Cardiology in the Young (2010), **20**, 220–222
doi:10.1017/S1047951110000053

Brief Report

Pregnancy-associated cardiomyopathy occurring in a young patient with nephropathic cystinosis

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Abstract Cystinosis is a rare autosomal recessive metabolic disorder characterised by an intracellular accumulation of cystine leading to severe organ dysfunction. It affects renal function, has extra-renal complications but has rarely been associated with cardiac disease. Renal transplantation and cysteamine have dramatically improved the prognosis in the nephropathic form. We present the case of a young adult Caucasian female diagnosed with nephropathic cystinosis and receiving haemodialysis who subsequently developed dilated cardiomyopathy. She presented with acute cardiac failure occurring early after stillbirth following an unplanned pregnancy when her cysteamine had been stopped. Transthoracic echocardiography showed typical features of dilated cardiomyopathy which was absent on pre-pregnancy scans. Investigations failed to identify an underlying cause for her cardiomyopathy. She responded to conventional treatment and currently has had full recovery of her cardiac function confirmed on follow-up echocardiography. As cardiomyopathy rarely co-exists with cystinosis, we believe that this case represents pregnancy-associated cardiomyopathy rather than direct involvement by her cystinosis, particularly as a minority of pregnant patients with associated cardiomyopathy develop heart failure early before the conventional period for peripartum cardiomyopathy. Patient characteristics and maternal outcomes are similar, albeit with higher risk of premature delivery suggesting the same underlying pathological process.

Keywords: Cardiomyopathy; pregnancy; cystinosis

Received: 26 August 2009; Accepted: 4 October 2009; First published online: 4 March 2010

CYSTINOSIS IS A RARE AUTOSOMAL RECESSIVE metabolic disorder characterised by an intracellular accumulation of cystine in various tissues leading to severe organ dysfunction in the most severe type which is nephrotoxic.[1] Renal symptoms predominate, but extra-renal deposition also occurs, typically involving the eyes, liver, skeletal muscles, and endocrine organs, but in only two case reports the heart.[2,3] Both renal transplantation and cysteamine, an aminothiol which depletes intracellular accumulation of cystine, have dramatically improved the prognosis in nephropathic cystinosis.[4]

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Case presentation

We present the case of a young adult Caucasian female, diagnosed with nephropathic cystinosis at the age of 3 years, which progressed to end stage renal failure by the age of 10 years, who developed dilated cardiomyopathy. She had undergone cadaveric renal transplantation which lasted for nearly 4 years but is currently receiving haemodialysis. She also has extra-renal complications including cystine crystal deposition in her sclera, hepatosplenomegaly, and short stature. However, she did not have clinical neurological involvement or myopathy. After confirmation of an unplanned pregnancy, her cysteamine was stopped followed by an uneventful still birth, 25-week gestation, culminating 1 week after with acute cardiac failure requiring hospitalisation.

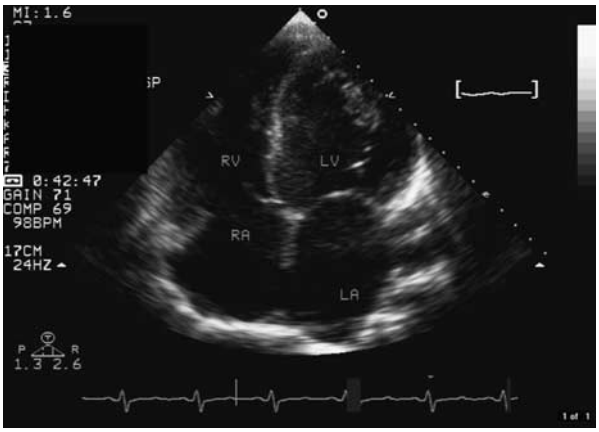

Figure 1.
Four-chamber view of transthoracic echocardiogram showing severe biventricular enlargement with left ventricular end diastolic diameter 6.7 centimetres.

Her chest X-ray confirmed pulmonary congestion and her electrocardiograph showed inferior wall ischaemia with troponin T level 0.11. Transthoracic echocardiography revealed severe biventricular enlargement, left ventricular end diastolic diameter 6.7 centimetre, with globally reduced and severe left ventricular systolic function, and moderately reduced right ventricular systolic function confirming dilated cardiomyopathy (Fig 1). Echocardiography before pregnancy was normal. Cardiac catheterisation showed normal coronary arteries but globally dilated and severely hypokinetic left ventricle with estimated cardiac output of 3.62 litres per minute with a cardiac index of 2.39 litres per minute per metre squared. Other routine investigations for known causes of cardiomyopathy were negative but cardiac biopsy was not performed.

She responded to conventional treatment for cardiac failure including diuretics, angiotensin converting enzyme inhibition, β-blockade and digoxin but was not a candidate for cardiac resynchronisation therapy. Cardiopulmonary exercise testing showed severely reduced aerobic capacity and early occurrence of anaerobic threshold compatible with dilated cardiomyopathy namely anaerobic threshold of 11.1 millilitres per kilogram per minute and peak oxygen consumption of 14.7 millilitres per kilogram per minute. She was referred for combined cardiac and renal transplant assessment, but at four months after hospital admission she had improved to New York Heart Association functional class II symptomatically and no longer wished to be considered and so this was deferred.

Her symptoms have continued to improve and her exercise capacity is currently back to pre-cardiomyopathy levels. Repeat echocardiography has shown favourable remodelling with normal left ventricular systolic function, regional wall motion and size, left ventricular end diastolic diameter 5.5 centimetre, with normal right cardiac size and function. In view of her improved cardiac function, she has been reinstated on the renal transplant list.

Discussion

The identified gene in cystinosis, *CTNS*, is found on chromosome 17p13. In the nephropathic form, free cystine accumulates in the lysosome due to a defect in transport across the lysosomal membrane with its poor solubility leading to crystal formation. The more benign forms have similar features to nephropathic cystinosis but with a slower rate of progression believed to be due to the inheritance of relatively less severe mutations in one or both alleles.[5] Diagnosis is made by measuring the cystine content of peripheral blood leucocytes of fibroblasts. Prenatal diagnosis testing is also available.

Early treatment with cysteamine attenuates decline in glomerular function and improves linear growth allowing increased survival into adulthood without the need for renal transplantation. It also helps prevent hypothyroidism indicating an effect on at least one of the extra-renal manifestations of cystinosis and should be continued after transplantation.[6] Diminished immune responsiveness induced by intracellular cystine accumulation may account for the greater success of renal transplantation in children with cystinosis than with other childhood causes of renal failure.[7]

With our patient, the cardiomyopathy could be directly related to her cystinosis, due to pregnancy-associated cardiomyopathy or an unconnected cardiomyopathy. Her cysteamine was stopped during her pregnancy to avoid foetal injury, and the subsequent cystine accumulation may have lead to cardiac deposition of cystine and dysfunction. Also the re-introduction of systemic cysteamine might have contributed in addition to her renal supportive care, β-blockers and angiotensin-converting enzyme inhibitors to the normalisation of her cardiac function. However, in only one reported case of cystinosis with associated cardiac failure did postmortem cardiac biopsy suggest possible extra-renal cardiac involvement. There was a high tissue cystine content and cystine-like crystals were found in the lysosomes of interstitial histiocytes adjacent to cardiomyocytes and in a single cardiac myocyte.[2] In another patient with nephropathic cystinosis, isolated non-compaction of the left ventricle was diagnosed after presenting with cardiac failure complicated by ventricular arrhythmias requiring implantation with an implantable cardioverter defibrillator, although endomyocardial biopsy was not performed.[3]

https://doi.org/10.1017/S1047951110000053 Published online by Cambridge University Press

Interestingly, skeletal muscle involvement is common as an extra-renal manifestation of cystinosis causing a progressive and distal vacuolar myopathy with muscle wasting, but this was not apparent in our patient.[8]

Alternatively, and as cardiomyopathy rarely co-exists with cystinosis, we believe that her cardiomyopathy was directly related to her pregnancy. Typically, the diagnostic criteria for peripartum cardiomyopathy are confined to the last gestational month and the first 5 months after delivery.[9] However, presentation with cardiac failure can occur before this period in approximately 20% and the diagnosis of pregnancy-associated cardiomyopathy has been coined for this group.[10] Comparison between early and late presentation revealed similar age, obstetric history, maternal outcome, left ventricular ejection fraction, and subsequent recovery in cardiac function, but higher rates of premature deliveries in the early onset group possibly related to the earlier onset of cardiac dysfunction or, alternatively, due to the unmasking of subclinical rcardiac disease by the haemodynamic changes of pregnancy. In our patient, previous cardiac disease was excluded by her relatively recent normal echo before pregnancy. The relatively rapid resolution of her cadiac failure favours pregnancy-associated cardiomyopathy rather than cardiomyopathy secondary to cystinosis which would be expected to be progressive, not transient.

Conclusion

Cardiomyopathy rarely co-exists with cystinosis and this case may represent either direct involvement by her cystinosis or pregnancy-associated cardiomyopathy. The latter is favoured due to the recovery in left ventricular function in our patient and the fact that a minority of pregnant patients with associated cardiomyopathy develop cadiac failure early before the conventional peripartum period. Patient characteristics and maternal outcomes are similar albeit with higher risk of premature delivery that was seen in our case suggesting the same underlying pathological process.

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