CASE REPORT

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Simultaneous Pancreatic and Kidney Transplant in Adult with Autosomal Dominant Polycystic Kidney Disease and Type I Diabetes Mellitus: Post Surgical Events and Genetic Review

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ABSTRACT

Autosomal dominant polycystic kidney disease (ADPKD) is a common inherited condition characterized by the growth of multiple bilateral cysts in the kidneys. We describe the case of a 35-year-old male with combined ADPKD and type 1 diabetes mellitus with a strong family history of both. At the age of 32, he developed end-stage kidney disease for which he underwent preemptive simultaneous pancreatic and kidney transplant, which in turn led to multiple perioperative complications. Evaluation of familial clustering of genetic disease is critical in genetic epidemiology and precision medicine as it enables estimation of lifetime disease risk and early assessment as well as detection of the disease among one's siblings.

Type 1 diabetes mellitus (T1DM) is a genetically heterogeneous autoimmune disease affecting about 0.3% of Caucasian populations.[1] Genetic studies of T1DM have focused on the detection of loci associated with increased susceptibility to this multifactorial phenotype.[1] Many patients eventually develop diabetic ketoacidosis, which can be a major risk of mortality.

Polycystic kidney disease (PKD) is one of the most common hereditary kidney diseases affecting the renal tubules. The affected individuals may carry autosomal dominant PKD (ADPKD) and autosomal recessive PKD (ARPKD). ADPKD has an estimated prevalence of 1:400 to 1:1000 live births.[2,3]

Genetically, ADPKD is a heterogeneous disease mainly caused by mutations in *PKD1* and *PKD2* genes, although 5–10% of ADPKD pedigrees remain either genetically unsolved or harbor rare mutations in other genes causing ADPKD-like phenotypes such as α-glucosidase neutral AB, *DNAJB11*, or hepatocyte nuclear factor 1β (*HNF1B*) gene.[4]

CASE REPORT

A 35-year-old man, with a known case of metabolic syndrome and a body mass index of 30 Kg/m^2, had hypertension since early adolescence and T1DM since the age of four years. His diabetes was being maintained on insulin, dyslipidemia on statin, and hyperuricemia on medications. He also had chronic kidney disease – secondary to his ADPKD. He developed end-stage kidney disease (ESKD) by the age of 32 years for which he underwent preemptive simultaneous pancreatic and kidney transplant from a deceased donor. He was discharged with a serum creatinine of 78 umol/L, estimated glomerular filtration rate > 90 mL/min/1.73 m^2, and suboptimal blood sugar of 10 mmol/L.

Two days later, the patient was readmitted with 38.8 °C fever, chills, generalized weakness, fatigue, and mild abdominal pain mainly around the umbilicus. He had no gastrointestinal symptoms, urinary tract symptoms, or other systemic symptoms. On examination, he was dehydrated, with blood

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pressure of 90/50 mmHg, pulse rate of 120/min, and respiratory rate of 22/min. Abdominal examination revealed mild distension and a well healed scar was visible extending from the umbilicus to the suprapubic region. There was mild tenderness below the umbilicus. On palpation, the kidney graft was non-tender. Laboratory investigation results at admission are shown in Table 1.

While the patient's blood cultures revealed no growth, his urine culture showed *Enterococcus faecium*, which was sensitive to vancomycin. The pus discharge from his surgical wound grew carbapenem-resistant *Klebsiella pneumoniae* ssp. (sensitive to tigecycline) and *Citrobacter freundii* (sensitive to cotrimoxazole). His chest X-ray revealed normal lung fields with prominent heart size. Abdominal X-ray revealed no abnormally, dilated bowel loops, or signs of free gas. Echocardiography showed mild pericardial effusion measuring 7 mm behind the right atrium and grade 1 diastolic dysfunction with an ejection fraction of 55%.

Figure 1 shows the patient's abdominal magnetic resonance imaging, with descriptions underneath.

Our multidisciplinary team decided on interventional drainage of the collection with a pigtail catheter which yielded 30 mL frank thick pus, whose culture yielded *K. pneumoniae* with sensitivity to cotrimoxazole and tigecycline. Ultrasound image post drainage showed the transplanted kidney (12 cm) with normal echotexture, no hydronephrosis, resistivity index of 0.54–0.58, and with 6 mL peri-graft collection. Abdominal computed tomography showed a significant reduction in the pre-drainage pelvic collection.

The pigtail catheter was removed after a week of no further drainage and a repeat ultrasound showed peri-graft collection of only 6 mL. The patient was managed with full course of intravenous antibiotics for three weeks. A month later, with his laboratory investigation results showing progressive improvement [Table 1], he was discharged on a small dose of insulin of 8 U/day, steroids tapered

Table 1: Laboratory investigations on admission, after intervention drainage, and discharge.

Laboratory	Normal value	Admission	After intervention drainage	Discharge
Hemoglobin, g/dL	11.5–15.5	11.0	11.1	10.0
Total WBC, 10 g/dL	2.2–10.0	7.4	4.5	7.9
Neutrophils, 10 g/dL	1–5	6.4	3.3	6.2
Platelets, 10 g/dL	140–400	204	292	387
Lymphocytes, 10 g/dL	0.5	0.6	1.0	1.3
Blood urea, mmol/L	2.5–6.7	5.6	12.3	11.7
Serum creatinine, umol/L	45–100	83	88	136
Serum sodium, mmol/L	135–145	137	133	137
Serum potassium, mmol/L	3.5–5.0	5.1	4.3	4.9
eGFR, mL/min/1.73 m^2	> 90	> 90	> 90	56
Serum insulin, pmol/L	20	227.3	64.3	64.3
Serum glucose, mmol/L	4.0–5.5	7.0	4.4	4.5
HbA_{1c}, mmol/mol	20–42	37	35	39
Lipase-1, U/L	13–60	226	226	74
Amylase in serum, IU/L	8–55	127	111	130
C-peptide, pmol/L	260–1710	2363	716	2994
Serum albumin, g/L	35–50	23	28	30
ALT, IU/L	0–40	12	14	18
Anti-islet Ab	Cut off > 1.0 is positive	> 20	–	–
C-Reactive protein, mg/L	<5	14.2	1.4	4.4
ESR, mm/hr	2–25	39	22	-
CMV PCR, copies/mL	Nil	55 247	< 100	< 100
BK PCR, copies/mL	Nil	Not detected	Not detected	Not detected

WBC: white blood cells; eGFR: estimated glomerular filtration rate; HbA1c: hemoglobin A1c; ; ALT: alanine transaminase; ESR: erythrocyte sedimentation rate; PCP: polymerase chain reaction.

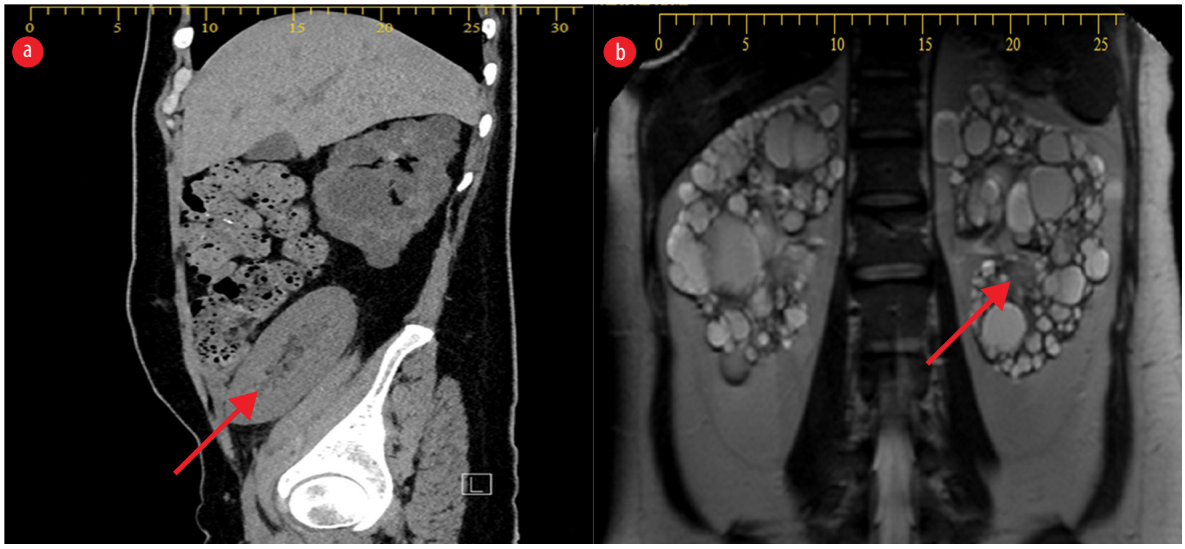
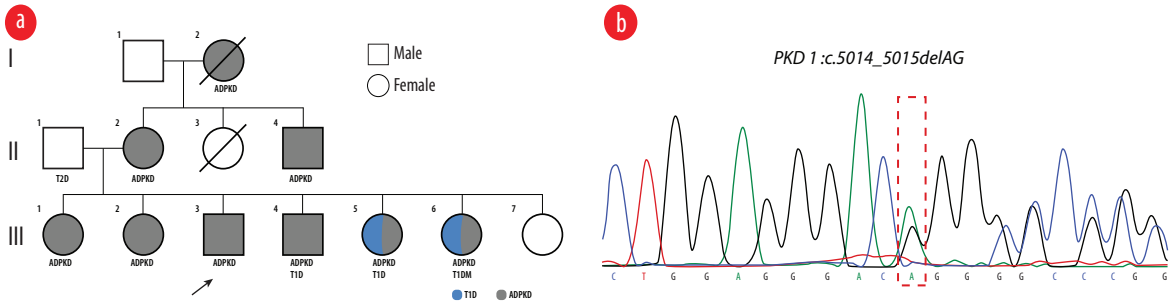


Figure 1: Abdominal MRI post kidney and pancreatic transplant. **(a)** The native kidneys show features of polycystic kidney disease, with innumerable variably sized renal cysts, replacing the normal renal parenchyma. The native pancreas is atrophied. The transplanted kidney is in the right iliac fossa (red arrow). **(b)** MRI of the abdomen shows multiple collections at the site of the transplanted kidney and pancreas, suggestive of abscess, likely infected hematomas. One of the collections is a large abdominopelvic, insinuating between the sigmoid and the transplanted pancreas (red arrow).

down to 2.5 mg once daily (OD). He was kept on tacrolimus 3 mg twice daily (BID), mycophenolate mofetil (CellCept) 1 g BID, and valganciclovir 900 mg OD. He continued to receive intervention tigecycline daily at our daycare facility.

Our patient had a strong family history of both ADPKD and DM. His father was diabetic without kidney disease and his mother had ADPKD without diabetes and underwent kidney transplant. One brother and two sisters of the patient had ADPKD; the brother had kidney transplant. Two other sisters had ADPKD with T1DM and were on insulin. A younger sister had neither ADPKD nor diabetes at the time assessment[Figure 2a].

The proband's sister III-1 underwent targeted next-generation sequencing panel that contains polycystic kidney disease associated genes (including *PKD1*, *PKD2*, *PKHD1*, *HNF1B*, *REN*, *UMOD*, and *MUC*), which revealed a heterozygous 2-bp deletion (NM_001009944.2; c.5014_5015delAG) in the coding region, exon 15, of the *PKD1* gene. This mutation was then verified by Sanger sequencing [Figure 2b]. It was also revealed that our proband, his mother and three sisters (III-2, III-5, and III-6) were all carriers.



Pedigrees were constructed and drawn using Progeny free online pedigree tool (Progeny Genetics LLC, Delray Beach, FL; www.progenygenetics.com). ADPKD: autosomal dominant polycystic kidney disease; T1D: type 1 diabetes; T2D: type 2 diabetes; PKD1: polycystic kidney disease 1. Squares specify males; circles specify females. Arow points to proband; filled squares and circles specify the affected individuals in the family.

Figure 2: Genetic evaluation diagram of the patient's family. **(a)** Pedigrees of the family showing the distribution of ADPKD, T1D and T2D among the members. **(b)** Genomic DNA Sanger chromatograms show heterozygous PKD1 c.5014_5015delAG; p.Arg1672fs*98 frameshift deletion.

DISCUSSION

Inherited and congenital kidney disease is an essential cause of ESKD in the Omani population which is characterized by high rate of consanguinity (56.3%).[5,6] Omani patients with inherited kidney disease start renal replacement therapy at a relatively young mean age of 29 years.[7,8]

Our patient, who had a strong family history of both T1DM and ADPKD, developed both these conditions in early childhood (caused by a heterozygous frameshift deletion mutation in *PKD1*) leading to early kidney failure. Enlarged kidneys with multiple bilateral cysts along with hepatic cysts and hypertension were the typical characteristics of ADPKD in his family for multiple generations. Our patient received a preemptive simultaneous pancreatic and kidney transplant from a deceased donor but multiple complications followed.

Both clinical investigations and molecular genetic analysis proved the diagnosis of ADPKD. He was found to carry a previously reported heterozygous 2-bp deletion (NM_001009944.2; c.5014_5015delAG) in exon 15 of the *PKD1* gene.[5] Mutations in PKD1 (16p13.3) account for around 85% of ADPKD patients and are expected to lead to ESKD by on average age of 53.3 years, much earlier than the average age of ESKD in patients with PKD2 (4q22.1) mutations (72.7 years).[9] Furthermore, truncating PKD1 mutations are linked with ESKD onset at younger ages than non-truncating mutations.[10] In agreement with these studies, our patient and several members of his family developed ESKD at younger ages (proband: 32 years, III-5: 35 years, and III-6: 34 years). Our patient's family history confirms a possible association between the mutation types and phenotypic outcome. Hence, the age of onset of renal failure can be influenced by the causal mutation, highlighting the importance of molecular genetic analysis for ADPKD patients.

Regarding T1DM, genetic susceptibility and environmental factors interact to form the basic element in its progression.[11] In the pedigree of our report, T1DM in combination with ADPKD was diagnosed in our patient and his two sisters (III-5 and III-6) who were all found positive for glutamic acid decarboxylase and anti-islet cell antibodies. It is rare for three or more siblings to develop T1DM, even though such cases have been reported in large families and in other populations.[12–14] The lifetime risk of developing T1D is increased in relatives depending on which human leukocyte antigen haplotypes are shared.[15,16] The lifetime risk in siblings of T1D-affected patients is unidentified, and our report of the family of our patient should inspire clinicians to evaluate their risks of diabetes.

CONCLUSION

We have described an Omani patient diagnosed with early-onset T1D and with a heterozygous frameshift mutation in the *PKD1* gene who developed ESKD in his early thirties. His family had a longtime history of ADPKD and T1D. The study of familial clustering of specific disease is an essential concept in genetic epidemiology that facilitates lifetime risk evaluation and early assessment, both in patients and their relatives. We recommend early genetic diagnosis in such cases to facilitate early treatment and thereby prevent the disease progression and the associated morbidity.

Disclosure

The authors declared no conflicts of interest. The study was approved by the Research and Ethical Review and Approval Committee of the Ministry of Health (MOH) in Oman (MH/DGP/R&S/PROPOSAL_APPROVED/18) and conducted per the Declaration of Helsinki. Informed consent was obtained from the patient and his family members.

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