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MORPHO-GENETIC VARIABILITY IN MYOCARDIAL TISSUE AFTER SEPTAL MYECTOMY IN PATIENTS WITH OBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY: A FOUR-CASE SERIES STUDY

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Abstract

Background and Objective: Obstructive hypertrophic cardiomyopathy (OHCMP) is a heterogeneous disease with strong genetic determination.

The study aimed to identify myocardial morphological features in OHCMP patients depending on genetic status and to assess correlations between morphology and mutations in key genes.

Materials and methods. A descriptive study included 4 OHCMP patients undergoing septal myectomy. Myocardial morphology was assessed using hematoxylin-eosin, PAS, and Masson Trichrome staining. Genetic testing was performed by next-generation sequencing (NGS), including 17 genes: ACTC1, DES, FLNC, GLA, LAMP2, MYBPC3, MYH7, MYL2, MYL3, PLN, PRKAG2, PTPN11, TNNC1, TNNI3, TNNT2, TPM1, TTR.

Results. Genetically positive patients (MYH7, GLA, PRKAG2) demonstrated a chaotic arrangement of cardiomyocytes, marked nuclear polymorphism, and fine-fibrous perivascular and pericellular myocardial fibrosis. Genetically negative and control patients showed a more ordered arrangement of cardiomyocytes, focal coarse-fibrous fibrosis, and no nuclear polymorphism. Regardless of genetic status, all patients showed signs of cardiomyocyte hypertrophy and dystrophy, as well as a positive PAS reaction.

Conclusion. Myocardial morphological features differ significantly depending on genetic status, underscoring the importance of integrating histological and genetic analyses for risk stratification and personalized management of OHCMP patients. These findings provide a foundation for further research and development of clinical recommendations for cascade screening and prognosis.

Keywords: *obstructive hypertrophic cardiomyopathy, genetic status, myocardial morphology, nuclear polymorphism, PAS reaction, cardiac fibrosis, NGS, personalized medicine.*

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Резюме

МОРФОГЕНЕТИЧЕСКИЕ ОСОБЕННОСТИ МИОКАРДА У ПАЦИЕНТОВ С ОБСТРУКТИВНОЙ ГИПЕРТРОФИЧЕСКОЙ КАРДИОМИОПАТИЕЙ ПОСЛЕ СЕПТАЛЬНОЙ МИЭКТОМИИ: АНАЛИЗ СЕРИИ ИЗ ЧЕТЫРЕХ СЛУЧАЕВ

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Предпосылки и цель: Обструктивная гипертрофическая кардиомиопатия (ОГКМП) является гетерогенным заболеванием с выраженной генетической детерминацией.

Цель исследования – выявить морфологические особенности миокарда у пациентов с ОГКМП в зависимости от генетического статуса и оценить корреляцию морфологии с мутациями ключевых генов.

Материалы и методы: Проведено описательное исследование с включением 4 пациентов с ОГКМП, подвергшихся септальной миоэктомии. Морфологический анализ миокарда включал окраски гематоксилином и эозином, PAS и Masson Trichrome. Генетическое тестирование осуществлялось методом секвенирования нового поколения (NGS), панель включала 17 генов: ACTC1, DES, FLNC, GLA, LAMP2, MYBPC3, MYH7, MYL2, MYL3, PLN, PRKAG2, PTPN11, TNNC1, TNNI3, TNNT2, TPM1, TTR.

Результаты: У генетически положительных пациентов (MYH7, GLA, PRKAG2) выявлено: хаотичное расположение кардиомиоцитов, выраженный полиморфизм ядер и тонковолокнистый периваскулярный и перицеллюлярный кардиосклероз. У генетически отрицательных и контрольных пациентов отмечалось более упорядоченное расположение кардиомиоцитов, грубоволокнистый очаговый фиброз и отсутствие полиморфизма ядер. Независимо от генетического статуса, у всех пациентов выявлялись признаки гипертрофии и дистрофии кардиомиоцитов, а также положительная PAS-реакция.

Выводы: Морфологические особенности миокарда существенно различаются в зависимости от генетического статуса, что подтверждает важность интеграции гистологического анализа и генетического тестирования для стратификации риска и персонализированного ведения пациентов с ОГКМП. Полученные данные могут служить основой для дальнейших исследований и разработки клинических рекомендаций по каскадному скринингу и прогнозированию течения заболевания.

***Ключевые слова**: гипертрофическая кардиомиопатия, обструктивная форма, генетические мутации, морфология миокарда, кардиомиоциты, кардиосклероз*

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Түйіндеме

ОБСТРУКТИВТІ ГИПЕРТРОФИЯЛЫҚ КАРДИОМИОПАТИЯСЫ БАР НАУҚАСТАРДА СЕПТАЛЬДЫ МИЭКТОМИЯДАН КЕЙІНГІ МИОКАРДТЫҢ МОРФОГЕНЕТИКАЛЫҚ ЕРЕКШЕЛІКТЕРІ: ТӨРТ ЖАҒДАЙДАН ТҰРАТЫН СЕРИЯНЫ ТАЛДАУ

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Кіріспе және мақсаты: Обструктивті гипертрофиялық кардиомиопатия (ОГКМП) – әртүрлі генетикалық детерминациясы бар ауру.

Зерттеудің мақсаты – ОГКМП науқастарында миокардтың морфологиялық ерекшеліктерін генетикалық статусқа байланысты анықтау және негізгі гендердің мутацияларымен корреляциясын бағалау.

Материалдар мен әдістер: Септальды миоэктомиядан өткен 4 науқасты қамтитын сипаттамалық зерттеу жүргізілді. Миокард морфологиясы гематоксилин-эозин, PAS және Masson Trichrome бояулары арқылы зерттелді. Генетикалық тестілеу жаңа буын секвенирлеу (NGS) әдісімен жасалды, панельге 17 ген кірді: ACTC1, DES, FLNC, GLA, LAMP2, MYBPC3, MYH7, MYL2, MYL3, PLN, PRKAG2, PTPN11, TNNC1, TNNI3, TNNT2, TPM1, TTR.

Нәтижелері: Генетикалық жағынан оң науқастарда (MYH7, GLA, PRKAG2) кардиомиоциттердің хаотикалық орналасуы, ядрелердің айқын полиморфизмі және ұсақталымды периваскулярлық және перицеллюлярлық кардиосклероз анықталды. Генетикалық жағынан теріс және бақылау тобындағы науқастарда кардиомиоциттердің тәртіпті орналасуы, ұсақталмаған ошақты фиброз және ядро полиморфизмінің болмауы байқалды. Генетикалық статусқа қарамастан, барлық науқастарда кардиомиоциттердің гипертрофия және дистрофия белгілері, сондай-ақ оң PAS-реакция анықталды.

Қорытынды: Миокард морфологиясының ерекшеліктері генетикалық статусқа байланысты айтарлықтай өзгереді, бұл ОГКМП науқастарын басқаруда гистологиялық талдау мен генетикалық тестілеуді біріктірудің маңызды екенін растайды.

***Түйінді сөздер:** обструктивті гипертрофиялық кардиомиопатия, генетикалық статус, миокард морфологиясы, ядро полиморфизмі, PAS-реакция, кардиосклероз, NGS, персонализирленген медицина.*

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Introduction

Hypertrophic cardiomyopathy (HCM) is a common genetic myocardial disorder characterized by unexplained left ventricular hypertrophy, myocyte hypertrophy and dysfunction, interstitial fibrosis, and highly variable clinical manifestations ranging from an asymptomatic course to the development of heart failure or sudden cardiac death. According to current evidence, a prevalence of approximately 1:500 is considered the most accurate estimate for clinical assessment and management of HCM [12]. The main morphological substrate of HCM is left ventricular wall thickening in the absence of conditions associated with congenital or acquired heart defects, arterial hypertension (AH), coronary artery disease (CAD), or other diseases that can contribute to myocardial hypertrophy [10].

The obstructive form of HCM (oHCM) is the most common variant requiring surgical intervention. The principal treatment options include transaortic septal myectomy (the Morrow procedure), less invasive transapical septal myectomy, or alcohol septal ablation. The objective of surgical treatment is the resection of a portion of the hypertrophied interventricular septum that causes left ventricular outflow tract (LVOT) obstruction and impairs normal blood flow from the heart into the aorta.

The histological appearance of resected interventricular septal tissue in HCM is characterized by myofiber disarray with hypertrophic cardiomyocytes exhibiting nuclear polymorphism, including nuclei of diverse shapes. Typically, these nuclei are deformed and surrounded by a perinuclear halo with glycogen accumulation in these regions. Microscopic examination also reveals cardiomyocyte disarray, clustering of mitochondria, and scarring of nuclear membranes [14, 17]. In addition, changes involve the walls of intramural arterioles, which show medial hypertrophy and intimal hyperplasia, leading to luminal narrowing and, presumably, reduced overall coronary capacity, thereby contributing to dystrophic morphological alterations. Contemporary histological and electron microscopy studies examining myocardial biopsies in various heart diseases – congenital and acquired defects, AH, and CAD – describe similar morphological patterns. Thus, efforts to differentiate these conditions from HCM based solely on morphology have not yielded definitive criteria [1]. Therefore, the morphological changes described in the literature for HCM cannot be considered strictly specific.

Current international guidelines highlight the importance of a multimodal approach to diagnosis and management, including genetic testing [7]. Genetically, HCM is predominantly inherited in an autosomal dominant manner and results from mutations in genes encoding sarcomeric proteins responsible for myocardial contraction. The most frequently implicated genes include MYH7 (β-myosin heavy chain), MYBPC3 (cardiac myosin-binding protein C), TNNT2 (troponin T), TNNI3 (troponin I), TPM1 (tropomyosin), MYL2, MYL3, and ACTC1 [4, 16, 19].

Mutations in MYH7 and MYBPC3 account for up to 60-70% of all genetically confirmed HCM cases [16, 19]. They are typically associated with pronounced asymmetric septal hypertrophy and substantial cardiomyocyte disarray, reflecting profound disruption of myocardial architecture [18]. Despite known associations between individual genes and morphological phenotypes, the direct correlation between genotype and structural manifestations remains incomplete. Carriers of the same mutations often exhibit a wide range of morphological and clinical features, indicating the influence of gene expression modifiers, epigenetic mechanisms, and hemodynamic factors on the development of the pathological phenotype [9, 11].

One of the key challenges in contemporary HCM morphology is the absence of standardized morphometric criteria for assessing histological changes. Different studies employ varying quantitative parameters to evaluate cardiomyocyte disarray, fibrosis severity, and cellular hypertrophy, complicating cross-study comparisons and hindering the development of unified diagnostic scales [13]. Furthermore, many morphological studies rely on limited clinical samples and do not always include genetically confirmed diagnoses, reducing the reliability of conclusions regarding genotype–phenotype correlations [15].

This study aims to determine morphological patterns according to genetic status by performing histological examination of myocardial tissue obtained during septal myectomy in four patients with obstructive hypertrophic cardiomyopathy.

Materials and Methods

The study was conducted at the Research Institute of Cardiology and Internal Diseases between 2020 and 2021. Four consecutive patients undergoing surgery for obstructive hypertrophic cardiomyopathy with available myocardial tissue and genetic data were included. Resected myocardial tissue underwent morphological analysis, and molecular genetic testing for hypertrophic cardiomyopathy – associated mutations was performed. A descriptive comparative analysis was used to assess differences in morphological and genetic findings; no formal statistical analysis was conducted due to the small sample size.

Morphological analysis

Following surgical septal myectomy, the resected interventricular septal myocardium was fixed in 10% buffered formalin (pH 7.2-7.4) for 24 hours and subsequently processed manually in isopropyl alcohol through a series of six graded steps, each for 60 minutes. The tissue was then embedded in paraffin using a Leica EG 1150 H embedding station to create paraffin blocks. Sections of 5 μm thickness were cut using a Leica RM 2125 RT microtome.

For general morphological assessment, sections (4-5 μm) were stained manually with Mayer's hematoxylin and 1% aqueous eosin (H&E, hematoxylin and eosin staining) to evaluate nuclear and cytoplasmic changes in cardiomyocytes, tissue architecture, and cellular disorganization. A periodic acid-Schiff (PAS) reaction was performed to detect glycogen accumulation, including its perinuclear distribution. PAS-positive structures, indicative of carbohydrate degeneration and energy metabolism disorders, were observed as cytoplasmic regions or extracellular elements stained pink-purple with varying intensity. Staining intensity and distribution were assessed semi-quantitatively using light microscopy at ×10 and ×40 magnifications.

Masson's Trichrome staining was used to differentiate muscle and connective tissue and to assess perivascular and pericellular fibrosis (collagen fibers stained blue/green, muscle fibers stained red). After staining, sections were mounted under coverslips using Biomount medium to

ensure long-term preservation and prevent fading. Microscopy and photographic documentation were performed using a Leica DM 1000 microscope.

Histological analysis of all prepared slides was conducted in the pathomorphology laboratory of the Research Institute of Cardiology and Internal Disease.

Genetic Testing

Molecular genetic testing was performed at the DLE Laboratory (Genética Humana, Doenças Raras e Genômica, Brazil) (https://www.dle.com.br/). Mutation profiling was conducted using next-generation sequencing (NGS), which targets specific regions of isolated DNA followed by massively parallel sequencing. This method offers high sensitivity for detecting single-nucleotide variants and small insertion-deletion variants in genes associated with HCM. The genetic panel employed in this study included 17 key genes implicated in the development of HCM: ACTC1, DES, FLNC, GLA, LAMP2, MYBPC3, MYH7, MYL2, MYL3, PLN, PRKAG2, PTPN11, TNNC1, TNNI3, TNNT2, TPM1, and TTR.

Prior to participation, all patients provided written informed consent, detailing the study objectives and procedural steps. Following consent, standard forms were completed, recording each patient's full name, date, and location of biopsy, and the attending physician's information (full name, phone number, and email address).

Biopsy samples were collected from all patients using the dried blood spot (DBS) method. Under sterile conditions, 1 ml of venous blood was drawn and evenly applied to diagnostic cards using a stencil, without exceeding the designated areas. The cards were left to dry at room temperature, protected from light, for three hours. Once dried, the diagnostic cards and signed consent forms were placed in specialized shipping envelopes and sent to the DLE Laboratory for NGS analysis.

For morphogenetic comparison, four patients were selected from those undergoing surgery for obstructive hypertrophic cardiomyopathy with known genetic testing results. The cohort included: one patient with a single identified mutation, one with three mutational variants, one with a negative test result, and one patient with unknown genetic status, used as a blinded control.

Ethics approval and consent to participate

This study was conducted in accordance with ethical standards and was approved by the Bioethical Commission of Kazakh National Medical University named after S.D. Asfendiyarov (Protocol #1071, dated March 31, 2021). Written informed consent was obtained from all participants.

Results

Histological analysis of myocardial tissue obtained after septal myectomy in four patients with OHCM revealed morphological differences that corresponded to the patients' genetic status (Fig. 1 - 4).

Morphological features of a MYH7 Gene-positive patient

Myocardial morphology of a MYH7 gene-positive patient (29 years old at the time of the study) is shown in Figures 1a–g.

H&E staining (Fig. 1a–b) demonstrated pronounced disruption of myocardial architecture, characterized by nuclear polymorphism, chaotic arrangement of muscle fibers with areas of side-to-side interweaving, the presence of multiple intermuscular bridges, end-to-side cardiomyocyte fusion, and longitudinally and transversely sheared muscle fiber bundles, resulting in a lobular myocardial structure (Fig. 1a, green arrow).

At ×40 magnification (Fig. 1b), marked multidirectionality of muscle fiber distribution was observed, including areas of interweaving, adhesion, and branching. Several cardiomyocytes appeared fragmented and dissociated, exhibiting nuclear polymorphism and uneven chromatin distribution (white arrows).

PAS staining (Fig. 1c) revealed enlarged, polymorphic nuclei with perinuclear glycogen accumulation (gray arrow). Masson's Trichrome staining (Fig. 1d) showed a fine, delicate network of perivascular and pericellular collagen fibers forming a "web-like" structure (black arrow) against a background of enlarged, randomly oriented cardiomyocytes (red arrow).

Morphological features in a gene-negative patient

A gene-negative patient (63 years old) (Fig. 2a-d) exhibited uneven hypertrophy of cardiomyocytes (Fig. 2a, green arrow), thickening of the arteriolar wall due to asymmetric hypertrophy of the muscular layer (Fig. 2a, blue arrow), and focal perivascular proliferation of course, mature connective tissue (Fig. 2a, black arrow). Some cardiomyocytes showed loss of transverse striations, foci of myocytolysis, and areas of cellular "melting".

At ×40 magnification (Fig. 2b), cardiomyocytes were arranged in a relatively orderly pattern, with no nuclear polymorphism observed (brown arrow). A few cardiomyocytes were fragmented and dissociated, but chromatin distribution remained uniform. Focal myocytolysis and small perivascular lymphocytic infiltrates were also noted (yellow arrow).

PAS staining (Fig. 2c) demonstrated enlarged nuclei with perinuclear glycogen accumulation (gray arrow). Masson's Trichrome staining (Fig. 2d) highlighted coarse fibrous connective tissue in perivascular foci (blue staining, black arrow) and red-stained, enlarged, orderly arranged cardiomyocytes (red arrow).

Morphological features in a MYH7, GLA, and PRKAG2 Gene-Positive Patient

A patient with positive molecular genetic testing for the MYH7, GLA, and PRKAG2 genes (female, 49 years old) exhibited the following myocardial morphological changes (Fig. 3a–d).

H&E staining (Fig. 3a) demonstrated markedly disorganized myocardial architecture, with chaotic muscle fiber distribution, areas of side-to-side interweaving, and multiple intermuscular bridges. Fibers were oriented in multiple directions, showing local adhesion, branching, and parquet-like interweaving. Cardiomyocytes were interconnected end-to-end, forming both longitudinally and transversely sheared muscle fiber bundles (Fig. 3a, green arrow).

An increased stromal component was observed due to the proliferation of mature connective tissue, predominantly perivascular and pericellular, forming a reticular network. Scattered lymphocytic infiltration was also noted in the stroma (Fig. 3a, yellow arrow). Some cardiomyocytes displayed uneven fragmentation, with foci of myocytolysis and areas of cellular "melting."

At higher magnification (×40, Fig. 3b), pronounced nuclear polymorphism was observed in cardiomyocytes, with uneven chromatin distribution and the appearance of characteristic “holey” nuclei (white arrows).

PAS staining (Fig. 3c) revealed enlarged and polymorphic nuclei with prominent perinuclear glycogen accumulation (gray arrow). Masson’s Trichrome staining (Fig. 3d) highlighted fine-fibrous collagen forming the perivascular and pericellular network (blue staining, black arrow) and intense red staining of enlarged, randomly arranged cardiomyocytes (red arrow).

Morphological features in a control patient with unknown genetic status

Histological examination of the surgical specimen from a patient with unknown genetic status (male, 33 years old) revealed the following myocardial changes (Fig. 4a-d).

Cardiomyocyte hypertrophy was unevenly expressed, but the myocardial fibers were generally arranged in an orderly fashion (Fig. 4a, green arrow). Perivascular and pericellular proliferation of coarse, mature connective tissue forming a reticular network was observed in the stroma (Fig. 4a, black arrow).

At higher magnification (×40, Fig. 4b), cardiomyocytes retained an organized architecture, and no nuclear polymorphism was detected. Some cells showed fragmentation and dissociation, but chromatin distribution remained uniform, and nuclear polymorphism was absent.

PAS staining (Fig. 4c) demonstrated enlarged nuclei with perinuclear glycogen accumulation (gray arrow). Masson’s Trichrome staining (Fig. 4d) highlighted blue-stained connective tissue forming a perivascular meshwork and red-stained, enlarged, orderly arranged cardiomyocytes (red arrow).

Comparative analysis of the histological specimens from four patients with a clinical diagnosis of OHCM revealed the following features (Table 1)

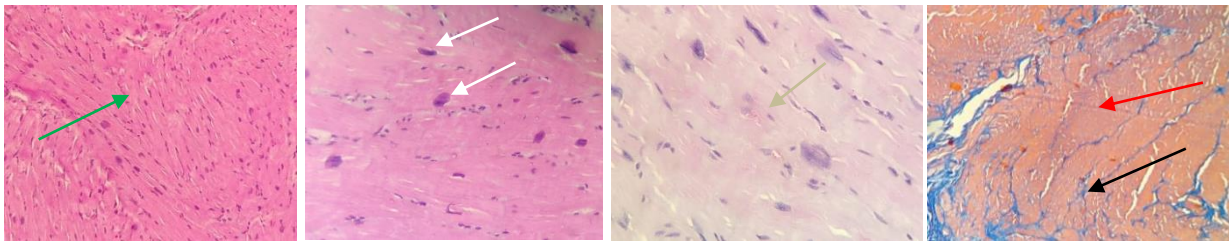

Figure 1a *Figure 1b* *Figure 1c* *Figure 1d*

Figure 1. Myocardial architectural abnormalities in a MYH7 gene-positive patient (male, 29 y): H&E staining ×10 (a), ×40 (b); PAS staining (c); Masson’s Trichrome staining (d).

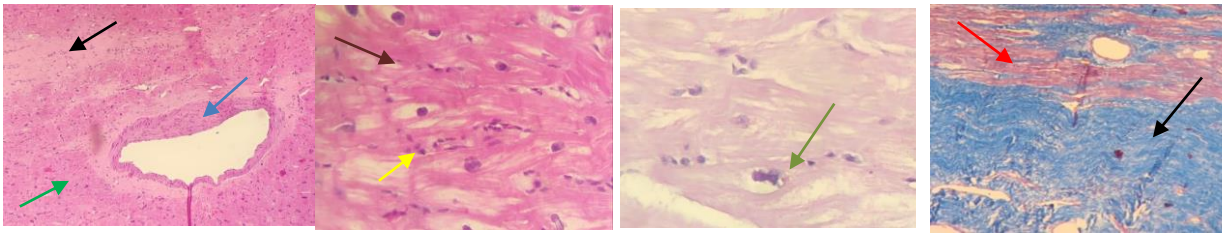

Figure 2a *Figure 2b* *Figure 2c* *Figure 2d*

Figure 2. Disruption of myocardial architecture in a gene-negative patient (male, 63 y): H&E staining ×10 (a), ×40 (b); PAS staining (c); Masson’s Trichrome staining (d).

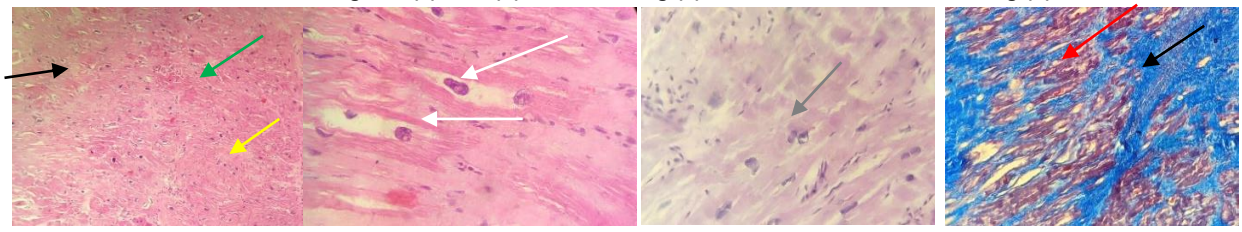

Figure 3a *Figure 3b* *Figure 3c* *Figure 3d*

Figure 3. Myocardial architectural abnormalities in a MYH7, GLA, and PRKAG2 gene-positive patient (female, 49 y): H&E staining ×10 (a), ×40 (b); PAS staining (c); Masson’s Trichrome staining (d).

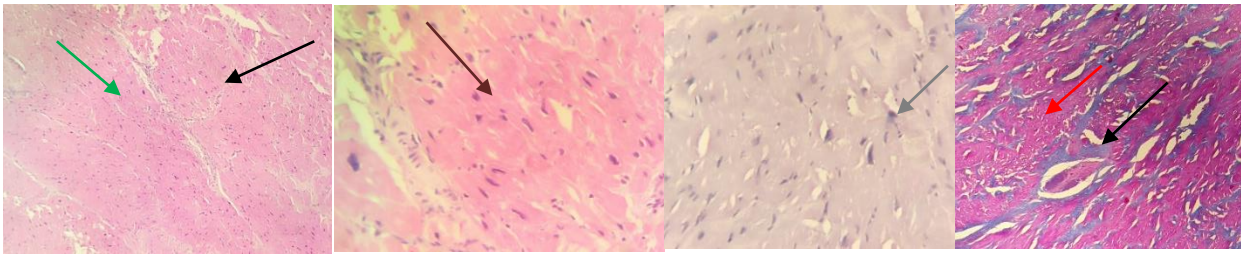

Figure 4a *Figure 4b* *Figure 4c* *Figure 4d*

Figure 4. Myocardial architectural changes in a control patient with unknown genetic status (male, 33 years old): H&E staining ×10 (a), ×40 (b); PAS staining (c); Masson’s Trichrome staining (d).

Table 1.

Comparative characteristics of myocardial morphological changes in patients with acute myocardial infarction depending on genetic status.

Genetic status Morphological features	MYH7 (+) (male, 29 y)	MYH7, GLA, PRKAG2 (+) (female, 49 y)	Unknown gene status - (male, 33 y)	Gene (-) (male, 68 y)
Cardiomyocyte hypertrophy with structural disorganization	+ Chaotic cardiomyocyte arrangement, “lobular” myocardium	+ Chaotic cardiomyocyte arrangement, “parquet-like” pattern	+ Ordered cardiomyocyte arrangement with uneven hypertrophy	+ Ordered cardiomyocyte arrangement with uneven hypertrophy
Nuclear polymorphism of cardiomyocytes	+	+ “holey” nuclei	-	-
Myocardial fibrosis	+ Fine-fibrous, delicate, perivascular, and pericellular, "web-like" type	+ Perivascular and pericellular, reticular	+ Perivascular and pericellular, reticular	+ Coarse fibrous, perivascular and focal
PAS staining	+	+	+ Mild	+
Vascular changes	-	-	-	+ Arteriolar wall hypertrophy
Pathological infiltration	-	+ Scattered, isolated lymphocytes	-	+ Focal lymphocytic infiltration
Cardiomyocyte dystrophy	+ Fine-droplet lipid and fine-granular dystrophy	+ Fine-droplet lipid and fine-granular dystrophy	+ Fine-droplet lipid and fine-granular dystrophy	+ Parenchymal fine-granular dystrophy

All patients demonstrated cardiomyocyte hypertrophy, parenchymal cardiomyocyte degeneration, positive PAS staining, and myocardial fibrosis. Patients with identified pathogenic mutations (MYH7; MYH7 + GLA + PRKAG2) exhibited more pronounced cardiomyocyte disorganization and nuclear polymorphism. Notably, the patient with three positive genetic mutations showed coarse-fibrous (dense) myocardial fibrosis, in contrast to the fine, delicate “web-like” fibrosis observed in the patient with a single genetic variant. Additionally, the patient with MYH7 + GLA + PRKAG2 exhibited the presence of “holey” nuclei in cardiomyocytes.

In contrast, the gene-negative patient and the control patient displayed a more orderly myocardial architecture, with uneven cardiomyocyte hypertrophy. In the control patient (male, 63 y), coarse-fibrous focal fibrosis was observed alongside focal lymphocytic infiltration and hypertrophy of the arteriolar muscular layer, which may reflect ischemic cardiomyopathy.

The primary distinction between genetically positive and negative patients was reflected in myocardial morphology: genetically positive patients exhibited pronounced chaotic cardiomyocyte arrangement, nuclear polymorphism, and fine-fibrous perivascular and pericellular fibrosis, whereas genetically negative patients showed orderly cardiomyocyte arrangement, absence of nuclear polymorphism, and coarse-fibrous, perivascular, and focal myocardial fibrosis.

Discussion

This descriptive study aimed to identify myocardial morphological features in four patients with obstructive hypertrophic cardiomyopathy undergoing septal myectomy, with consideration of their genetic profiles for key HCM-associated genes.

Morphological Characteristics and Relationship with Genotype

The observed morphological changes demonstrate a clear dependence of myocardial structure on the presence of pathogenic mutations in the MYH7, GLA, and PRKAG2 genes. Patients with genetically confirmed mutations exhibited pronounced alterations in myocardial architecture, including chaotic cardiomyocyte arrangement, nuclear polymorphism, intermuscular bridge formation, and parquet-like fiber disorganization. These features reflect the structural disorientation of myocardial fibers characteristic of hereditary HCM and are recognized morphological markers of sarcomeric mutations [6].

Furthermore, gene-positive patients demonstrated “holey” cardiomyocyte nuclei and perinuclear glycogen accumulation on PAS staining, indicative of disrupted carbohydrate metabolism and cellular energy degeneration, which is particularly characteristic of metabolic HCM variants, such as PRKAG2 [3]. Perivascular and pericellular fine-fibrous “spiderweb” fibrosis in these patients may represent compensatory myocardial remodeling in response to chronic metabolic stress.

In contrast, patients without identified mutations displayed relatively ordered myocardial architecture, moderate cardiomyocyte hypertrophy, and focal coarse-

fibrous fibrosis, likely secondary to ischemic or hemodynamic factors, including age-related changes. The absence of pronounced nuclear polymorphism and metabolic alterations supports the predominantly secondary nature of these morphological changes.

Data Integration and Clinical Significance

These findings are consistent with previous studies demonstrating disrupted fiber organization, interstitial fibrotic replacement, and nuclear polymorphism as hallmarks of genetically determined HCM [20]. Fine-fibrous reticular fibrosis and metabolic markers (glycogen accumulation, "holey" nuclei) are characteristic of metabolic/genetic subtypes, whereas coarse focal fibrosis and preserved cardiomyocyte architecture are more typical of non-genetic secondary forms.

From a clinical perspective, such morphological patterns hold diagnostic and prognostic significance. Their presence may serve as an indirect indicator of a hereditary form of HCM, which is particularly valuable in settings with limited access to molecular genetic testing. These patterns aid in distinguishing primary (hereditary) from secondary (hemodynamic or ischemic) forms of HCM and may indicate an increased risk of disease progression and adverse outcomes. Early identification of at-risk asymptomatic individuals via molecular and clinical cascade screening, along with optimal risk stratification for sudden cardiac death, can facilitate timely preventive interventions to mitigate irreversible myocardial remodeling [5, 8, 16].

Integrating morphological analysis with genetic and clinical assessments enables more accurate individualized risk stratification and management of HCM patients and their relatives. This approach underscores the importance of combining histopathological, genetic, and clinical data when interpreting identified variants. Thus, the observed differences reinforce the notion that myocardial morphological features can serve as indirect markers of genetically determined forms of hypertrophic cardiomyopathy, particularly in the absence of molecular genetic testing.

Strengths and Limitations

This study provides valuable insights into the relationship between myocardial morphological changes and genetic variants in patients with obstructive hypertrophic cardiomyopathy in Kazakhstan. Analysis of these well-characterized cases highlights genotype–phenotype correlations, demonstrating how particular genetic variants manifest as distinct structural myocardial patterns. These observations enhance understanding of disease heterogeneity, support the identification of patients likely to harbor pathogenic mutations, and may inform risk stratification and management of both patients and their first-degree relatives.

However, several limitations should be acknowledged. The descriptive nature of the study and the small sample size (four patients) limit the generalizability of the findings, reflecting the high costs and logistical challenges of combined morphological and genetic testing. Additionally, the interpretation of results may be affected by the routine collection and storage of biopsy material prior to analysis. Finally, morphological data were obtained exclusively from myectomy specimens, without longitudinal or dynamic clinical follow-up. Further studies with larger cohorts and integrated clinical, genetic, and morphological analyses are warranted to validate these patterns and clarify their prognostic significance.

Future directions

Future research should expand the patient cohort, implement quantitative fibrosis assessment, and investigate correlations between genotype and phenotype. Enlarging the sample size and applying advanced sequencing technologies may reveal novel disease markers. Integrating morphological, genetic, and clinical data will provide a foundation for developing personalized diagnostic and therapeutic strategies for HCM patients and their families.

Conclusion

Overall, the morphological data indicate that myocardial structure in OHCM patients varies according to genetic status. Distinct patterns – disrupted myocardial architecture, nuclear alterations, metabolic markers, and fibrosis characteristics – can complement clinical and genetic diagnostics. These findings underscore the importance of integrating histopathology, genetics, and clinical information to guide individualized management of HCM. Further studies with larger cohorts and high-sensitivity genetic analyses are needed to validate these patterns and deepen understanding of HCM pathogenesis.

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