CASE REPORT

Old-Age Onset Progressive Cardiac Contractile Dysfunction in a Patient with Polycystic Kidney Disease Harboring a PKD1 Frameshift Mutation

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Summary

A 70-year-old man with dyspnea was admitted to our department and received standard therapy for recurrent heart failure. He was diagnosed with polycystic kidney disease (PKD) in his thirties and received hemodialysis for 4 years before undergoing renal transplantation at age 45. Although his left ventricular ejection fraction (LVEF) was preserved in his 50s, LVEF decreased progressively from 61% to 24%, while left ventricular diastolic dimension (LVDd) increased from 54 mm to 65 mm between 63 and 69 years of age. Right ventricular endomyocardial biopsy demonstrated myocardial disarray and interstitial fibrosis. Genetic analysis identified a heterozygous frameshift mutation in PKD1, which encodes polycystin-1, a major causative gene of PKD. We detected PKD1 protein expression in myocardial tissue by immunostaining. Recent epidemiological studies and animal models have clarified the pathological correlation between ventricular contractile dysfunction and PKD1 function. Here, we present a case of old-age onset progressive cardiac contractile dysfunction with a PKD1 gene mutation.

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Key words: Cardiomyopathy, Genetic analysis

Dilated cardiomyopathy (DCM) is an intractable disease characterized by left ventricular chamber dilation and thinning, leading to mechanical and electrical dysfunction. The prognosis of end-stage heart failure caused by DCM remains poor even with maximum medical therapy. The etiology of DCM is variable and can be related to viral infection, chronic alcoholic intake, cardiotoxic drug use, metabolic disease, and genetic mutations; however, the majority of DCM patients are still diagnosed as idiopathic.1,2 The differential diagnosis of secondary cardiomyopathy has grown in importance because the diagnosis may facilitate a specific therapy targeting the upstream pathological basis, such as immunosuppressive therapy for sarcoidosis and enzyme replacement therapy for Fabry disease.2,4,5

Case Report

A 70-year-old man was admitted to our department because of general fatigue and worsening dyspnea. An electrocardiogram on admission showed sick sinus syndrome (SSS), and his heart rate was 40 beats per minute. He was diagnosed as acute exacerbation of chronic heart failure due to bradycardia and received permanent pacemaker transplantation and standard medical therapies. It was his fifth admission due to worsening of heart failure. The left ventricular contractile function of the patient decreased rapidly after his 60s and he was hospitalized repeatedly with a diagnosis of DCM. The disease progressed rapidly to inotropic dependency, and his clinical

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Recent epidemiological studies5 and researchers using animal models6 have helped elucidate the pathological correlation between ventricular contractile dysfunction and the function of PKD1, mutations which are major causes of inherited autosomal dominant polycystic kidney disease (PKD). Here, we present the case of a patient with old-age onset progressive cardiac contractile dysfunction with PKD who harbors a heterozygous frameshift mutation in PKD1.

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PROGRESSIVE CARDIAC CONTRACTILE DYSFUNCTION IN PKD

A

63 yo

LVEF: 61%
LVDD: 54mm

69 yo

LVEF: 24%
LVDD: 65mm

B

64 yo

70 yo

Figure 1. A: Transition of left ventricular ejection fraction (LVEF) and left ventricular diastolic dimension (LVDD) from 63 to 69 years of age. B: Transition of electrocardiogram from 64 to 70 years of age. yo indicates years old.

course over the past few years appeared to differ from typical heart failure cases.

The patient was diagnosed with polycystic kidney disease (PKD) in his thirties and received hemodialysis for 4 years until undergoing renal transplantation at 45 years of age. The patient’s son was also diagnosed with PKD. After renal transplantation, he no longer required dialysis. He also presented small hepatic cysts because of PKD, but did not complain of subjective symptoms. He was diagnosed as suffering from angina pectoris due to left circumflex occlusion (LCx) 13 with collateral flow at 53 years of age and underwent percutaneous coronary intervention (PCI). At age 63, LVEF and LVDD evaluated by echocardiography were 61% and 54 mm, respectively. At age 64, LVEF was suddenly reduced to 40%, although he showed no chest pain or symptoms related to heart failure. Exercise stress TI-201 cardiac scintigraphy demonstrated a global perfusion defect and incomplete redistribution both at the LV anterior-septal and posterior wall. Therefore, we first suspected ischemic cardiomyopathy due to the progression of coronary disease as a cause of the reduced LVEF. However, neither re-stenosis nor progression of the stenotic lesion was detected by coronary angiography.

We started β-blocker (carvedilol) administration to improve the patient’s reduced contractile function, but over the next 6 years, LVEF evaluated by echocardiography gradually and progressively decreased from 61% to 24%, and LVDD enlarged significantly from 54 mm to 65 mm (Figure 1A). Electrocardiography showed decreased QRS voltage in all leads over this period (Figure 1B). BMIPP scintigraphy at age 66 also showed a global decrease in cardiac tracer uptake. Right ventricular endomyocardial biopsy demonstrated myocardial disarray and interstitial fibrosis (Figure 2) and neither periodic acid-Schiff staining nor Congo red staining indicated secondary cardiomyopathy. His blood pressure remained within normal limits over the past few years (Figure 3), suggesting that hypertensive heart disease is not the primary cause of the contractile dysfunction. The clinical course, diagnostic imaging, and pathological findings suggested that the progressive contractile dysfunction may be caused by some myocardial disorder, and we diagnosed his heart failure as an idiopathic DCM. Over the past few years, the frequency of hospitalization has increased and renal function has deteriorated in proportion to the reduced LVEF (Figure 3). His heart failure symptoms have become resistant to standard medical therapy, and during his current course
of hospitalization, he could not be weaned off the inotropic agent because of the severe advanced heart failure with reduced LVEF.

Recent rapid advances in comprehensive genome analysis have elucidated the genetic basis of cardiomyopathy not only in familial but also in sporadic cases.7-10) Progressive contractile dysfunction in this patient may be due to a myocardial disorder, thereby prompting us to perform a genetic screen, although there was no familial history of DCM. We obtained written informed consent from the patient and analyzed his genome using amplicon sequencing targeting 404 cardiovascular genes. Among cardiomyopathy-related genes, we identified two non-synonymous variants in TTN encoding titin. We also identified a heterozygous frameshift mutation in exon 38 in PKD1 (c.11143delC, p.L3715fs) (Figure 4A) which was already reported as a confirmed pathogenic mutation in the Autosomal Dominant Polycystic Kidney Disease (ADPKD) Mutation Database (http://pkdb.pkdcure.org). PKD1 encodes polycystin-1, a large membrane protein with 11 transmembrane domains (Figure 4B) that localizes to the primary cilium in kidney cells and acts as a mechanosensor that regulates calcium influx.6,11,12) Mutations in PKD1 are identified in around 85% of ADPKD cases.11) Pkd1 is also expressed in murine heart tissues and cardiac specific knockout of Pkd1 results in decreased cardiac function.10) A recent epidemiological study demonstrated that PKD1 frameshift mutations in patients with ADPKD are associated with cardiomyopathy onset.12) To determine whether the PKD1 protein is expressed in the heart tissue of the patient presented in this case, we immunostained a myocardial biopsy sample obtained from his right ventricle with a monoclonal antibody that can detect the PKD1 protein in human kidney tissues.13) As shown in Figure 4C, positive signals were detected in the cytoplasm, especially around the nuclear periphery of troponin-positive cardiomyocytes in the heart tissue.

**Amplicon sequence analysis:** The use of patient-derived samples and the genomic analysis were approved by the Ethics Committee of Osaka University Hospital, and written informed consent was obtained from the patient. For genomic analysis, we used an Ion Ampliseq Cardiovascular Research Panel (10,430 PCR amplicons covering 404 genes known to harbor mutations affecting cardiovascular function. Gene list is shown in Supplemental Table I), and sequence run was performed using Ion PGM with 318 Chips. Sequencing data were analyzed using TorrentSuite (version 5.2.2, Life Technologies). Among the identified 1,626 variants (average read depth: 183.0), synonymous mutations without amino acid changes were excluded. Variants were classified to be benign when present in the Human Genetic Variation Database (HGMD) or ESP 6500 database with an allele frequency more than 1%. After filtering, among cardiomyopathy-related genes, we found 2 non-synonymous variants in TTN. We also identified a heterozygous frameshift mutation in PKD1 which was not reported in either the HGMD or ESP 6500 database. Detailed variant information is shown in Supplemental Table II.

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**Figure 2.** Masson trichrome staining of right ventricular endomyocardial biopsy sample. Scale bar: 200 μm.

**Figure 3.** Clinical course of patient from 64 to 70 years of age.
Figure 4. A: Direct Sanger sequence of the genomic DNA obtained from this patient. In the mutated allele, 11143delC caused a frameshift and resulted in protein truncation at amino acid 3824. B: Schematic of PKD1 structure from N-terminus (N) to C-terminus (C) with 11 transmembrane domains. X indicates the location of 11143delC. C: Immunofluorescence staining of right ventricular endomyocardial biopsy sample using anti-PKD1 (Abcam ab74115, RRID: AB_1925337) and anti-troponin I (Abcam ab47003, RRID: AB_869982) antibodies. Nuclei were stained with Hoechst. Scale bar: 50 μm.

Discussion

We admitted an old-age onset DCM patient who demonstrated progressive cardiac contractile dysfunction in his 60s. During early stages when his cardiac contractile function first started to decrease, we suspected myocardial ischemia as the cause of the cardiac dysfunction. However, we later believed a myocardial disorder other than cardiac ischemia to be the primary cause of the progressive contractile dysfunction for the following reasons. First, coronary angiography did not detect the progression of coronary stenosis, and his past history of coronary artery disease could not account for the global decrease in tracer uptake detected by RI scintigraphy. Second, the progressive contractile dysfunction that rapidly led to inotrope dependency over several years in spite of the preservation of LVEF in his 50s could not be fully explained by his past clinical course. After the differential diagnosis of secondary cardiomyopathy, the patient was diagnosed with idiopathic DCM and we presumed that the identified frameshift mutation in the PKD1 gene may be associated with the progression of contractile dysfunction because of the following review regarding the cardiac manifestation of ADPKD and molecular function of the PKD1 gene.

Prevalence of ADPKD and cardiac manifestation: ADPKD is a multisystemic disease characterized by the progressive development of bilateral renal cysts, resulting in enlargement of the kidney volume due to cystic formations and decline in glomerular filtration rate. ADPKD represents the fourth most common cause of end-stage renal disease (ESRD) in Western countries and occurs worldwide in people of all races. In Japan, the annual incidence rates for ESRD caused by ADPKD in men and women are 5.6 and 4.0 per million, respectively. ADPKD is characterized by the development of renal cysts and various extrarenal manifestations, including hepatic and pancreatic cysts, intracranial aneurysms, and aortic root dilatation. Importantly, cardiovascular diseases are the leading cause of mortality in patients with ADPKD. Among the cardiac manifestations, mitral valve prolapse (MVP) is most commonly observed in ADPKD patients. Hypertension and left ventricular hypertrophy are also associated with ADPKD. In this case, we detected mild mitral regurgitation, but not MVP, by echocardiography. The blood pressure of the case remained within the normal limit and echocardiography did not detect left ventricular hypertrophy in the past clinical course before the manifestation of cardiac dysfunction. The pathological association between ADPKD and cardiomyopathy has not been fully elucidated. Cases of hypertrophic obstructive cardiomyopathy (HOCM), hypertrophic cardiomyopathy (HCM), or left ventricular noncompaction (LVNC) with ADPKD were previously re-
ported. A recent epidemiological study that assessed the association of PKD with cardiomyopathy surveying 667 patients diagnosed with ADPKD31 clarified that among the 58 patients with available echocardiography data, 39 (5.8%) had idiopathic DCM, 17 (2.5%) had HOCM, and 2 (0.3%) had LVNC. The mean ages of diagnosis of IDCM and HOCM are 53.3 and 59.9 years old, respectively. In this epidemiological study, among the 9 patients with PKD mutations, 6 had a truncating mutation, suggesting that ADPKD patients may be predisposed to cardiomyopathies. In our case, we sequentially observed the cardiac function over several years and found rapidly progressive contractile dysfunction in our patient diagnosed with ADPKD harboring a truncating mutation in PKD1 by genetic analysis. A family history of PKD or cardiac manifestation was not apparent in his parents or grandparents. We speculate that these family members had medically undiagnosed PKD, or this patient with PKD might be a sporadic case with de novo mutation in PKD1 as previously reported.31

Molecular function of PKD1 gene: ADPKD is caused by gene mutations in PKD1 encoding polycystin-1 (around 85% of the cases) and PKD2 encoding polycystin-2 (around 15% of the cases).32-35 Studies using genetically modified mice clarified that polycystin-1 regulates tubular morphology in both developing and adult kidney.36,37 Polycystin-1 and polycystin-2 co-distribute in the primary cilia of kidney epithelium and contribute to fluid-flow sensation as a mechanosensor that regulates calcium influx.38 The molecular functions of these genes in heart tissue have been proposed recently. Experimental research using pkd2 mutant zebrafish and the human ADPKD database clarified that pkd2 modulates intracellular calcium cycling and PKD2 mutations are associated with the onset of idiopathic DCM.39 More recently, experimental research using genetically modified mice has demonstrated that cardiac specific knockout of PKD1 results in decreased cardiac function and a decreased α1CL-type calcium channel protein level, suggesting that PKD1 is a cardiomyocyte mechanosensor that regulates L-type calcium channels.40 Although PKD1 protein is expressed in various tissues including kidney, to the best of our knowledge, there are no reports regarding the distribution of PKD1 in human heart tissue. We detected PKD1 expression in the cytoplasm around the nuclear periphery of cardiomyocytes in the patient’s heart tissue. The subcellular locations of PKD1 are reported to be the plasma membrane, junctional complexes, or sarcoplasmic reticulum.41,42 Further studies are required to determine the precise intracellular localization of PKD1 in human cardiomyocytes. The C-terminal region of PKD1 translocates to the nucleus, activates downstream signaling,43,44 and promotes calcium channel stabilization in cardiomyocytes.45 The 11143delC mutation identified in this case causes a frameshift in the reading frame and results in truncation of the encoded protein at amino acid residue 3824; full-length PKD1 contains 4303 amino acids. The point of truncation is located in the intermediate region between the 6th and 7th transmembrane domains of PKD1 (Figure 4B), which could thereby cause the loss of the entire C-terminal region of PKD1. Therefore, impaired intracellular signaling and dysregulated calcium flux in cardiomyocytes may underlie the contractile dysfunction in this case. Although both epidemiological studies and animal models have clarified the pathological correlation between ventricular contractile dysfunction and PKD1 function, not all the ADPKD patients manifest cardiomyopathy. In this case, the patient’s son was diagnosed with PKD but does not have cardiac manifestation at present. Genetic variants of TTN identified in this case may affect the cardiac function, because TTN truncating variants are one of the major causes of DCM cases.46,47 ADPKD is the most common group of inherited kidney cystic diseases, shown to affect between 1/400 and 1/1000 of the population,48 and the estimated prevalence from Japan was 1 in 4033,49 suggesting the clinical significance of screening of the cardiac function of these cases. Although the causal relationship between PKD1 frameshift mutations and progressive contractile dysfunction has not yet been proven, genetic screening potentially provides important information about the mechanisms of progressive cardiac dysfunction in patients with ADPKD.

Disclosures
Conflicts of interest: None.

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Supplemental Files 

Supplemental Tables I, II 
Please see supplemental files; https://doi.org/10.15364/hij.18-184