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CASE REPORT

CLINICAL CASE

Treatment of RAF1-Related Obstructive Hypertrophic Cardiomyopathy by MEK Inhibition Using Trametinib

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ABSTRACT

RASopathies cause nonsarcomeric hypertrophic cardiomyopathy via dysregulated signaling through RAS and upregulated mitogen-activated protein kinase activity. We provide the first report of the successful treatment of an adult with RAF1-associated hypertrophic cardiomyopathy using trametinib, a MEK inhibitor. (J Am Coll Cardiol Case Rep 2024;29:102379) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

An 18-year-old male presented in infancy with clinical features of Noonan syndrome and severe obstructive hypertrophic cardiomyopathy (HCM). Early treatment in childhood consisted of beta-blockers to reduce the peak left ventricular outflow tract (LVOT) gradient below 50 mm Hg. At age 6 years, disopyramide was required and reduced the LVOT gradient from 100 to 15 mm Hg. Over the next decade, the patient enjoyed an improved quality of life and catch-up in physical growth while on medical therapy with beta-blockers and disopyramide. There was slow progression of peak LVOT gradients which at times were severe, ranging from 50 to 100 mm Hg. By the age of 17 years, there was significant progression of LVOT obstruction that culminated in a peak LVOT gradient of 213 mm Hg.

LEARNING OBJECTIVES

- To develop a differential diagnosis for causes of sarcomeric and nonsarcomeric HCM.
- To understand the role of genetic testing to identify disease mechanisms and precision treatments.
- To understand the role of trametinib in the treatment of RAF1- or RIT1-associated HCM.

Clinical examination findings included the following: blood pressure 112/54 mm Hg, heart rate 70 beats/min, height 155 cm, and weight 51 kg. The extremities were warm and well perfused. Apex size

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ABBREVIATIONS AND ACRONYMS

HCM = hypertrophic cardiomyopathy

LVOT = left ventricular outflow tract

and position were normal. S_1 and S_2 heart sounds were normal. There was a grade 3/6 systolic ejection murmur at the left upper sternal border.

PAST MEDICAL HISTORY

The patient was diagnosed with Noonan syndrome with severe obstructive HCM and a left ventricular (LV) apical aneurysm. Additionally, the patient had ectatic coronary arteries and obstructive sleep apnea.

DIFFERENTIAL DIAGNOSIS

We considered sarcomeric and nonsarcomeric causes of HCM. Among the nonsarcomeric causes are syndromic and metabolic cardiomyopathies like RASopathies, Andersen-Fabry disease, Friedreich ataxia, glycogen storage disease, and amyloidosis.

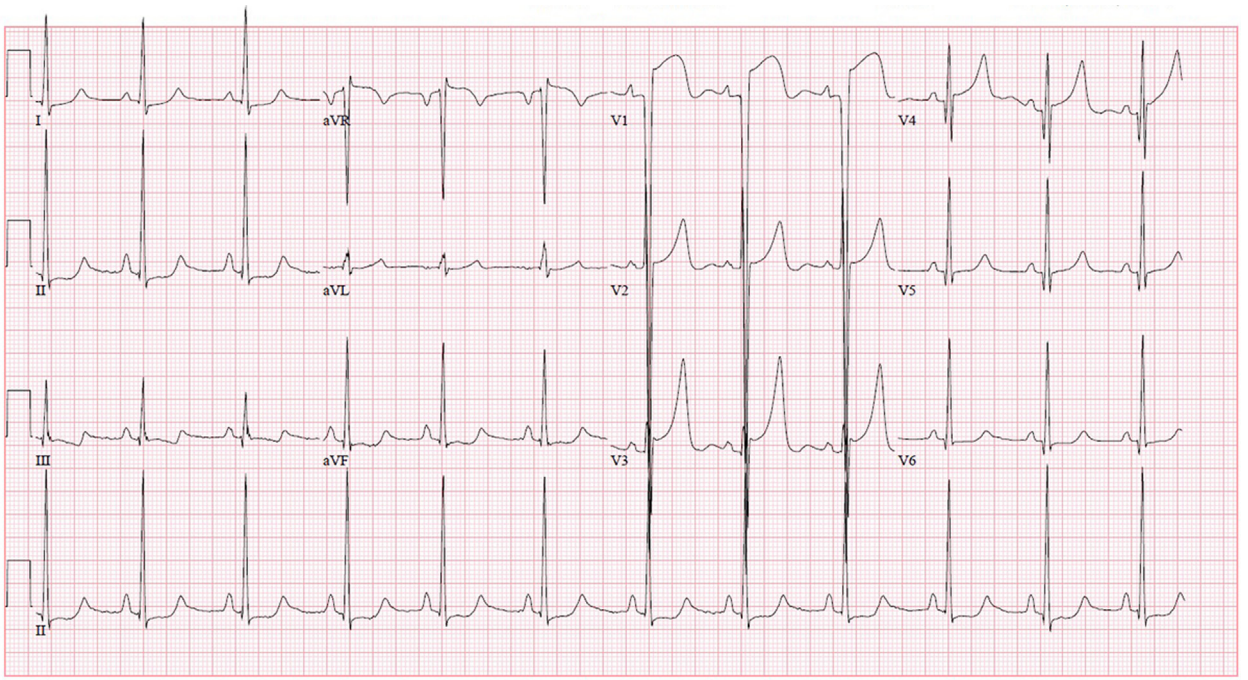
INVESTIGATIONS

Electrocardiogram (**Figure 1**) showed normal sinus rhythm, right atrial abnormality, left ventricular hypertrophy with repolarization abnormality, and nonspecific T-wave abnormality.

Echocardiography (Video 1) showed severe concentric left ventricular hypertrophy, normal LV ejection fraction, maximal ventricular septal wall thickness of 25 mm, and systolic anterior motion of the mitral valve with leaflet-septal contact and a peak LVOT gradient of 213 mm Hg (**Figure 2**).

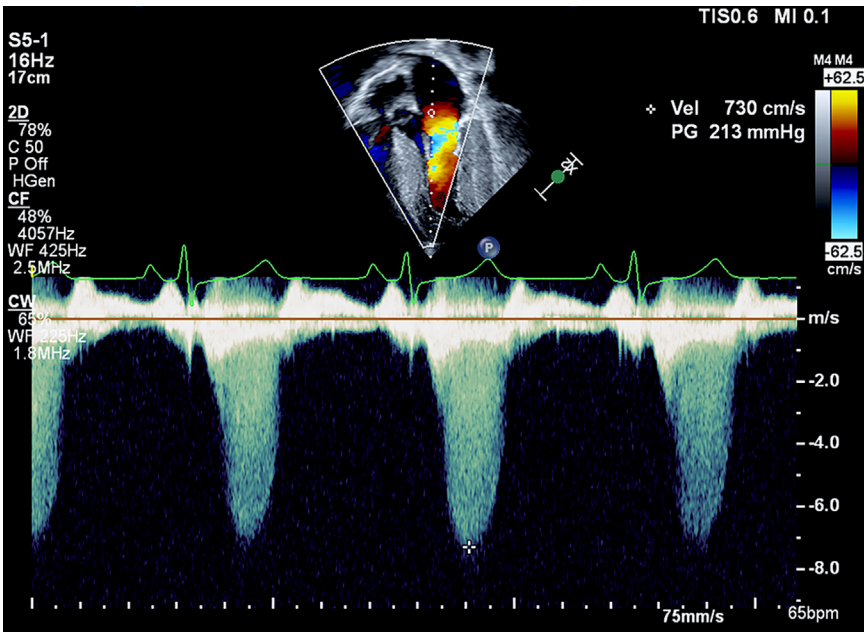
Cardiac magnetic resonance cine imaging and late gadolinium enhancement imaging showed septal dominant hypertrophy with a maximal wall thickness of 36 mm, leading to systolic anterior motion of the mitral leaflets, an LV apical aneurysm, and a small (approximately 9%) burden of late gadolinium enhancement (**Figure 3**).

FIGURE 1 Electrocardiogram Showing Left Ventricular Hypertrophy



Electrocardiogram shows normal sinus rhythm, right atrial abnormality, left ventricular hypertrophy with repolarization abnormality, and nonspecific T-wave abnormality.

FIGURE 2 **Echocardiogram Showing an LVOT Gradient of 213 mm Hg**



Transthoracic echocardiogram (apical 3-chamber) spectral Doppler assessment showing a peak left ventricular outflow tract gradient of 213 mm Hg while on therapy with beta-blockers and disopyramide.

Gene testing showed a heterozygous pathogenic missense RAF1 c.770C>T (p.Ser257Leu) de novo variant.

MANAGEMENT

The RAF1 c.770C>T (p.Ser257Leu) variant is not present in population databases and is associated with a high penetrance of severe obstructive HCM through enhanced MEK activity.

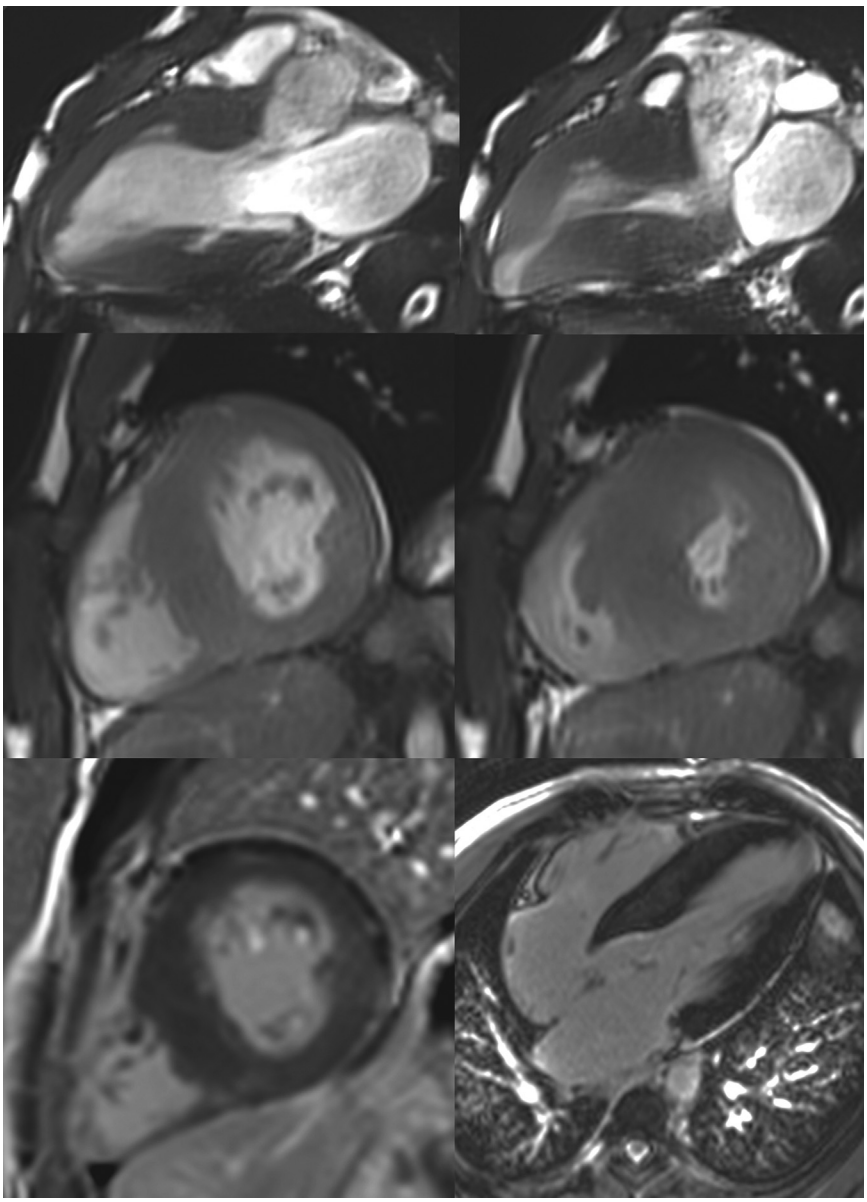
We trialed targeted therapy with trametinib, a highly selective MEK inhibitor that is approved for treatment of cancers arising from perturbations in the RAS- mitogen-activated protein kinase (MAPK) pathway that similarly result in increased MEK activity. We started with a reduced dose of 0.01 mg/kg orally daily to minimize side effects, with the option to increase the dose to treatment effect. Treatment with trametinib 0.5 mg orally daily dramatically reduced the LVOT gradient from 211 to 41 mm Hg on follow-up echocardiography (**Figure 4**, Video 2) and led to an improvement in biomarkers (**Table 1**). Cardiac magnetic resonance imaging showed no objective differences with respect to maximal wall thickness or global LV mass; however, a visible reduction in severity of SAM was present on the 3-chamber view (**Figure 5**, Video 3).

DISCUSSION

RASopathies cause nonsarcomeric HCM via dysregulated signaling through RAS and up-regulated MAPK activity. Compared with sarcomeric HCM, RASopathy-associated HCM presents at an earlier age, with more ventricular obstruction, and with higher rates of hospitalization and intervention.[1] The mechanism of hypertrophy in RASopathies depends on the associated gene mutation. RAF1 and RIT1 mutations enhance MEK activity and result in profound hypertrophy.

Trametinib is a highly selective MEK inhibitor that is approved for treatment of cancers arising from disturbances in the RAS-MAPK pathway. Trametinib

FIGURE 3 **Cardiac Magnetic Resonance Imaging Showing Severe Ventricular Hypertrophy**

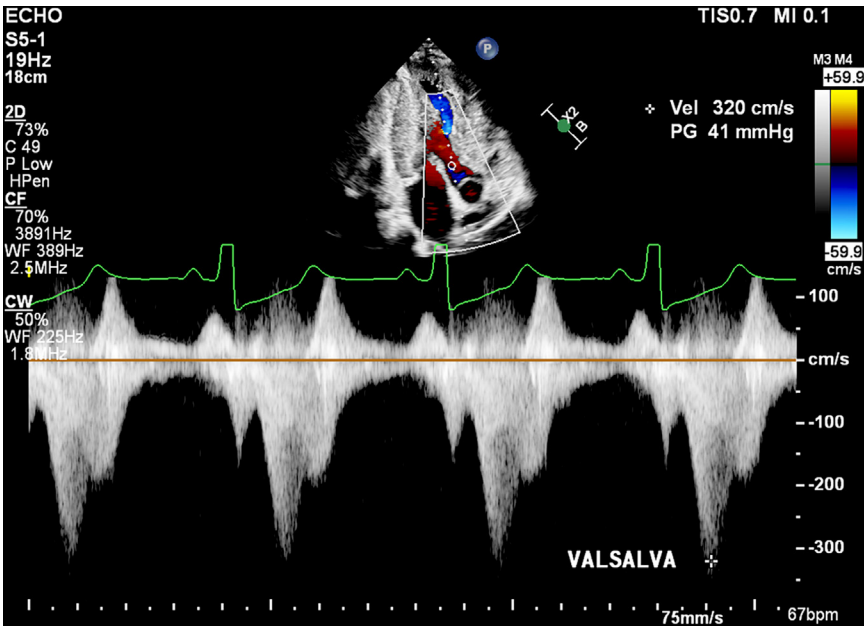


Cardiac magnetic resonance imaging with late gadolinium enhancement showing septal dominant hypertrophy with a maximal wall thickness of 36 mm, leading to systolic anterior motion of the mitral leaflets, a left ventricular apical aneurysm and a small (approximately 9%) burden of late gadolinium enhancement.

was successfully used to reverse ventricular hypertrophy and LVOT obstruction in 2 cases of RIT1-mutated Noonan syndrome within 4 months of initiating therapy.[2] Subsequently, trametinib was used to successfully treated a newborn with the RAF1c.770C>T (p.Ser257Leu) variant.[3]

We describe the successful treatment of RAF1-associated HCM with a MEK inhibitor. To our knowledge, this is the first report of treatment with trametinib for an adult with HCM. We highlight the value of precision therapies via a genotype-based determination of the mechanism of disease.

FIGURE 4 Echocardiogram Post-Trametinib Showing a Marked Improvement in the LVOT Gradient



Transthoracic echocardiogram (apical 3-chamber) spectral Doppler assessment showing a peak left ventricular outflow tract gradient of 41 mm Hg following treatment with trametinib.

FOLLOW-UP

The LVOT gradient remained stable at 18-month follow-up. We avoided septal reduction therapy by implementing targeted therapy with trametinib.

TABLE 1 Clinical and Laboratory Parameters Pre-treatment and Post-Treatment With Trametinib

	Pre-trametinib	Post-trametinib
Blood pressure, mm Hg	112/54	124/50
Weight, kg	51	64
Hematocrit	0.45	0.45
Albumin, g/L	41	37
Creatinine, μmol/L	82	79
N-terminal pro–B-type natriuretic peptide, ng/L	2,237	991

CONCLUSIONS

We describe the first successful use of trametinib for treating an adult with RAF1-associated Noonan syndrome and HCM through MEK inhibition. Precision therapies hold promise for RASopathies and other causes of non-sarcomeric HCM.

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The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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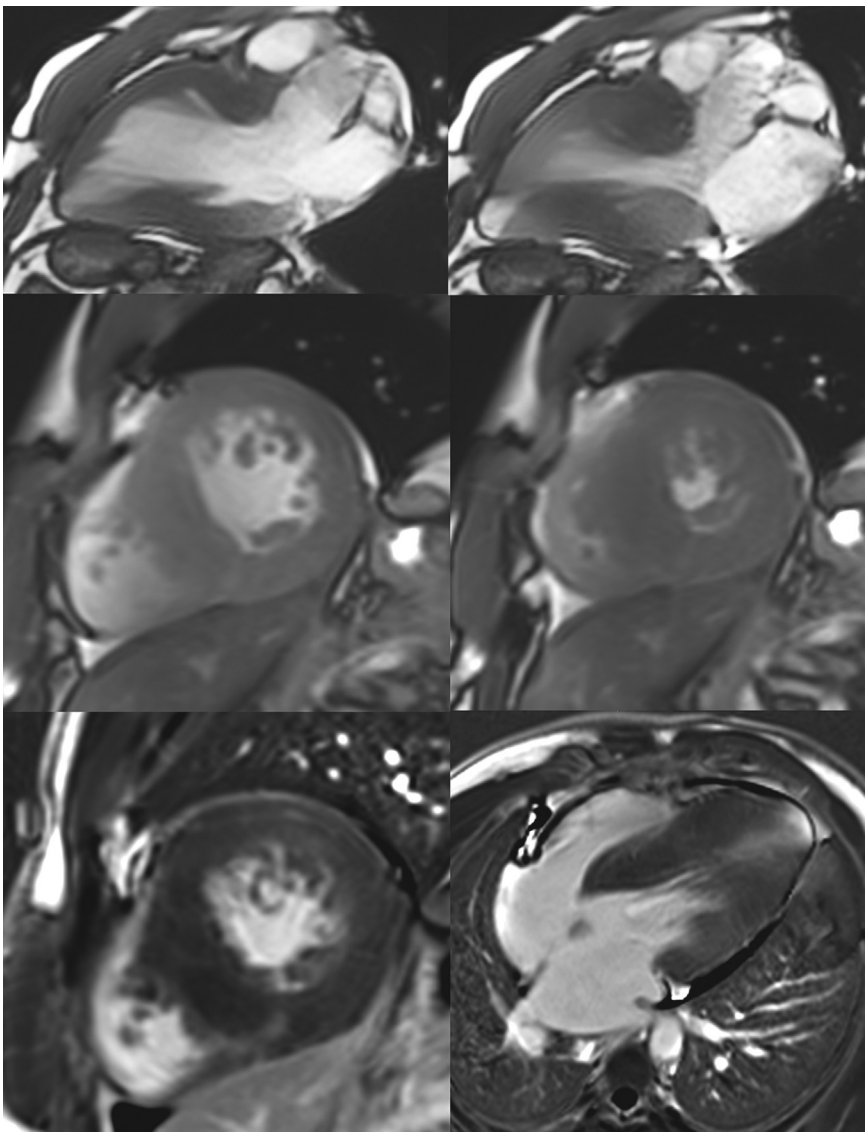
FIGURE 5 Cardiac MRI After Treatment With Trametinib



Cardiac magnetic resonance imaging following treatment with trametinib showed no objective differences with respect to maximal wall thickness, global left ventricular mass, left ventricular aneurysm, or myocardial fibrosis; however, a visible reduction in severity of systolic anterior motion was present.

REFERENCES

1. Arbelo E, Protonotarios A, Gimeno JR, et al, ESC Scientific Document Group. 2023 ESC guidelines for the management of cardiomyopathies. *Eur Heart J*. 2023;44(37):3503-3626. https://doi.org/10.1093/eurheartj/ehad194

2. Calcagni G, Adorisio R, Martinelli S, et al. Clinical presentation and natural history of hypertrophic cardiomyopathy in RASopathies. *Heart Fail Clin*. 2018;14(2):225-235. https://doi.org/10.1016/j.hfc.2017.12.00

3. Mussa A, Carli D, Giorgio E, et al. MEK inhibition in a newborn with RAF1-associated Noonan syndrome ameliorates hypertrophic cardiomyopathy but is insufficient to revert pulmonary vascular disease. *Genes (Basel)*. 2021;13(1):6. https://doi.org/10.3390/genes13010006

KEY WORDS cardiovascular genetics, hypertrophic cardiomyopathy, Noonan syndrome, RASopathies

APPENDIX For supplemental videos, please see the online version of this paper.