Case Study: Transthyretin Amyloidosis presenting as HCM

Clinical Overview
A 48 year-old male presents to his cardiologist with complaints of shortness of breath. An echocardiogram reveals concentric left ventricular hypertrophy (LVH). Full panel testing was ordered for hypertrophic cardiomyopathy (HCM). A heterozygous mutation was found in the TTR gene, which is known to cause transthyretin (TTR) amyloidosis. Concentric hypertrophy is a finding that can be associated with TTR amyloidosis. Full gene sequencing of TTR detects more than 99% of TTR-amyloidosis causing mutations.

Patient Information:
Age: 48 Specimen: Blood
Referral diagnosis: Concentric left ventricular hypertrophy. Patient has normal weight and no history of smoking or hypertension.
Family history: Patient has no siblings. His family history is notable for his mother diagnosed with LVH in the setting of hypertension and a maternal uncle who died at age 62 of renal disease. Paternal family history is unremarkable.

Diagnostic Summary:
POSITIVE. Heterozygous Thr79Lys mutation in TTR. GeneDx tests not only for genes associated with isolated HCM, but also genes associated with multisystem disorders such as amyloidosis, Danon disease, and Fabry disease. Distinguishing the different genetic causes of heart muscle thickening is extremely important, as the treatment for HCM can differ markedly depending on the etiology.

HCM gene sequencing panel: Sequence analysis of 18 genes associated with HCM revealed the Thr79Lys mutation in the TTR gene, associated with familial transthyretin (TTR) amyloidosis. The patient also had a cardiac MRI revealing delayed enhancement, consistent with amyloid deposits in the heart (cardiac amyloidosis). Transthyretin (TTR) amyloidosis is an autosomal dominant disorder caused by the deposition of insoluble amyloid fibrils around peripheral nerves and in various tissues, including the heart muscle. Based on the predominant organ involvement, several distinct subtypes have been reported. Cardiac amyloidosis usually presents after age 50, though there can be variability in the age of onset. The echocardiogram reveals left ventricular hypertrophy with preserved systolic function. In a subset of families with cardiac amyloidosis, peripheral neuropathy may be completely absent or very mild.1

Diagnostic Implications:
Hypertrophy of the left ventricle is a finding common to several conditions, including athlete’s heart, hypertensive heart disease, Fabry disease, cardiac amyloidosis, cardiac sarcoidosis, or when all other conditions are excluded, idiopathic hypertrophic cardiomyopathy. Genetic testing as part of a clinical evaluation can define the diagnosis and assist in determining appropriate management. The patient was counseled for management of cardiac amyloidosis, with consideration of a liver transplant to minimize disease progression.

The patient’s family members were also tested for the Thr79Lys mutation. Those who tested negative have a significantly reduced risk of developing cardiac amyloidosis in the future. Those who are positive for the TTR mutation are at increased risk of developing amyloidosis in the future, and will be advised to follow up with a cardiologist, nephrologist and neurologist for medical management advice.

References:
1. Dubrey, SW et al. 2011 Heart 97:75e84