ESC HEART FAILURE
ESC Heart Failure 2020; **7**: 721–726
Published online 20 February 2020 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12650

CASE REPORT

Double-chambered right ventricle complicated by hypertrophic obstructive cardiomyopathy diagnosed as Noonan syndrome

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Abstract

We present a case of double-chambered right ventricle (DCRV) complicated by hypertrophic obstructive cardiomyopathy (HOCM) in *KRAS* mutation-associated Noonan syndrome. The diagnosis was incidental and made during diagnostic testing for an intradural extramedullary tumour. Spinal compression, if not surgically treated, may cause paralysis of the extremities. We decided to pursue pharmacological therapy to control biventricular obstructions and reduce the perioperative complication rate. We initiated treatment with cibenzoline and bisoprolol; the doses were titrated according to the response. After 2 weeks, the peak pressure gradient of the two RV chambers decreased from 101 to 68 mmHg, and the LV peak pressure gradient decreased from 109 to 14 mmHg. Class 1A antiarrhythmic drugs and β-blockers decreased the severe pressure gradients of biventricular obstructions caused by DCRV and HOCM. The patient was able to undergo surgery to remove the intradural extramedullary tumour, which was diagnosed as schwannoma.

Keywords Adult congenital heart disease; Double-chambered right ventricle; Obstructive hypertrophic cardiomyopathy; Pharmacological therapy; Noonan syndrome

Received: 16 October 2019; Revised: 27 January 2020; Accepted: 29 January 2020
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Introduction

Double-chambered right ventricle (DCRV) is a heart defect in which the right ventricle is separated into proximal high-pressure and distal low-pressure chambers.[1] The overall incidence of all type of congenital heart diseases is 0.5–2.0%.[2] Most DCRV cases are diagnosed during childhood or adolescence, and the defect is resolved at that time; DCRV is rarely present in adulthood.[3] Noonan syndrome is a genetic multisystem disorder characterized by distinctive facial features, developmental delay, learning difficulties, short stature, and congenital heart disease.[4]

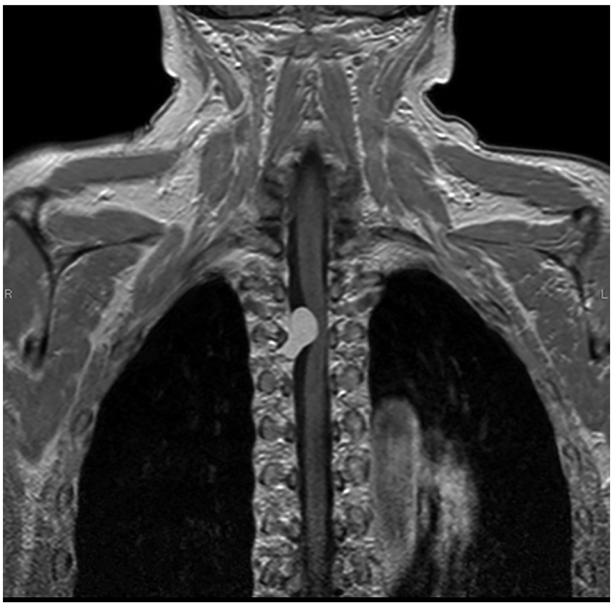
The understanding of the gene mutation in the RAS-MAPK signalling pathway that causes Noonan syndrome has greatly increased in the past decade, and the involvement of some genes (*PTPN11*, *KRAS*, etc.) has been reported.[5] *KRAS* mutations account for approximately 2.0% of the reported Noonan syndrome cases, but the phenotype and natural history are unclear.[6] We found no published report in the literature describing Noonan syndrome caused by *KRAS* mutation (p. K5E) presenting with DCRV associated with hypertrophic obstructive cardiomyopathy (HOCM) and pharmacological therapy that decreased the biventricular obstruction.

Case report

A 47 year-old woman was diagnosed with ventricular septal defect (VSD) during early infancy. When she was 16 years

old, her VSD was found to have spontaneously closed. No other cardiac disease was present; therefore, she was lost to cardiology follow-up for multiple years. However, when she was older (>40 years), she experienced slight exertional dyspnoea and began visiting an orthopaedic surgery centre because of worsening leg numbness, where she was diagnosed with an intradural extramedullary tumour (*Figure 1*). Although there was an urgent need for surgery, physical assessment revealed severe obstruction in the right ventricular outflow tract (RVOT) and left ventricular outflow tract (LVOT). Her height was only 145 cm. She had facial features suggestive of Noonan syndrome, including wide-set eyes and low-set ears. During physical examination, auscultation detected a Levine scale III/VI systolic ejection murmur over the second left intercostal space.

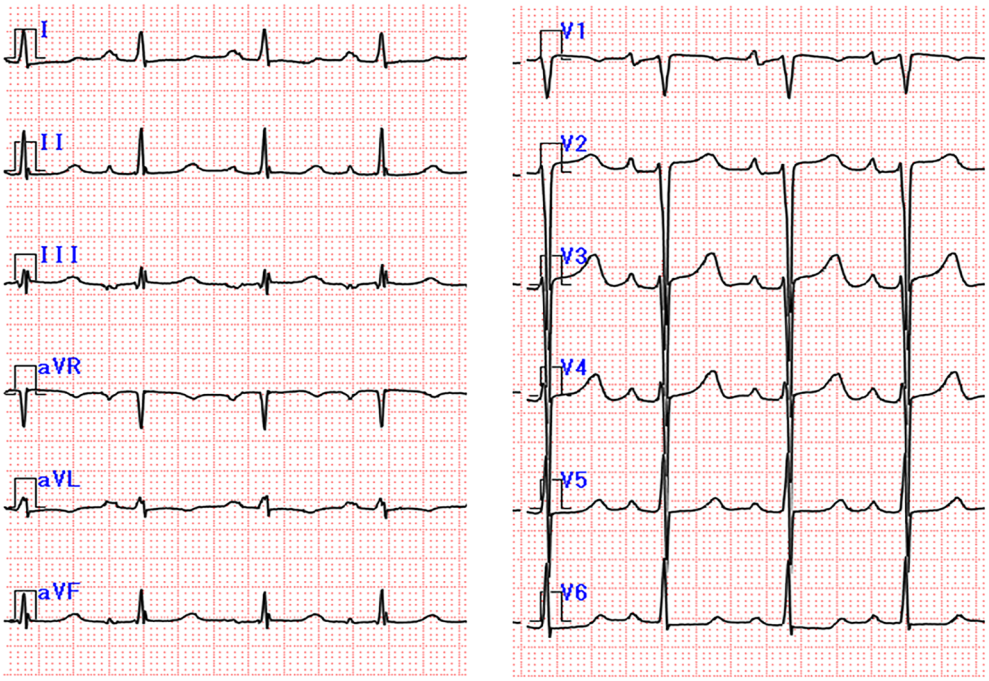
Figure 1 Gadolinium-enhanced magnetic resonance imaging shows the intradural extramedullary tumour.



Electrocardiography showed sinus rhythm, left atrium load, and intraventricular conduction disturbance in leads II, III, and aVF (*Figure 2*). A chest X-ray showed enlargement of the cardiac silhouette; moreover, high concentration of B-type natriuretic peptide (562.5 pg/mL) was detected. The transthoracic echocardiogram (TTE) examination revealed RV hypertrophy and midcavitary stenosis because of an abnormal cord-like structure in the RV (see Supporting Information, *Video S1*). No residual VSD was observed. The peak pressure gradient of the two RV chambers was increased (97 mmHg), suggesting DCRV. There was no significant stenosis in the pulmonary valve. Moreover, TTE revealed left ventricular hypertrophy (17 mm) (Video S2) causing LVOT obstruction with a peak gradient of 101 mmHg.

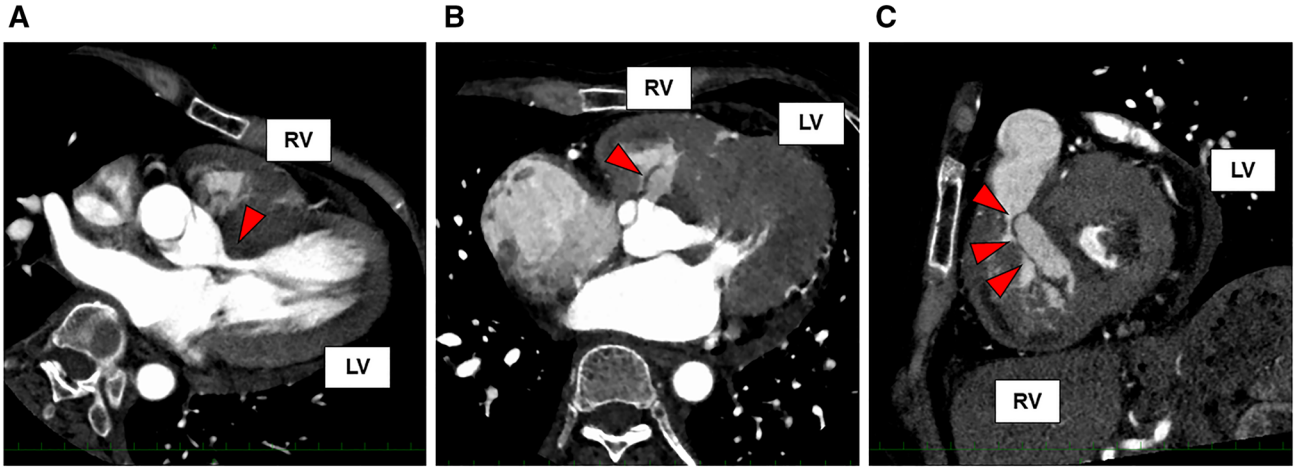
Enhanced computed tomography (CT) showed LVOT obstruction (*Figure 3A*) and cord-like sequencing of the

Figure 2 Electrocardiogram on admission.



DOI: 10.1002/ehf2.12650

Figure 3 Enhanced computed tomography shows (A) LV hypertrophy causing left LVOT obstruction (arrowhead), (B) cord-like structure sequencing of the anterior tricuspid valve leaflet (arrowhead), and (C) RV (three arrowheads). LV, left ventricle; LVOT, left ventricular outflow tract; RV, right ventricle.



anterior tricuspid valve leaflet and right ventricle (*Figure 3B* and *3C*). Furthermore, gadolinium-enhanced cardiovascular magnetic resonance imaging revealed late gadolinium enhancement (LGE) at the right ventricular junction (*Figure 4A*, *Video S3*), RV and LV hypertrophy, an abnormal cord-like structure, redundant chordae tendineae in the RV chamber, and a flow void sign at the RV and LV outflow tracts (*Figure 4B* and *4C*).

Right ventriculography showed RV outflow obstruction caused by the abnormal cord-like structure (*Figure 5A* and *5B*, *Video S4*). A simultaneous pressure study found that peak pressure gradients of the RV and LV were 94.8 and 110.8 mmHg, respectively (*Figure 6A*). Coronary angiogram did not show ischemic heart disease. However, generalized wall thickness was observed despite the absence of indicators revealed by physical examination, blood examination, and endomyocardial biopsy, suggesting secondary myocardial disease and nonbacterial endocarditis.

An intravenous injection of disopyramide (50 mg) dramatically reduced the RV and LV peak pressure gradients without decreasing blood pressure (LVOT from 110.8 to 64.6 mmHg; RVOT from 94.8 to 74.9 mmHg) (*Figure 6B*). The final diagnosis was DCRV caused by an abnormal cord-like structure sequence of the anterior tricuspid valve leaflet and RV complicated by HOCM.

Even though the symptoms from spinal cord compression were progressing to paralysis of the extremities and warranted orthopaedic surgery as soon as possible, haemodynamic stability should be ensured to reduce the perioperative complication rate. We initiated and titrated

Figure 4 Gadolinium-enhanced cardiovascular magnetic resonance imaging shows (A) late gadolinium enhancement at the RV junction (arrowhead) and (B,C) a flow void sign at the LV and RV outflow tracts (arrowhead). LV, left ventricle; RV, right ventricle.

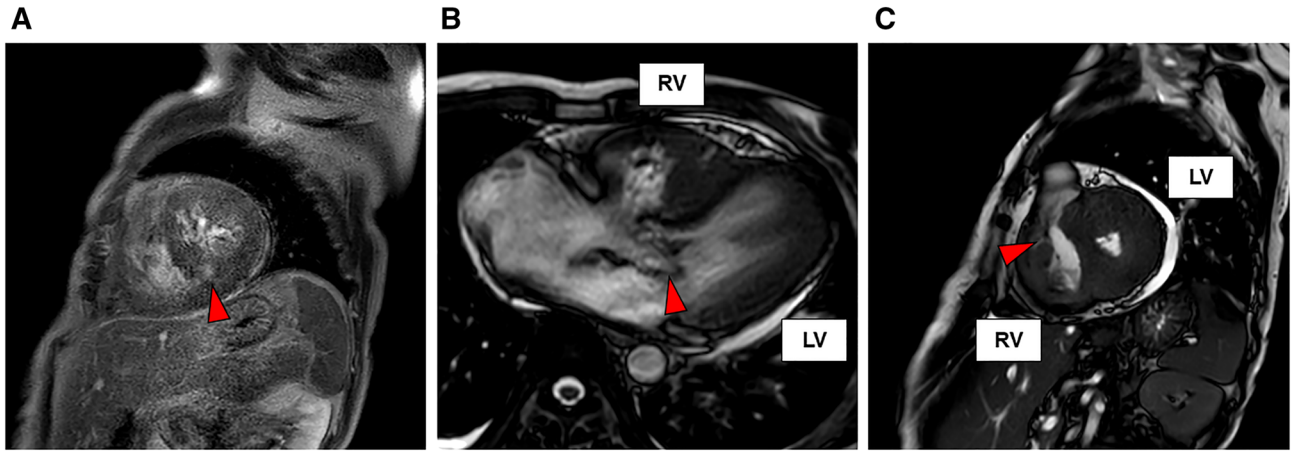


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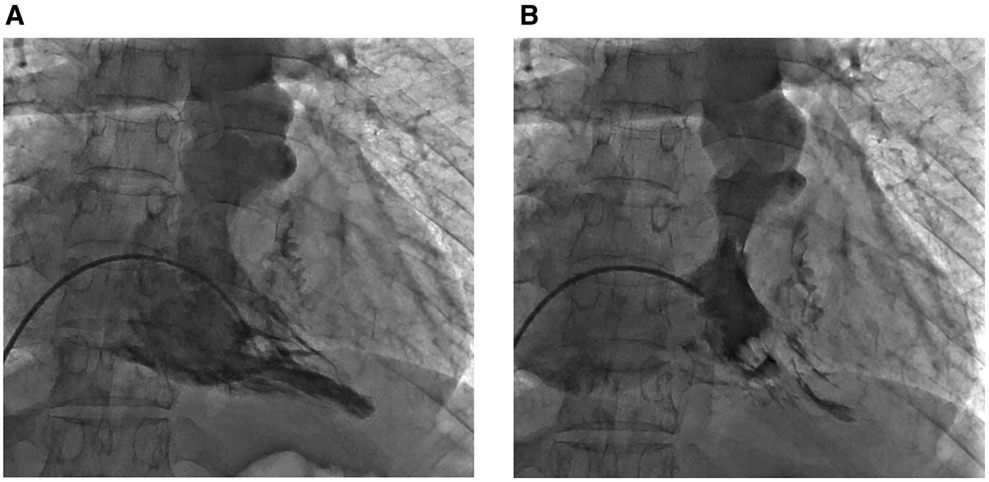
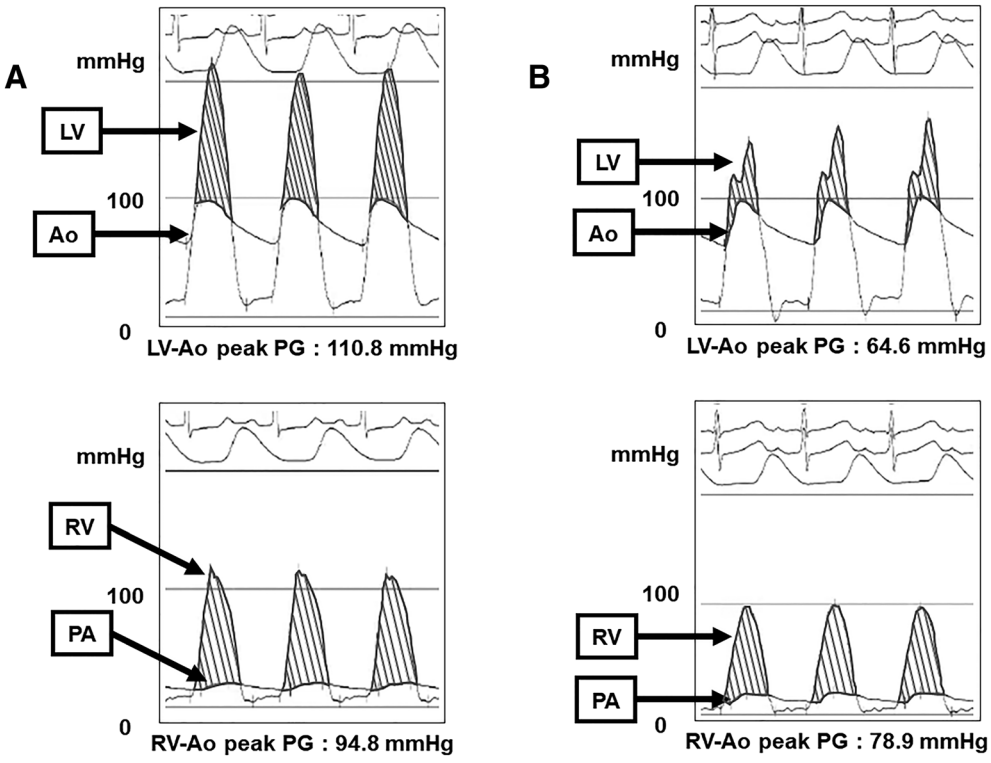
Figure 5 Right ventriculography of the (A) systolic and (B) diastolic phases shows right ventricular hyperkinetic contraction and outflow obstruction.



bisoprolol (up to 5 mg) and cibenzoline (up to 300 mg) to reduce RV and LV obstructions. After 2 weeks, TTE showed that the RV and LV peak pressure gradients decreased by 33 and 95 mmHg, respectively (*Video S5*), whereas blood pressure was preserved. During this period, brain natriuretic peptide levels significantly decreased (562.5 to 140.6 pg/mL). At that point, the patient could undergo surgery to remove the intradural extramedullary tumour, which was diagnosed as schwannoma. After surgery, the patient continued to be followed-up at our institution.

Because of her characteristic facial features and medical history, she was advised to undergo genetic screening for

Figure 6 Intracardiac pressure on heart catheterization: (A) control and (B) after intravenous injection of disopyramide (50 mg). Ao, aorta; LV, left ventricle; PA, pulmonary artery; RV, right ventricle; PG, pressure gradient.



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Noonan syndrome or related disorders, which revealed a *KRAS* mutation, c.13A>G, p.K5E. *KRAS* germline mutations have been identified in patients with Noonan syndrome or cardio-facio-cutaneous syndrome. Finally, the patient was diagnosed as having Noonan syndrome by her clinical manifestations.

Discussion

Double-chambered right ventricle is characterized by intraventricular pressure gradients greater than 20 mmHg in the RV. The mechanism of obstruction in DCRV may be due to anomalous muscle bands, hypertrophied endogenous trabecular tissue, or an aberrant moderator band. Most patients with DCRV have coexisting cardiac lesions such as VSD (60–90%), pulmonary valve stenosis (~40%), atrial septal defect (~17%), and double-outlet RV (~8%).[2] However, no previous case reports described DCRV coexisting with severe LVOT obstruction. The primary aim of this case was to achieve intradural extramedullary tumour excision due to the progressive symptoms of spinal cord compression. To decrease the surgical risk, a decrease in the severe pressure gradients of RVOT and LVOT obstruction was achieved through class 1A antiarrhythmic drugs and β-blocker use.

It has been advocated that multimodalities, such as cardiovascular magnetic resonance, provide important anatomical information[7,8] We found that the RVOT obstruction was induced not only by RV hypertrophy but also by the abnormal cord-like structure sequencing of the anterior tricuspid valve leaflet, which is termed DCRV. However, the main cause of LVOT obstruction was LV hypertrophy. This may provide an explanation of why the RVOT obstruction seemed more prominent and why the negative inotropic effect was stronger in the LV. Two reports evaluating the area of LGE have been published. First, Rudolph et al.[9] showed that LGE of the RV junction was common in hypertrophic cardiomyopathy (HCM). The same authors also reported that increased afterload induced LGE at the area of maximum wall thickness.[9] Additionally, Blyth et al. showed that most patients with increased RV afterload due to pulmonary hypertension present with LGE within the RV junction.[10] showed Therefore, the present case, which showed LGE within the RV junction, is consistent with the aforementioned findings of LV primary HCM and compensatory RV hypertrophy. Even though the RVOT gradient remained, the most relevant clinical parameter for the risk of perioperative complications was LVOT obstruction, which was adequately reduced by pharmacological therapy.

Noonan syndrome is the most common syndromic cause of congenital heart disease after trisomy 21.[2] A genetic mutation of the RAS-MAPK signalling pathway has been highlighted as a cause of cardiac hypertrophy associated with Noonan syndrome.[11] Previous reports indicated how mutations in the *PTPN11* gene induces cardiac hypertrophy and cardiovascular diseases.[12,13] However, the intracellular role of *KRAS* mutation in Noonan syndrome is largely unknown.[14]

In conclusion, this case describing Noonan syndrome caused by *KRAS* mutation (p.K5E) presenting with DCRV and HOCM is educational and practical for clinicians. Although surgical myectomy is the first-choice procedure,[15] we also considered performing emergent spinal cord surgery. Evaluations using multiple imaging modalities provide important anatomical information and help determine the appropriate treatment strategy. This case demonstrated an interesting finding of a good response to pharmacological therapy. This *KRAS* mutation–associated Noonan syndrome showed gradient-worsening hypertrophic cardiomyopathy with concomitant intradural schwannoma. We should remember that Noonan syndrome is often progressive; therefore, medical treatment should be continued.

Acknowledgement

We thank the patient for providing consent to publish her case.

Conflict of interest

None declared.

Funding

This work was supported by grants-in-aid for Young Scientists B from the Japan Society for the Promotion of Science (S.T., 17K16015)

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Video S1. Transthoracic echocardiogram showing RV hypertrophy and mid-cavitary stenosis due to an abnormal cord-like structure in the RV. RV = right ventricle.
Video S2. Transthoracic echocardiogram showing left ventricle hypertrophy (17 mm).
Video S3. Magnetic resonance imaging showing RV and LV hypertrophy, an abnormal cord-like structure, and the flow void sign at the RV outflow tracts. RV = right ventricle; LV = left ventricle.

Video S4. Right ventriculography showing right ventricular outflow tract obstruction caused by the right ventricle stenosis and the abnormal cord-like structure.

Video S5. Transthoracic echocardiogram after pharmacological therapy.

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