

[CASE REPORT]

Renal Squamous Cell Carcinoma-related Polymyositis in a Patient with Autosomal Dominant Polycystic Kidney Disease

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Abstract:

A 74-year-old Japanese woman diagnosed with autosomal dominant polycystic kidney disease (ADPKD) was admitted to our institute for the further examination of right-side groin pain developing in the past week. The patient was diagnosed with polymyositis (PM). Diagnostic imaging showed a mass lesion measuring 8 cm and a renal stone in the right kidney. Immediately following surgical resection of the right kidney, the patient's serum CK decreased to the normal range. A histopathological analysis showed well-differentiated squamous cell carcinoma. In conclusion, this case showed a close relationship between the occurrence of squamous cell carcinoma and the development of PM in an ADPKD patient.

Key words: autosomal dominant polycystic kidney disease, polymyositis, squamous metaplasia, squamous cell carcinoma, paraneoplastic syndrome, renal pelvis cancer

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is a multisystem hereditary disease characterized by the formation of cysts in the ductal organs (1). Although renal cell carcinoma (RCC) is known to be a complication of ADPKD, renal pelvis malignancy in ADPKD is rare, with few cases being investigated and reported (2, 3).

Polymyositis (PM) is a rare, autoimmune, idiopathic, inflammatory myopathy involving the muscles. It presents with proximal skeletal muscle weakness and evidence of muscle inflammation. It is well known that an association exists between inflammatory myopathy, including PM, and cancer. The increased frequency of cancer in patients with inflammatory myopathy is consistent with the concept that paraneoplastic processes linked to oncogenesis and autoimmunity contribute to the disease in a subset of PM cases.

However, the association between PM and renal pelvic cancer is rare (4, 5).

To our knowledge, this is the first report of the development of PM as paraneoplastic syndrome, following the occurrence of renal pelvis squamous cell carcinoma (SCC), in a 74-year-old ADPKD patient.

Case Report

A 74-year-old Japanese woman was admitted to our institute for further examination of general malaise, including bilateral femoral muscle pain and right-side groin pain, all of which began a month prior to this admission. A diagnosis of ADPKD with renal stone and renal hemorrhaging had been confirmed by computed tomography (CT) for the right lower flank pain when she was 38 years old. In the following years, CT for the flank pain had been repeated. The patient's medical history included appendicitis at 22 years old,

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Table. Laboratory Data.

Serum	Patient	Reference range
White blood cell (μL)	9,500	3,200 - 7,900
Hemoglobin (g/dL)	8.9	11.3-15.0
Platelet ($\times 10^3/\mu\text{L}$)	277	155-350
Total protein (g/dL)	7.1	6.9-8.4
Albumin (g/dL)	3.2	4.1-5.1
Total Bilirubin	0.3	0.3-1.1
Urea nitrogen (mg/dL)	63	8-21
Creatinine (mg/dL)	3.1	0.6-1.0
eGFR (mL/min/1.73 m ³)	12.1	≥ 90
C-reactive protein (CRP)	5.5	<0.3
Erythrocyte sedimentation rate (mm) *2 hours rate	74	<30
Aspartate aminotransferase (IU/L)	41	11-38
Alanine transaminase (IU/L)	44	6-50
Lactate dehydrogenase (IU/L)	538	103-190
Triglyceride (mg/dL)	107	40-149
Total cholesterol (mg/dL)	167	142-248
High-density lipoproteins cholesterol (mg/dL)	46	40-90
Low-density lipoproteins cholesterol (mg/dL)	69	65-139
Creatinine kinase (IU/L)	1,509	<100
Myoglobin ($\mu\text{g/L}$)	>3,000	<106
Aldolase (U/L)	5.9	2.7-7.5
Glucose (mg/dL)	99	
Hemoglobin A1c (%)	5.7	4.9-6.0
Thyroid stimulating hormone ($\mu\text{IU/mL}$)	1.094	0.50-4.30
Free thyroxine (ng/dL)	0.92	0.70-1.70
Intact-PTH (pg/mL)	133	15-65
Immunoglobulin G (mg/dL)	1,425	861-1,747
Immunoglobulin A (mg/dL)	169.8	93-393
Immunoglobulin M (mg/dL)	115.5	33-183
Complement activities50 (U/mL)	58	31-58
Complement3 (mg/dL)	104	73-138
Complement4 (mg/dL)	42	11-31
Antinuclear antibody (ANA)	8.3	<40
Anti-Jo-1 antibody (U/mL)	<1	<1
Rheumatoid factor (IU/mL)	4	<14
Anti-ARS antibody (U/mL)	negative	negative
Anti-MDA5 antibody (U/mL)	negative	negative
Anti-Mi-2 antibody	negative	negative
Anti-TIF1- γ antibody	negative	negative
Anti Ku antibody	negative	negative
Anti-PM-Scl100 antibody	negative	negative
Anti-PM-Scl75 antibody	negative	negative
Anti SRP antibody	negative	negative
Anti-PL-7 antibody	negative	negative
Anti-PL-12 antibody	negative	negative
Anti-OJ antibody	negative	negative
Anti-EJ antibody	negative	negative
Anti-Ro-52 antibody	negative	negative
Urinary RBC sediment (/HPF)	1-5	<1
Urinary RBC sediment (/HPF)	1	<1
Urine protein qualitative	1+	-
Urinary protain (g/day)	5.14	<0.15
(24 hours urine) Creatinine clearance (mL/min)	9.9	<1.0

ARS: anti-aminoacyl tRNA synthetase, MDA5: melanoma differentiation-associated protein 5, TIF1- γ : anti-transcriptional intermediary factor-1 gamma, SRP: signal recognition particle

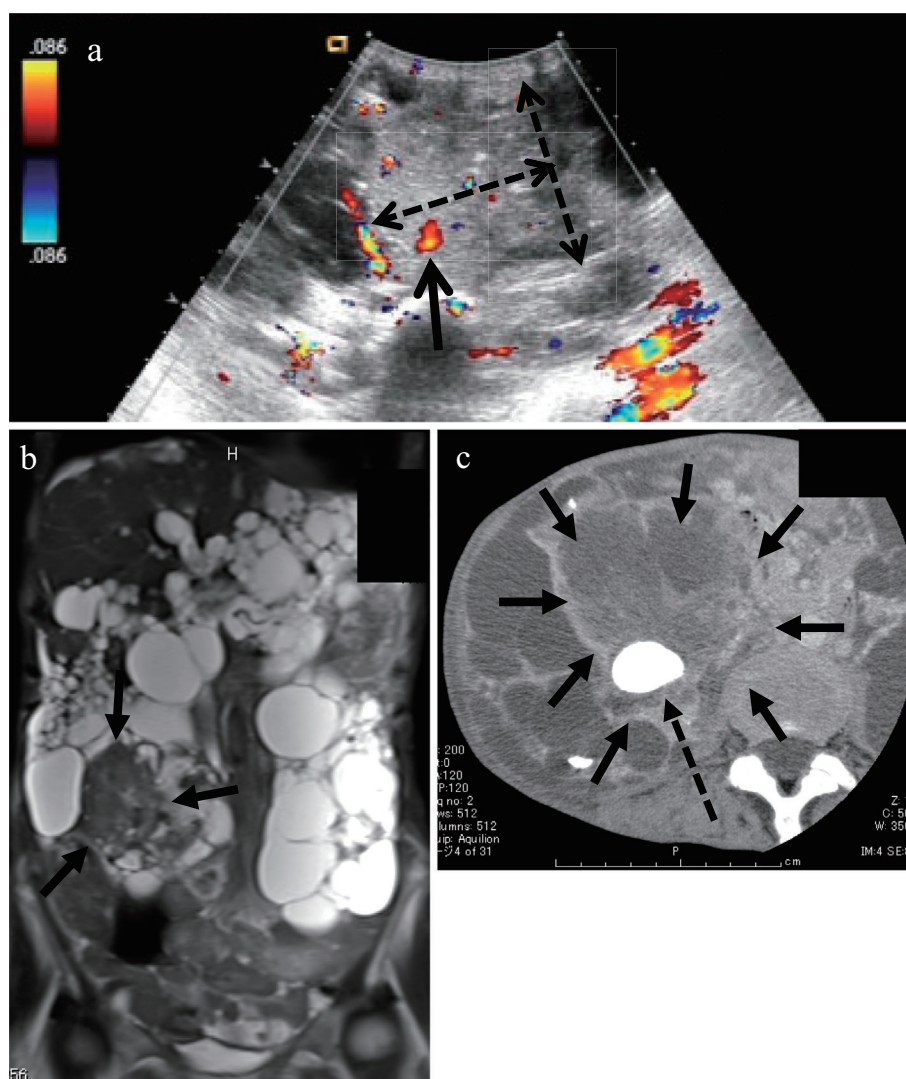


Figure 1. Ultrasonography findings. a: An 8-cm mass lesion (dotted arrow) in the lower portion of the right kidney. Color Doppler signal indicates vascularity within the mass (black arrows). b: Magnetic resonance imaging (MRI) showed hypointensity on T2-weighted imaging (black arrows). c: Computed tomography (CT) after the administration of contrast media showed that the tumor margin and parenchyma were enhanced compared with multiple renal cysts (black arrows). A renal stone 30 cm in size was seen in the center of the mass (dotted arrow).

retinal detachment at 62 years old, and sudden deafness at 63 years old. The patient's younger and older brothers, and two older sisters had also been diagnosed with ADPKD.

On admission, the patient's height was 155 cm with a body weight of 39.3 kg. Her blood pressure was 170/102 mmHg, and her body temperature was 37.3°C. Bilateral pitting edema was notable, and proximal muscle pain without muscle weakness was noted, particularly in the femoral muscles bilaterally.

The laboratory data were: white blood cells (WBCs) 9,500/ μ L; CRP 5.5 mg/dL; CK 1,509 IU/L; and myoglobin >3,000 μ g/L. Blood urea nitrogen was 63 mg/dL, creatinine was 3.1 mg/dL, and the estimated glomerular filtration rate (eGFR) was 12.1 ml/min/1.73 m². CEA was 72.2 U/mL, and CA125 was 216 U/mL. The patient tested negative for all myositis-related antibodies, including anti-aminoacyl tRNA-synthetase enzyme (ARS), anti-melanoma differentiated-

associated gene 5 (MDA5), anti-nuclear matrix protein 2 (Mi-2), and anti-transcriptional intermediary factor-1-gamma (TIF-1- γ) (Table).

A muscle biopsy from the right biceps was performed, and magnetic resonance imaging (MRI) revealed high-intensity T2 with mild myogenic changes observed by electromyography (EMG). Lymphocytes infiltrating the surrounding myofibers stained positive for cluster of differentiation 8 (CD8). Scattered necrotic muscle fibers and variable sizes of muscle fibers were noted. The patient was consequently diagnosed with PM.

Diagnostic imaging showed that the kidneys had been replaced by numerous bilateral cysts. A mass lesion measuring approximately 8 cm in size and including a stone 3 cm in size, surrounded by multiple cysts, was noted on the lower portion of the right kidney. Ultrasonography showed vascularity with color-Doppler (Fig. 1a), MRI showed hypointen-

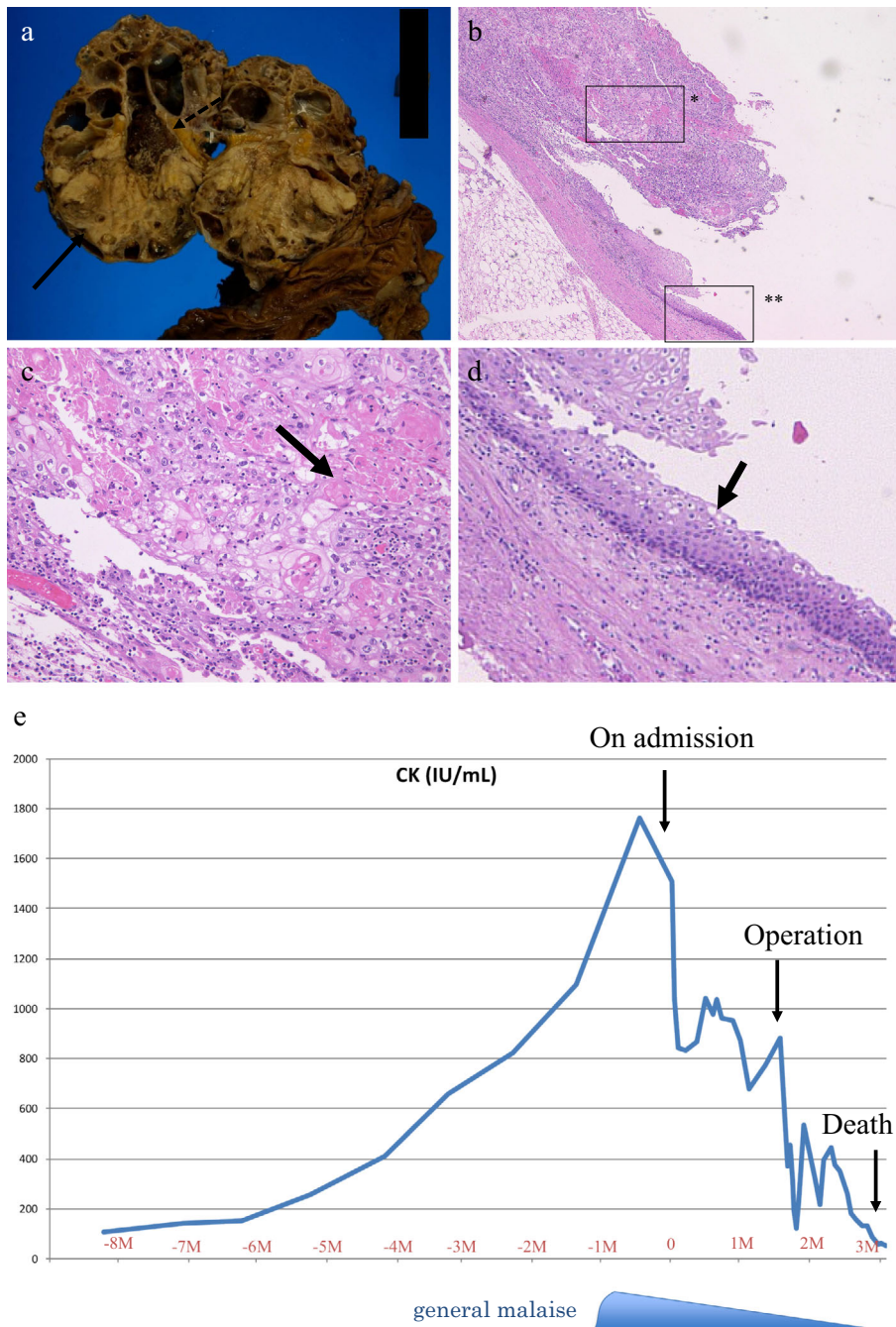


Figure 2. Histology of the surgical specimen. a: A solid mass (arrow) measuring 90×80×90 mm and a renal stone measuring 40×30×20 mm in size were observed in the lower pole of the kidney. b: Microscopy shows well-differentiated squamous cell carcinoma [Hematoxylin and Eosin (H&E) staining ×40]. c: Magnification of figure 2b (*) shows cancer nests of squamous cell carcinoma (H&E staining ×120). d: Magnification of figure 2b (**) shows squamous metaplasia of renal pelvis mucosa (arrow) (H&E staining ×120). e: Clinical course. The patient started to feel general malaise one month before admission. The operation was performed after one and a half months. The CK level gradually decreased after the operation and was within the normal range when she died from intractable hepatic cyst infection.

sity on T2-weighted imaging (Fig. 1b), and CT showed enhancement after the administration of contrast media (Fig. 1c). Renal cancer was suspected, and consequently, open right nephrectomy and ileocecal resection were performed. Immediately after surgical resection, the patient's CK dropped to 122 IU/L and continued to slowly decrease

to a normal range of 52 IU/L. This CK range was maintained until the death of the patient.

Histopathology of the surgical specimen

Regarding the gross diameter and circumference, the excised right kidney measuring 15×10×9 cm had a renal pelvis

stone measuring 40×30×20 mm in the center. A yellowish-white to white solid mass measuring 90×80×90 mm was observed in the lower pole of the kidney (Fig. 2a). A diagnosis of well-differentiated squamous cell carcinoma (SCC) was made following a microscopic analysis. This diagnosis was confirmed by cancer nests of squamous epithelial cell pearls with eosinophilic cytoplasm, indicating keratinization (Fig. 2b, c). These cancer nests appeared to be developing further into squamous metaplasia of the renal pelvis mucosa (Fig. 2b, d). A small portion of the tumor was poorly differentiated. Renal carcinoma cells were not present.

Clinical course

Following surgery, the patient remained hospitalized due to a poor condition. She ultimately died two months after surgery because of intractable hepatic cystic infection (Fig. 2e).

Discussion

An inherited multi-system disorder, ADPKD is characterized by renal and extra-renal fluid-filled cyst formation and increased kidney volume, both of which eventually result in end-stage renal disease (1). A nation-wide cohort study from Taiwan comparing 8,692 individuals with and without ADPKD, showed an increased risk of renal cancer [adjusted sub-hazard ratio 2.45 (95% confidence interval (CI) 1.29-4.65); $p=0.006$], liver cancer [1.49 (95% CI 1.04-2.13); $p=0.030$], and colon cancer [1.63 (95% CI 1.15-2.30); $p=0.006$] in the ADPKD patients (6). Among the cases of renal cancers related to ADPKD, the most common malignancy was RCC. In a previous study of 240 ADPKD patients undergoing renal surgery, 10 patients (4.2%) were papillary RCC, 5 (2.1%) were clear cell RCC, and 1 (0.4%) were papillary noninvasive urothelial cancer (7). Interestingly, renal pelvis squamous cell carcinoma remains rare among ADPKD patients, as squamous cell carcinoma does not occur in renal tissue without squamous metaplasia. The coexistence of renal pelvis SCC in ADPKD patient has only been described in one case report by Xie et al. They reported a 35-year-old man with ADPKD who had the thrombosis formation of SCC in the inferior vena cava; however, in that case, no renal stone was observed (8). Patients with ADPKD are known to be more predisposed to stone formation than non-ADPKD patients (9). Levine et al. also noted in their CT analysis of 84 ADPKD patients that 19 had renal stones (10). This tendency is caused by a structural abnormality secondary to cyst growth, renal tubular stasis, metabolic disorders, or a combination of these factors (11).

There are several case studies of chronic renal stones in non-ADPKD patients that developed into squamous metaplasia and ultimately led to SCC (12, 13). Paonessa reported the case of a 70-year-old woman, showing that chronic renal calculi carry a risk of inducing the development of squamous metaplasia, which may lead to SCC of the renal collecting system (12). Jain et al. reported four cases of co-

existing staghorn stones and a well-differentiated SCC of renal pelvis (13). A close relationship between renal stone-related squamous metaplasia and SCC can be applied to non-ADPKD patients. Therefore, preventing the formation of renal stones may help reduce the risk of developing renal SCC.

PM is an idiopathic inflammatory myopathy, characterized by proximal skeletal muscle weakness and muscle inflammation. The association between malignancy and inflammatory myopathies has been reported by several epidemiologic studies (4, 5). The highest risk for malignancy has been reported in association with DM, and the relative risk for malignancy in PM has been reported to be lower than that in DM (14). In particular, adult patients with DM positive for anti-TIF1- γ are more likely to develop malignancy than those with DM negative for anti-TIF1- γ (15). Our patient was negative for anti-TIF1- γ antibody. We were unable to discuss the relationship between PM and negativity for anti-TIF1- γ , because this relationship has not been reported. Hill et al. reported that adenocarcinomas of the cervix, lung, ovaries, pancreas, bladder, and stomach, accounted for approximately 70% of the cancers associated with inflammatory myopathies. The risk of squamous cell cancers and adenocarcinomas was not increased in patients with PM. However, the risk of hematological and lymphatic malignant diseases was increased two-fold (16).

In conclusion, a 74-year-old Japanese patient with a history of ADPKD and renal stone presented with PM and squamous cell carcinoma of the right kidney. Following surgical resection of the right kidney, PM decreased. The findings of this clinical case report indicate that renal SCC secondary to renal stone-related squamous metaplasia can develop among ADPKD patients, and may result in the development of PM via paraneoplastic mechanisms.

This case study was conducted in accordance with the Declaration of Helsinki. The patient provided her informed consent for the publication.

The authors state that they have no Conflict of Interest (COI).

References

1. Nishimura H, Ubara Y, Nakamura M, et al. Renal cell carcinoma in autosomal dominant polycystic kidney disease. *Am J Kidney Dis* **54**: 165-168, 2009.
2. Kumar S, Cederbaum AI, Pletka PG. Renal cell carcinoma in polycystic kidneys: case report and review of literature. *J Urol* **124**: 708, 1980.
3. Keith DS, Torres VE, King BF, Zincki H, Farrow GM. Renal cell carcinoma in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* **4**: 1661, 1994.
4. Chen YJ, Wu CY, Huang YL, Wang CB, Shen JL, Chang YT. Cancer risks of dermatomyositis and polymyositis: a nationwide cohort study in Taiwan. *Arthritis Res Ther* **12**: R70, 2010.
5. Sigurgeirsson B, Lindelöf B, Edhag O, Allander E. Risk of cancer in patients with dermatomyositis or polymyositis. A population-based study. *N Engl J Med* **326**: 363, 1992.

6. Yu TM, Chuang YW, Yu MC, et al. Risk of cancer in patients with polycystic kidney disease: a propensity-score matched analysis of a nationwide, population-based cohort study. *Lancet Oncol* **17**: 1419, 2016.
7. Jilg CA, Drendel V, Bacher J, et al. Autosomal dominant polycystic kidney disease: prevalence of renal neoplasias in surgical kidney specimens. *Nephron Clin Pract* **123**: 13-21, 2013.
8. Xie J, Zhang X, Wang W, Li H. Case report of renal pelvis squamous cell carcinoma with tumor embolus in autosomal dominant polycystic kidney disease. *Medicine (Baltimore)* **95**: e4597, 2016.
9. Higashihara E, Aso Y, Shimazaki J, Ito H, Koiso K, Sakai O. Clinical aspects of polycystic kidney disease. *J Urol* **147**: 329-332, 1992.
10. Levine E, Grantham JJ. Calcified renal stones and cyst calcifications in autosomal dominant polycystic kidney disease: clinical and CT study in 84 patients. *AJR Am J Roentgenol* **159**: 77-81, 1992.
11. Nishiura JL, Neves R, Eloi S, Cintra S, Ajzen S, Heilberg I. Evaluation of nephrolithiasis in autosomal dominant polycystic kidney disease patients. *Clin J Am Soc Nephrol* **4**: 838-844, 2009.
12. Paonessa J, Beck H, Cook S. Squamous cell carcinoma of the renal pelvis associated with kidney stones: a case report. *Med Oncol* **28** (Suppl): S392-S394, 2011.
13. Jain A, Mittal D, Jindal A, et al. Incidentally detected squamous cell carcinoma of renal pelvis in patients with staghorn calculi: case series with review of the literature. *ISRN Oncol* **2011**: 620574, 2011.
14. Buchbinder R, Forbes A, Hall S, Dennett X, Giles G. Incidence of malignant disease in biopsy-proven inflammatory myopathy. A population-based cohort study. *Ann Intern Med* **134**: 1087-1095, 2001.
15. Trallero-Araguás E, Rodrigo-Pendás JÁ, Selva-O'Callaghan A, et al. Usefulness of anti-p155 autoantibody for diagnosing cancer-associated dermatomyositis: a systematic review and meta-analysis. *Arthritis Rheum* **64**: 523-532, 2012.
16. Hill CL, Zhang Y, Sigurgeirsson B, et al. Frequency of specific cancer types in dermatomyositis and polymyositis: a population-based study. *Lancet* **357**: 96-100, 2001.

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