A case of congenital left ventricular diverticulum in a patient with autosomal dominant polycystic kidney disease: possible mechanistic link between polycystin and ventricular diverticulum

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Abstract

A 40-year-old woman had been followed as an outpatient to manage chronic kidney disease secondary to autosomal dominant polycystic kidney disease (ADPKD). Atrial premature contraction was found incidentally on an electrocardiogram during her regular follow-up examination. Subsequent transthoracic echocardiography detected an abnormal structure located very close to the left ventricular outflow tract (23 mm long × 15 mm wide in diastole). The structure was finally diagnosed as congenital left ventricular diverticulum (CLVD) using transesophageal echocardiography, contrast-enhanced computed tomography, and magnetic resonance imaging. Although CLVD occasionally causes intraventricular coagulation, lethal arrhythmia, and congestive heart failure, the size and location of her diverticulum remained unchanged over time and a 24-h Holter electrocardiogram showed no lethal arrhythmias. Accordingly, neither anticoagulation therapy nor surgical resection of the diverticulum was performed. To the best of our knowledge, ours is the first case of CLVD in a patient with ADPKD. Because gene abnormalities in polycystin coding are mechanistically related to the development of colonic diverticulum and abnormal cyst formation in ADPKD patients, we suspected that CLVD and abnormal cyst formation were related to the same gene abnormality in ADPKD. More case reports, case series studies, and basic research are required to determine whether CLVD in ADPKD is mechanistically associated with abnormal polycystin or just a coincidence.

Keywords Atrium · Autosomal dominant polycystic kidney disease · Congenital left ventricular diverticulum · Polycystin

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most frequently inherited renal disease leading to end-stage kidney disease. ADPKD occurs in approximately 1 in every 400–1000 live births [1]. Approximately 80% of families with ADPKD have an abnormality on chromosome 16 (*PKD1* locus), and most of the remaining families (14%) have a different defect that involves a gene on chromosome 4 (*PKD2* locus) [2]. *PKD1* and *PKD2* genes encode the proteins polycystin-1 and polycystin-2, respectively, and defects cause diverse abnormalities [3]. ADPKD is primarily characterized by expanding cysts in the kidney, liver, pancreas, and spleen. Patients with ADPKD also often have complications related to a variety of other abnormalities including cerebral aneurysm, cardiac valve disease, and colonic diverticula, many of which are consistent with a generalized defect in epithelial cell differentiation and extracellular

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matrix function as a primary expression of the genetic abnormality [1, 2, 4].

Congenital left ventricular diverticulum (CLVD), originally described in 1838 [5] at autopsy by O'Bryan, is a rare congenital malformation/anomaly described as a localized protrusion of endocardium and myocardium from the free wall of the left ventricle and occasionally of the atrium [6]. In general, CLVD is discovered incidentally during routine transthoracic echocardiography (TTE). In adult populations, the incidence was reported as approximately 0.4% in autopsy series of cardiac death, and approximately 0.26% in non-selected patients undergoing cardiac catheterization [6]. CLVD in ADPKD patients has not been reported previously, and the association between ADPKD and CLVD remains unclear.

We describe a patient with ADPKD who was incidentally diagnosed with CLVD originating from the left ventricular outflow tract and protruding into the left atrium. To the best of our knowledge, ours is the first case of CLVD observed in an ADPKD patient.

Case report

A 40-year-old woman with chronic kidney disease secondary to ADPKD was followed as an outpatient at our hospital since she was 25 years old. Her grandfather, mother, aunt, and cousin also suffered from ADPKD, and her mother and aunt had been undergoing hemodialysis. Her ADPKD-associated complications included polycystic kidneys, and contrast-enhanced computed tomography (CT) imaging showed numerous kidney cysts with no obvious solid contents (Fig. 1a). Multiple cysts in the liver were also seen on non-contrast-enhanced X-ray CT (Fig. 1b), consistent with

typical ADPKD. Cerebral aneurysm was not detected by magnetic resonance imaging (MRI), and the presence of a colonic diverticulum was not examined by colonoscopy or barium enema.

At age 40, the patient underwent a scheduled medical checkup, and an electrocardiogram incidentally revealed atrial premature contraction. She was then transferred to the department of cardiovascular medicine in our hospital. On presentation, her height was 161 cm, and her weight was 57 kg. She was alert, with a blood pressure of 126/74 mmHg, heart rate of 64 beats per minute, and body temperature of 36.6 °C. No heart murmur was detected, and respiratory auscultation was clear. Laboratory data on admission revealed: hemoglobin: 10.7 g/dL; white blood cell count: 5600/ μ L; platelet count: 24.0×10^4 / μ L; serum albumin: 4.2 g/dL; blood urea nitrogen: 29 mg/dL; serum creatinine: 1.75 mg/dL; and estimated glomerular filtration rate (eGFR): 27.2 mL/min/1.73 m². A urine dipstick test was negative for proteinuria and hematuria. Urinary sediment examination revealed 1–5 red blood cells/high power field and 0–50 white blood cells/high power field. Chest X-rays were unremarkable, and an electrocardiogram showed a sinus rate of 64 beats per minute with no ST-T change. TTE revealed normal left ventricular function (ejection fraction; 71%), internal diameters and wall motions, and trivial mitral regurgitation. However, an abnormal structure was seen in the left atrium (Fig. 2a, b), measuring 23 mm long $\times$ 15 mm wide in diastole (Fig. 2c). Color Doppler TTE revealed that the lesion received blood flow for only a moment in systole (Fig. 2d). The patient then underwent MRI and contrast-enhanced CT imaging, which revealed an abnormal structure in the left atrium proximal to the anterior leaflet of the mitral valve (Fig. 3a), and inflow of contrast agent from the left ventricle (Fig. 3b). A three-dimensional stereoscopic

Fig. 1 Plain and contrast-enhanced computed tomographic (CT) imaging of the abdomen. Numerous cysts in bilateral kidneys are seen in axial CT images. **a** Obvious solid ingredients are not observed; **b** multiple cysts in the liver

Fig. 2 Transthoracic echocardiography findings. An abnormal structure is seen in the left atrium in diastole (a) and systole (b). In each image, the CLVD is indicated by a white arrow. c Lesion measured

23 mm long $\times$ 15 mm wide in diastole. d Color Doppler sonographic image showing inflow of blood to the lesion. CLVD, congenital left ventricular diverticulum

Fig. 3 Contrast-enhanced computed tomographic (CT) imaging of the heart. a Axial CT image showing the CLVD receiving inflow of contrast medium from the left ventricle. The CLVD is indicated by a white arrow. b Inflow portion appears pedunculated in the sagittal image. The CLVD is indicated by a black arrow. c Three-dimensional

stereoscopic image of the CLVD during systole, excluding structures other than the ascending aorta, left ventricle, and coronary arteries. The CLVD is indicated by a white arrow. CLVD, congenital left ventricular diverticulum

image of the CLVD is shown in Fig. 3c. Initially, the lesion resembled a left atrial diverticulum; however, based on the imaging findings, we diagnosed CLVD. In MRI, the walls constituting a CLVD have equal signal strength to the left ventricle, and the size remains essentially unchanged regardless of systole or diastole (Fig. 4a, b).

Although we considered initiating anticoagulation therapy, the risk of thrombus formation in the CLVD was considered low, because the position of the CLVD exposed it to high-pressure blood flows. Therefore, we did not initiate anticoagulation therapy. No clinically important arrhythmia was detected during 24-h of Holter electrocardiographic monitoring (total beats: 83,981 beats; mean, 65 beats per minute; ventricular premature contraction: 1 beat with no ST-T change). At 4 and 12 months after hospitalization, no change in the size of the left ventricular diverticulum was detected by TTE. Accordingly, surgical

resection of the CLVD was not performed, and because the patient's blood pressure at home and in-hospital was consistently lower than 130/80 mmHg, antihypertensive drugs including renin–angiotensin–aldosterone system inhibitors were not prescribed.

During 4 years of follow-up, her renal function showed a gradually decreasing eGFR of 5.6 mL/min/1.73 m² per year. At age 44, she developed uremic symptoms and blood laboratory testing revealed: BUN: 132 mg/dL; serum creatinine: 8.3 mg/dL; and eGFR: 4.8 mL/min/1.73 m². Accordingly, she underwent hemodialysis for 4 h, three times weekly. At this time, there was still no increase in the size of the left CLVD, which we continue to regularly follow. She is scheduled for periodic cardiographic evaluation to determine whether she needs further therapy based on the status of her CLVD.

Fig. 4 Magnetic resonance imaging (MRI) of the heart. T1-weighted image of the CLVD during systole (a) and diastole (b). In each image, the CLVD is indicated by a red arrow. Walls constituting the

CLVD are depicted with equal signal to the left ventricle. The size of the CLVD did not change dramatically regardless of systole or diastole. CLVD, congenital left ventricular diverticulum

Discussion

We report a case of CLVD located proximal to the anterior leaflet of the mitral valve and potentially associated with ADPKD. Because the size of the diverticulum did not change over time, the position of the CLVD exposed it to high-pressure blood flows, and the CLVD was causing neither fatal arrhythmia nor abnormal cardiac function, she did not receive surgical resection or anticoagulation therapy and undergoes periodic follow-up for early detection and intervention for potentially fatal cardiac complications.

The major extra-renal complications of ADPKD are cerebral aneurysms, hepatic and pancreatic cysts, colonic diverticula, and cardiac valve disease. Among these, cardiac disease and valvular abnormalities of unclear clinical significance can be detected by cardiac ultrasonography in 25–30% of patients with ADPKD. The most common abnormalities include mild mitral valve prolapse and aortic regurgitation [7]. Generalized abnormalities in collagen and extracellular matrix may be responsible for the valve disease in ADPKD [7]. Dissections and aneurysms of the ascending thoracic aorta have also been associated with ADPKD [8]; however, ADPKD patients are rarely complicated by CLVD. Our patient experienced multiple bilateral kidney cysts and trivial mitral valve regurgitation, but not cerebral aneurysm. The most striking complication in our patient was the left ventricular diverticulum detected incidentally, and our primary interest was whether the diverticulum was a

coincidental complication or mechanistically linked to her gene abnormality.

PKD1 and *PKD2* genes encode the proteins polycystin-1 and polycystin-2, respectively [3]. Polycystin-1 is a membrane protein localized at sites of cyst formation, including renal tubular epithelium. Possible roles of polycystin-1 include the regulation of protein–protein, cell–cell, and cell–matrix interactions and intracellular signaling pathways involved in regulating cell proliferation and survival [9]. Polycystin-2 is expressed in the distal tubules, collecting ducts, and thick ascending limb [10] and is involved in cell calcium signaling [11]. Adhesion deficiencies of cell–cell or cell–matrix are also caused by polycystin-1 abnormalities. Polycystin-2 abnormalities decrease intracellular calcium concentration, which leads to elevations in cyclic AMP, causing cysts to form and grow progressively [9–11].

CLVD is a rare cardiac malformation consisting of a localized protrusion of endocardium and myocardium from the free wall of the left ventricle [5]. The reported incidence of CLVD is approximately 0.4% in an autopsy series following cardiac death, and approximately 0.26% in non-selected patients undergoing cardiac catheterization [6]. Possible etiologies of CLVD include abnormalities during embryogenesis or acquired malformations in utero, including coronary artery abnormalities, viral infection, or arrhythmia-related vascular accidents [12]. CLVD has been classified as fibrous or muscular type, based on pathophysiological findings. The muscular type is contractile and originates from left ventricular apical, inferior, or posterior lesions. In contrast, the

fibrous type is not contractile and originates from the base of the left ventricle [13]. The terms ventricular diverticulum and ventricular aneurysm are often used interchangeably [14], especially when the lesion projects to the outside of the heart. Histological examinations show that a true congenital diverticulum is always composed of epicardium, myocardium, and endocardium, whereas an aneurysm may appear as a defect or as the absence of muscle [15].

The association between CLVD and gene abnormalities in *PKD1* and *PKD2* is an intriguing subject of debate. PCKD, including ADPKD, is generally a clinical diagnosis based on family history and imaging studies; therefore, we did not perform a mutation analysis in our patient. This is a limitation in our study when we suggest a possible link between abnormal polycystin and the development of left ventricular diverticulum. Notably, polycystin is expressed in smooth muscle cells and is believed to be associated with the development of gastrointestinal diverticula including colonic diverticula [16]. In addition, the development of atrial and ventricular diverticula is closely related to abnormal smooth muscle, which suggests that CLVD is caused by abnormal polycystin. This may not have been reported previously, because CLVD is diagnosed incidentally, and most cases are clinically silent, often leading to underdiagnosis. However, more case reports and basic research are required to determine whether CLVD in ADPKD is related to abnormal polycystin.

In our patient, neither cerebral aneurysm nor colonic diverticulum were detected. In general, not all PCKD patients develop complications related to abnormal polycystin such as colonic diverticulum and cerebral aneurysm, although the reasons remain unclear. A possible explanation is that other factors during neonatal organogenesis may determine the development of complications in PCKD patients with polycystin mutations, which lead to the relatively low rate of colonic diverticulum, cerebral aneurysm, or mitral valve regurgitation [17]. Namely, polycystin gene mutations are not the decisive factor in the development of cerebral aneurysm and colonic diverticulum, unlike polycystic kidneys. With this assumption, some PCKD patients develop cerebral aneurysm, and others develop mitral valve regurgitation. Likewise, only some PCKD patients develop CLVD. As we described, many PCKD cases are clinically silent, and if not examined very carefully, patients may be underdiagnosed. This might partially explain why our patient developed CLVD as a complication but neither cerebral aneurysm nor colonic diverticulum, which are more commonly observed in PCKD patients.

Morphologically, a diverticulum has a narrow connection with a ventricle, and this connection is wider in aneurysms. Further differentiating the two, although diverticula contract synchronously with the ventricle, aneurysms show a paradoxical expansion [15]. In our patient, the lesion was

located proximal to the anterior leaflet of the mitral valve, and not outside the heart. In addition, the lesion appeared to consist of thin myocardial fibers based on CT (Fig. 3a, b) and MRI (Fig. 4a, b), and the lesion had a narrow connection (Fig. 3b). Finally, although the lesion did not contract synchronously with the ventricles and appeared to admit blood flow during systole, it did not expand during systole (Fig. 2a, b); the lesion size remained essentially unchanged regardless of systole or diastole (Fig. 4a, b). Based on these findings, we diagnosed the lesion as CLVD, not as an aneurysm.

CLVD is often clinically silent, but may be associated with serious complications such as systemic embolism, fatal ventricular arrhythmias, congestive heart failure, cardiac rupture, and sudden death [12]. Although the fundamental treatment of CLVD is surgical resection, there are few reports on the natural prognosis of this disease, and there is no established therapy. We considered initiating anticoagulation therapy or surgical resection in our patient, based on past reports [18]. Related to this decision, we diagnosed her CLVD as the fibrous type based on the position of the lesion and the absence of contractility. Systemic thromboembolism often occurs as a complication of the fibrous type [14]; however, given that the location of her CLVD was exposed to high-pressure blood flows, the probability of thrombus formation in the CLVD was low. In addition, because her CLVD did not involve lethal arrhythmia, and there was no tendency to expand, we tentatively concluded that there was no indication for surgery at that time. 4 years later, at age 44 years, dialysis therapy was initiated. Because survival is relatively longer in Japanese ADPKD patients who undergo dialysis therapy [19], it is necessary to follow the CLVD periodically.

In summary, to our knowledge, our case is the first report of CLVD in a patient with ADPKD. Although there are no known reports of the relationship between a CLVD, development of cardiac tissue, and *PKD1* or *PKD2* abnormalities, we suspected that the CLVD in our patient was caused by abnormal polycystin. More case reports and case series, and basic research are required to determine whether CLVD in ADPKD is mechanistically associated with abnormal polycystin or just a coincidence. In addition, it may be necessary for all PCKD patients to receive detailed morphological cardiac assessment by ultrasonography to detect CLVD.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

Human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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