The proprotein convertase furin is required to maintain viability of alveolar rhabdomyosarcoma cells

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Abstract: Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children. Success of current therapies is still limited and outcome is particularly poor for metastatic alveolar rhabdomyosarcoma (aRMS). We previously identified the proprotein convertase furin as potential target for specific drug delivery with RMS-homing peptides. Furin is a protease that converts inactive precursor proteins into bioactive proteins and peptides. In this study, we investigate the biological role of furin in aRMS progression in vitro and in vivo. Furin expression was confirmed in over 86% RMS biopsies in a tissue microarray (n=89). Inducible furin silencing in vitro led to significant impairment of cell viability and proliferation in all investigated aRMS cell lines, but not in MRC5 fibroblasts. Furthermore, the aRMS cell lines Rh3 and Rh4 revealed to be very sensitive to furin silencing, undergoing caspase-dependent cell death. Notably, furin silencing in vivo led to complete remission of established Rh4 tumors and to delayed growth in Rh30 tumors. Taken together, these findings identify furin as an important factor for aRMS progression and survival. Thus, we propose furin as a novel therapeutic target for treatment of aRMS.

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CARDIOVASCULAR FLASHLIGHT

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Cardiac amyloidosis: still challenging

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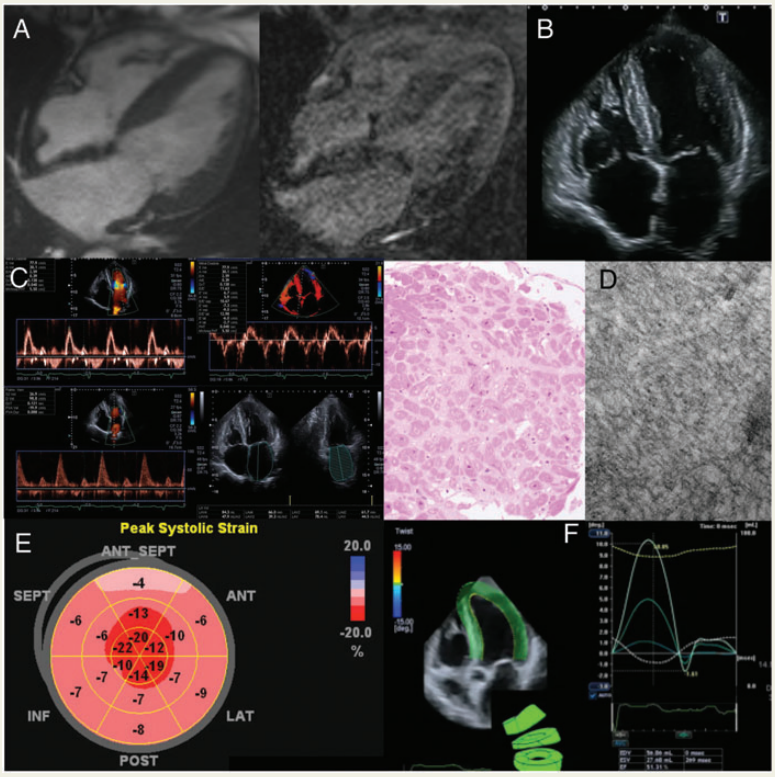
A 67-year-old men complaining of rapidly progressive dyspnoea was hospitalized with a first episode of biventricular cardiac decompensation at a local hospital. Initial evaluation revealed a hypertrophic ventricle with preserved ejection fraction, a restrictive filling pattern and dilated atria as well as a diffuse and patchy midventricular late gadolinium enhancement in MRI (*Panel A*). Therefore, some form of hypertrophic or restrictive cardiomyopathy was suspected. No signs for systemic diseases were found, particularly not for haemochromocytosis or multiple myeloma (immune-electrophoresis). Symptomatic heart failure treatment was initiated with a loop diuretic and a follow-up with a cardiologist was scheduled.



Echocardiography some weeks later showed symmetrical thickening of the left and right ventricles with normal ejection fraction, an increased echogenicity with a granular sparkling appearance, as well as dilated and immobile atria (*Panel B*; Supplementary material online, *Video S1*). Furthermore, LV-inflow pattern, tissue Doppler images, and pulmonary vein inflow was notable for severe diastolic dysfunction (restrictive filling pattern; *Panel C*). Cardiac amyloidosis was suspected and the patient was referred to the 'amyloidosis network' of the University Hospital Zurich for endomyocardial biopsy. Although cardiac biopsies showed an increased interstitial matrix (*Panel D*, left), Congo-Red staining did not show typical green birefringence by polarizing microscopy and immunohistochemical stainings for AL amyloid and transthyretin-related amyloid were negative. However, in electron microscope the morphology and arrangement of the interstitial fibrils were characteristic for amyloid (*Panel D*, right). Typical for amyloidosis, an advanced 3D-echocardiography then clearly demonstrated a baso-apical gradient with preserved systolic function at the apex, a relative apical sparing in speckle-tracking longitudinal strain pattern (*Panel E*; Supplementary material online, *Video S2*), and decreased LV torsion (*Panel F*).

These observations prompted to reevaluate initial assessment and recheck for multiple myeloma. Indeed, serum electrophoresis and bone marrow biopsy revealed a lambda-clonal plasma cell neoplasia, and AL-amyloidosis type lambda was diagnosed. This case illustrates difficulties diagnosing cardiac amyloidosis and highlights the value and importance of advanced echocardiography in the diagnosis of cardiac amyloidosis.

Supplementary material is available at *European Heart Journal* online.