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MINI-FOCUS ISSUE ON CARDIOMYOPATHIES AND GENETIC COUNSELING

BEGINNER

CASE REPORT: CLINICAL CASE

Cardiac Myxoma in a Patient With Hypertrophic Cardiomyopathy

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ABSTRACT

We report a rare case of concomitant hypertrophic cardiomyopathy and cardiac myxoma without LEOPARD syndrome. Additionally, 6 similar cases were systemically reviewed, and the characteristics of this first-ever studied patient group were summarized. (**Level of Difficulty: Beginner.**) (J Am Coll Cardiol Case Rep 2020;2:378–83) © 2020 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

A 55-year-old male patient was referred to the authors' Institute for Cardiomyopathies for evaluation due to thickened left ventricular walls detected by an external echocardiography examination. At presentation, the patient was asymptomatic. He had no shortness of breath, angina pectoris, or palpitations. His family history revealed that his father died due to sudden cardiac death (SCD) at 55 years of age. The patient's physical examination was unremarkable. His heart sounds were normal, and no murmurs at rest or after provocation, using the Valsalva maneuver, could be heard. There were no neurologic deficits or abnormal skin pigmentation.

MEDICAL HISTORY

The patient had well-controlled arterial hypertension and was an active smoker with 20 pack-years.

DIFFERENTIAL DIAGNOSIS

Based on the information above, the differential diagnosis included hypertensive heart disease, hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy, storage disease, and coronary heart disease.

INVESTIGATIONS

The patient's electrocardiography (ECG) was positive for the Sokolow-Lyon index, and showed giant T-wave inversions and ST-segment depressions in the precordial leads (**Figure 1A**). His blood test results revealed elevated concentrations of N-terminal pro-B-type natriuretic peptide (NT-proBNP) (1,165 ng/l) and high-sensitivity cardiac troponin T (hs-cTnT) (66 ng/l). A cardiac magnetic resonance (CMR) study was scheduled, because a potential cardiomyopathy was suspected. The CMR results showed a notably

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, or patient consent where appropriate. For more information, visit the *JACC: Case Reports* author instructions page.

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LEARNING OBJECTIVES

- Hypertrophic cardiomyopathy and myxoma can occur simultaneously. LEOPARD syndrome is an important differential diagnosis defined by lentigines in combination with at least 2 other hallmarks: electrocardiographic conduction abnormalities, ocular hypertelorism, structural cardiac abnormalities, abnormal genitalia, retarded growth, and deafness. Further investigations on the genetic associations between HCM and myxoma, other than the known RAS/MAPK pathway, are requested.
- Each imaging modality provides specific information about cardiomyopathy and cardiac tumors, and modalities are complementary, i.e., 1) echocardiography provides information about tumor location, morphology, and attachment site in the heart, whereas CMR allows for detailed tumor-tissue characterization); 2) although CMR is the de facto standard mode for cardiomyopathies and cardiac tumors, it missed the atrial myxoma in this case, because the protocol was optimized for cardiomyopathy. This underlines the importance of multi-modality approaches for cardiac tumors and cardiomyopathies alike.

hypertrophied left ventricle (maximal wall thickness of 26 mm) with an ejection fraction of 79% and diffuse positive late gadolinium enhancement (LGE) in the hypertrophied regions. The hypertrophy pattern indicated an apical type of HCM. In the in-house transthoracic echocardiogram, an additional broad-based mass attached to the interatrial septum was seen in the left atrium (**Figures 1B and 1C**). Neither the gradient across the mitral valve (due to myxoma) nor the elevated left ventricular outflow tract (LVOT) gradient were present. The subsequent transesophageal echocardiogram revealed a friable multilobular tumor (approximately 26 × 16 × 16 mm) originating from the fossa ovalis (FO) in the left atrium (**Figure 2**), consistent with a myxoma. The heart catheterization results showed no evidence of coronary heart disease. Thus, the elevated hs-cTnT concentration was attributed to myocardial injury due to HCM. The elevated NT-proBNP concentration suggested heart failure. Because of the lack of specific dermatologic abnormalities (i.e., lentigines) and other clinical hallmarks (hypertelorism, conduction abnormalities, sensorineural deafness), LEOPARD syndrome was ruled out.

MANAGEMENT

The patient was promptly referred to the cardiac surgery department. A tumor resection (**Figure 3A**) with reconstruction of the FO with a pericardial patch was conducted without complications. Septal myectomy was not necessary, because no LVOT obstruction was detected at rest or after provocation.

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DISCUSSION

The most common symptoms of cardiac myxoma includes obstructive symptoms of the mitral valve (e.g., congestive heart failure, syncope, and SCD) and embolic events (e.g., stroke). Thus, diagnosis of a cardiac myxoma is usually followed by an immediate surgical tumor resection. Echocardiography provides essential information for location, morphology, and attachment to the adjacent structures of the myxoma. Aside from conventional transthoracic echocardiograms, transesophageal echocardiograms offer superior image resolution, especially of the posterior left atrial wall, atrial septum, and right atrium (1). Notably, CMR has evolved as the principal imaging modality in assessing cardiac tumors due to its superior capabilities of tissue characterization (2). However, in the present case, the CMR did not reveal the presence of a myxoma. This is because the suspicion of a cardiac tumor was not raised prior to the CMR, and consequently, the tumor-specific protocol (e.g., first pass perfusion imaging) was not implemented. When the CMR images were retrospectively reviewed, a slightly hypointense tumor-occupying region could be seen at the interatrial septum in the left atrium but was barely discriminated from normal flow phenomenon (**Figures 4A and 4B**).

Interestingly, the patient's condition was diagnosed with both cardiac myxoma and HCM, without LEOPARD syndrome. To further explore the occurrence of both, systematic reviews of Medline (1970 to 2019) and Cochrane Central Register of Controlled Trials (Cochrane Library Issue 3 of 12, March 2019) were undertaken. All publications, either original articles or reviews, reporting at least 1 case of concomitant atrial myxoma and HCM were eligible for inclusion. In total, 6 case reports (including the

ABBREVIATIONS AND ACRONYMS

ECG = electrocardiogram
FO = fossa ovalis
HCM = hypertrophic cardiomyopathy
hs-cTnT = high-sensitivity cardiac troponin T
LGE = late gadolinium enhancement
LVOT = left ventricular outflow tract
NT-proBNP = N-terminal pro-B-type natriuretic peptide
SCD = sudden cardiac death

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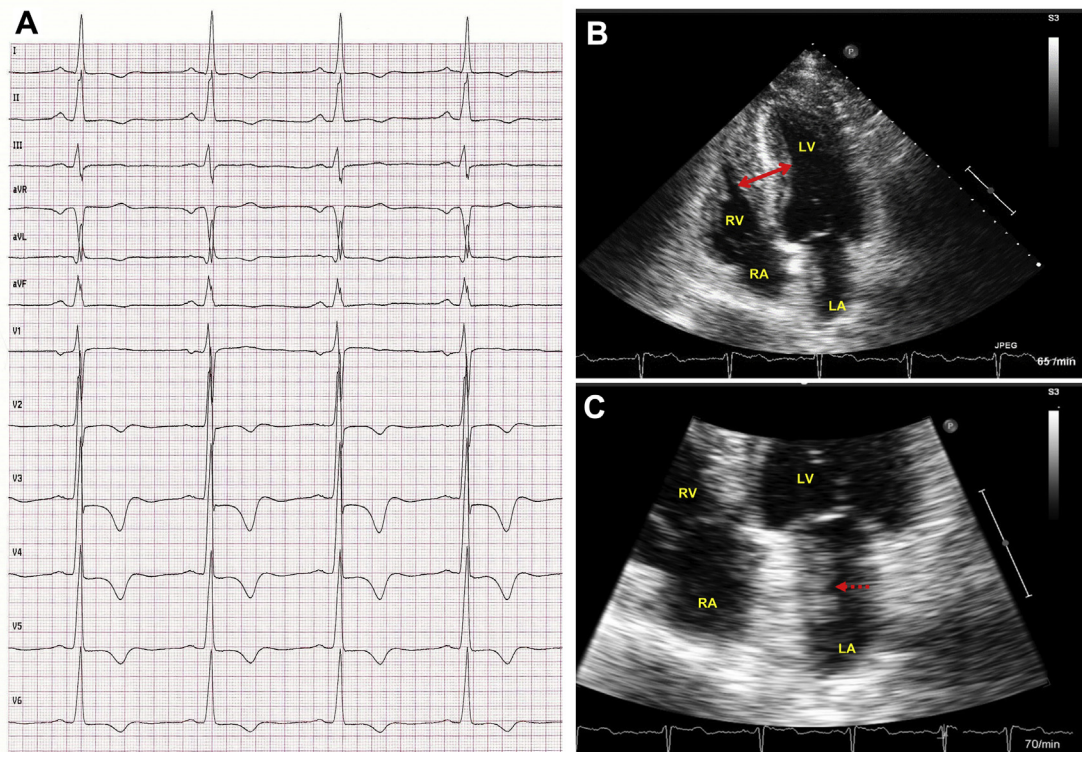
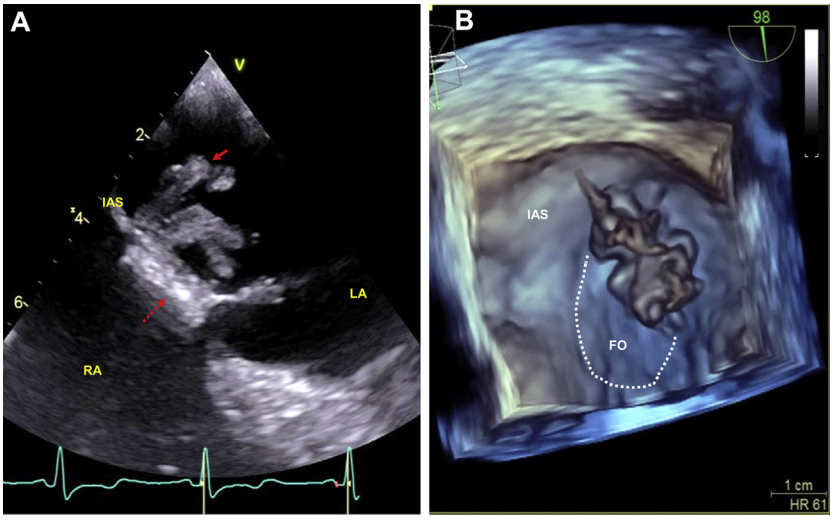
FIGURE 1 Electrocardiography and Transthoracic Echocardiogram



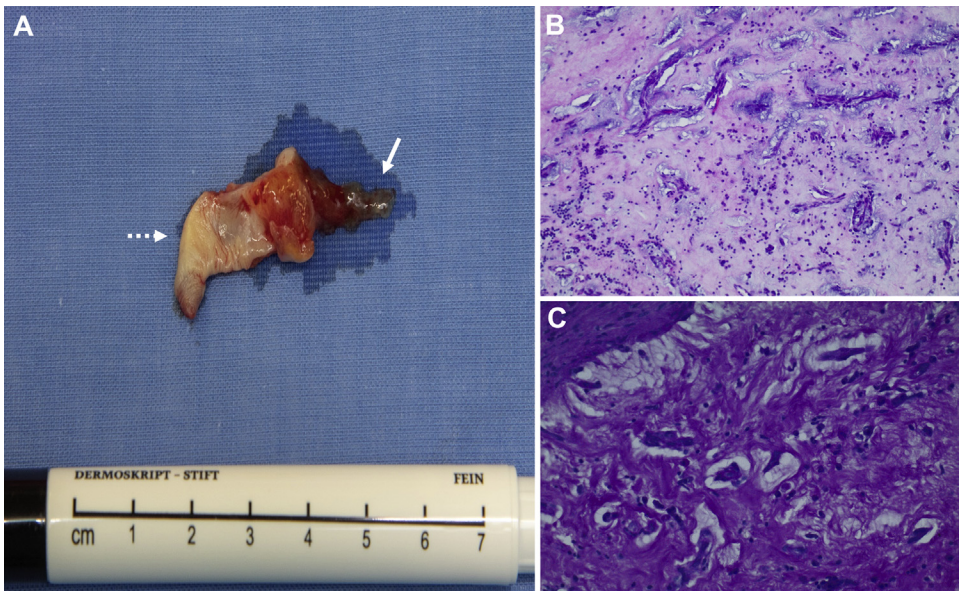
(A) A 12-lead ECG shows giant T-wave inversions and ST-segment depressions in the precordial leads. **(B)** Transthoracic echocardiography shows a hypertrophied LV with a thickened interventricular septum **(red arrow)**. **(C)** A broad-based mass **(dotted red arrow)** is shown attached to the interatrial septum in the LA. ECG = electrocardiography; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

FIGURE 2 Transesophageal Echocardiogram



Transesophageal echocardiogram demonstrates **(A)** a friable multilobular tumor **(solid red arrow)** originating from the fossa ovalis (FO) **(dotted red arrow)**. **(B)** A 3-dimensional transesophageal echocardiogram visualizes the myxoma in the left atrium. The border of the FO is denoted **(dotted white line)**. FO = fossa ovalis; LA = left atrium; IAS = interatrial septum; RA = right atrium.

FIGURE 3 Excised Cardiac Myxoma



(A) Photograph shows part of the excised cardiac myxoma **(solid white arrow)**. Other parts of the tumor were already suctioned away during the surgery because of the tumor's friability. The resected fossa ovalis is also shown **(dashed white arrow)**. **(B)** Microscopy confirmed the features of a cardiac myxoma: an abundant myxoid stroma with inflammatory cells, small vessels, and small elongated tumor cell groups (H&E stain; ×100 original magnification). **(C)** Myxoid stroma with inflammatory cells and isolated siderophages (periodic acid-Schiff stain; ×200 original magnification). H&E = hematoxylin and eosin.

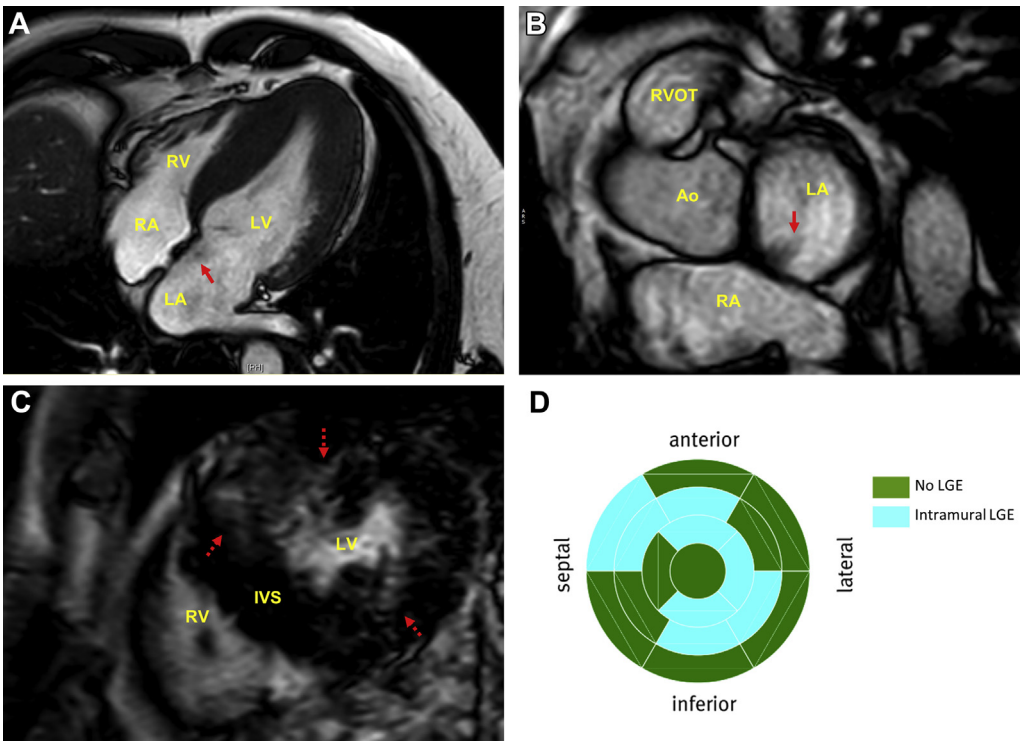
present case) met inclusion criteria. Figure 5 summarizes the selection process of eligible studies. Patient data are presented in Table 1. The patients were between 45 and 75 years of age with a median 55 years of age (95% confidence interval: 46 to 71 years of age) at the time of first diagnosis. Four of 6 patients were male. The tumor was located in the left atrium in all patients. Three patients were asymptomatic at presentation, whereas 1 experienced an embolic stroke, 1 had chest pain and dyspnea, and 1 had recurrent syncope and dyspnea. None of them had LEOPARD syndrome. None of the patients had a family history of myxoma, but 2 patients had familial HCM.

HCM and cardiac myxoma are both rare diseases. Therefore, the intriguing question is whether there is a pathophysiological link between hypertrophic signaling in ventricular cardiomyocytes and neoplasm formation of mesenchymal cells. Convergence of both diseases has been described in LEOPARD syndrome, caused by germline mutations in the RAS/MAPK pathway proteins (3). Interestingly, generally, the activation of the RAS/MAPK pathway is integral to the pathogenesis of HCM (4). Moreover, the *RAS* oncogene is the most common oncogene in humans, and an overactivation of *RAS* signaling leads to neoplasm formation. Thus, the authors surmise that the concomitance of HCM and cardiac myxoma in the present patient and other cases without LEOPARD syndrome could be due to an unreported form of *RAS*opathies. Further genetic studies in these patients can potentially elucidate the puzzling pathogenetic mechanism.

FOLLOW-UP

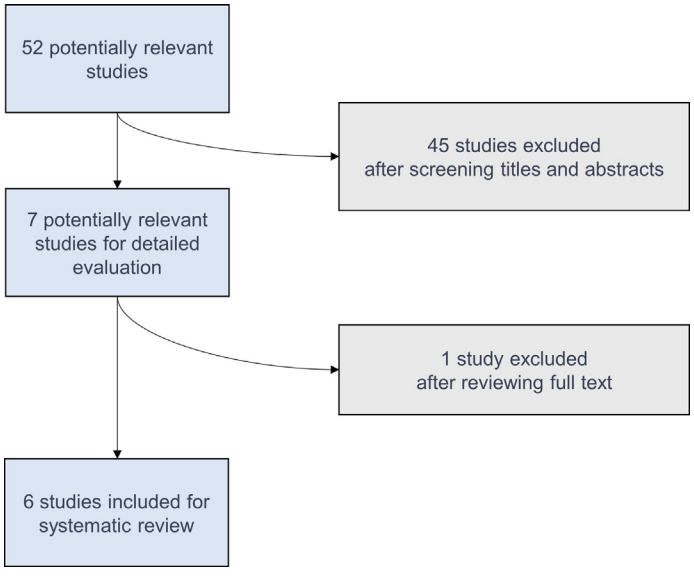
The patient was discharged 6 days after the surgery without complications. The histology report confirmed the diagnosis of a myxoma with regressive changes (Figures 3B and 3C). We recommended a 48-h ambulatory ECG to evaluate the risk of SCD and the indication of an ICD therapy, as recommended by the 2014 European Society of Cardiology guidelines for

FIGURE 4 Cardiac Magnetic Resonance in 4-Chamber Views and Short Axis



(A and B) SSFP cine sequences of the 4-chamber views and short axis respectively. The slightly hypointense tumor-occupying region **(red arrow)** is hardly differentiable from normal flow phenomenon. **(C)** Phase-sensitive inversion-recovery sequence shows diffuse intramural LGE **(dotted red arrow)**. **(D)** An illustration summarizing the distribution of LGE. Ao = ascending aorta; IVS = interventricular septum; LA = left atrium; LGE = late gadolinium enhancement; LV = left ventricle; RA = right atrium; RV = right ventricle; RVOT = right ventricular outflow tract; SSFP = steady-state free precession.

FIGURE 5 Flow Chart of Studies Inspected in the Systematic Review



diagnosis and management of HCM (5). During the patient's next visit, his 5-year risk of SCD will be estimated by using the HCM Risk-SCD formula (6) in combination with his LGE findings. A genetic investigation was suggested to the patient, who preferred to consider this important test after his recovery from the surgery.

CONCLUSIONS

This is the first study to systematically review the concomitance of cardiac myxoma and HCM without LEOPARD syndrome. Most of these patients were middle-aged males with HCM and myxoma in the left atrium. The underlying pathophysiological mechanisms require further investigation.

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TABLE 1 Cases With Concomitant Cardiac Myxoma and HCM

First Author (Year, Country) (Ref. #)	Age at Diagnosis, yrs	Sex	Tumor Size, mm	Tumor Location	Attachment Site	TIA or Stroke	Chest Pain, Dyspnea or Syncope	Family History of Myxoma	Family History of HCM or SCD	LVOT Gradient >30 mm Hg	Mode of Diagnosis
Hiasa et al. (1981, Japan) (7)	55	M	80 × 50 × 35	LA	NA	No	No	No	No	NA	TTE
Kanemoto et al. (1992, Japan) (8)	67	M	45 × 35 × 30	LA	IAS	No	Dyspnea and syncope	No	No	No	TTE
Abdou et al. (2013, U.S.) (9)	71	F	22 × 12	LA	IAS	No	No	No	Yes	No	CMR
Kałużna-Oleksy et al. (2014, Poland) (10)	46	F	37 × 27 × 16	LA	IAS	Stroke	No	NA	NA	NA	TTE
Padmanabhapillai (2016, India) (11)	63	M	33 × 20	LA	IAS	No	Chest pain and dyspnea	No	No	No	TTE
Gi et al. (2019, Germany)	55	M	26 × 16 × 16	LA	IAS	No	No	No	Yes	No	TTE

CMR = cardiac magnetic resonance; HCM = hypertrophic cardiomyopathy; IAS = interatrial septum; LA = left atrium; LVOT = left ventricular outflow tract; NA = not available; TIA = transient ischemic attack; SCD = sudden cardiac death; TTE = transthoracic echocardiogram.

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KEY WORDS cardiac myxoma, echocardiography, hypertrophic cardiomyopathy, imaging, LEOPARD syndrome