Everolimus-responsive dilated cardiomyopathy in tuberous sclerosis

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The cardiac feature of tuberous sclerosis (TSC) is a rhabdomyoma, but rare cases with dilated cardiomyopathy have been reported. Constitutive activation of mTOR complex 1 (mTORC1) by mutations in TSC1 or TSC2 is responsible for formation of tumours such as renal angiomyolipoma (AML) in TSC. Everolimus, an mTORC1 inhibitor, is the only available agent for treatment of AML.

A 29-year-old woman who had been diagnosed as having TSC during childhood was admitted for heart failure. Computed tomography showed bilateral giant renal AML (Panel A), echocardiography revealed dilatation of both ventricles and reduced left ventricular ejection fraction (Panel B, Supplementary material Online, Video S1), and NT-proBNP level was elevated to 4386 pg/mL. Endomyocardial biopsy showed hypertrophic cardiomyocytes with vacuoles, but significant inflammation or fibrosis was not observed (Panel C). Phosphorylation of ribosomal protein S6 (Rps6), a marker of mTORC1 activation, was detected in several cardiomyocytes (Panel D), indicating up-regulation of mTORC1 activity in cardiomyocytes. She was treated with 10 mg of everolimus per day in addition to 5 mg/day of enalapril.

One year later, renal tumour volume was clearly reduced (Panel E). In addition, ventricular dimensions and systolic function were improved (Panel F, Supplementary material Online, Video S2) with reduction of NT-proBNP level (185 pg/mL). Repeated endomyocardial biopsy showed negligible phosphorylation of Rps6 and improvement of histological changes in cardiomyocytes (Panels G and H).

This case suggests that aberrant activation of mTORC1 in cardiomyocytes contributes to the development of dilated cardiomyopathy in TSC, which is treatable by everolimus.

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