Immunosuppressive treatment in fulminant myocarditis and gene expression pattern associated with, but no histological confirmation of giant cell myocarditis

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Abstract

A healthy woman with acute onset of pulmonary oedema and severely depressed left ventricular function underwent endomyocardial biopsy under the clinical suspicion of fulminant myocarditis. While awaiting the results of biopsy, the situation deteriorated to Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) and extracorporeal membrane oxygenation was implanted. Finally, immunohistochemistry in biopsy specimen corresponded to fulminant lymphocytic myocarditis, although active myocarditis was excluded. Furthermore, gene expression profiling identified giant cell myocarditis although multinuclear cells were absent. This prompted the start of immunosuppression with cortisone and cyclosporine. The patient fully recovered.

Keywords  Myocarditis; Endomyocardial biopsy

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Introduction

Idiopathic giant cell myocarditis is a rapid progressive disease with an enormously high mortality because of pump failure or arrhythmias.1 In many cases, clinical course is acute to fulminant, and time span between clinical presentation and start of treatment should be as short as possible. The diagnostic tool of choice is endomyocardial biopsy (EMB) showing typical granulomas of giant cells in histology. However, repeat EMBs are frequently necessary delaying initiation of treatment.2 Treatment consists of immunosuppression including cortisone and cyclosporine.

Here, we present a case of a young woman with fulminant myocarditis in whom gene expression profiling of giant cells was helpful in diagnosing the disease.

Case report

A previously healthy woman (26 years) was admitted via helicopter because of sudden onset of massive dyspnoea, nausea, and vomiting following a respiratory infection 2 weeks ago. The patient had no fever. Because of the acute beginning of dyspnoea, pulmonary embolism was excluded by computed tomography. The patient was then admitted to the intensive care unit for treatment.

She was intubated and mechanically ventilated with initially high positive end expiratory pressure that led to respiratory stabilization. Echocardiography revealed a massive depression of left ventricular function with an ejection fraction (LV-EF) of 25%, while right ventricular function was normal. Inotropic therapy including levosimendan (0.05 μg/kg/min) and...
norepinephrine (0.2 μg/kg/min) was started. Laboratory values at admission are given in Table 1.

Invasive cardiologic workup including coronary angiography and EMB was performed the following day under the suspicion of fulminant myocarditis to differentiate between lymphocytic, eosinophilic, or giant cell myocarditis. Coronary arteries were normal. After EMB, echo showed an even more depressed LV-EF (15%), and the dose of norepinephrine necessary to stabilize circulation increased further (up to 0.5 μg/kg/min). Overall, cardiogenic shock progressively deteriorated (INTERMACS-1). This prompted the implantation of an extracorporeal membrane oxygenation (ECMO) in a veno-arterial manner.

After 5 days on ECMO and inotropes, the patient was stable, but LV-EF still was poor (15%). Preliminary results of EMB showed no viral genome and no giant cells in histology (three EMBs, although lymphocytes and macrophages were present; Figure 1(A)).

Quantification of immunohistochemical stainings by digital image analysis in two additional EMBs yielded the following values: CD3+: 32 per mm² (normal values (NV) <7 per mm²), CD11a/LFA-1+: 187 per mm² (NV <14.0 per mm²), CD11b/Mac-1+: 487 per mm² (NV <35 per mm²), area fraction of human leukocyte antigen class I: 14.8% (NV <5.5%), and CD54/ICAM-1-AF: 7.56% (NV <1.2%), demonstrating a massive elevation of lymphocytes and macrophages (Figure 1(B)–(D)) and expression of adhesion molecules (no perforin-positive cytotoxic cells have been present).

Immunohistochemical composition of cellular infiltrates corresponded to fulminant lymphocytic myocarditis, although active myocarditis (i.e. myocytolysis) was excluded. However, as histological proof of multinuclear giant cells or eosinophilic cells was not successful, a myocardial gene expression profiling using a set of 16 altered genes was performed. The results suggested the presence of multinucleated giant cells in the myocardium as key feature for giant cell myocarditis. This diagnostic approach was suitable to differentiate this disease from active lymphocytic myocarditis (Figure 2).

With this information, the recommended therapy for giant cell myocarditis was started with a high cortisone-dose (10 mg/kg body weight for 3 days followed by 4 weeks at 1 mg/kg body weight) in combination with cyclosporine. After 3 days of high-dose cortisone and cyclosporine, LV-EF increased from 15% to 55%, and ECMO was explanted. The patient was extubated and transferred to the normal ward after another 4 days.

| Table 1 Laboratory values out of range at admission |
|----------------------------------|------------------|
| Value                                    | Normal range     |
| Leucocytes (G/L)                  | 23 500           | <11 300          |
| CK (U/L)                          | 186              | <145             |
| hs troponin T (pg/mL)             | 1012             | <14              |
| Lactate (mmol/L)                  | 3.4              | <2.2             |
| pH                                | 7.29             | 7.37–7.45        |
| FiO2 (%)                          | 85               | 21               |
| paO2 (mmHg)                       | 54               | 71–104           |
| paCO2 (mmHg)                      | 48               | 32–43            |
| O2 saturation (%)                 | 83               | 95–98            |

CK, creatinkinase; hs troponin, high-sensitivity troponin; FiO2, fraction of inspiratory oxygen; paO2, arterial pressure of oxygen; paCO2, arterial pressure of carbon dioxide.

Figure 1  (A) Histology with atrophic myocytes (mean diameter: 14 μm) in regular arrangement. Blood vessels displaying thickened walls and normal endothelia. In the surrounding of vessels slight fibrosis, fatty tissue and small numbers of lymphocytes and macrophages are present. No eosinophils or multinuclear giant cells. No signs of myocyte necrosis or apoptosis. Endocardium normal (not shown). Hematoxylin and eosin stain. (B)–(E) Immunohistochemical examination including digital imaging analysis in other biopsies displays increase of T-lymphocytes (CD3 32 cells/mm², B), LFA-1 positive cells (LFA-1 187 cells/mm², C), and macrophages (MAC-1 468 cells/mm², D), but no multinuclear giant cells and no cytotoxic perforin-positive cells (E). Positive cells are stained by brown-red peroxidase reaction product.
Overall, the patient left the hospital after 4 weeks to start cardiac rehabilitation. Treatment at discharge consisted of methylprednisolone (1 mg/kg for 4 weeks, followed by a decline of 10 mg every 2 weeks until 10 mg will be reached), cyclosporine (trough level 100–150), pantoprazole 40 mg, calcium plus vitamin D, ramipril, eplerenone, and bisoprolol. This treatment was continued for 12 months with repeated visits at our outpatient clinic. All echocardiographic parameters stayed within normal ranges, throughout this time, and the patient returned to work after 10 months.

Discussion

Our case clearly shows the dilemma of diagnosing idiopathic giant cell myocarditis. Histological proof of multinucleated giant cells is the gold standard, but a recent publication showed that only 68% of first EMBs are diagnostic and repeat EMBs are necessary to confirm diagnosis.2 In our case, repeat EMB has been discussed but gene expression profiling, a method previously published by Lassner and coworkers, proved beneficial and a repeat biopsy could be avoided.3,4 However, the complete lack of myocytolysis (i.e. histological confirmation of myocarditis) in our patient was surprising. Nevertheless, lymphocytic myocarditis could be diagnosed with immunohistochemical tools.

We cannot completely rule out that LV-EF may have recovered by prolongation of ECMO and inotropic therapy. However, the finding of gene profiles of giant cells in biopsy specimen prompted the initiation of treatment for giant cell myocarditis and LV-EF recovered within 48 h. We think that a full recovery without immunosuppression is highly unlikely.

As shown here, the new technique of gene expression profiling may be helpful in patients with fulminant myocarditis to confirm the presence of giant cells in specimen without historical evidence of the disease, laying path to early initiation of immunosuppression and avoidance of repeat EMBs as shown in our case report.

Therefore, we conclude that gene expression profiling of giant cell myocarditis in patients with fulminant myocarditis and negative historical findings may be helpful laying path to tailored immunosuppressive treatment for this disease.

Conflict of interest

Drs Lassner and Schultheiss report a patent pending named ‘Verwendung von microRNAs oder Genen als Marker zur Identifizierung, Diagnose und Therapie einzelner nicht-ischämischer Kardiomyopathien oder Speichererkrankungen’ in Germany. The other authors have nothing to declare.

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