Familial right ventricular dysplasia with biventricular involvement and inflammatory infiltration

Bruno Pinamonti, Daniela Miani, Gianfranco Sinagra, Rossana Bussani, Furio Silvestri, Fulvio Camerini, and the Heart Muscle Disease Study Group

Abstract
The aetiology of right ventricular dysplasia/cardiomyopathy is presently unknown. A genetic background has been suggested, but myocarditis may play a part in its pathogenesis. Two familial cases of right ventricular dysplasia, one of whom had also a diagnosis of myocarditis, are reported. Both patients presented with ventricular arrhythmias. The father subsequently had a “flu-like” syndrome, heart failure, and biventricular dysfunction; “active” myocarditis was found at endomyocardial biopsy. Then the patient died suddenly. The daughter developed progressive biventricular dysfunction; then she was resuscitated from a cardiac arrest, and subsequently died suddenly. In both patients necropsy showed severe right ventricular atrophy and fibroadipose substitution, associated with biventricular fibrosis. Inflammatory infiltration was also present in the first patient. This study shows the association of right ventricular dysplasia and myocarditis in the same family. These cases may represent a link between inherited and acquired (“inflammatory”) forms of the disease.

Keywords: right ventricular dysplasia, myocarditis, familial cardiomyopathy

The aetiology of arrhythmogenic right ventricular dysplasia/cardiomyopathy remains unclear.1 In fact, although a familial occurrence has been reported and a genetic pattern suggested,2 non-familial forms are relatively frequent. Moreover inflammatory infiltrates were described in biopsies of some of these patients,3 4 suggesting an inflammatory mechanism in the pathogenesis of the disease.4

We describe two familial cases, father and daughter, affected by this disease. Both initially presented with apparently idiopathic ventricular arrhythmias. The father had left ventricular dysfunction and congestive heart failure. At endomyocardial biopsy active myocarditis was diagnosed. The daughter, during follow up, developed right ventricular dysfunction with subsequent left ventricular involvement. Both patients died suddenly. In both postmortem examination disclosed an extensive fibroadipose substitution of the right ventricular myocardium compatible with right ventricular dysplasia, associated with diffuse inflammatory infiltrates in the father. The possible links between familial disease, inflammation, and pathological changes in the pathogenesis of the disease are discussed.

Case reports

CASE 1
The first patient was first evaluated when he was 29 year old because of ventricular arrhythmias. The electrocardiogram showed a first degree atioventricular block, left anterior hemiblock, and T wave inversion from V1 to V3 with frequent multiform ventricular extrasystoles. He subsequently developed an advanced atioventricular block and was treated with permanent pacemaker and amiodarone.

Table 1 Echocardiographic and haemodynamic data

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>M mode echo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDD/LVESD (cm)</td>
<td>5-4/3-0</td>
<td>6-1*/5*</td>
</tr>
<tr>
<td>SF (%)</td>
<td>44</td>
<td>18**</td>
</tr>
<tr>
<td>RVEDD (cm)</td>
<td>1-2</td>
<td>2-4</td>
</tr>
<tr>
<td>Cross sectional echo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVEDA/RVES (cm²)</td>
<td>23/15</td>
<td>26/18</td>
</tr>
<tr>
<td>RV SFA (%)</td>
<td>35*</td>
<td>31*</td>
</tr>
<tr>
<td>LV EDV/LV ESV (ml)</td>
<td>114/85</td>
<td>43/18</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>26*</td>
<td>58</td>
</tr>
<tr>
<td>Haemodynamics:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV pressure (mm Hg)</td>
<td>135, 0/5</td>
<td>100, 0/10</td>
</tr>
<tr>
<td>LVVEDV (ml/m²)</td>
<td>63</td>
<td>101**</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>61</td>
<td>38*</td>
</tr>
<tr>
<td>RV pressure (mm Hg)</td>
<td>22, 0/2</td>
<td>23, 0/2</td>
</tr>
<tr>
<td>CI (mm²/min/m²)</td>
<td>2-6</td>
<td>3-2</td>
</tr>
<tr>
<td>MPWP (mm Hg)</td>
<td>6</td>
<td>9</td>
</tr>
</tbody>
</table>

*Abnormal data.
LV, left ventricle; RV, right ventricle; EDD, end diastolic diameter; ESD, end systolic diameter; SF, shortening fraction; EDV, end diastolic volume; ESV, end systolic volume; EF, ejection fraction; CI, cardiac index; MPWP, mean pulmonary wedge pressure.
Physical examination, chest x rays, M mode echocardiogram, and cardiac catheterisation were normal (table).

Three years later he had a “flu-like” syndrome and was admitted with severe heart failure.

Echocardiography showed biventricular dysfunction and bialtrial enlargement (table).

Endomyocardial biopsy from the right ventricle showed “active” myocarditis according to the Dallas criteria (fig 1).

The patient improved clinically after a treatment with prednisone, azathioprine, digoxin, and diuretics. However, biventricular dysfunction persisted and subsequent biopsies showed marked interstitial and subendocardial fibrosis. Seven months later the patient was resuscitated from an out of hospital cardiac arrest. Heart failure recurred and he died suddenly at the age of 35.

At postmortem examination all four chambers were dilated. The anterior and lateral walls of the left ventricle in the middle and apical portions and the right ventricular walls were thinned and replaced by fibrous and adipose tissue. In some areas of the anterior wall the myocardium was completely absent and a transillumination was evident (fig 2A). There was an aneurysm in the middle third of the interventricular septum and areas of fatty infiltration. Microscopically, multifocal areas of inflammatory infiltration were present in both ventricles, associated with severe adipose substitution and moderate fibrosis (fig 2B).

CASE 2

The daughter of the first patient was first seen when she was 12 because of complex ventricular arrhythmias.

The ECG showed negative T waves from V1 to V4 and frequent polymorphic ventricular extrasystoles. Non-sustained ventricular tachycardia was documented during Holter monitoring and during an effort test. An echocardiogram showed an apical hypokinesis of the right ventricle, with a normal left ventricle (table). Intracardiac pressures and left ventricular function were normal at cardiac catheterisation. Endomyocardial biopsy from the right ventricle showed only a mild atrophy of the myocytes with mild fibrosis and inflammatory infiltration. The patient was subsequently treated with amiodarone.

An echocardiogram performed one year later (1985) showed a worsening of right ventricular function and the appearance of septal hypokinesis and a mild decrease in left ventricular ejection fraction (table).

Three years later, while playing volleyball, she had a cardiac arrest caused by ventricular fibrillation. She was resuscitated with no neurological sequelae. A new echocardiogram showed a severe right ventricular dysfunction with multiple akinetic wall bulges and a further deterioration of left ventricular function with diffuse hypokinesis but without significant dilatation (table); there was also an akinetic bulge at mid septal level (fig 3).

The patient had a slowly progressive increase in dyspnoea and peripheral oedema.
and was found dead at home at the age of 18, six years after the initial evaluation.

At necropsy there were severe degenerative changes caused by the long interval (three days) between death and the examination. The right ventricle was markedly dilated, with severe wall thinning and extensive fibrous and adipose substitution. The left ventricle was moderately enlarged and showed a localised wall thinning at the apex and a small septal aneurysm.

Microscopically, multifocal areas of atrophied myofibres, severe fibrosis, and moderate adipose substitution were present in both ventricles.

Discussion

Right ventricular dysplasia is an idiopathic heart muscle disorder, characterised by fatty or fibrofatty replacement of right ventricular myocardium. The aetiology of the disease is still unknown, but, in many cases, it appears to be an inherited disorder with familial incidence. Recently Rampazzo et al9 localised the gene involved in the genesis of the disease on chromosome 14q23-q24. However, others suggested that right ventricular dysplasia may be at least in some cases the consequence of a previous myocarditis.4,5,10-13

In fact inflammatory infiltrates are not uncommon in histological specimens from these patients.

Fontaine et al10 in a review of 27 patients with right ventricular dysplasia found inflammatory infiltrates in eight, whereas Thiene et al14 classified the disease, from a pathological point of view, into lipomatous and fibrolipomatous. Because they found that the fibrolipomatous pattern was frequently associated with inflammatory infiltrates, necrotic myocytes, fibrosis, and aneurysms, they regarded this form as the possible expression of a chronic myocarditis, in which infectious and/or immunological factors could have a pathogenetic role. These observations are supported by the experimental study by Matsumori and Kawai15 who found that BALB/c mice infected with Coxsackie virus B3 developed selective right ventricular myocarditis with myocardial cell destruction, followed by acute mononuclear cell infiltration and later right ventricular aneurysms. Moreover, the case described by Zolezzi et al16 can be regarded a clinical example of myocarditis with predominant right ventricular involvement. Zolezzi et al interpreted the right ventricular abnormalities as being secondary to myocarditis, whereas others17,18 thought that the inflammatory infiltrates were a reaction to a damaged myocardium.

Familial cases are difficult to explain in this context. Familial cases of myocarditis have seldom been described,11,12,13 though sometimes they were associated with right ventricular dysplasia.11,12 A genetic predisposition and susceptibility to infections, or a familial cardiomyopathy with superimposed inflammation can be hypothesised. O'Connell et al18 found a deficiency of suppressor lymphocyte function in a patient with familial myocarditis. In this case the inherited factor could be a deficiency in immunoregulation and host response.

In this report we describe two patients (father and daughter) who died suddenly when young. The familial association, the relatively rapid clinical deterioration, the malignant ventricular arrhythmias with aborted sudden death and the pathological findings suggest that they both had the same disease. The daughter had symptoms and echocardiographic findings compatible with right ventricular dysplasia and left ventricular...
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