Case Series

Identification of recurrent *MYH7* variant hypertrophic cardiomyopathy patients in Korea: a case series

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Background: Hypertrophic cardiomyopathy (HCM) is a genetically heterogeneous cardiac disorder often caused by variants in sarcomeric genes such as *MYH7*. The p.Tyr134His variant in *MYH7* has previously been reported only once in a Korean HCM patient and was classified as a variant of uncertain significance (VUS), with no further supporting evidence available. This study adds to the literature by providing additional clinical and genetic evidence for this rare variant, suggesting a possible Korean-specific founder effect.

Case Description: We identified eight unrelated Korean patients with HCM, all carrying the heterozygous *MYH7* NM_000257.4:c.400T>C (p.Tyr134His) variant. These patients underwent exome sequencing across multiple clinical centers in South Korea. Clinical presentations varied from asymptomatic cases to those with arrhythmia, syncope, or structural changes such as asymmetric septal hypertrophy. No other pathogenic variants in known cardiomyopathy genes were identified in all eight patients. The variant was absent in major public and Korean population databases but present only in Korean HCM patients from our in-house cohort. *In silico* tools, including REVEL, AlphaMissense, and 3Cnet, consistently predicted deleterious effects.

Conclusions: Our findings provide clinical and population-level evidence supporting the pathogenicity of the p.Tyr134His variant in *MYH7*, potentially representing a rare Korean-specific founder mutation. However, as functional studies have not yet been performed, the pathogenic mechanism remains unconfirmed. Therefore, while current evidence remains of uncertain significance, further experimental

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validation may provide additional evidence to reclassify the variant as likely pathogenic.

Keywords: Hypertrophic cardiomyopathy (HCM); *MYH7*; exome sequencing; Korean genetics; case series

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Introduction

Hypertrophic cardiomyopathy (HCM) is a genetically heterogeneous disorder characterized by thickening of the left ventricular wall (1). HCM is one of the most common inherited cardiomyopathies with an estimated prevalence of 0.02% in the United States and 0.03% in Korea (2,3). Over 60 genes have been identified to be associated with HCM, with an average molecular diagnosis yield of 30% (4).

Genes associated with HCM often code for different components of the cardiac sarcomere. The *MYH7* gene (NM_000257.4, MIM: 160760), located in 14q11.2, encodes the thick filament within the sarcomere. A pathogenic variant found in *MYH7* has been primarily associated with autosomal dominant HCM (MIM: 192600). Together with pathogenic variants in *MYBPC3*, another sarcomere protein-coding gene, pathogenic variants in *MYH7* are known to be the major contributors to familial HCM, accounting for 33% of all molecular diagnoses made (1). HCM caused by pathogenic variants in sarcomere genes is associated with a higher risk of adverse outcomes and morbidity compared to patients with negative test results (5,6). Positive sarcomere gene testing results have been linked to higher incidences of atrial fibrillation, ventricular tachycardia, and heart failure (5,6). Early monitoring and possible device intervention are often necessary for patients with sarcomere-related HCM (5). Therefore, understanding the genetic cause underlying HCM can provide important indications for patients' prognosis.

In this case series, we described eight HCM patients from Korea who share the heterozygous NM_000257.4:c.400T>C (NP_000248.2:p.Tyr134His) variant in *MYH7*. Although the variant was not reported in ClinVar, it had previously been described as a variant of uncertain significance (VUS) by Kim *et al.* from a Korean HCM patient, suggesting that the variant may be specific to the Korean population (7). We present this article in accordance with the AME Case Series reporting checklist (available at https://cdt.amegroups.com/article/view/10.21037/cdt-2025-188/rc).

Highlight box

Key findings

- Eight unrelated Korean patients with hypertrophic cardiomyopathy (HCM) were found to share the same heterozygous *MYH7* missense variant, NM_000257.4:c.400T>C (p.Tyr134His).
- The variant is absent from large population databases and all Korean control datasets, and is predicted to be damaging by multiple algorithms.
- The variant is thought to be Korean-specific founder variant that may expand the genetic and clinical spectrum of *MYH7*-related HCM.

What is known and what is new?

- Most pathogenic *MYH7* variants are missense, yet many remain variants of uncertain significance because they lack sufficient evidence.
- This is the first multi-center report aggregating eight probands with the same p.Tyr134His variant with multiple patients.
- It highlights a potential founder effect in the Korean population and demonstrates the power of data sharing for variant reclassification.

What is the implication, and what should change now?

- Clinical laboratories and cardiologists in East Asia especially in Korea should look for p.Tyr134His variant.
- Meanwhile, patients carrying this allele should undergo surveillance, although a highly malignant course is not anticipated.

Case presentation

Eight patients with HCM were enrolled for clinical exome sequencing at 3billion, Inc. (Seoul, South Korea) between 2021 and 2023. Patients underwent exome sequencing (*Table 1*). Clinical evaluation was performed by clinicians across seven different hospitals and clinics across the Republic of Korea. All procedures performed in this case series were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki and its subsequent amendments. Written informed consent was obtained from the patients for the publication of this case series and accompanying

Table 1 Clinical information of NM_000257.4:c.400T>C variant carriers

Patient #	Age (years), sex	ECG	LVH morphology (concentric, asymmetric, atypical)	LVEF	Clinical characteristics	Family history
1	43, male	LVH, T wave inversion	Concentric remodeling	60%	Left ventricular hypertrophy, dilated LV, chest discomfort	Family history of hypertrophic cardiomyopathy and dilated cardiomyopathy
2	61, male	LVH, T wave inversion	Concentric remodeling	62%	Left ventricular hypertrophy, palpitation, cardiomegaly	Family history of hypertrophic cardiomyopathy
3	69, female	LVH, T wave inversion	Asymmetric	65%	Left ventricular hypertrophy	No family history
4	53, female	LVH, T wave inversion	Asymmetric	55%	Left ventricular hypertrophy, heart failure	Family history of coronary artery disease
5	70, female	LVH, T wave inversion	Apical	67%	Left ventricular hypertrophy	Family history of sudden death
6	53, female	LVH, T wave inversion	Asymmetric	NP	Proteinuria, left ventricular hypertrophy	No family history
7	67, male	LVH, T wave inversion	Asymmetric	46%	Left ventricular hypertrophy, arrhythmias	Family history of sudden death
8	40, male	LVH, T wave inversion	NP	62%	Left ventricular hypertrophy, proteinuria	Family history of hypertrophic cardiomyopathy
Previously reported in Kim *et al.* 2020	Unknown	–	–	–	Hypertrophic cardiomyopathy	–

ECG, electrocardiogram; LV, left ventricular; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; NP, not provided.

images. A copy of the written consent is available for review by the editorial office of this journal.

Exome sequencing was performed at 3billion, Inc., Illumina NovaSeq system (San Diego, CA, USA) was used for sequencing as 150 bp paired-end reads, generating a mean depth of coverage of 100× with greater than 98% 20× target region. Sequencing data analysis was performed at 3billion, Inc. following the CAP/CLIA validated standard operating protocol. Alignment to the human reference genome was done using BWA-MEM2, and samtools v1.15 was used for BAM file sorting and marking duplicates (8,9). The exome data were aligned to either GRCh37 or GRCh38. Recalibration and variant calling for single-nucleotide variants (SNVs) and small insertion/deletion variants (INDELs) were performed using GATK v4.2.14. Structural variants (SVs) were analyzed using CoNIFER v0.2.2, MANTA v1.6.0, and 3bCNV, an internally developed tool (10-12). Variants were annotated, filtered, and classified using EVIDENCE v4 (Seoul, South Korea), which incorporates Ensembl Variant Effect Predictor for annotation and the American College of Medical Genetics and Genomics (ACMG) guideline for classification (13-15).

Clinical presentation of eight patients

Patient 1

A 41-year-old male presented with T wave inversion on electrocardiogram (ECG) (*Figure 1A*). Coronary computerized tomography (CT) showed no significant disease. Despite large body size (170 cm, 113 kg) and mild hypertension [initial blood pressure (BP) 146 mmHg, well-controlled], marked left ventricular hypertrophy (LVH) was noted. He had a family history of HCM. Septal thickness remained ~15 mm after BP control.

Patient 2

A 61-year-old male with palpitations and T wave inversion on ECG (*Figure 1B*). Coronary CT was unremarkable. He had frequent ventricular premature beats responsive to beta-blockers and a family history of HCM. Echocardiography

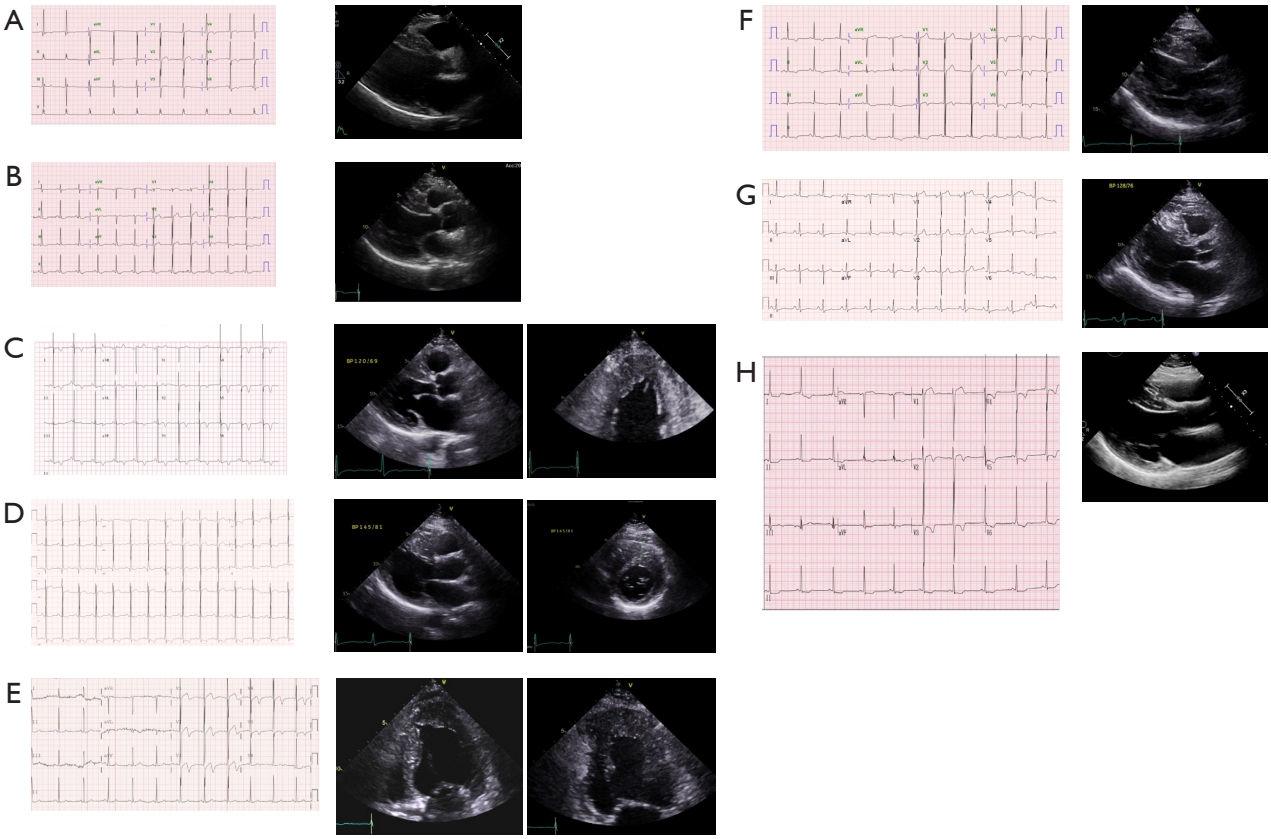

Figure 1 Electrocardiography and echocardiogram from the patient with NM_000257.4:c.400T>C (NP_000248.2:p.Tyr134His) variant. (A) Patient 1; (B) patient 2; (C) patient 3; (D) patient 4; (E) patient 5; (F) patient 6; (G) patient 7; (H) patient 8.

showed global myocardial thickening (max 14 mm) with normal left atrial size.

Patient 3

A 69-year-old female with chest discomfort and an abnormal outside echocardiogram. History of diabetes and hyperlipidemia; no family history of cardiac disease. Echo revealed asymmetric LVH (septum 14 mm, apex 15 mm). ECG showed T wave inversion (I, II, V3–V6) (*Figure 1C*). Global longitudinal strain (GLS) was 12.8%; N-terminal pro B-type natriuretic peptide (NT-proBNP) was 900.1 pg/mL. Peak VO_2 was reduced (8.42 mL/kg/min), confirming HCM.

Patient 4

A 53-year-old female with one-month exertional chest pain and dyspnea. Two siblings had coronary stents, but no family history of sudden cardiac death. Coronary CT showed minimal stenosis. NT-proBNP was 1,482 pg/mL. ECG showed LVH with ST depression and T wave inversion (V3–V6). Echo showed asymmetric LVH (septum 22 mm) (*Figure 1D*), with no outflow obstruction; GLS 10.7%. Stress echo showed no diastolic dysfunction, but ST depression (II, III, aVF).

Patient 5

A 70-year-old female presented with dizziness. ECG showed LVH with T wave inversion; troponin was elevated. Her father had a sudden death. Echo showed apical LV thickening (max 21 mm) with left atrial enlargement (43 mm), suggesting diastolic dysfunction (*Figure 1E*).

Patient 6

A 53-year-old female was incidentally found to have LVH and T wave inversion on ECG before surgery (*Figure 1F*). She was asymptomatic, with no known family history of HCM. Coronary CT was unremarkable. The echo showed asymmetric septal hypertrophy (max 20 mm) and left atrial enlargement, without mitral valve systolic anterior motion or outflow obstruction.

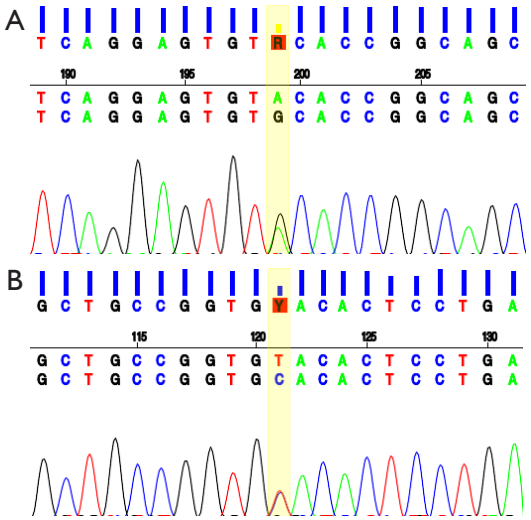

Figure 2 Sanger sequencing data of NM_000257.4:c.400T>C (NP_000248.2:p.Tyr134His) variant of family 1.

Patient 7

A 67-year-old male diagnosed with HCM since age 24 presented with dizziness and syncope. His father died suddenly in his 40s; three brothers have LVH. Holter showed non-sustained ventricular tachycardia (VT). Cardiac magnetic resonance imaging (MRI) showed asymmetric septal hypertrophy (max 18 mm) from base to apex with right ventricular involvement and myocardial fibrosis (*Figure 1G*). Ejection fraction (EF) was 46%. He underwent implantable cardioverter-defibrillator (ICD) implantation for secondary prevention.

Patient 8

A 66-year-old patient with a diagnosis of HCM (*Figure 1H*). His sister had HCM but was unavailable for testing. No history of HCM-related interventions such as myectomy or ICD.

Interpretation of the disease-causing MYH7 variant

To identify genetic causative variants, eight patients underwent exome sequencing. No clinically significant copy number variants (CNVs) or SVs were identified. Upon inspection of SNVs and small INDELs, all eight patients carried the same heterozygous missense variant, NM_000257.4:c.400T>C (NP_000248.2:p.Tyr134His) located in exon 5 of the *MYH7* gene (*Table 1*). Sanger sequencing was performed for patient I to confirm the variant (*Figure 2*).

The variant is located outside of the known myosin head domain, amino acids 181–937, that are statistically more likely to be disease-associated, as suggested by the ACMG/AMP *MYH7* framework group (13). The variant was absent in the gnomAD v4.1 and TopMED, the two largest available databases from presumed healthy individuals (https://gnomad.broadinstitute.org/) (16,17). The variant was also absent in the Korean Genome and Epidemiology Study (KoGES) database and the Korean Variant Archive (KOVA) database, containing 5,000 genome sequencing data and 1,896 genome and 3,409 exome sequencing data from presumed healthy Koreans, respectively (18,19). The variant was only identified in Korean individuals from an in-house database, which contains exome and genome data from over 50,000 healthy and rare disease patients, and was absent from other ethnicities. To the best of our knowledge, the variant was only reported once by Kim *et al.* 2020 in one Korean HCM patient and was classified as a (VUS) (7). No additional causative variants were identified in other cardiomyopathy-related genes for all patients.

The variant was predicted to be deleterious by multiple *in silico* algorithms. Two publicly available predictors, REVEL (0.89) and AlphaMissense (0.996), both predicted deleterious effects (20,21). Additionally, our in-house *in silico* predictor, 3Cnet, which outperforms REVEL, also suggested a damaging effect (0.97) (22). Neither spliceAI nor Pangolin predicted any splicing changes (23,24).

p.Tyr134His variant is enriched in Korean HCM patients

To evaluate whether the prevalence of the variant in HCM patients is significantly increased compared to the prevalence in controls, we performed an odds ratio evaluation utilizing the HCM patient cohort. HCM patient cohort used for statistical analysis consisted of 4,508 non-syndromic HCM Korean patients who underwent exome sequencing between 2021 and 2025. The inclusion criteria for the cohort included exhibiting LVH as a primary phenotype and being predicted as an East Asian from the genetic data. Patients who did not meet these criteria were excluded. Our cohort were between the ages of 19–98 years, with a median age of 58 years. Sixty-five percent (2,943/4,508) of patients were male, and 28.2% of the patients had received a molecular finding using exome (1,273/4,508). Similar to previous studies, *MYBPC3* (432/1,273) and *MYH7* (244/1,273) variants accounted for the majority of the variants identified.

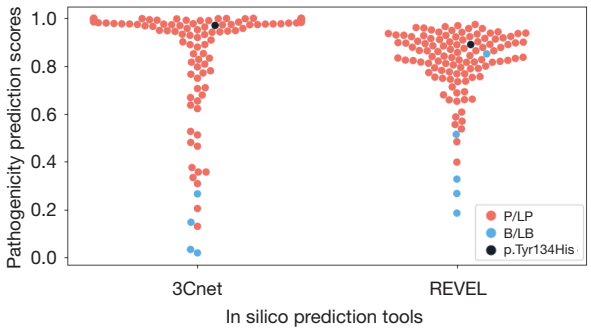

Figure 3 *In silico* score distribution of ClinVar curated pathogenic *MYH7* variants. Only ClinVar curated 1 star (or higher) likely P/LP or B/LB missense variants were used. The REVEL and 3Cnet score for variant NM_000257.4:c.400T>C (NP_000248.2:p.Tyr134His) is marked as black. B/LB, benign/likely benign; P/LP, pathogenic/likely pathogenic.

As the NM_000257.4:c.400T>C (NP_000248.2:p.Tyr134His) variant was absent from the control database, we performed odds ratio estimation utilizing ethnicity-matched gnomAD v4.1 controls after performing Haldane-Anscombe correction. The estimated odd ratio for NM_000257.4:c.400T>C (NP_000248.2:p.Tyr134His) was 84.76 [8.5/4,500.5 *vs.* 0.5/22,439.5; 95% confidence interval (CI): 4.89–1,468.87].

Discussion

Pathogenic variants in the *MYH7* and *MYBPC3* genes are two major contributing genes in familial HCM patients, accounting for over 33% of molecularly diagnosed patients (25). These two genes are also included in the secondary findings list provided by the ACMG, as mortality caused by sudden cardiac death and heart failure can be prevented through intervention (26). Compared to *MYBPC3*-related HCM, where the known pathogenesis mechanism is haploinsufficiency caused by loss-of-function variants, most of the pathogenic variants in *MYH7*-related HCM are missense (13). Thus interpretation of novel *MYH7* variants is often challenging as they often have to rely on *in silico* predictions as the sole source of evidence. This generates a heavy VUS burden for the *MYH7* gene and a high discordance rate among different clinical laboratories (27,28). Patients and physicians with novel VUS genetic testing results have a difficult time, as they are often stuck between dismissing the variant or performing further investigation to reclassify the variant.

In this case series, we identified the NM_000257.4:c.400T>C (NP_000248.2:p.Tyr134His) variant in eight unrelated HCM patients. The variant was previously reported as a VUS due to insufficient evidence. In this study, we have identified the variant in 8 unrelated probands with HCM, providing an odds ratio of 84.76, suggesting that the variant is enriched in the Korean HCM cohort. The variant was absent in gnomAD v4.1, Topmed, KoGES, and KOVA databases, suggesting the variant is a rare variant among the population. In addition, the variant was only identified from the Korean HCM cohort and no other databases, suggesting that the variant could be a Korean-specific founder variant. Although their use is limited, multiple *in silico* algorithms have also identified the variant as deleterious (REVEL: 0.89, 3Cnet: 0.97, AlphaMissense: 0.996). Compared to other pathogenic and likely pathogenic variants from *MYH7* from ClinVar, the variant's prediction score separated correctly with pathogenic variants (*Figure 3*, Table S1). In conclusion, our study provides additional clinical and population-based evidence supporting the pathogenicity of the variant.

However, our study is limited to a cohort from the South Korean population. Therefore, it's unclear if the variant could be causative for HCM in different ethnic groups. Furthermore, although the odds ratio was estimated to be 84.76, the lower limit of the 95% confidence interval was 4.89, which is insufficient for reclassification of the variant in accordance with the guideline provided by the Clingen HCM working group. Therefore, the variant remains of uncertain significance at this time. Additional studies and functional studies are needed to truly understand the pathogenicity of the variant (13).

Patients 1 and 2 have been followed for five years, during which time they have remained stable without significant changes in their ECGs or left ventricular wall thickness. Patient 3 has been under observation at another hospital without any significant worsening of symptoms. Patient 4 has been followed in the outpatient clinic for six months with no notable changes in symptoms. Patient 5, a 70-year-old female with a family history of sudden death, presented initially with dizziness, but no further follow-up data are available. Patient 6 had a maximal septal thickness of 20 mm, but no late gadolinium enhancement was detected on cardiac MRI. She remained asymptomatic, with no non-sustained ventricular tachycardia on the annual 24-hour Holter ECG and no other high-risk features over the 5-year follow-up period after diagnosis. Patient 7, who had a strong family history of HCM and sudden death, received an ICD for secondary prevention of sudden cardiac death and is

currently under close monitoring. Patient 8 has a diagnosis of HCM, a sister with HCM, and a father who died from presumed arrhythmic events at age 42, yet no follow-up data are available for patient 8. Overall, it is expected that the clinical course associated with the NM_000257.4:c.400T>C (NP_000248.2:p.Tyr134His) variant may not be highly malignant. The degree of LVH was moderate, and considering the family history, sudden cardiac arrest is not anticipated compared to other pathogenic variants. However, there remains a potential risk for arrhythmias or other cardiac complications in these patients. Furthermore, clinical data for the patient were insufficient to correlate the variant with a more detailed clinical phenotype at this time. Thus, continuous monitoring and appropriate medical interventions remain essential for long-term management. Further research, including functional studies, is needed to confirm these observations and clarify the long-term prognosis associated with this variant.

Conclusions

We identified heterozygous NM_000257.4:c.400T>C (p.Tyr134His) variant in *MYH7* in eight unrelated Korean patients with HCM. The variant was absent from large population reference datasets. A case–control analysis involving 4,508 Korean HCM cases demonstrated significant enrichment of the variant (odds ratio =84.76; 95% CI: 4.89–1,468.87). Multiple *in-silico* predictors support a deleterious effect, and no additional cardiomyopathy-related variants were identified in these patients, suggesting a potential causal role. However, due to a wide confidence interval and the lack of functional evidence, the variant remains classified as a VUS currently. These data provide evidence toward a possible Korean-specific founder variant and emphasize the need for functional studies and validation in larger, multi-ethnic cohorts to confirm its pathogenicity.

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Footnote

Reporting Checklist: The authors have completed the AME Case Series reporting checklist. Available at https://cdt.amegroups.com/article/view/10.21037/cdt-2025-188/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this case series were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki and its subsequent amendments. Written informed consent was obtained from the patients for the publication of this case series and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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