Underdiagnosed Roifman Syndrome Manifested as Non-ischemic Cardiomyopathy: A Case Report

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PURPOSE

- To recognize the association between non ischemic cardiomyopathy and genetic disorder Roifman syndrome
- To underscore the importance of whole genome sequencing in the diagnosis

METHODS

- We reported a case with underdiagnosed Roifman syndrome manifested as non-ischemic cardiomyopathy

RESULTS(CASE)

- A 20-year-old male who was born with microcephaly and later as a child developed retinitis pigmentosa, recurrent ear infection, adrenal and thyroid insufficiency consistent with APS type 2. He presented with one month of worsening dyspnea on exertion and a near syncope episode.
- He was hypotensive (81/40 mmHg), tachycardiac (112 bpm) and hypoxic (85% on room air).
- TSH was significantly elevated 70 mU/L. NT pro-BNP was 5340 pg/mL. A transthoracic echocardiogram (TTE) revealed left ventricular ejection fraction (LVEF) of 20% and severe left ventricle (LV) dilation. Cardiac catheterization ruled out obstructive coronary artery disease and cardiac MRI revealed nonspecific non ischemic cardiomyopathy with LVEF of 32% without infiltration or inflammation. Cardiac endomyocardium biopsy showed no histopathological abnormality.
- He was managed with mechanical ventilation for respiratory support, diuresis with inotropes (dobutamine) along with mechanical cardiac support with Impella (CP and RP) for cardiogenic shock, thyroid and steroid hormone replacement. He was then slowly weaned off mechanical cardiac support, pressors, and inotropes and started with guideline-directed medical therapy (GDMT). Unfortunately, his heart function didn't improve despite normalization of thyroid function. Then he underwent MitraClip implantation for severe mitral regurgitation (Figure 1) , and an automatic implantable cardioverter defibrillator (AICD) implantation.

FIGURES

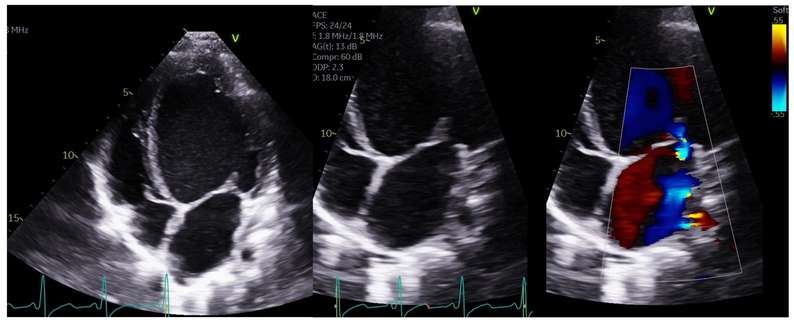

Figure 1. Echocardiogram at 3-month follow-up showed dilated LV (LVIDd 6.4cm) and severe LV systolic dysfunction (LVEF 21%). Status post MitraClip implantation with residual moderate mitral regurgitation.

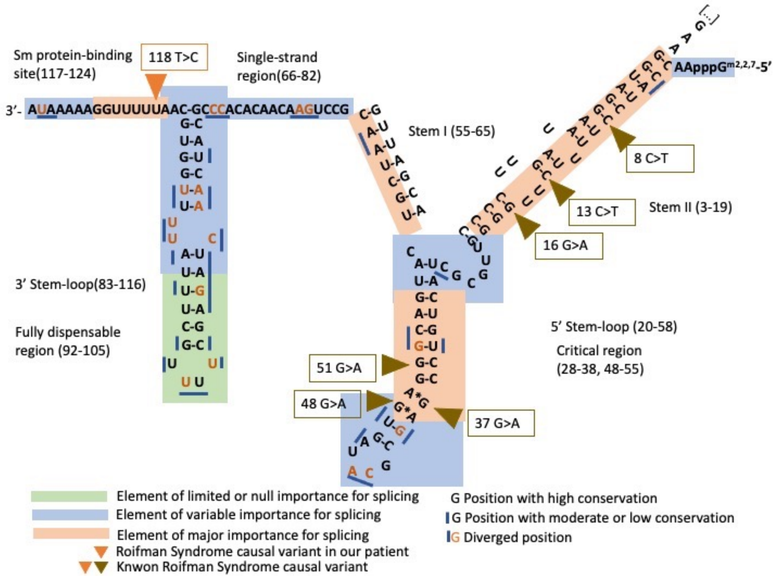

Figure 2 U4ATAC snRNA secondary structure elements, evolutionary conservation status of each nucleotide position and Roifman Syndrome causal variants (orange and brown triangles) (modified from Merico et al [1]). The pathogenic variant in RNU4ATAC (NR_023343.1:n.118T>C) is marked in orange box with orange triangle.

RESULTS(CASE)

- Initial Invitae cardiomyopathy comprehensive panel which we use commonly for cardiomyopathy-related genetic disorders screening was unable to detect any pathogenic variants.
- whole genome sequencing from Baylor Genetics for Undiagnosed Disease Network (UDN) was performed and revealed a compound heterozygous pathogenic variant in RNU4ATAC (NR_023343.1:n.118T>C, autosomal recessive (AR) inheritance, heterozygous, mother is heterozygous and father is negative, pathogenic, Figure 2) which was considered to be pathogenic for Roifman syndrome and would explain this patient's complicated medical history. His younger sister's whole genome sequencing report revealed the same results.

CONCLUSIONS

- Our patient broadens further the association between non ischemic cardiomyopathy and genetic disorder Roifman syndrome.
- We underscore that cardiomyopathy might be part of the clinical manifestations of Roifman syndrome. In patients with non-ischemic cardiomyopathy but without clear etiology, associated with other clinical features like, spondyloepiphyseal dysplasia, immunodeficiency, growth retardation, or retinal anomaly, genetics should be involved and Roifman syndrome should be considered as a part of the differential diagnoses as other manifestations might be subtle and undiagnosed.
- The whole genome sequencing should be performed instead of the traditional cardiomyopathy comprehensive panel alone for the diagnosis confirmation.
- Meanwhile, in patients Roifman syndrome, cardiac manifestations should be monitored during their lifetime as it might be a later presentation.

- Disclosures: Nothing to disclose by any authors
- Reference

[1] Merico D, Roifman M, Braunschweig U, Yuen RK, Alexandrova R, Bates A, Reid B, Nalpathamkalam T, Wang Z, Thiruvahindrapuram B, Gray P, Kakakios A, Peake J, Hogarth S, Manson D, Buncic R, Pereira SL, Herbrick JA, Blencowe BJ, Roifman CM, Scherer SW. Compound heterozygous mutations in the noncoding RNU4ATAC cause Roifman Syndrome by disrupting minor intron splicing. Nat Commun. 2015 Nov 2;6:8718.