ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Mulibrey Nanism: A Case with Heart Failure

Mulibrey Nanism: Bir Kalp Yetersizliği Olgusu

ABSTRACT

Mulibrey Nanism is a rare genetic disorder characterized by a variety of systemic manifestations, including cardiac involvement. We report the case of a 26-year-old male who underwent partial pericardiectomy for constrictive pericarditis at age 4 and presented to our cardiology clinic with heart failure symptoms. Examination revealed dysmorphic features characteristic of Mulibrey Nanism such as short stature, macrocephaly, and hypertelorism. Genetic testing identified a homozygous likely pathogenic mutation in the *TRIM37* gene. The patient's heart failure was managed through a multidisciplinary approach, involving consultations with various specialties to address and diagnose the syndrome's complex multisystem pathologies. This case underscores the importance of including Mulibrey Nanism in the differential diagnosis of patients with a history of constrictive pericarditis at an early age and dysmorphic features, as well as the necessity of a multidisciplinary approach to manage the diverse manifestations of this rare genetic disorder.

Keywords: Arrhythmias, atrial fibrillation, constrictive pericarditis, heart failure, Mulibrey nanism, pericarditis

ÖZET

Mulibrey Nanism kardiyak tutulum da dahil birçok sistemik bulguyla ortaya çıkabilen nadir bir genetik hastalıktır. Bu olgu bildirisinde kliniğimize kalp yetersizliği semptomları ile başvuran, 4 yaşında konstriktif perikardit sebebiyle parsiyel perikardiyektomi ameliyatı geçirmiş 26 yaşındaki erkek hastayı sunmaktayız. Hastanın detaylı muayenesinde Mulibrey Nanism ile uyumlu bulgular olan kısa boy, hipertelorizm ve makrosefaliye sahip olduğunu gözlemledik. Genetik testler sonucu *TRIM37* geninde homozigot patojen mutasyon saptandı. Hastanın kalp yetersizliği multidisipliner bir yaklaşım ile tedavi edildi, ayrıca hastalığın farklı sistemik patolojilerinin tanı ve tedavisi için birçok uzmanlık alanına konsültasyonlarda bulunuldu. Bu olgu özellikle dismorfik bulguları olan ve genç yaşta konstriktif perikardit öyküsü olan hastalarda Mulibrey Nanism sendromunun ayırıcı tanıda bulunması gerektiğine ve bu tip hastaların multidisipliner bir yaklaşım ile tanı ve tedavisinin sağlanmasının gerekliliğine dikkat çekmektedir.

Anahtar Kelimeler: Aritmiler, atriyal fibrilasyon, konstriktif perikardit, kalp yetmezliği, Mulibrey nanizmi, perikardit

CASE REPORT
OLGU SUNUMU

Ahmet Yiğit Temizhan[1]
Mehmet Numan Çolakoğlu[2]
Meryem Kara[1]
Etga Köprücü[1]
Ahmet Korkmaz[1]
Serkan Topaloğlu[1]
Feride Pınar Altay[3]
Ekin Yiğit Köroğlu[3]
İnci Elif Erbahçeci Timur[4]
Nagihan Uğurlu[4]
Ahmet Temizhan[1]

[1]*Department of Cardiology, Ankara Bilkent City Hospital, Ankara, Türkiye*
[2]*Department of Radiology, Ankara Bilkent City Hospital, Ankara, Türkiye*
[3]*Department of Endocrinology, Ankara Bilkent City Hospital, Ankara, Türkiye*
[4]*Department of Ophthalmology, Ankara Bilkent City Hospital, Ankara, Türkiye*

Corresponding author:
Ahmet Yiğit Temizhan
✉ ytemizhan@windowslive.com

Received: July 02, 2023
Accepted: November 02, 2023

Cite this article as: Temizhan AY, Çolakoğlu MN, Kara M, et al. Mulibrey nanism: A case with heart failure. *Turk Kardiyol Dern Ars.* 2024;52(6):464-467.

DOI:10.5543/tkda.2023.95443

Mulibrey (muscle, liver, brain, eye) Nanism, an autosomal recessive syndrome, is characterized by a triangular face, often accompanied by macrocephaly, gracility, muscular hypotonia, a distinctive voice, an enlarged liver, elevated venous pressure, and yellowish dots and pigment dispersion in the ocular fundi. Pericardial constriction is a common feature of this syndrome, and early pericardiectomy has been linked to improved mortality.[1,2] Furthermore, congestive heart failure is a major determinant of prognosis.[3] Consequently, cardiological evaluation, treatment, and follow-up are crucial for this patient group.

The syndrome is associated with the *TRIM37* gene on chromosome 17q22-q23, which encodes the peroxisomal protein *TRIM37*. This protein is a potential target for specific modulators in ubiquitin-dependent protein degradation.[4] The exact prevalence of the syndrome is unknown, with approximately 150 cases reported worldwide.[5]

Case Report

A 26-year-old male was referred to the cardiology outpatient clinic with dyspnea, bilateral leg edema, massive ascites, and a significant reduction in exercise capacity over the last month. The patient reported mild effort limitation, dyspnea, and abdominal bloating for five years; however, he did not seek cardiology consultation until four months ago when his symptoms worsened. He worked at a grocery store but had been unable to work for the last month due to his symptoms. Four months prior he was diagnosed with heart failure with a mildly reduced ejection fraction at the cardiology outpatient clinic, and prescribed furosemide, carvedilol, and spironolactone. He underwent a partial pericardiectomy at age four due to constrictive pericarditis after being admitted to pediatrics with severe dyspnea and cyanosis. Six months ago, he underwent penile revascularization surgery for erectile dysfunction and was prescribed acetylsalicylic acid and dipyridamole as antiaggregants. He had been taking acetylsalicylic acid, dipyridamole, spironolactone, and furosemide 40 mg twice a day but discontinued carvedilol due to dizziness.

On physical examination, he was 145 cm tall and weighed 55 kilograms, with a high-pitched voice and characteristic signs of Mulibrey Nanism (Figure 1): hypertelorism, macrocephaly, broad forehead, low nasal bridge, facial triangularity, hepatomegaly, bilateral pretibial edema, massive ascites, pericardial friction rub, jugular venous distension, and pulmonary rales up to the mid lung segments. Mulibrey Nanism syndrome was suspected, and the patient was referred for genetic testing of the *TRIM37* gene via whole genome sequencing. DNA was isolated from peripheral blood, and all exons and exon-intron boundaries were sequenced using the Illumina MiSeq next-generation sequencing system (Illumina, USA) and confirmed with Sanger sequencing. Annotated variants are classified according to American College of Medical Genetics and Genomics (ACMG) criteria using in-silico tools and are thoroughly investigated through online databases such as HGMD, Mutation Taster, SIFT, Polyphen, and ClinVAR. We identified a causative homozygous *TRIM37* mutation in the proband, c.1894_1895delGA (p.Glu632LysfsTer25), which results in a premature stop codon. His parents were not related, and he had no relatives with a similar phenotype; however, genetic testing was recommended for his first-degree relatives due to the oncogenic potential of the gene in question. Nonetheless, none of the relatives agreed to testing. The patient consulted with multiple specialties regarding the manifestations of Mulibrey Nanism Syndrome. An ophthalmological consultation confirmed bilateral yellow discoloration and yellow dots in the mid-periphery of the retina (Figure 2). An endocrinological consultation diagnosed him with type 2 diabetes mellitus, hypothyroidism, hypergonadotropic hypogonadism, and growth hormone deficiency. His renal ultrasonography revealed renal cysts.

ABBREVIATIONS

ACMG	American College of Medical Genetics and Genomics
ECG	Electrocardiogram
MRI	Magnetic resonance imaging
NT-proBNP	N-terminal brain natriuretic peptide
PASP	Pulmonary arterial systolic pressure
TAPSE	Tricuspid annular plane systolic excursion

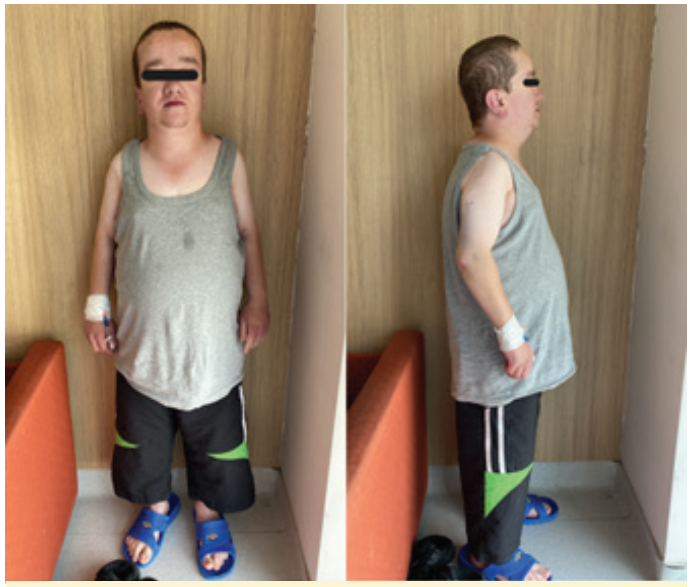

Figure 1. Characteristic findings of Mulibrey Nanism: hypertelorism, macrocephaly, broad forehead, low nasal bridge, facial triangularity, hepatomegaly, bilateral pretibial edema, and ascites.

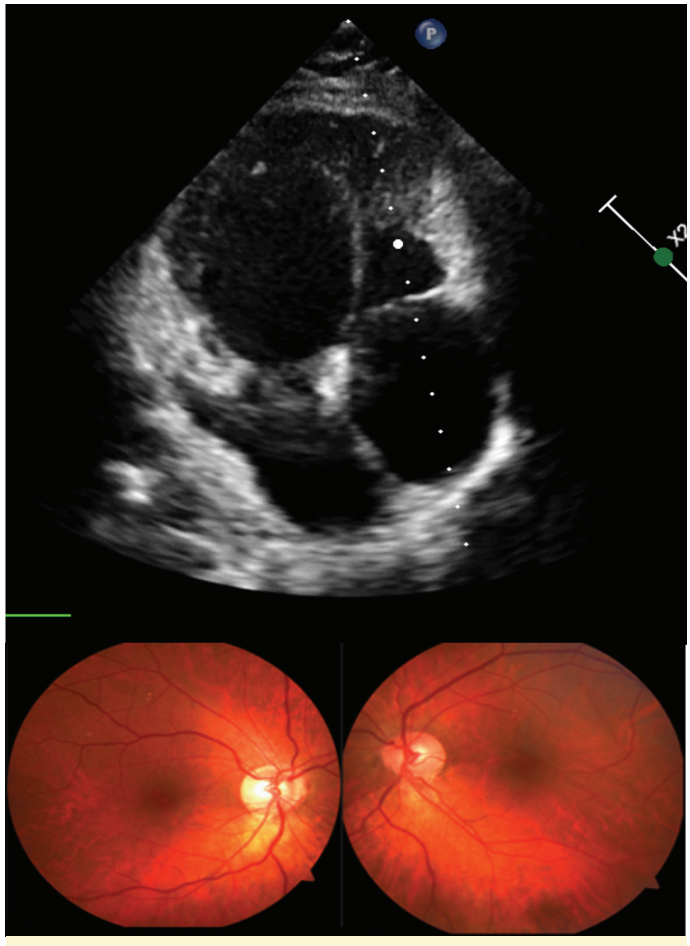

Figure 2. Echocardiography revealing a highly echogenic, thickened pericardium attached to the posterior left atrium and left ventricle. Fundoscopy shows bilateral yellow discoloration and yellow dots in the mid-periphery of the retina.

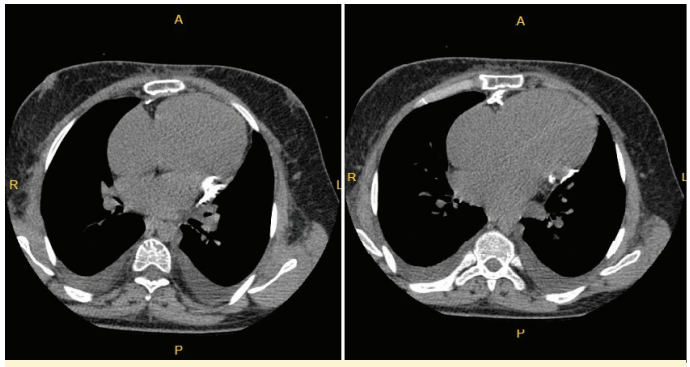

Figure 3. Contrast-enhanced cardiac CT scan displaying residual calcified constrictive pericardium attached to the posterior left atrium, extending to the posterior left ventricle.

Upon admission, his bloodwork showed an elevated N-terminal brain natriuretic peptide (NT-proBNP) level of 720 ng/dL, with no other significant findings. His admission electrocardiogram (ECG) displayed a sinus rhythm with a heart rate of 88 bpm. Transthoracic echocardiography indicated interventricular and posterior wall thickness of 10 mm, a left atrial diameter of 38 mm, and mildly dilated right atrium and ventricle (Figure 2). The left ventricular ejection fraction was 45%. Doppler velocity tracing showed mild mitral regurgitation, second-degree tricuspid regurgitation, and an estimated pulmonary arterial systolic pressure (PASP) of 42 mmHg. His right ventricular function was slightly impaired, with a tricuspid annular plane systolic excursion (TAPSE) of 9 cm/s. He was started on IV furosemide treatment. On the night of admission, he reported palpitations and dyspnea, and an ECG showed atrial flutter. IV metoprolol tartrate (5 mg/mL) was administered, and oral treatment with bisoprolol 5 mg along with anticoagulation using warfarin was initiated. During hospitalization, 600 mg of IV furosemide was combined with 25 mg of spironolactone, 500 mg of acetazolamide, and 10 mg of dapagliflozin given orally, but adequate diuresis was not achieved. Therefore, suspecting renal tamponade caused by massive ascites, we decided to perform a paracentesis to relieve the pressure on the renal capsule.[6] This procedure was successfully completed, and 4 liters of fluid were drained over two days, after which adequate diuresis was achieved. As the congestion began to resolve, a decision was made to perform an atrial flutter ablation because the patient was highly symptomatic. A transesophageal echocardiography was conducted to exclude an intracardiac thrombus; however, an artifact caused by the pericardium attached to the posterior atrium rendered the imaging non-diagnostic. Cardiac magnetic resonance imaging (MRI) was considered, but the patient could not undergo the procedure due to claustrophobia. Consequently, we performed a cardiac computed tomography scan to exclude any thrombus formation, which confirmed the absence of a thrombus and revealed remnants of calcified constrictive pericardium attached to the posterior left atrium and left ventricle from a previous pericardiectomy (Figure 3). After excluding thrombus formation, ablation of the cavotricuspid isthmus was carried out successfully, significantly improving the patient's symptoms. He was discharged the next day, weighing 38 kilograms and symptom-free. His discharge prescription included spironolactone 75 mg, acetazolamide 500 mg, dapagliflozin 10 mg, bisoprolol 5 mg, levothyroxine 100 mcg, warfarin 2.5 mg once daily, and furosemide 80 mg twice daily, all taken orally. Three months post-discharge, the patient was free of ascites with an oral diuretic regimen, maintained a class 1 functional capacity, and had an NT-proBNP value of 99 ng/dL. Control echocardiography showed complete recovery of left ventricular function, some improvement in right ventricular function, mild tricuspid regurgitation, a PASP of 29 mmHg, and normal right ventricular systolic function. The patient provided informed consent for this case report.

Discussion

During the patient's medical examination, he mentioned a previous diagnosis of achondroplasia as the cause of his short stature and dysmorphic features. However, given his history of constrictive pericarditis from early childhood, we considered another clinical entity that could cause such specific pathology early in life, leading to the diagnosis. The gene mutation detected in the patient (c.1894_1895delGA(p.E632Kfs*25) (p.Glu632LysfsTer25)) was also found in another Turkish Mulibrey Nanism patient[7] whose parents carried the same mutation in a heterozygous form, leading to a homozygous mutation in the patient in question. They were first cousins; however, our patient's parents denied any degree of relativity. Since they refused genetic testing, it remains uncertain whether the mutation was inherited from the parents or is a de novo mutation. The mutation is significant as it leads to haploinsufficiency by inducing an early stop codon. Moreover, carriers of this gene should be screened for malignancies due to the association of the mutation with a wide variety of tumors.[4] Although the precise pathophysiology remains unclear, the constrictive pericarditis resulting from fibrosis in the pericardium may be linked to altered ubiquitin-dependent protein degradation caused by the mutation in the *TRIM37* gene.[4]

Regarding the medical management of the patient, he experienced congestion resistant to diuretics, which was attributed to right ventricular dysfunction, as indicated by echocardiographic findings. Consequently, we explored alternative methods to alleviate congestion. In this case, we suspected renal tamponade due to massive ascites in the abdomen, but refrained from performing paracentesis until after maximizing the diuretic combination, which eventually led to successful diuresis once the pressure overload on the kidneys was relieved. Additionally, restoring sinus rhythm was crucial in managing this case. We opted for anticoagulation with warfarin due to concerns about the bleeding risks associated with other oral anticoagulants, given that hepatopathy is a recognized feature of Mulibrey Nanism.[8]

Conclusion

Mulibrey Nanism is a distinct congenital syndrome where constrictive pericarditis significantly influences the prognosis. Nonetheless, after pericardiectomy, surviving adult patients may present with symptoms of heart failure, which require a multidisciplinary treatment approach.

Informed Consent: The patient provided informed consent for the case report.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept –A.Y.T., M.N.Ç., A.T.; Design – A.Y.T., M.N.Ç.; Supervision – A.T.; Materials – A.Y.T., A.T.; Data Collection and/or Processing – M.K., E.K., A.K., S.T., F.P.A., E.Y.K., İ.E.T.; Analysis and/or Interpretation – A.Y.T., M.N.Ç.; Literature Review – A.Y.T., M.N.Ç.; Writing – A.Y.T., M.N.Ç.; Critical Review – A.T.

Use of AI for Writing Assistance: QuillBot was used to check spelling mistakes.

Conflict of Interest: The corresponding author declare that the authors have no conflicts of interest to declare.

Funding: The authors declared that this study received no financial support.

References

1. Perheentupa J, Autio S, Leisti S, Raitta C, Tuuteri L. Mulibrey nanism, an autosomal recessive syndrome with pericardial constriction. *Lancet.* 1973;2(7825):351–355. [CrossRef]
2. Cordova Sanchez A, Vasigh M, Carhart R. The importance of early pericardiectomy in Mulibrey Nanism syndrome, a case report. *J Investig Med High Impact Case Rep.* 2022;10:23247096221077816. [CrossRef]
3. Sarkola T, Lipsanen-Nyman M, Jalanko H, Jokinen E. Pericardial constriction and myocardial restriction in pediatric Mulibrey Nanism: A complex disease with diastolic dysfunction. *CJC Open.* 2021;4(1):28–36. [CrossRef]
4. Brigant B, Metzinger-Le Meuth V, Rochette J, Metzinger L. TRIMming down to TRIM37: Relevance to inflammation, cardiovascular disorders, and cancer in Mulibrey Nanism. *Int J Mol Sci.* 2018;20(1):67. [CrossRef]
5. OrphaNet. Mulibrey Nanism. Updated January 2019. Accessed May 22, 2024. https://www.orpha.net/en/disease/detail/2576#:~:text=Mulibrey%20nanism%20(MUL)%20manifests%20neonatally,Psychomotor%20development%20is%20mainly%20normal.
6. Boorsma EM, Ter Maaten JM, Voors AA, van Veldhuisen DJ. Renal compression in heart failure: The Renal Tamponade hypothesis. *JACC Heart Fail.* 2022;10(3):175–183. [CrossRef]
7. Doğancı T, Yüksel Konuk BE, Alpan N, et al. A novel mutation in TRIM37 is associated with mulibrey nanism in a Turkish boy. *Clin Dysmorphol.* 2007;16(3):173–176. [CrossRef]
8. Sivunen J, Karlberg S, Kivisaari R, et al. Liver pathology and biochemistry in patients with mutations in TRIM37 gene (Mulibrey Nanism). *Liver Int.* 2022;42(6):1369–1378. [CrossRef]