The Pathology of Subaortic Membranes: An Analysis of 83 Surgically Resected Cases with Molecular Genetic Correlation

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Background: Subaortic membranes (SAM) are subvalvular collections of fibro(muscular) tissue that result in fixed obstruction. The pathogenesis of subaortic membranes (SAM) remains obscure and while both congenital and acquired forms have been identified, the latter is thought to be more common. Phenotypic overlap exists with other forms of outflow obstruction, such as hypertrophic cardiomyopathy (HCM) and differentiating between them is important given the heritable implications of cardiomyopathic states. Herein, histopathologic and molecular genetic features of a population of 83 surgically resected cases of SAM are evaluated.
Design: Formalin-fixed paraffin embedded (FFPE) tissue was obtained on 83 patients having undergone surgical resection of a discrete or tunnel SAM (2009-2015). Clinical information and hemodynamic data was abstracted from the medical record. Light microscopic features, including myocyte disarray, myocyte hypertrophy, and interstitial fibrosis were semiquantitatively scored. Extracted genomic DNA underwent Agilent SureSelect targeted capture of 54 genes associated with cardiomyopathies, followed by sequencing on the Illumina MiSeq platform. Variants were classified according to established guidelines.
Results: 83 patients (54 women) were included in the study, with a mean age of 49.8 years (range, 4-80). 77 cases of SAM were discrete membranous, while 6 were tunnel-type. Myocyte hypertrophy was absent or mild in 6 cases, moderate in 53 and severe in 23 cases. Interstitial fibrosis was absent or mild in 56 cases, moderate in 25, and severe in 1. Myocyte disarray was absent or mild in 75 cases and moderate in 7. The majority of genetic variants identified were benign polymorphisms; however, 4 pathogenic/likely pathogenic and 77 variants of unknown significance were identified (average, 1.7/case). Of the pathogenic/likely pathogenic variants, mutations in *PTPN11* were present in 2 cases, *MYH7* mutation in 1, and *SOS1* in 1 case. 25 cases were believed clinically to have concomitant HCM, though none of those carried a molecular genetic mutation compatible with such. No histopathologic or clinical parameter appeared to correlate with identified pathogenic mutations.
Conclusions: Hitherto, this is the first systematic survey of SAMs to evaluate their histopathologic features. Additionally, it is the largest series of cases of SAMs to undergo molecular genetic interrogation to evaluate for concomitant cardiomyopathy or syndrome. Histologic findings alone did not appear to be a predictor of underlying genetic variation to help in evaluation for a cardiomyopathic or syndromic state.