Renal cell carcinoma of native kidney in allogeneic transplant recipient with acquired cystic kidney disease – case report and literature review

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ABSTRACT
Acquired cystic kidney disease (ACKD) develops in patients with end-stage renal insufficiency, irrespective of the primary reason of renal dysfunction. The risk of cancer development in this group of patients is many times higher than that in the general population. We present a case of an allogeneic kidney transplant recipient with ACKD, in whom, during a follow-up visit 10 years after transplantation, a tumor in the native kidney was found. After computer tomography the patient was qualified for left-side nephrectomy. Histology confirmed the presence of a tumor built of clarocellular kidney cells in the T1 N0 M0 stage of advancement. We present the diagnostic management algorithm in renal transplant recipients before and after transplantation and review the current literature.

INTRODUCTION
Acquired cystic kidney disease (ACKD) is a pathology developing in primarily normal kidneys during the end stage of insufficiency (ESRD – end stage renal disease). ACKD was first described by Dunhill in 1977. The disease develops in dialyzed patients, but may also appear in patients with renal insufficiency that are not yet qualified for dialysis. ACKD develops irrespectively of the type of dialyses and the severity of cystic transformation in the kidney increases with progressing insufficiency and duration of dialysis treatment. ACKD of a native kidney may develop in kidney transplant recipients and the incidence increases with time after transplantation. There are reports suggesting the effect of immunosuppressive treatment on the development of ACKD. One of the most serious complications of ACKD is development of cancer in the native kidney. It is estimated that the risk of renal cancer among patients with ACKD increases 15 to 100 times in comparison to the general population. The disease oftentimes comprises both kidneys and in about 50% is multifocal. Then treatment of choice is resection of the affected kidney.

We present an allogeneic kidney recipient, in whom, during follow-up visit 10 years after transplantation, a tumor in the native kidney was found (on histology: RCC – renal cell carcinoma) with coexisting ACKD.

CASE REPORT
Patient S.L., aged 45 years, hemodialyzed from 1993 due to end stage renal insufficiency in the course of glomerulonephritis (not confirmed by biopsy). In September 1998 in the Department of Urology and Kidney Transplantology, M. Pirogow District Hospital, he received a kidney transplant from a donor with brain death, complicated with a single episode of transplant rejection in October 1998. Primary tri-drug immunosuppression was based on cyclosporine (Neoral), azathioprine (Imuran) and prednisone (Encorton), and then converted to tacrolimus (Prograf) and mycophenolic acid (Myfortic). On 08.17.2008 the patient was admitted to the Department of Urology and Kidney Transplantology, M. Pirogow District Hospital, Łódź (case no: 6713/2017) because of a tumor in the native kidney confirmed by imaging studies. Ultrasound and then two stage CT of the abdominal cavity (Figs. 1 and 2) performed in August 2008 showed numerous cysts in the cortex up to 16mm diameter in both cirrhotic native kidneys, and in addition in the lower pole of the left native kidney a tumor 20 mm in diameter protruding the external contour. The transplanted kidney was normal in ultrasound and CT.

The patient was qualified for resection of the left native kidney. Renal parameters before surgery were as follows: urea 152.0 mg/dl, creatinine 3.4 mg/dl, uric acid 10.5 mg/dl, Na 139.0 mmol/l, K 3.8 mmol/l, Cl 111.0 mmol/l. Left lumbar incision was used to reach the kidney and visualize its lower pole with tumor. The kidney was removed together with the tumor and adipose capsule. The post-operative course was uneventful; the patient did not require dialysis. He was discharged on the 8th postoperative day, in good general condition, with healed wound, and lab results: 24-hour urine 4000 ml, urea 171.0 mg/dl, creatinine 3.8 mg/dl, uric acid 10.3 mg/dl, Na 139.0 mmol/l, K 4.2 mmol/l, Cl 108.0 mmol/l.

Histology (sample no. 24881/08) revealed tumor of the lower pole of the left kidney 15 mm in diameter – microscopically Carcinoma de celulas renalibus (typus clarocellularis) – I° malignancy acc. to Fuhrman, not involving the connective tissue kidney capsule. Renal hilus had no histooncological lesions; tumor was in stage of advancement pT1a.

DISCUSSION
Renal cancer in the native kidney in patients with acquired cystic kidney disease, and also in renal transplant recipients, is becoming more common due to lengthening of the follow up period of patients after transplantation.

Neoplastic processes occurring in patients after renal transplant may be divided into three groups:

1. Neoplastic diseases present before transplantation and detected in the first year after transplantation. In the described recipient there were no neoplasms before transplantation or in the first year after the procedure.
2. Neoplasms transferred with the kidney – there is a possibility of random transfer of neoplastic cells together with the transplanted organ. Because of this possibility the National Transplantation Council introduced, in 2006, a standard of imaging studies and neoplastic markers panel obligatorily performed in all donors. The protocol of organ collection comprises physical examination of the donor and intraoperative examination. If a neoplastic disease is detected in a donor, control of all recipients of organs from the same donor is obligatory. Additionally, the serum of the donor is stored for 5 years after transplantation. In the presented case there were no tumors in the transplanted kidneys within the whole period after transplantation.


In organ recipients, apart from monitoring of the functions of new organs, screening towards neoplasms is a must because of immunosuppressive treatment. The group of kidney transplant recipients is a risk group for tumors in native kidneys; they constitute about 90% of renal neoplasms diagnosed in this group [6]. The etiology of cancer development in the native kidney after renal transplantation is not known, but significant risk factors include, among others, acquired cystic kidney disease, which increases the risk of renal cancer in kidney recipients by over 4 times [10, 12]. The incidence of ACKD is closely connected with the duration of end stage renal disease – after 10 years 80% of dialyzed patients suffer from ACKD [1]. ACKD is diagnosed if cystic lesions are present in more than 25% of kidney parenchyma visible on ultrasound. Another described criterion is demonstrating the presence of at least 3 cysts in each kidney in a patient with end stage renal disease if the genetic background of cysts is excluded. ACKD is usually asymptomatic – sometimes the presence of cysts is suggested by lumbar pain, hematuria, or abdominal pain. The pathogenesis of ACKD has not been fully elucidated, but it is connected with the activation of proto-oncogenes, which may be responsible for the development of renal cell carcinoma. Literature reports contain contrasting data on the effect of allogenic kidney transplant on the development of ACKD. According to some authors it leads to the development and progression of ACKD in native kidneys, but there are reports of rapid regression of ACKD in native kidneys after successful kidney transplantation. It is possible that such discrepancies result from other important factors affecting the course of disease, one of which undoubtedly is immunosuppression in patients after organ transplantation. Literature abounds in contrasting reports about the effect of immunosuppressive treatment on the development of neoplasms (including renal cell carcinoma in native kidneys) in kidney recipients [7, 10]. In the majority of reports it is suggested that long term immunosuppression and treatment of acute graft rejection significantly increases the risk of neoplasm development in the observed patients. Other significant risk factors of neoplastic diseases in kidney recipients include: patient’s age (significant increase of relative risk in age groups after 45 and 60 years – 2-fold and 4-fold, respectively), neoplastic disease in the past (almost 2.3-fold risk increase), and splenectomy (almost 2-fold risk increase) [3, 9].

Cancer in the native kidney with ACKD in patients after allogenic transplantation is more common than in the general population. 10-year risk of malignancy in native kidneys of kidney recipients is about 20% and is over 15-fold higher than that in the general population, although even a 100-fold risk increase has been described in literature [1, 7, 10, 11]. Kliem et al., in their material of 2,372 kidney recipients, found tumor of the native kidney in 12 patients (7.8% of all malignant tumors detected) accompanied, in 73% of cases, by ACKD in native kidneys [10]. According to Doublet et al. in...
a group of 129 kidney recipients followed up regularly, renal cancer was seen in 5 patients (3.9%) [7]. Heinz-Peer et al. in the group of 385 kidney recipients during follow up detected tumors in native kidneys in 7 patients, in whom RCC was found in 6 patients, and 5 out of 6 patients with histologically confirmed RCC had ACKD (83.3%) [5]. Schwarz et al. among 916 kidney recipients found RCC in 8 patients; 7 of them had ACKD (87.5%); in 1 patient tumor in the transplanted kidney was found [12]. In our material of 350 transplanted kidneys (transplantations between 1996 and 2007) native kidney cancer was found in 3 patients.

Despite many potential risks for kidney recipients, constant improvements in the standards of care of post transplant patients and new immunosuppressive treatment regimes have significantly increased the life expectancy among kidney recipients within the last three decades. Currently it is twice as long that of dialyzed patients, irrespectively of the age of patients. Due to significant cumulative risk of neoplasms in native kidneys among allogenic kidney recipients and ageing of the population of patients within the renal transplantation program, neoplasms (including renal tumors) may soon become the leading reason of late deaths among patients after kidney transplantation.

Current recommendations of the American Society of Transplantation and European Dialysis and Transplant Association do not include any algorithm of treatment in terms of prophylactic management aimed at early detection of native kidney cancer in the discussed group of patients. However, both sets of recommendations point to the necessity of screening, but with no clear suggestions as to the frequency of examinations. Recommendations by the Committee of the American Society of Transplantation do not state the optimal frequency of ultrasound screening towards tumors in native kidneys and routine imaging studies in this respect are not recommended [8], European Best Practice Guidelines for kidney transplantation leave the decision as to screening imaging studies, such as ultrasound of native kidneys, to the physician and do not specify margin values suggested for these examinations and time intervals between examinations: „All renal transplant recipients should have regular ultrasonography of their native kidneys (when applicable) for screening of renal cell carcinomas, which are observed at much higher incidence in both dialyzed and transplanted patients” [4].

It seems reasonable to systematize suggestions included in the above mentioned recommendations and construct a program of prophylactic management.

CONCLUSIONS

The number of transplanted kidneys increases and the life span of transplanted organs becomes longer. At the same time the follow up period of kidney transplant recipients increases too. There is a need for close monitoring of recipients regarding neoplasms in native kidneys. It seems necessary to design a study aimed at development of appropriate guidelines.

Thorough presentation of screening diagram in the studied group of patients exceeds the span of this publication; it would require detailed calculation of screening costs to statistical increase in the patients’ life expectancy. Despite this fact, in patients from the discussed group, initially regular control ultrasound scans of the urinary system may be indicated every 12 months, irrespectively of the time from transplantation. In kidney recipients with ACKD ultrasound studies should be combined with control CT, as ultrasound is not sufficiently accurate for exact proper evaluation of lesions in kidneys containing multiple cysts [2]. The suggested scheme of control examinations with mean linear tumor growth rate described in literature – about 1 cm/year – in the studied group of patients would allow for the detection of renal cancer in its early stage and make effective radical treatment possible [5].

REFERENCES


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