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Right ventricular dilated cardiomyopathy associated with primary biliary cirrhosis

F. ALFONSO*, A. L. P. CAFORIO†, J. DEL TORO*, E. TORRECILLA*, M. REY* AND P. DE RABAGO*

**Cardiac Department, Fundacion Jimenez Diaz University of Madrid, Spain and †Deparment of Cardiological Sciences, St George's Hospital Medical School, University of London, U.K.*

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A case of right ventricular dilated cardiomyopathy associated with primary biliary cirrhosis is described. The patient was a middle aged woman, who initially complained of fatigue and itching. The diagnosis of primary biliary cirrhosis was made based on clinical, biochemical and histological evidence of the disease. Seven years later severe right-sided heart failure developed. The diagnosis of right ventricular dilated cardiomyopathy was made based on echocardiographic and angiographic evidence of a globally dilated and poorly contracting right ventricle. Left ventricular function was within normal limits. Autoimmune serology screening at this time revealed the presence of organ-specific cardiac antibody (titre 1/20) and of antinuclear antibody (titre 1/80) by indirect immunofluorescence. There were no findings of mitochondrial antibody or other non-organ specific or organ-specific antibodies. Overall, this assessment demonstrates autoimmunity in both hepatic and heart muscle disease in a patient with primary biliary cirrhosis and right ventricular dilated cardiomyopathy.

Introduction

Primary biliary cirrhosis (PBC) is an autoimmune disorder, characterized by chronic destruction of the intrahepatic bile ducts[1]. The diagnosis is based upon a suggestive clinical history, cholestatic liver function tests, raised serum IgM, and typical hepatic biopsy features[2]. In such patients mitochondrial antibodies have been detected in a proportion varying from 83 to 93%[3].

Right ventricular dilated cardiomyopathy is a rare condition, which probably represents one end of the spectrum of dilated cardiomyopathy (DCM)[4–8]. The involvement of autoimmunity in the pathogenesis of DCM is controversial[9]; however, the recent demonstration of organ-specific circulating cardiac antibodies in a quarter of such patients[10] is consistent with autoimmune pathogenesis.

Autoimmune disorders are frequently associated in genetically predisposed individuals[11]. In the present study we describe the association of right ventricular cardiomyopathy and PBC.

Case report

A 52-year-old woman was admitted with right-sided heart failure. Ten years before she had complained of fatigue and anorexia, with subsequent development of intense pruritus. Cholestatic liver function tests were abnormal. Biliary duct obstruction was ruled out by abdominal ultrasonography and endoscopic retrograde cholangiography. Two percutaneous needle biopsies performed in different university hospitals were both highly suggestive of PBC (atypical biliary ducts surrounded by giant cells and hepatic granulomata with normal central veins) (Fig. 1). A diagnosis of PBC with negative mitochondrial antibody was made and she remained stable on cholestyramine. Seven years later she developed ankle oedema, progressive dyspnoea and palpitation.

On physical examination blood pressure was 110/70 mmHg, heart rhythm was regular and heart rate was 60 b.min^{-1}; mild jaundice was present. Jugular venous pressure was elevated with a prominent 'v' wave. On auscultation there was a grade 3/6 systolic murmur in the tricuspid area, which increased during inspiration. The liver edge was palpable 5 cm below the costal margin. The tip of the spleen could be felt and mild ascites was also present.

LABORATORY INVESTIGATIONS

These showed haemoglobin 12 g.100 ml^{-1}; white blood cells (WBC) 4400.mm^{-3}; platelets 110 000.mm^{-3}; serum bilirubin 2 mg.100 ml^{-1}; serum aspartate aminotransferase 120 U; serum alkaline phosphatase 272 U; gamma-glutamil transpeptidase 263 U; total proteins 7 g.100 ml^{-1} (albumin 2·6 g.100 ml^{-1} and gamma-globulins 2·25 g.100 ml^{-1}).

Immunological investigations were performed in two reference centres for diagnostic autoimmune serology tests, both with specific interest in cardiac autoimmunity (Prof P. A. Berg, Tübingen and Prof G. F. Bottazzo, London). Serum IgG and IgM were increased (2370 mg.dl^{-1} and 324 mg.dl^{-1} respectively) and IgA were normal (298 mg.dl^{-1}). Smooth muscle, nuclear, liver/kidney microsomal, gastric parietal cell, reticulin and mitochondrial antibodies from anti-M1 to anti-M6, including the PBC-specific subtype anti-M2 were assessed by indirect immunofluorescence[3,12,13]. Thyroid (thyroglobulin and microsomal) antibodies were assessed by passive haemoagglutination using commercial kits.

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Correspondence: Alida L. P. Caforio, MD, Research Fellow, Department of Cardiological Sciences, St George's Hospital Medical School, Cranmer Terrace, London SW17 0RE, U.K.

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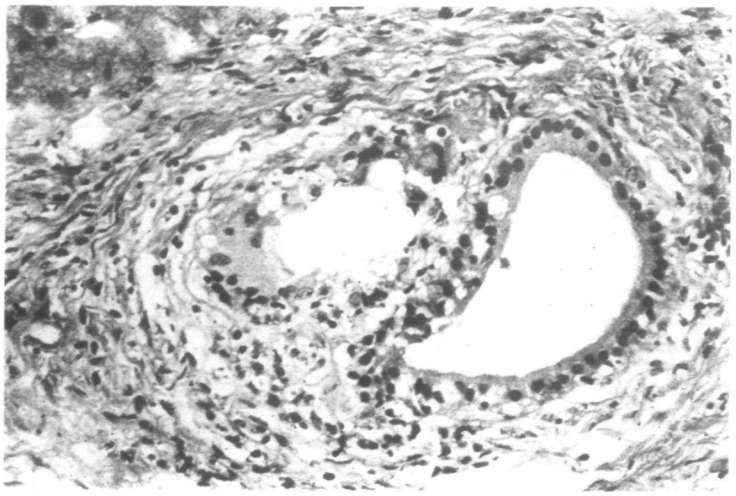

Figure 1 Damaged bile duct with vacuolized epithelium and periductal hepatic granuloma.

Anti-heart autoantibody screen was performed on frozen cryostat sections of normal O blood group human atrium, ventricle and skeletal muscle using indirect immunofluorescence[10]. The anti-adenine nucleotide translocator (ANT) antibody[15] and the mitochondrial antibody subtypes anti-M4, anti-M6, anti-M8, anti-M9, the PBC-specific subtype anti-M2, and the cardiac-specific subtype anti-M7[14], were assessed by enzyme-linked immunosorbent assay. Neither anti-ANT antibody nor mitochondrial antibody of any subtype was detected in either laboratories. Antinuclear antibodies and organ-specific cardiac antibodies, which reacted with the cytoplasm of myocytes, but not with skeletal muscle[10] were detected by immunofluorescence. The antibody titre was 1/20 for organ-specific cardiac antibody and 1/80 for antinuclear antibody. Serum was negative for all the remainder antibody specificities tested.

The electrocardiogram (ECG) revealed sinus rhythm with T wave inversion on right precordial leads. Chest X-ray showed moderate cardiomegaly and distension of the upper lobe veins. Severe enlargement of the right atrium and right ventricle was seen at two-dimensional echocardiography (Fig. 2). The tricuspid valve was in its normal position in the annulus and the dilated right ventricle was globally hypocontractile. No focal akinetic areas were seen. Left-sided cardiac chambers and valves were normal. Angiographic left ventricular ejection fraction was normal (66%), while right ventricular dilatation and depression of systolic function was confirmed (Fig. 3). Pressures (mmHg) were as follows: left ventricular 100/90, pulmonary artery 26/8; capillary wedge pressure 11; right ventricular 27/8; right atrial 8. Endomyocardial biopsy was not performed. A diagnosis of right ventricular cardiomyopathy was made and treatment with digoxin and diuretics was initiated. At follow-up the patient's main complaint was that of palpitation, and atrial tachycardia was documented. The arrhythmia was successfully treated with propafenone and pacemaker insertion.

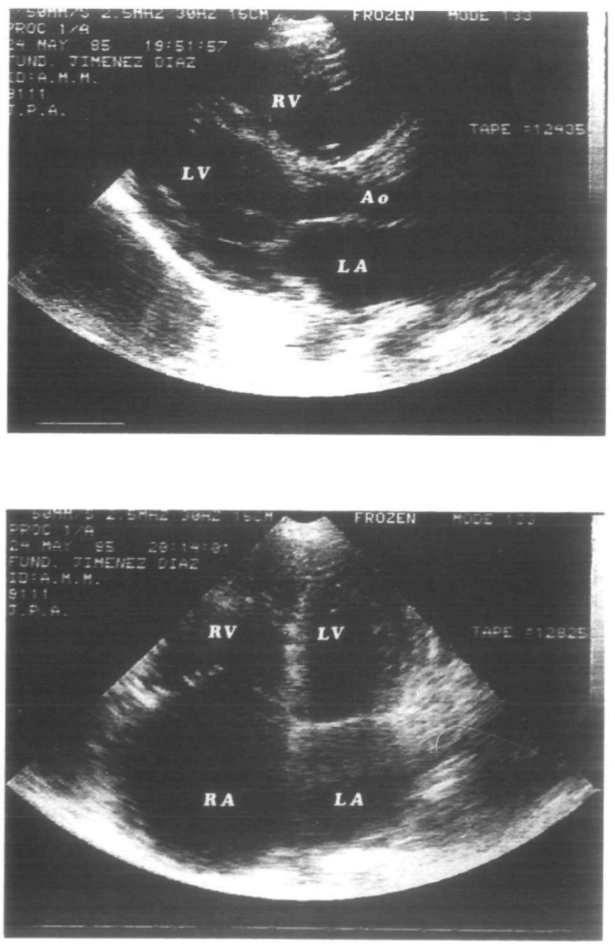

Figure 2 Parasternal long axis view (top) and four-chamber apical view (bottom) showing severe enlargement of the right ventricle (RV) and right atrium (RA). The tricuspid valve is normally positioned and both the left ventricle (LV) and left atrium (LA) are normal. Ao = aorta.

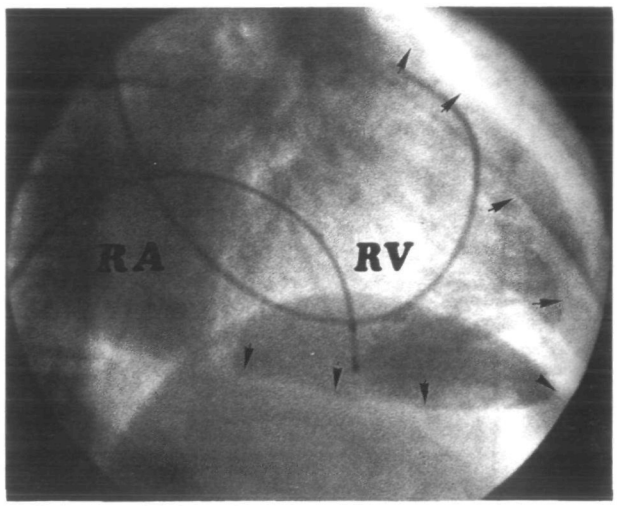

Figure 3 Right ventricular angiogram revealing the dilated right ventricle (RV) and right atrium (RA), in the absence of localized areas with abnormal motion Moderate tricuspid regurgitation was also present.

Discussion

We have described an unusual case of right ventricular cardiomyopathy associated with PBC. The diagnosis of PBC, which is of autoimmune origin, was based on clinical features, biochemical evidence of cholestasis and typical hepatic biopsy findings[2]. The absence of mitochondrial antibody does not exclude the diagnosis, particularly in view of typical histology and raised IgM titres, which were both present in this patient; it is well established that 5 to 10% of patients with PBC are antibody-negative[3]. The possibility of reduction in antibody titres with disease progression should also be considered in this patient with longstanding disease; it has been shown that the prevalence of mitochondrial antibody in PBC is higher (90–100%) when the test is performed at a pre-symptomatic stage[16,17].

The diagnosis of right ventricular cardiomyopathy was based on echocardiographic and angiographic evidence of a dilated and poorly contracting right ventricle[18,19]. The clinical presentation in our patient was similar to that reported in Fitchett's series of patients with right ventricular cardiomyopathy[4,5]; one of these patients also had PBC. These authors suggested that right ventricular cardiomyopathy is one end of the spectrum of dilated cardiomyopathy rather than a separate entity. Further studies are needed to clarify whether the same applies to an overlapping clinical condition termed right ventricular dysplasia, in which the changes in the right ventricle may be related to abnormalities in the development of ventricular myocardium. In some of these cases, characterized by the occurrence of ventricular tachycardia and by localized dome-shaped areas of dilatation, which may exhibit paradoxical systolic motion, the term arrythmogenic right ventricular dysplasia has been used[20–22]. The presence of exercise-induced abnormalities in left ventricular function in many such patients has again suggested that there may be a generalized myocardial disease[23].

Our patient had circulating organ-specific cardiac antibodies by indirect immunofluorescence. The concomitant absence of mitochondrial antibodies allowed us to detect organ-specific cardiac antibodies. In fact, if mitochondrial antibodies are present, they produce cytoplasmic staining on both human cardiac and skeletal muscle, as well as on rat liver and kidney[12,13], which makes assessment of cardiac-specific antibodies impossible.

Organ-specific cardiac antibodies are novel serological markers of autoimmunity to the heart. They have been detected in 26% of patients with DCM and are virtually absent in other cardiac disease, in heart failure due to myocardial infarction, and in normal subjects[10]. The finding of organ-specific cardiac antibodies in this patient with right ventricular cardiomyopathy and PBC is consistent with the interpretation that in this case autoimmunity is involved in both myocardial and hepatic disease. This is not surprising in view of the fact that autoimmune disorders are frequently associated with genetically predisposed individuals[11]. It also reinforces the concept that right ventricular cardiomyopathy may not be a distinct entity from DCM[4,5].

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