drug reactions occurred. The two-year follow-up was uneventful.

## Discussion

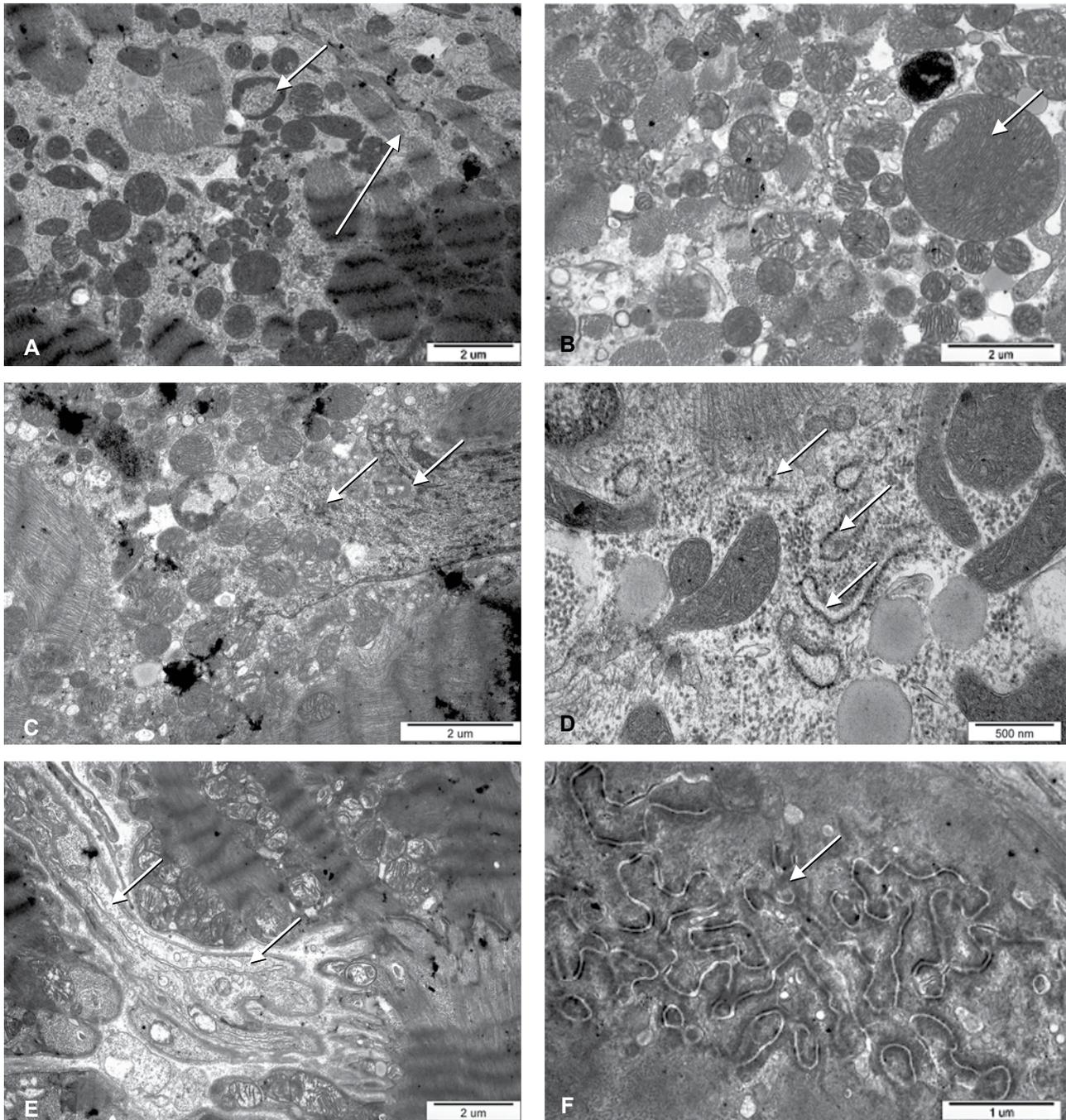
The clinical presentation of DCM caused by CAD includes, apart from the typical symptoms, those suggesting HF and arrhythmia, and is burdened with a risk of sudden death.<sup>6</sup> Similar manifestations can be



**Figure 2.** Heart tissue from a patient with a history of myocardial infarction and viral cardiomyopathy. Arrows show (A) myocytolysis in haematoxylin & eosin staining, (B) fibrosis in Masson's trichrome staining. Cellular infiltration was evaluated to investigate the inflammatory process: (C) leucocytes (LCA – leucocytes cell antigen), (D) macrophages (CD68 – CD68 antigen). Low number of leucocytes (below  $14/\text{mm}^2$ ).

observed in patients with DCM of viral background. In patients, especially older ones, who have ECG abnormalities, elevated cardiac enzymes, and clinical signs of CAD, an aetiology of left ventricular dilatation other than CAD is very rarely considered. Analysis of our case suggests that, when a patient shows no clinical improvement or when clinical worsening occurs despite treatment in accordance with guidelines, additional diagnostics should be considered. Diagnosis based on clinical presentation, physical examination, laboratory tests and echocardiography is sufficient neither for definitive confirmation nor for exclusion of viral cardiomyopathy. Neither can CMR in patients with DCM exclude inflammation or virus persistence in the heart tissue.<sup>7</sup> Moreover, CMR sensitivity is significantly lower in patients who present with

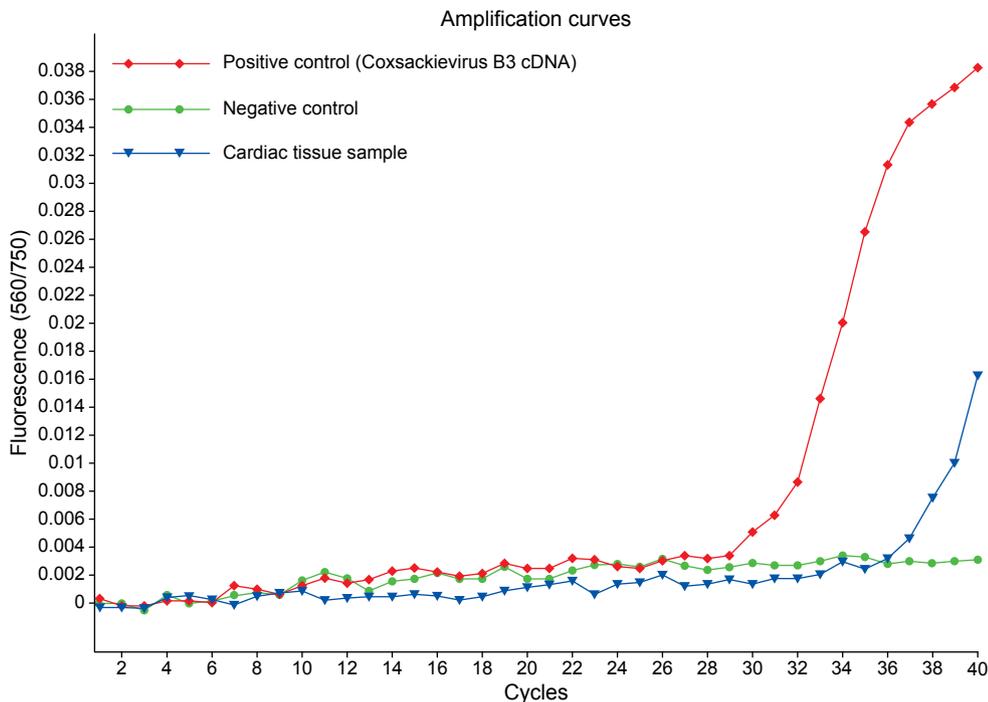
non-acute onset of a disease, because one of the Lake Louise criteria (oedema) is not fulfilled in most cases.<sup>8,9</sup> The only available method for the definite confirmation of viral cardiomyopathy, important for decisions about therapy, is a virological examination of the EMB.<sup>10</sup> Histopathological and immunohistochemical examinations of the heart tissue *per se* are insufficient for a diagnosis of viral presence in the heart tissue. The lack of inflammation does not rule out a detrimental influence of the virus on the myocardium.<sup>11</sup> The presence of the virus, or its components, in the heart tissue, even without a concomitant local immune response (determined by standard histopathological examination) can elicit the fibrosis, hypertrophy and degeneration of the cardiomyocytes observed in DCM.<sup>12</sup> Moreover, the structural changes mentioned



**Figure 3.** Electron microscopy showing ultrastructural changes in the heart tissue in a patient with viral cardiomyopathy after myocardial infarction. A: disorganised myofibrils with ring mitochondria. B: mitochondria with membrane fusion and circular cristae. C: interrupted nuclear envelope. D: wide sarcoplasmic reticulum. E: closed microvessels. F: increased density of intercalated discs.

above are also observed in the heart tissue after MI. Therefore, to establish the diagnosis of viral cardiomyopathy in patients with CAD (especially those with a history of MI) based only on histopathological analysis seems uncertain or even impossible. Thus, PCR analysis of biopsy samples should be performed in each pa-

tient with suspected viral heart damage in order to detect the presence of a viral genome. The virus can be detected with electron microscopy, yet the changes we observed in this case could suggest viral presence in the heart tissue, even though viral particles themselves were not identified.<sup>7,13</sup>



**Figure 4.** Amplification chart of qualitative real-time polymerase chain reaction for detection of human enterovirus in an endomyocardial biopsy sample obtained from the patient.

Taking into consideration all the available information it seems impossible to determine the exact time of onset of viral infection in our case. We presume that both diseases (MI and viral cardiomyopathy) occurred independently from each other. The observed HF exacerbation could have been caused by the presence of HEV in the heart tissue. We suspect that HEV can also influence the structure and function of both cardiomyocytes and extracellular matrix in the heart after MI. HEV could be yet another factor, apart from CAD, that causes dilatation of the left ventricle and HF progression. Therefore, the diagnosis of viral cardiomyopathy should be taken into account in all patients with a suspicion of viral presence, even in those with coronary artery lesions. The effectiveness of the treatment with interferon- $\beta$ , which may lead to clearance of HEV from heart tissue, indicates the importance of direct techniques of virus detection in EMB samples.<sup>5,14</sup>

## Conclusion

This case proves that the presence of CAD does not exclude viral cardiomyopathy, which can lead to HF progression and can be successfully treated with interferon- $\beta$ .

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