Simultaneous Pancreatic/Kidney Transplant in Adult with Autosomal Dominant Polycystic Kidney Disease and Type I Diabetes Mellitus

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Abstract

Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common inherited kidney diseases characterized by the growth of multiple bilateral cysts in the kidneys. Symptoms of ADPKD differ in severity and age of onset, but usually developed in adulthood between the age of 30 and 40, causing progressive renal function impairment and end stage kidney disease (ESKD). We described a 35-year-old gentleman with a combined familial ADPKD and type 1 diabetes mellitus (T1D). He has strong family history of T1D and ADPKD which was genetically proved by positive PKD1 gene frameshift deletion (NM_001009944.2; c.5014_5015delAG, p.(Arg1672fs*98)). He developed ESKD by the age of 32-years and underwent a preemptive simultaneous pancreatic and kidney transplant from deceased donor with multiple complications perioperatively. This paper reports a rare familial T1D in concordance with ADPKD, resulting in progressive decline of kidney function. Evaluation of familial clustering of genetic disease is critical concept in genetic epidemiology and precision medicine that helps in lifetime disease-risk estimation and early assessment and detection of disease in other siblings.

Keywords: Autosomal dominant polycystic kidney disease (ADPKD); type 1 diabetes mellitus (T1D); end stage kidney disease (ESKD); simultaneous pancreatic and kidney transplant; genetic disease.

Introduction

Type 1 diabetes mellitus (T1D), previously known as insulin-dependent diabetes mellitus (IDDM), is a disorder of glucose homeostasis characterized by susceptibility to ketoacidosis (DKA) in the lack of insulin therapy caused by destruction of pancreatic beta-cells. It is a genetically heterogeneous autoimmune disease affecting about 0.3% of Caucasian populations ¹. Genetic studies of T1D have focused on the detection of loci associated with increased susceptibility to this multifactorial phenotype.

Polydipsia, polyuria, and weight loss are the typical phenotype of diabetes mellitus as a consequence from hyperglycemia-induced osmotic diuresis and secondary thirst. These derangements can lead to long-term complications mainly affecting the eyes, kidneys, nerves, and blood vessels. Many patients may present with DKA, which can be a major risk of mortality. Celiac and thyroid diseases are the major autoimmune diseases associated with T1D.
Polycystic kidney disease (PKD) is one of the most common hereditary kidney diseases affecting the renal tubules. It consists of autosomal dominant (ADPKD) and autosomal recessive PKD (ARPKD). It is estimated that ADPKD is affecting over 10 million individuals worldwide, with a prevalence of 1:400 to 1:1,000 live births. Currently, between 7-15% of patients commencing renal replacement therapy (RRT) in the developed countries has ADPKD, demonstrating a significant public health burden.

Genetically, ADPKD is a heterogeneous disease and mutations in PKD1 and PKD2 are the major causes of ADPKD, although 5-10% of ADPKD pedigrees remain as either genetically unsolved or harbour rare mutations in other genes causing ADPKD-like phenotype, such as α-glucosidase neutral AB (GANAB), DNAJB11 or hepatocyte nuclear factor 1b (HNF1B) gene.

We herein report an interesting case of a 35-year-old man who has familial ADPKD combined with familial T1D with subsequent preemptive simultaneous pancreatic and kidney transplant.

Case Presentation

A 35-year-old gentleman, a well-known case of metabolic syndrome with background of obesity with body mass index (BMI) of 30, hypertension diagnosed since childhood (at age of 13-14 Y old), T1D since early childhood (diagnosed at age of 4 Y) was kept on insulin, dyslipidemia on statin and hyperuricemia on medications. Also, he had chronic kidney disease (CKD) — secondary to his autosomal dominant polycystic kidney disease (ADPKD).

His estimated glomerular filtration rate (eGFR) was kept stable > 90 ml/min till the age of 20 years, after which his kidney function showed gradual deterioration, and his eGFR reaches 11 by the age of 32 years. He was advised for preparation of renal replacement therapy (RRT) with options of transplantation, hemodialysis, or peritoneal dialysis. Therefore, he underwent a preemptive simultaneous pancreatic and kidney transplant from a deceased donor. However, he developed a history of long duration of fever for more than one month postoperative and he was treated by antibiotic (Imipenem/moxifloxacin) while inpatient post operation.

He was discharged, with serum creatinine of 78 umol/L, e GFR >90 ml/min/1.73m2 and suboptimal blood sugar of 10 mmol/L. Discharge medications after transplantation included Cyclosporine 75 mg BID, Mycophenolate sodium (Myfortic) 360 mg BID, Prednisolone 10 mg QD and Vildagliptin 25 mg QD. Two days later, he was readmitted with fever of 38.8 Celsius. On admission, he had fever, chills, generalized weakness and fatigue with mild abdominal pain mainly around the umbilicus. He had neither gastrointestinal symptom like nausea, vomiting, diarrhea, urinary tract symptoms nor any other systemic symptoms. On examination he was feverish with a temperature of 38.8°C, dehydrated, hypotensive (Bp:90/50 mmHg), tachycardiac (pulse rate:120/min) and tachypneic (respiratory rate: 22/min). Abdominal examination revealed mild distension and well healed scar extending from the umbilicus to suprapubic region. There was mild tenderness below the umbilicus. While on the right iliac fossa there was non-tender palpable kidney graft.

His investigations at admission time are shown in Table 1, revealing that the patient was anemic, low transferrin and high ferritin with neutrophilia and lymphopenia. His serum creatinine was 83 umol/L. with e GFR of >90 ml/min/1.73 m2, his fasting serum glucose was 7.0 mmol/L, glycated hemoglobin -HBA1C 5.5%, insulin serum level 227.3 pmol/L, C-Peptide of 2363 pmol/L, Amylase of 127 IU/L (n= 8-55) and Lipase-1 of 226 U/L (n=13-60).

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Normal Value</th>
<th>On admission</th>
<th>On discharge</th>
<th>Lab after intervention drainage</th>
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<td>Hemoglobin</td>
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<td>10.0 (g/dl)</td>
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<td>2.2-10 (10 *g/dl)</td>
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<td>Neutrophils</td>
<td>1- 5 (10 *g/dl)</td>
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<td>6.2 (10 *g/dl)</td>
<td>3.3 (10 *g/dl)</td>
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<td>204 (10*g/dl)</td>
<td>387 (10*g/dl)</td>
<td>292 (10*g/dl)</td>
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<td>Lymphocytes</td>
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<td>0.6 (10 *g/dl)</td>
<td>1.3 (10 *g/dl)</td>
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<td>Serum Sodium</td>
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<td>137 (mmol/L)</td>
<td>137 (mmol/L)</td>
<td>133 (mmol/L)</td>
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<td>Unit 2</td>
<td>Unit 3</td>
<td>Unit 4</td>
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<tr>
<td>Serum</td>
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<td>e GFR</td>
<td>&gt;90ml/min/1.73m2</td>
<td>&gt;90ml/min/1.73m2</td>
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<td>Serum Insulin</td>
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<td>227.3 (pmol/L)</td>
<td>64.3 (pmol/L)</td>
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<td>4.5 (mmol/L)</td>
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<td>HbA1C</td>
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<td>35 mmol/mol</td>
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<td>Lipase-1</td>
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<td>226 (U/L)</td>
<td>74 (U/L)</td>
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<td>8-55 (Iu/L)</td>
<td>127(Iu/L)</td>
<td>130 (Iu/L)</td>
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<td>C-Peptide</td>
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<td>2363 (pmol/L)</td>
<td>2994 (pmol/L)</td>
<td>716 (Pmol/L)</td>
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<td>18 (Iu/L)</td>
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<td>C-Reactive protein</td>
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<td>14.2 (mg/L)</td>
<td>4.4 mg/L</td>
<td>1.4 (mg/L)</td>
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<td>55247 (copies/ml)</td>
<td>&lt;100 (copies/ml)</td>
<td>&lt;100 (copies/ml)</td>
</tr>
<tr>
<td>BK PCR</td>
<td>Nil (copies/ml)</td>
<td>Below detection</td>
<td>Below detection</td>
<td>Below detection</td>
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</table>

His blood cultures revealed no growth, his urine culture grew Enterococcus faecium, which was sensitive to vancomycin. Also, the pus discharge from his surgical wound grew Carbapenem resistance Klebsiella Pneumoniae ss. Pneumoniae, which was sensitive to Tigecycline and Citrobacter Freundii which was sensitive to Septrin. His chest X-ray revealed normal lung fields with prominent heart size. Abdominal x-ray revealed no abnormal dilated bowel loops with no signs of free gas. Echocardiography showed mild pericardial effusion measuring 7 MM behind right atrium and grade1 diastolic dysfunction with an ejection fraction of 55%. Figure 1C-D summaries the Magnetic Resonance Image (MRI), which shows multiple collections at the site of the transplanted kidney and pancreas, suggestive of abscess, likely infected hematomas.
Figure 1: Clinical and genetic evaluation of the family with ADPKD and concurrent T1D. A. Pedigrees of the index Omani family showing the distribution of ADPKD, T1D and T2D among family members. Squares specify males; circles specify females. Arrows point to proband; filled squares and circles specify affected individuals in the family. Pedigrees were constructed and drawn using Progeny Free Online Pedigree Tool (Progeny Genetics LLC, Delray Beach, FL, www.progenygenetics.com). B. Genomic DNA Sanger chromatograms showing heterozygous PKD1 c.5014_5015delAG; p.Arg1672fs*98 frameshift deletion. C. Abdomen Magnetic Resonance Image (MRI) image from patient III-4 post kidney and pancreatic transplant. It revealed that the native kidneys are showing features of polycystic kidney disease, with innumerable variably sized renal cysts, replacing the normal renal parenchyma of the kidneys, some of them are hemorrhagic. The native pancreas is atrophic. The transplanted kidney is in the right iliac fossa, with a longitudinal axis of about 8.8 cm, it is of smooth outline and it is of normal parenchymal signal intensity. No evidence of pelvicalyceal system dilatation. D. Magnetic Resonance Image (MRI) of the abdomen clearly shows multiple collections at the site of the transplanted kidney and pancreas, suggestive of abscess, likely infected hematomas. One of the collections is large abdominopelvic, insinuating between the sigmoid and the transplanted pancreas, midline in location extending to the right iliac fossa between the pancreas and the external iliac vessels, then crossing the renal pelvis, and extending superiorly reaching the anterior surface of the kidney, situated between the kidney, caecum and terminal ileum with a depth of 3.1 cm. Another collection was seen posterior to the transplanted pancreas and medial to the right iliac vessels of 3.8x3.5x3.3 cm that is reaching up to the above-mentioned collection.

MRI showed the native polycystic kidneys, with innumerable variably sized renal cysts, replacing the normal renal parenchyma of the kidneys, some of them are hemorrhagic. The native pancreas is atrophic. The transplanted pancreas is in the lower abdomen at midline position with no pancreatic duct dilatation but distorted because of adjacent collections, with surrounded small bowel adhesions. The transplanted kidney is in the right iliac fossa with a longitudinal axis of 8.8 cm with no evidence of pelvicalyceal system dilatation. There were multiple collections seen at the site of the renal and pancreatic transplants, suggestive of abscess, likely infected hematomas, one of the collections is large abdominopelvic, insinuating between the sigmoid and the transplanted pancreas, midline in location extending to the right iliac fossa between the pancreas and the external iliac vessels, then crossing the renal pelvis, and extending superiorly reaching the anterior surface of the kidney, situated between the kidney, caecum and terminal ileum with a depth of 3.1 cm. Another collection was seen posterior to the transplanted pancreas and medial to the right iliac vessels of 3.8x3.5x3.3 cm that is reaching up to the above-mentioned collection.

Multidisciplinary teams decided for interventional drainage of the collection with a Pig Tail insertion. The interventional radiologist drained 30 ml of frank thick pus that was sent for culture and sensitivity that showed Klebsiella Pneumoniae, which was sensitive to Septrin and Tigecycline.

Post drainage, the ultrasound showed a transplant kidney of 12 cm, normal echotexture, no hydronephrosis, resistivity index of 0.54-0.58, small 6 ml peri-graft collection, previous collection could not be seen with no definitive collection.

Abdominal Computerized Tomography was done after drainage showed a significant resolution of the previously noted pelvic collection with pigtail drainage tube in situ with small collection 2.2x1.9x1.8 cm in the posterior component, with no other sizeable collection.

Pig tail was removed after a week of no further drainage and a repeat ultrasound showed peri-graft collection of only 6 ml. He was managed along with disciplinary teams including infectious disease, and transplant surgeons with full course of intravenous antibiotics for 3 weeks and follow up CT reviewed by surgeons and ID team.

He was discharged a month later, on a small dose of insulin of 8 U/day with tapering down of his steroids to 2.5 mg OD. He was kept on Tacrolimus 3 mg BID, Cellcept (MMF) 1 gm BID and Valganciclovir 900 mg OD.

He continued his antibiotics of tigecycline on daily base at day care ward. His laboratory investigations, as shown in table 1, showed a progressive improvement with normal eGFR > 90 ml/min/1.73m2, serum glucose 4.4 mmol/L on insulin R 30 U/day, normal CRP 1.4, with normal total WBCs 4.5 and undetected CMV/BK-PCR.

He has strong family history of both ADPKD and diabetes mellitus. His father is diabetic without kidney disease, and his mother has ADPKD without diabetes and had a kidney transplant at age of 32 years. One brother and two sisters had ADPKD, where the brother had kidney transplant at age of 59 years. Another two sisters have
ADPKD with type 1 diabetes on insulin. A younger sister has neither ADPKD nor diabetes till now. The family tree is shown in figure 1A.

Proband’s sister III-1 underwent targeted next-generation sequencing (NGS) 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 1B). The extended family was screened for the offending mutation described above using Sanger sequencing and revealed that our proband, his mother and another 3 sisters (III-2, III-5 and III-6) are carriers.

This 2-bp deletion leads to frameshift and premature termination (p.Arg1672fs*98). It has not been found in ExAC, or gnomAD databases. However, it is classified as definitely pathogenic variant in the PKD mutation database(http://pkdb.mayo.edu/) and it is reported in multiple publications including that by Rossetti et al.

Discussion

ADPKD (OMIM# 173900) is an autosomal dominant form of polycystic kidney disease, has the typical manifestations of renal cysts, liver cysts, and intracranial aneurysm. Severe and chronic pain and nephrolithiasis are frequent complications and renal function failure is the most serious renal complication, which occurs in approximately 75% of patients by the age of 70 years. The typical age of onset is in middle life, but it is broadly variable ranging from as early as first decade to as late as eighth decade the range is from infancy to 80 years.

Similar to many countries, inherited and congenital kidney disease is an essential cause of ESKD in our population characterized by high rate of consanguinity. Recently, it was reported that genetic kidney diseases comprise 5% of all causes of ESKD and ADPKD is the most prevalent genetic kidney disease causing ESKD, accounting for 2% of total ESKD population. In Oman, patients with inherited kidney disease start RRT at a younger age (mean age, 29 years), being more prevalent in the pediatric and early age group compared to the elderly patients (≥65 years).

In the present paper, we report a patient who had T1D at age of 4 with ADPKD caused by a heterozygous frameshift deletion mutation in PKD1 leading to early kidney failure. His maternal-side family had a history of ADPKD throughout three generations. His father had no history or clinical symptoms associated with kidney disease, however he developed T2D with higher age. Our patient started to have symptoms of T1D since early childhood and was diagnosed at 4 years. Furthermore, enlarged kidneys with multiple bilateral cysts along with hepatic cysts and hypertension are the typical characteristics of ADPKD in this family for multiple generations. Our patient received a preemptive simultaneous pancreatic and kidney transplant from deceased donor that led to multiple complications.

Diagnosis of ADPKD is typically based on family history, ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI). Nevertheless, genetic testing can assist the diagnosis where the renal phenotypes are unclear, in the lack information of family history and in categorizing donors for transplantation. Both clinical investigations and molecular genetic analysis prove the diagnosis of ADPKD in our patient. Genetically, our patient was found to carry a previously reported heterozygous 2-bp deletion (NM_001009944.2; c.5014_5015delAG) in exon 15 of the PKD1 gene. Mutations in PKD1 (16p13.3) accounts for around 85% of ADPKD patients and are expected to lead to ESKD by, on average, age 53.3 years, which is earlier than the average age of ESKD in patients with PKD2 (4q22.1) mutations (72.7 years). Furthermore, truncating PKD1 mutations are linked with ESKD onset at younger ages than non-truncating mutations. In agreement with these studies, our patient and his family developed ESKD at younger ages earlier than 50 years of age (proband: 32 years, III-5: 35 years and III-6: 34 years), although their mother developed renal failure at 56 years. This family 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.

Diabetes mellitus (DM) is a major public health burden. With the global tendency of growing incidence and prevalence of diabetes, the number is predicted to reach 285 million cases in 2025. The incidence and prevalence of T1DM is rather variable in different countries, but recent meta-analysis study estimated the worldwide incidence of T1D is 15 per 100 000 population and the prevalence of T1D is 9.5 per 10 000 people. In Oman, the incidence and prevalence of T1D, which constitutes about 5%–15% of all cases and often involve children, is
not known, may be due to poor registration and absence of disease suspicion and follow-up. The only available study documenting the incidence of childhood T1DM (aged 0–14 years) in Oman is dating back to over two decades ago, in which Soliman et al. reported an incidence rate of 2.45 and 2.62 per 100,000 per year in 1993 and 1994 17.

It is well recognized that interaction between genetic susceptibility and environmental factors comprises the basic element in progression of T1D 18. The genetic contribution is abundantly suggested by the comparatively high degree of familial clustering among patients with T1D, although there is no recognizable pattern of inheritance 19. The major genetic determinants, associated with 40% of the genetic susceptibility, map to the major histocompatibility complex (MHC) at chromosome6p21, even though other susceptibility gene markers outside the MHC, including the insulin gene, have also been associated to T1D risk with different degrees 18. A simultaneous clinical manifestation of T1D in siblings is rare as most incidences are sporadic rather than familial. In the pedigree of our report, T1Din combination with ADPKD was diagnosed in our patient and his two sisters (III-5 & III-6), who are all positive for glutamic acid de carboxylase and anti-islet cell antibodies. It is rare for three or more siblings to develop T1D, even though such cases had been reported in large families and in other populations 20-22. Although it is estimated that approximately 85% of new cases of T1D occur in persons without an affected first-degree relative, the life-time risk of developing T1D is increased in relatives depending on which HLA haplotypes are shared 23, 24. The lifetime risk in siblings of T1D affected patients is unidentified and our report of this family will inspire clinicians to evaluate the risks of diabetes in siblings of patient with T1D.

The epidemiological data suggested that the lifetime risk of progressing ESKD for T1D patients is varying from as low as 10–15% to as high as 25–30% 25, 26. Consequently, not every T1D patient may develop progressive nephropathy that eventually requires dialysis or transplantation. This is a result of several factors, including the competing cardiovascular risk of death as well as blood glucose and pressure control. Different studies from varying populations have shown that the risk of ESKD has declined constantly over time and that the progression of diabetic nephropathy and renal failure is slower than before among patients with T1D. There is strong evidence that achieving the best metabolic control (A1c <7%) along with treating hypertension (<130/80 mmHg or <125/75 mmHg if proteinuria >1.0 g/24 h and increased serum creatinine), using drugs with blockade effect on the renin-angiotensin-aldosterone system, and treating dyslipidemia (LDL cholesterol <100 mg/dl) are successful strategies for preventing the development of microalbuminuria, in delaying the development to more complex stages of nephropathy and in decreasing cardiovascular mortality in patients with T1D 25. In their studies of Finnish population, Helve et al. (2018), showed that ESKD developed more slowly, at which within 30 years from the diagnosis of T1D approximately 7.0% of the patients developed renal failure and those less than 5 years old at the time of diagnosis had the lowest risk of ESKD after diagnosis 27.

Conclusion

We describe a patient diagnosed early-onset T1D and with a heterozygous frameshift mutation in the PKD1 gene who developed ESKD at his earlier30s. His family has longtime history of ADPKD in addition to familial T1D. The study of familial clustering of specific disease is an essential concept in genetic epidemiology that would facilitate lifetime risk evaluation and early assessment and detection of other siblings. Also, this report highlights the significance of early genetic diagnosis in implementing precision medicine to establish early treatment and prevent the disease progression and associated morbidity.

Acknowledgments

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Disclosure of potential conflicts of interest

The study was approved by the Scientific Research Committee at the Royal Hospital and SQUH, Muscat, Oman and certify that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments ethical standards. https://mohcsr.gov.om/my-researches/
Availability of data and material

No more Data available publicly but can be requested from the corresponding author in a reasonable time.

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Conflict of Interest

Authors declare no conflict of interest.

Authorship and Disclosures

Each person listed as an author has participated sufficiently in the intellectual content, the analysis of data, and/or the writing of the manuscript to take public responsibility for it. Each author has reviewed the manuscript, believes it represents valid work, and approves it for submission.

References


