

# Mitral regurgitation in patients with hypertrophic cardiomyopathy: a case series

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Background	Mitral regurgitation (MR) is a frequent occurrence in hypertrophic cardiomyopathy (HCM), often explained by valvular or sub- valvular abnormalities as part of a broad HCM phenotype spectrum.	
Case summary	In this case series, we present two HCM cases diagnosed with systolic anterior motion of the anterior mitral valve (MV) leaflet and left ventricular outflow tract (LVOT) obstruction. Both cases had abnormal sub-valvular abnormalities that led to deterioration of LVOT obstruction and MR. The series highlights the need for close collaboration within a multidisciplinary team, with a special em- phasis on the need for a personalized treatment strategy when considering septal reduction therapy and/or MV surgery.	
Discussion	Mitral regurgitation is linked to adverse cardiac outcomes, often contributing towards symptoms, poor functional capacity, hospi- talization, and advanced therapies. Complex and interlinked biomechanical factors lead to MR, often co-existing with LVOT ob- struction. Multimodality imaging with echocardiography (transthoracic and transoesophageal) and cardiac magnetic resonance imaging plays a key role in determining the aetiology of MR in HCM. This case series highlights the role of this comprehensive assessment, paving the way for a personalized treatment pathway for patients.	
Keywords	Hypertrophic cardiomyopathy • Mitral regurgitation • LVOT obstruction • Echocardiography • Cardiac MRI • Case report • Case series	
ESC curriculum	2.3 Cardiac magnetic resonance • 2.2 Echocardiography • 6.5 Cardiomyopathy • 8.1 Sports cardiology	

#### Learning points

- Multimodality imaging plays a key role in determining the mechanisms of mitral regurgitation (MR) in hypertrophic cardiomyopathy (HCM).
- The mechanisms of MR in HCM will ultimately dictate the best therapeutic approach, thereby providing a personalized treatment strategy.

# Introduction

Hypertrophic cardiomyopathy (HCM) is the second most common inherited cardiomyopathy affecting ~1 in 200 to 1 in 500 adult subjects.<sup>1</sup> The presence of mitral regurgitation (MR) in HCM is associated with adverse cardiac outcomes.<sup>2,3</sup> The aetiology of MR in HCM is often attributed to intrinsic mitral valve (MV) pathologies or systolic anterior

motion (SAM) of the anterior MV leaflet. Other abnormalities of the MV apparatus, such as papillary muscle displacement and abnormal papillary muscle insertion, have also been reported.<sup>2</sup> The mechanism of MR in HCM will dictate the management strategy, which is why a multimodality assessment in such cases is paramount. The case series presented in this manuscript will depict the comprehensive assessment that is inevitably required in such cases.

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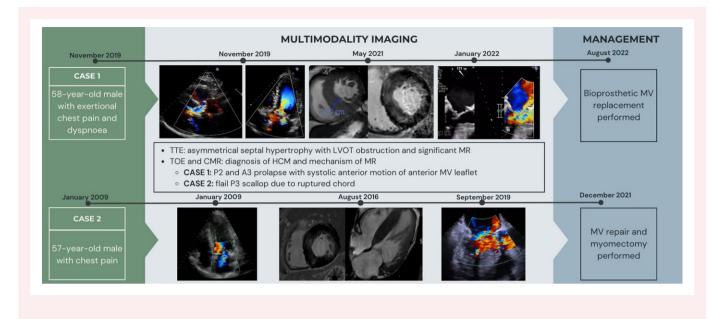
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## Summary figure



## Case 1

A 58-year-old Caucasian male presented to the emergency department with exertional chest pain and dyspnoea. He was known to suffer from obstructive sleep apnoea and hypertension. On examination, he had a loud ejection systolic murmur loudest at the left sternal edge in the fourth/fifth intercostal space. A resting 12-lead ECG showed firstdegree atrioventricular block, P-wave satisfying criteria for left atrial enlargement, and QRS complexes satisfying voltage criteria for left ventricular hypertrophy (LVH). There was downsloping ST-segment depression and T-wave inversion (TWI) in the inferolateral leads. Transthoracic echocardiography (TTE) showed concentric LVH with a septal bulge (maximal LV wall thickness 19 mm; Figure 1A-E). Septal hypertrophy and SAM of the MV led to significant left ventricular outflow tract (LVOT) obstruction (peak gradient 84 mmHg during Valsalva) and moderate MR. Invasive coronary angiography while on atenolol 12.5 mg daily revealed a distal LAD lesion, deemed significant with invasive coronary physiological assessments (iFR 0.87). Despite stenting the LAD, symptoms kept getting worse, eventually leading to significant functional limitations. The patient's NYHA class went up to 3, failing to improve after increasing atenolol to 12.5 mg BD. Repeat TTE and bicycle stress echocardiography confirmed the persistence of LVOT obstruction (160 mmHg during Valsalva).

A cardiac magnetic resonance (CMR) showed normal biventricular size and function on cine imaging. Maximal left ventricular wall thickness was 24 mm in the interventricular septum, with diffuse patchy mid-wall fibrosis on post-contrast imaging in hypertrophied segments (*Figure 2A–D*). There was early SAM of the anterior MV leaflet leading to moderate MR with a regurgitant fraction of 20% and a regurgitant volume of 23 mL (see Supplementary material). Left ventricular outflow track obstruction was again appreciated on phase contrast flow imaging. Genetic testing (using Cardio Pro kits by 4 bases on the MiSeq Illumina Platform, which includes 203 genes) did not identify any HCM-causing variants. The HCM Risk-SCD 5-year sudden cardiac death risk score was 3.6% (low risk).

Transoesophageal echocardiography (TOE) was performed to better characterize the functional and anatomical mechanisms contributing towards LVOT obstruction, and MR had several features consistent with complex degenerative disease (*Figure 3D* and *E*). There was P2 and A3 prolapse, together with mild SAM leading to severe MR consisting of multiple jets. The case was discussed in an inherited cardiomyopathy multidisciplinary team (MDT) meeting. The multimodality imaging assessment of the MV led the team to opt for MV surgery instead of a myectomy.

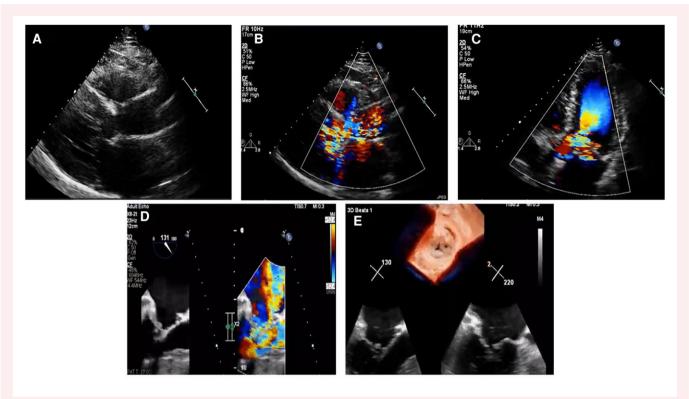
A few weeks later, he was admitted for investigation of possible MV endocarditis. He presented with a vasculitic rash and splinter haemorrhages. A repeat TOE whilst awaiting surgical intervention showed prolapse of P2/P3 with a probable perforation of the posterior leaflet, with a regurgitant jet passing through the perforation (*Figure 3A* and *B*). Serology and immunology markers all came back negative. A cardiac computed tomography also failed to confirm the presence of a perforation; an abscess was also ruled out. In the absence of any of the Modified Duke Criteria for infective endocarditis, the diagnosis was eventually dismissed.

A Bicarbon<sup>TM</sup> fitline MV replacement (27 mm) was performed later that year. Histopathological analysis of the MV revealed myxomatous degeneration, with no evidence of vegetations. His symptoms post-operatively improved significantly (*Figure 4*). A post-operative TTE showed no MR, with complete resolution of LVOT obstruction (maximum gradient 29 mmHg).

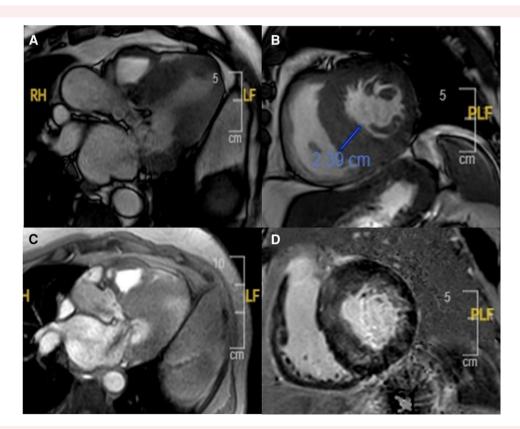
In conclusion, we present a case of HCM that was complicated with symptomatic LVOT obstruction and SAM-related MR (*Table 1*). Degenerative changes in the MV and prolapse of the posterior leaflets also contributed towards the mechanism of MR. Clinical features and worsening symptoms lead to a clinical suspicion of endocarditis. The patient was then referred for MV surgery, with resolution of symptoms and LVOT obstruction post-operatively. He remained asymptomatic and had no detectable LVOT obstruction up to 2 years post-operatively.

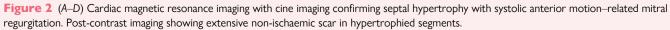
#### Case 2

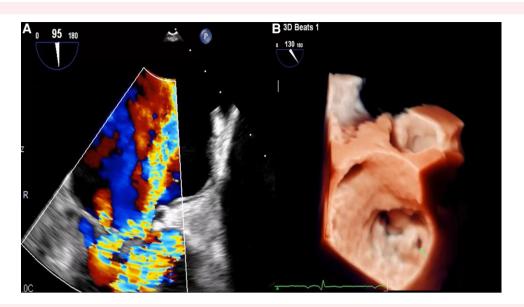
A previously healthy 57-year-old Caucasian male was admitted to ED after two short, self-resolving episodes of chest pain, thought to be musculoskeletal pains. On examination, an ejection systolic murmur was identified, loudest at the left sternal edge in the fourth/fifth intercostal space. A resting 12-lead ECG showed first-degree



**Figure 1** (A–E) Transthoracic echocardiography showing septal hypertrophy, systolic anterior motion of the anterior mitral valve leaflet and significant mitral regurgitation secondary to P2 and A3 prolapse.







**Figure 3** (A and B) Transoesophageal echocardiography showing mitral valve P2/P3 prolapse with suspected perforation (green arrow) of the posterior leaflet giving mitral regurgitation.

#### Table 1 Timeline for Case 1

Case 1			
Initial TTE (diagnosis of HCM)	6 November 2019		
Coronary angiography	9 November 2019		
PCI to LAD	25 November 2019		
Repeat TTE	3 November 2020		
Bicycle stress echocardiography	17 March 2021		
CMR	27 May 2021		
Initial TOE	10 January 2022		
TOE in view of clinical suspicion of	16 February 2022		
infective endocarditis			
MV replacement	24 August 2022		
Follow-up TTE	14 September 2024		

atrioventricular block, left axis deviation, and shallow TWI in Leads I/aVL. Transthoracic echocardiography showed preserved LV size and function, asymmetrical septal hypertrophy with a maximal LV wall thickness of 20 mm, absence of LVOT obstruction, and mild-to-moderate MR with a moderately dilated left atrium. He was followed up with repeat TTEs over the following years, which did not show any interval changes.

A CMR performed years later confirmed maximal LV wall thickness of 18 mm (septum) with SAM. There was mild MR and left atrial dilatation. Post-contrast imaging also showed limited focal non-ischaemic fibrosis in hypertrophied segments (*Figure 5A* and *B*). Transthoracic echocardiography subsequently identified a resting peak LVOT gradient of 63 mmHg. The mechanism of LVOT obstruction was at that time unclear. Valsartan 160 mg daily was switched to atenolol 25 mg daily.

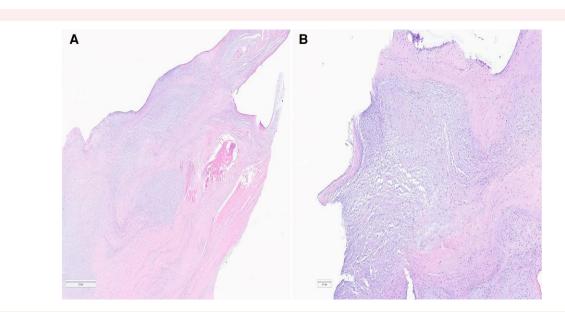
Admission to the hospital with pulmonary oedema prompted an inpatient TTE, which showed a new eccentric jet of MR. Transoesophageal echocardiography exhibited degenerative changes of the MV with a ruptured chordae to the posterior MV leaflet (PMVL), which led to a flail P3 scallop with posteromedial commissural involvement, causing severe MR (*Figure 6A* and *B*) (see Supplementary material). Systolic anterior motion of the sub-valvular apparatus to the AMVL causing significant LVOT obstruction was also appreciated, reaching a peak gradient of 75 mmHg at rest on a repeat TTE 2 years later. Genetic analysis (same panel as previous case) did not identify a pathogenic variant causing the HCM.

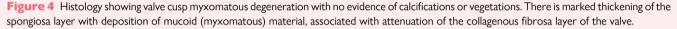
The absence of ongoing cardiogenic shock, the COVID-19 pandemic, and the absence of a dedicated myectomy service in the caring institution led to an inevitable delay in referral to the cardiothoracic team. A decision for surgery was then made after discussion at an inherited cardiomyopathy MDT meeting. He underwent MV repair and myectomy. Complete heart block was present post-operatively. He was then implanted with a permanent pacemaker. Post-operative TTE exhibited resolution of the LVOT obstruction with a well-repaired MV and minimal MR.

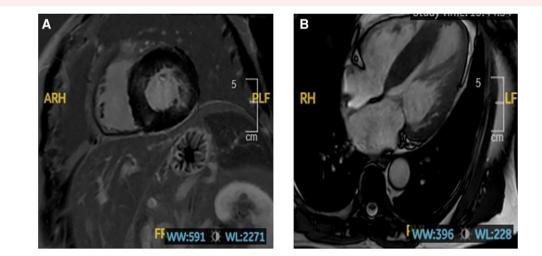
In conclusion, the second case depicts a patient with gene-negative obstructive HCM who presented with acute pulmonary oedema secondary to MV chordal rupture (*Table 2*). This also led to worsening of SAM and LVOT obstruction. The patient was referred for MV repair and a myectomy, complicated with post-operative complete heart block requiring permanent pacing. There was otherwise an excellent post-operative recovery, with symptom resolution and normalization of LVOT gradients and correctly functioning MV in a post-operative TTE.

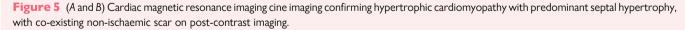
## Discussion

Mitral regurgitation is a frequent finding in HCM. The functional and structural mechanisms of MR in this patient subgroup are often driven by intrinsic MV anomalies and SAM of the anterior MV leaflet.<sup>2</sup> Mitral regurgitation in HCM also contributes to significant morbidity. A prospective study of 176 patients with HCM by Tesic *et al.*<sup>2</sup> showed that moderate-to-severe MR was associated with a worse functional classification, poor cardiovascular outcome, and an important predictor for atrial fibrillation.<sup>2,3</sup> Whilst treatment of HCM has been mainly focused









on the management of LVOT obstruction, MR itself requires a thorough evaluation.

Intrinsic MV apparatus abnormalities are broadly classified into valvular and sub-valvular abnormalities (including papillary muscles). Up to two-thirds of HCM cases often manifest elongated MV leaflets.<sup>4</sup> Although the exact aetiology of elongated MV leaflets has yet to be explored, it is likely a pre-clinical manifestation of the disease, often present even in genotype-positive phenotype-negative individuals.<sup>5</sup> Intuitively, one can postulate that excess MV leaflet tissue might lead to a prolapse. Chronic excessive strain on the MV leaflets may lead to an additional fibrous layer on top of the leaflets and an increased elastic fibre in a spongiosa layer of the valve leaflet in patients with HCM.<sup>4</sup> Mitral valve leaflet remodelling, particularly an additional layer of fibrous

layer on top of original leaflets, was seen in an ex vivo study mimicking MV prolapse and in some human tissue of MV prolapse.<sup>6</sup> To date, there are not many studies analysing the prevalence of MV prolapse in patients with HCM. However, a few previous studies suggest that MV prolapse might be present in up to 3% of patients with HCM.<sup>7</sup>

Geometric changes of the MV annulus may also be present in HCM. Dilatation of the annulus, shape, angulation, and calcification can all contribute towards the mechanism of MR in HCM. Mitral valve chordal rupture is also implicated in the mechanism of MR in HCM. This appears to be a rare phenomenon, present in 1% of patients with HCM.<sup>7</sup> Advancing age and hypertension appear to be important risk factors driving this pathology. Myxomatous degeneration is frequently observed, often involving the PMVL. Rupture may reduce or eliminate



Figure 6 (A and B) Degenerative changes of the mitral valve with a ruptured chord and flail P3 callop causing severe mitral regurgitation.

#### Table 2 Timeline for Case 2

Case 2	
Initial TTE (diagnosis of HCM)	17 January 2009
Repeat TTEs	2013 and 2016
CMR	11 August 2016
Repeat TTEs	2017, 2018, and 2019
TOE	13 September 2019
Repeat TTEs	March 2020, November 2020, and
	May 2021
MV repair and myomectomy	18 December 2021
Follow-up TTE	13 January 2022

LVOT obstruction, a classical finding in the literature, potentially evading the need for septal reduction therapy because of a paucity of symptoms.<sup>8</sup>

Anomalies in the sub-valvular are also implicated in the aetiology of MR in HCM. Papillary muscle abnormalities (anteroapical or anterior displacement, double bifidity) are frequently observed.<sup>9</sup> Direct papillary muscle insertion into the anterior MV leaflet and abnormal chordal attachment to the anterior MV leaflet are also occasionally seen in HCM.<sup>10</sup> Both might lead to LVOT obstruction. The displaced papillary muscle would be in direct contact with the septum, leading to tenting of the anterior MV leaflet. Systolic anterior motion of the anterior MV leaflet is seen mostly at mid-to-late systole of the cardiac cycle and leads to dynamic obstruction of LVOT. This phenomenon can be observed in 60%-70% of individuals with HCM.<sup>11</sup> The mechanism of SAM was previously thought to be owing to a Venturi effect because of a narrower LVOT (secondary to septal hypertrophy). Although this theory was widely accepted, it failed to explain how SAM can be seen even prior to the LV systolic ejection. In fact, a vector flow mapping study of patients with HCM by Ro et al.<sup>12</sup> showed that in some HCM cases, early SAM begins when an isovolumetric vortical flow within the LV affects the posterior surfaces of the MV leaflet from below. Some circles, in

fact, refer to this phenomenon as diastolic SAM. Systolic anterior motion of the anterior MV leaflet leads to a lack of coaptation with the tip of the PMVL. This typically leads to a posteriorly directed eccentric jet of MR.

The discrepancy in MR severity estimation based on the imaging modality adds another dimension of complexity. This is now well established, as has been described in Case 1 of this series. Mitral regurgitation quantification by CMR certainly seems promising in being able to offer superior prognostic value in predicting various endpoints when compared with TTE. Cardiac magnetic resonance is, however, very dependent on the variability in volumetric analysis according to the placement of the basal slice, dependent on the plane used to measure aortic flow and the presence of non-compensated Eddy current-induced fields.<sup>2,3</sup> The presence of a very eccentric jet may be a reason for the discrepancy in MR severity assessment between echocardiography and CMR. The absence of standardized CMR criteria for MR severity, unlike in echocardiography, is another reason for heterogeneity in MR severity reporting. A multimodality strategy, with a clinical evaluation in the appropriate context, is thus always recommended.

Medical therapy with beta-blockers, calcium channel blockers, or disopyramide is often a first-line option in patients with HCM with symptomatic LVOT obstruction and MR. Mavacamten is a first-in-class cardiac myosin adenosine triphosphatase (ATPase) inhibitor, offering a novel approach to treating MR in patients with HCM by directly addressing the molecular mechanisms of myocardial contractility. Guidelines recommend using it as an adjunct to traditional therapies or as a standalone alternative in those individuals who are intolerant to other medical therapies (Class IIa indication as per latest 2023 ESC cardiomyopathy guidelines).<sup>13</sup> By reducing LVOT obstruction, Mavacamten has been shown to reduce the severity of MR. In EXPLORER-HCM, 9% of the treatment arm had improvement in MR following the initiation of Mavacemten.<sup>14</sup> A reduction in SAM and improved MR was again demonstrated in the treatment arm of the VALOR-HCM trial.<sup>15</sup> Mavacamten is specifically advised for patients with an ejection fraction (EF) >55%, and its use should be discontinued if there is a (i) significant drop in EF and/or (ii) development of heart failure symptoms. This targeted modulation of myocardial contractility is another step towards a more personalized approach to treating LVOT obstruction and MR in HCM. Subjects who remain symptomatic despite medical therapy would have to be considered for septal

reduction therapies. Determining the mechanism of MR in these patients is important to establish the most appropriate surgical approach, opting for MV repair (with or without myectomy) whenever possible.<sup>13</sup>

# Lead author biography



Dr Mark Abela is a cardiology registrar practicing at Mater Dei Hospital. He has finished speciality training in cardiology and has undergone a fellowship in Sports Cardiology and Inherited Cardiac Conditions at St George's Hospital in London. His main academic and clinical interests are athletic cardiac adaptation, cardiac screening, inherited cardiac conditions, and cardiac rehabilitation. He has presented at several local and international congresses. He is the lead investigator for the nationwide

cardiac screening programme in Maltese Adolescents BEAT-IT. He is currently a nucleus member within the ESC committee for Sports Cardiology and Exercise. He is also the national cardiovascular disease prevention coordinator in Malta for the ESC.

# Supplementary material

Supplementary material is available at European Heart Journal – Case Reports online.

**Consent:** The authors confirm that informed consent has been obtained for both patients. The authors also confirm that compliance with COPE guidelines has been adhered to.

Conflict of interest. None declared.

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### Data availability

Data has been presented in the main manuscript. We have also included additional supporting files as supplementary data.

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