Acquired Cystic Kidney Disease and Renal Cell Cancer after Transplantation: Time to Rethink Screening?

John D. Scandling

Adult Kidney and Pancreas Transplant Program, Palo Alto, California

Clin J Am Soc Nephrol 2: 621-622, 2007. doi: 10.2215/CJN.02000507

Acquired cystic kidney disease (ACKD) may have been first described more than a century ago (1). Its recognition as a disease of consequence in patients who undergo long-term maintenance hemodialysis was in the 1970s (2). In the ensuing three decades, repeated cross-sectional studies have corroborated early findings that this disease affects one third or more of long-term (≥3 yr) hemodialysis patients and that approximately 20% of those with ACKD will have renal cell carcinoma, representing a prevalence of approximately 5% (3). Age, male gender, and duration of dialysis are primary risk factors. It may occur less frequently in those who are on peritoneal dialysis and may regress after transplantation (4). Its pathogenesis is not understood but may relate to the activation of proto-oncogenes, which may also be responsible for the subsequent development of renal cell carcinoma (5).

Transplantation carries risk for cancer, more so as the years of exposure to the immunosuppressive agents accrue. Kidney transplant recipients in the United States have been shown to carry a 15-fold risk for kidney cancer (which would include non–renal cell cancers as well) in the first 3 yr after transplantation when compared with the general US population and a 39% higher risk for developing kidney cancer in those years in comparison with transplant candidates who are still on the waiting list (6).

Recommendation to screen patients with ESRD for ACKD and renal cell cancer has not been uniform because of their limited life expectancy (7). Screening kidney transplant candidates for ACKD and kidney cancer is recommended by the North American and European professional transplantation societies, but the guidelines as to who should be screened are vague. The guideline of the American Society of Transplantation recommends screening patients who are at high risk for renal cell carcinoma but does not define high risk (8). The guideline of the European Renal Association–European Dialysis and Transplant Association recommends screening of candidates who have been long-term dialysis patients but does not define long-term (9). It is not known whether these guidelines are followed in practice.

The two societies differ in their recommendation for screening after kidney transplantation. The American society guideline does not recommend screening (10). The European society guideline recommends screening but with the qualifier that it be done "when applicable," which is not defined (11). Again, the adherence to this guideline in practice is unknown.

In this issue, Schwarz *et al.* (12) report their findings of ACKD and renal cell cancer in a cross-sectional study of a large population of kidney transplant recipients who were anywhere from having recently received a transplant to 33 yr after transplantation. The mean duration of dialysis was 4 to 5 yr, and the mean time since transplantation was 9 yr. Of 916 eligible patients, 561 (61%) participated and underwent ultrasound of the native kidneys. Of these, 129 (23%) were found to have ACKD, defined as more than three cysts in both kidneys. Eight (1.4%) patients had newly diagnosed renal cell cancer, seven of whom had ACKD. An additional 19 patients in the group studied had a history of formerly diagnosed renal cell cancer, 18 of whom had ACKD. Together, these 27 patients with renal cell cancer represented 4.8% of the 561 patients studied. The prevalence of renal cell cancer in those with ACKD was approximately 20% and >50% in those with complex cysts (Bosniak categories IIF, III, and IV) (13). These prevalences of renal cell cancer in a cohort of patients with ESRD and renal cell cancer in the presence of ACKD corroborate the findings of previous studies of both dialysis and transplant patients (3).

Schwarz *et al.* found that older age, male gender, a history of heart disease, larger kidneys, and greater kidney calcifications were associated with ACKD. There was no association with duration of dialysis, time since transplantation, or immunosuppressive regimen. Curiously, both duration of dialysis and time since transplantation were shorter in those with renal cell cancer. The type of renal cell cancer was clear cell carcinoma in 58% and papillary carcinoma in 42% (one patient had both types). All patients were asymptomatic at diagnosis, and only one was found to have a metastasis, a lung metastasis in a patient with clear cell carcinoma. All were treated successfully with surgical resection. The benign course in these patients was in distinct contrast to an earlier report from the same institution, wherein metastatic disease and mortality were more common (14). Their relatively benign course was thought to be related to earlier detection, small size of cancer at detection, the overrepresentation of papillary *versus* clear cell carcinoma in ACKD and lower proliferative activity in renal cell cancer associated with ACKD.

Schwarz *et al.* recommend a screening and management pro-

Published online ahead of print. Publication date available at www.cjasn.org.

Correspondence: Dr. John D. Scandling, Adult Kidney and Pancreas Transplant Program, 750 Welch Road, Suite 200, Palo Alto, CA 94304. Phone: 650-723-7929; Fax: 650-723-3997; E-mail: jscand@stanford.edu

ISSN: 1555-9041/204–0621

tocol in transplant recipients, incorporating the Bosniak renal cyst classification system (13):

1. All recipients: Yearly ultrasound screening of the native kidneys.
2. ACKD and Bosniak category I or II cysts (benign simple cysts): Twice yearly ultrasound screening, computed tomography scan if progression evident.
3. ACKD and Bosniak category IIF (F for follow-up) cysts (moderately complex cysts): Quarterly ultrasound screening and yearly computed tomography or magnetic resonance imaging scan, nephrectomy if progression evident even if not reaching category III or IV.
4. ACKD and Bosniak category III ("indeterminate" cystic masses) or IV (clearly malignant cystic masses): Nephrectomy.

Life expectancy after transplantation has improved with advances in the discipline over recent decades so that it is now well more than double that of a patient on dialysis regardless of age (15). In 2004, the expected remaining lifetime of a US transplant recipient 50 to 54 yr of age, which was the average age of the patients with renal cell cancer in the report by Schwarz *et al.*, was 17 yr. Cancer may soon be the leading cause of death late after transplantation (16). Despite the low prevalence of renal cell cancer in ESRD, the relatively benign course of the affected patients in the report by Schwarz *et al.*, and the possibility of lesser cancer risk with newer immunosuppressive regimens (17), it is time to rethink the published guidelines and consider screening all kidney transplant candidates and recipients for ACKD and renal cell cancer.

Disclosures

None.

References

1. Gehrig JJ Jr, Gottheiner TI, Swenson RS: Acquired cystic disease of the end-stage kidney. *Am J Med* 79: 609–620, 1985
2. Dunnill MS, Millard PR, Oliver D: Acquired cystic disease of the kidneys: A hazard of long-term intermittent maintenance haemodialysis. *J Clin Pathol* 30: 868–877, 1977
3. Chapman AB, Rahbari-Oskoui FF, Bennett WM: Acquired cystic disease of the kidney in adults. *UpToDate* version 15.1. Available online: http://www.uptodate.com. Accessed May 10, 2007
4. Lien YH, Hunt KR, Siskind MS, Zukoski C: Association of cyclosporin A with acquired cystic kidney disease of the native kidneys in renal transplant recipients. *Kidney Int* 44: 613–616, 1993
5. Oya M, Mikami S, Mizuno R, Marumo K, Mukai M, Murai M: C-jun activation in acquired cystic kidney disease and renal cell carcinoma. *J Urol* 174: 726–730, 2005
6. Kasiske BL, Snyder JJ, Gilbertson DT, Wang C: Cancer after kidney transplantation in the United States. *Am J Transplant* 4: 905–913, 2004
7. Sarasin FP, Wong JB, Levey AS, Meyer KB: Screening for acquired cystic kidney disease: A decision analytic perspective. *Kidney Int* 48: 207–219, 1995
8. Kasiske BL, Cangro CB, Hariharan S, Hricik DE, Kerman RH, Roth D, Rush DN, Vazquez MA, Weir MR; for the American Society of Transplantation: The evaluation of renal transplant candidates: Clinical practice guidelines. *Am J Transplant* 1[Suppl 2]: 3–95, 2001
9. EBPG Expert Group on Renal Transplantation, European Renal Association-European Dialysis and Transplant Association: Evaluation, selection and preparation of the potential transplant recipient. *Nephrol Dial Transplant* 15[Suppl 7]: 3–38, 2000
10. Kasiske BL, Vazquez MA, Harmon WE, Brown RS, Danovitch GM, Gaston RS, Roth D, Scandling JD Jr, Singer GS; for the American Society of Transplantation: Recommendations for the outpatient surveillance of renal transplant recipients. *J Am Soc Nephrol* 11[Suppl 15]: S1–S86, 2000
11. EBPG Expert Group on Renal Transplantation, European Renal Association-European Dialysis and Transplant Association: Long-term management of the transplant recipient. *Nephrol Dial Transplant* 17[Suppl 4]: 3–67, 2002
12. Schwarz A, Vatandaslar S, Merkel S, Haller H: Renal cell carcinoma in transplant recipients with acquired cystic kidney disease. *Clin J Am Soc Nephrol* 2: 750–756, 2007
13. Israel GM, Bosniak MA: An update of the Bosniak renal cyst classification system. *Urology* 66: 484–488, 2005
14. Kliem V, Kolditz M, Behrend M, Ehlerding G, Pichlmayr R, Koch KM, Brunkhorst R: Risk of renal cell carcinoma after kidney transplantation. *Clin Transplant* 11: 255–258, 1997
15. US Renal Data System: *USRDS 2006 Annual Data Report: Atlas of End-Stage Renal Disease in the United States*, Vol 1, Bethesda, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2006, p 136
16. Dantal J, Pohanka E: Malignancies in renal transplantation: An unmet medical need. *Nephrol Dial Transplant* 22[Suppl 1]: i4–i10, 2007
17. Campistol JM, Albanell J, Arns W, Boletis I, Dantal J, de Fijter JW, Mortensen SA, Neumayer H-H, Oyen O, Pascual J, Pohanka E, Schena FP, Seron D, Sparacino V, Chapman JR: Use of proliferation signal inhibitors in the management of post-transplant malignancies: Clinical guidance. *Nephrol Dial Transplant* 22[Suppl 1]: i36–i41, 2007

See the related article, "Renal Cell Carcinoma in Transplant Recipients with Acquired Cystic Kidney Disease," on pages 750–756.