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High mortality from urothelial carcinoma despite regular tumor screening in patients with analgesic nephropathy after renal transplantation

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Abstract Patients with end-stage renal failure due to analgesic nephropathy have an increased risk of developing a urothelial carcinoma. To determine the impact of renal transplantation on the frequency of urothelial carcinomas, we analyzed 2072 patients who underwent 2371 renal transplantations between 1968 and 1993, including 78 (3.8 %) with clinically proven analgesic nephropathy. Before and after transplantation a regular tumor screening was performed in patients with analgesic nephropathy by urine cytology and abdominal sonography. In 11 of the 78 patients with analgesic nephropathy (14.1 %; age 51–66 years, 40–108 months after initiation of dialysis treatment, 5–77 months after transplantation), a urothelial carcinoma of the native urinary tract, especially the kidneys, was diagnosed. Therapy comprised nephroureterectomy (n = 6), transurethral resection (n = 6) and/or cystectomy (n = 2). Seven patients died due to tumor progression 16.3 (4–33) months postoperatively and one patient died due to a perioperative complication. Despite regular tumor screening after transplantation, the diagnosis of a urothelial carcinoma was made very late, leading to a high tumor-related mortality. As a consequence, we suggest that a bilateral nephroureterectomy should be performed prophylactically in patients with proven analgesic nephropathy. In addition, a cystoscopy with lavage cytology testing of the bladder should be performed twice a year.

Key words Analgesic nephropathy, urothelial carcinoma, kidney transplantation · Kidney transplantation, urothelial carcinoma · Urothelial carcinoma, kidney transplantation

Introduction

The prevalence of analgesic nephropathy among patients on renal replacement therapy lies in the range of 4 %–5 % in Germany [25]. Accordingly, the frequency of analgesic nephropathy among patients on the waiting list for renal transplantation in Hannover currently runs as high as 4.1 % (36/886 patients). The development of urothelial carcinomas in patients with analgesic nephropathy is a well-known complication which has been proven by numerous prospective studies [1–4, 6, 10, 13, 15, 16, 18, 20]. Autopsy studies have revealed a prevalence of up to 10 % of urothelial carcinomas in patients with analgesic nephropathy [1, 10, 15, 18]; multifocal growth was shown in up to 30 % [7]. The latent period before a urothelial carcinoma becomes clinically apparent is about 20 years and depends on the cumulative dose of analgesics ingested [3, 17].

The renal transplant patient with analgesic nephropathy carries an increased risk of developing a urothelial carcinoma due, on the one hand, to the long course of the disease and, on the other, to the immunosuppressive regimen. As data about frequency, clinical course and prognosis of urothelial carcinomas after renal transplan-

Table 1 Characteristics of renal transplant patients with analgesic nephropathy ($n = 78$) (*RTx* renal transplantation, *MP* methyl-prednisolone, *ATG* antithymocyte globulin)

	Without urothelial carcinoma ($n = 67$)	With urothelial carcinoma ($n = 11$)	*P*
Female : Male	2.7 : 1	4.5 : 1	
Age at RTx (years)	54 (29–68)	51 (40–63)	NS
Time on hemodialysis (months)	49 (5–240)	34 (13–77)	NS
Graft function (months)[a]	63 (2–198)	49 (20–106)	NS
Time on hemodialysis and graft function (months)	109 (31–268)	98 (61–139)	NS
Long-term immunosuppression:			
Azathioprine/prednisolone	13.4 %	18.2 %	
Cyclosporin A/prednisolone	70.1 %	72.7 %	
Triple drug therapy	16.4 %	9.1 %	
Rejection episodes:	19.4 %	27.3 %	
Treated with i.v. MP	$n = 13$	$n = 3$	
Treated with i.v. ATG	$n = 3$	–	

[a] In case of death or graft loss: time from RTx to death or graft failure. In case of urothelial carcinoma: time from RTx to first diagnosis of carcinoma

tation in larger patient populations are sparse, we retrospectively studied the long-term outcome of all of our renal transplant patients with analgesic nephropathy. The relevance of regular tumor screening (urine cytology, abdominal ultrasound) for the early detection of urothelial carcinomas in these patients was also studied.

Patients and methods

This retrospective study comprises all patients who received a renal graft between December 1968 and May 1993 at the Medizinische Hochschule Hannover. After transplantation, all patients were seen 2–12 times per year in our outpatient clinic. At each appointment, the following data were recorded: body weight, blood pressure, electrolytes, creatinine, urea, serum protein, electrophoresis, liver enzymes, full blood count, clotting screen, creatinine clearance, urine protein, and urine sediment. In addition, in patients with end-stage renal failure due to analgesic nephropathy, urine cytology testing was performed 2–4 times/year and an abdominal ultrasound, with special regard to the native kidney, was carried out 1–2 times/year. In the case of a positive or doubtful finding during ultrasound examination, a computer tomography scan and a retrograde ureteropyelography with lavage cytology testing were initiated.

The diagnosis of analgesic nephropathy was based on the exclusion of other renal diseases, on a characteristic past history (> 1.5 kg of mixed analgesics containing phenacetin or paracetamol), on clinical findings, and on renal ultrasonography. Abdominal ultrasonography, urine cytology and, whenever possible, cystoscopy and retrograde ureteropyelography were performed in all patients with analgesic nephropathy before they were placed on the waiting list for renal transplantation.

In the long run, all renal transplant patients received either azathioprine (1.5–2.5 mg/kg per day) or cyclosporin A (trough level 100–150 ng/ml) plus prednisolone (7.5 mg/day maintenance dose) as immunosuppressive medication. About 20 % of the patients had triple drug immunosuppression in the long-term course [prednisolone 7.5 mg/day, azathioprine 1–2 mg/kg per day, and low-dose cyclosporin A (trough level 50–90 ng/ml)]. Episodes of biopsy-proven acute graft rejection were treated with intravenous bolus doses of 0.5–1.0 g methyl-prednisolone on 3–5 consecutive days, depending on the response to therapy. In cases where there was no response to this therapy, additional immunosuppressive therapy was given, either with antithymocyte globulin (ATG; 5 mg per kg per day for 5 consecutive days) or with OKT 3 (5 mg/day for 7 consecutive days). Cyclosporin trough levels in whole blood were measured 12 h after the last dose using a monoclonal specific RIA kit (Sandoz, Basel, Switzerland). In addition, the results of laboratory tests carried out by other institutions, as well as specimens sent in at roughly 4-week intervals, were available to determine the cyclosporin trough level.

Statistical calculations were carried out using the Wilcoxon rank-sum and Mann-Whitney U-tests, and values given represent the median, with the range given in brackets in each case. A P value less than 0.05 indicates a significant difference between the groups.

Results

A total of 2371 renal transplantations were performed in 2072 patients in our center between December 1968 and May 1993; 184 of these patients received kidneys donated by living relatives. Seventy-eight patients (3.8 %; 20 men, 58 women; 1:2.9) had clinically proven analgesic nephropathy and were included in the study. The exact cumulative dose of ingested analgesics could only be calculated in a minority of cases. None of the patients had been nephrectomized prior to transplantation.

The characteristics of all renal transplant patients with analgesic nephropathy are shown in Table 1. There was no significant difference between patients without ($n = 67$) and with ($n = 11$) detectable urothelial carcinoma with respect to age at the time of renal transplantation, duration of pretransplant hemodialysis, duration of graft function, or duration of pretransplant hemodialysis plus graft function. Likewise, the immunosuppressive regimens, frequency of rejection episodes, and fre-

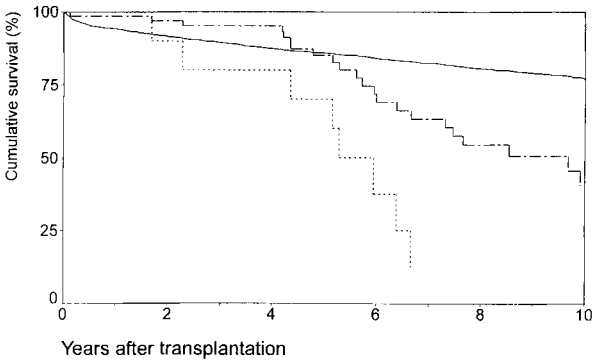

Fig. 1 Cumulative patient survival after renal transplantation in patients with analgesic nephropathy with urothelial carcinoma (n = 11; - -) and without urothelial carcinoma (n = 67; — · —) compared to all renal transplant patients with other renal diseases (n = 1994; ——) between 1968 and 1993 (Kaplan Meier estimation)

quency of steroid pulse therapy were comparable. An antibody therapy for rejection was given only in the patient group without urothelial carcinoma.

Of the 67 patients without urothelial carcinoma, 49 (73.1 %) are currently alive with a functioning graft (median serum creatinine 130 μmol/l, range 71–539 μmol/l), 7 (10.5 %) went back on dialysis treatment within 2–95 (median 26) months after renal transplantation. Nine patients (13.4 %) died 3–115 (median 69) months after transplantation. The cause of death was cardiovascular disease (myocardial infarction, cerebral infarction) in five cases. Two patients suffered from malignant disease other than urothelial carcinoma (bronchial carcinoma, colonic carcinoma) and two patients died from septic complications (pneumonia, diverticulitis).

Findings that led to further diagnostic steps in 11 patients (14.1 %) with analgesic nephropathy were macrohematuria in five cases, doubtful findings on cytology testing (PAP IIID) in three cases, suspicious findings on ultrasound examination of the native kidneys in two cases, and lumbar bone pain in one case. The age of the 11 patients with proven urothelial carcinoma at diagnosis of the tumor was 55.8 (51–66) years; time from start of dialysis and time from transplantation to the diagnosis of the tumor was 70.5 (40–108) months and 32.1 (5–77) months, respectively. The localizations of the carcinomas were: renal pelvis (n = 3); bladder (n = 5); renal pelvis and bladder (n = 2); and renal pelvis, ureter and bladder (n = 1). All urothelial carcinomas were found in the native kidneys of the transplant recipients; no cancer was found in any of the grafts. Three of the six patients with transitional cell carcinomas of the renal pelvis showed a superficial growth of a highly differentiated urothelial carcinoma; a carcinoma in situ was found in one case, and two patients presented with a muscle infiltrating tumor (≥ pT2), with lymph node metastases in one case. All seven patients who presented with a tumor of the bladder showed moderate to low differentiation on histologic grading with muscle infiltration (≥ pT2 grade II–III). In one patient, lymphatic spread was found at the time of presentation.

Therapeutically, unilateral nephroureterectomy was performed in five patients and bilateral nephroureterectomy in one patient. A transurethral tumor resection and/or total cystectomy with construction of an ileum conduit was carried out in six and two patients, respectively. Either radiation therapy (with protection of the transplant kidney) or palliative chemotherapy with carboplatin was administered to one of two patients with local relapse of the tumor.

Seven patients (63.6 %) died due to tumor progression 16.3 (4–33) months postoperatively. One patient died of a pulmonary embolism in the direct postoperative phase. One patient died 3 years after operation with a functioning graft in the course of repeated cerebral infarctions. Two patients are alive 10 and 36 months postoperatively, one of them with a functioning renal graft (serum creatinine < 100 μmol/l) after cystectomy and construction of an ileum conduit; the second is back on dialysis due to chronic graft rejection.

Patient survival in renal transplant recipients with analgesic nephropathy but without urothelial carcinoma (n = 67) did not differ essentially from that of all renal transplant patients with other renal diseases (n = 1994) between 1968 and 1993. However, patient survival among renal transplant recipients with analgesic nephropathy and urothelial carcinoma (n = 11) was markedly worse than that in the other two groups (Fig. 1).

Discussion

The development of a urothelial carcinoma in patients with longstanding analgesic nephropathy is a well-known complication [1–4, 6, 10, 13, 15, 16, 18, 20]. Yet, there are only few data concerning the incidence of urothelial carcinomas in these patients after renal transplantation [1, 11, 24, 26]. In our renal transplant population, a urothelial carcinoma was detected in 13 out of 2072 patients (0.63 %) in the native urinary tract. It is particularly worth noting that none of the urothelial carcinomas was found in any of the grafted kidneys. All but two of these patients suffered from analgesic nephropathy. Thus, the prevalence of urothelial carcinomas after renal transplantation without preceding analgesic nephropathy (0.1 %) is comparable to that in other studies [24]. The incidence of a urothelial carcinoma after renal transplantation in the patients with analgesic nephropathy (14.1 %) is comparable to the general incidence of up to 10 % of urothelial carcinomas in end-stage renal disease patients with analgesic nephropathy [1, 10, 15, 18]. We can confirm neither the very low [24] nor the very high incidence [11] found by other investigators.

The difference may lie in the strictness of the selection criteria for the inclusion of patients with a history of chronic ingestion of analgesics.

The percentage of urothelial carcinomas with respect to all malignant tumors in our transplant population is around 9.2 %. This is markedly higher than is generally expected for urothelial cancers in renal transplant recipients [22, 23] and may be explained by the higher percentage of patients with analgesic nephropathy in our population.

According to recently reported data [23] and our findings, the development of a urothelial carcinoma in patients with analgesic nephropathy is independent of the kind of long-term immunosuppression administered and is not influenced by the treatment of rejection episodes, even under antibody therapy (Table 1). Patient age, time on dialysis and time after transplantation obviously did not play decisive roles in tumor genesis in our study. Thus, our findings are in agreement with studies showing that the most important factor in the development of a urothelial carcinoma in the renal transplant patient is the cumulative dose of analgesics taken [3, 17].

The fact that frequent and regular urinary cytology and abdominal ultrasound led to the diagnosis of a urothelial carcinoma in only one-third of all of our cases leads as to believe that this method of tumor screening is insufficient, especially since all cases with positive findings showed an advanced stage of the disease.

The early detection of urothelial carcinomas by cytology from spontaneous urine is hampered by a high rate (22 %–67 %) of false-negative results [9, 14]. Only muscle-infiltrating, middle-to-low differentiated carcinomas of the urinary bladder will lead to a sensitivity and specificity of 95 % using urine cytology [27]. On the other hand, the detection of tumor cells from the upper urinary tract is dependent upon remaining diuresis, which will not be present in most of the patients. Who have been on dialysis for a long time. In this respect it is important that, in contrast to patients without renal disease, in whom 90 % of tumors of the urinary tract are restricted to the bladder, 7 % to the renal pelvis, and 3 % to the ureter, in patients with analgesic nephropathy, only about 50 % of the tumors affect the bladder, but 30 %–40 % the renal pelvis, and 5 %–15 % the ureter [18]. Our findings confirm this distribution. We cannot, however, confirm that a reversed distribution of the tumors in the urinary tract exists, with a bladder to renal pelvis ratio of 1:11 in analgesic-associated tumors as compared to 15:1 in analgesic-independent tumors of the urinary tract [20]. We do agree with other studies [7] that the tendency toward multifocal tumor growth must be pointed out.

Technical investigations like abdominal ultrasonography and computer tomography lack sensitivity and specificity for tumors of the upper urinary tract with a staging below pT3 because both absent urinary flow (lack of radio-opaque dye secretion) and differentiation from secondary renal cysts make a diagnosis difficult [8, 19, 21]. Retrograde ureteropyelography and ureteropyeloscopy are additional diagnostic means for the detection of urinary tract tumors. With the help of a ureteropyeloscopy, a tumor of the upper urinary tract can be detected up to 85 % of the time. Yet, due to the need for general anesthesia and the danger of rupturing the renal pelvis as a consequence of decreased elasticity in end-stage renal disease, this investigation should be rejected as a standard procedure in end-stage renal disease [5]. Retrograde ureteropyelography in conjunction with a lavage cytology taken from each ureter separately will lead to the best results as far as tumor detection is concerned. However, the ureteropyelography cannot clearly distinguish between papillomatous changes and papillary necrosis [12, 14].

In summary, after renal transplantation the risk of developing urothelial carcinomas in the native urinary tract, particularly in the native kidneys, of patients with analgesic nephropathy is rather high and is associated with a high tumor-related mortality. Because of this and the high rate of false-negative results of preventive urological tumor screening, we suggest that a unilateral or bilateral nephroureterectomy should be performed in patients with analgesic nephropathy, especially those with a high cumulative dose of analgesics. Nowadays, the sequelae of bilateral nephrectomy, i. e., renal anemia and arterial hypotonia, can be prevented by regular administration of erythropoietin. Thus, we have already changed our pretransplant strategy in these patients. Patients who do not consent to the operation or who cannot be operated on without risk due to medical reasons should undergo a retrograde ureteropyelography and a lavage cytology of each ureter every 1–2 years while waiting for a kidney transplant. Once transplantation has been carried out, the remaining native kidney should be removed and a cystoscopy with lavage cytology should be performed every 6–9 months.

References

1. Ballé C, Schollmeyer P (1990) Morbidity of patients with analgesic-associated nephropathy on regular dialysis treatment and after renal transplantation. Klin Wochenschr 68: 38–42
2. Bengtsson U, Angervall L, Ekman H, Lehmann L (1968) Transitional cell tumors of the renal pelvis in analgesic abusers. Scand J Urol Nephrol 2: 145–150
3. Bengtsson U, Johansson S, Angervall L (1978) Malignancies of the urinary tract and their relation to analgesic abuse. Kidney Int 13: 107–113

4. Blohme I, Johansson S (1981) Renal pelvic neoplasms and atypical urothelium in patients with end-stage analgesic nephropathy. Kindey Int 20: 671–675
5. Blute ML, Segura JW, Patterson DE, Benson RC, Zincke H (1989) Impact of endourology on diagnosis and management of upper urinary tract urothelial cancer. J Urol 141: 1298–1301
6. Brunner FP, Richtmann L, Thiel G, Dubach UC (1978) Tumoren der ableitenden Harnwege und Analgetikaabusus. Schweiz Med Wochenschr 108: 1013–1019
7. Charbit L, Gendreau MC, Mee S, Cukier J (1991) Tumors of the upper urinary tract: 10 years of experience. J Urol 146: 1243–1246
8. Ekman P (1990) Tumors of the upper urinary system: diagnostic procedures. In: Murphy G, Khoury S, Chateloin C, Denis L (eds) Recent advances in urological cancers. Diagnosis and treatment. III: Upper tract. Pergamon, New York, pp 151–154
9. Eriksson O, Johansson S (1976) Urothelial neoplasms of the upper urinary tract. A correlation between cytologic and histologic findings in 43 patients with urothelial neoplasms of the renal pelvis or ureter. Acta Cytol 20: 20–25
10. Gonwa TA, Corbett WT, Schey HM, Buckalew VM (1980) Analgesic-associated nephropathy and transitional cell carcinoma of the urinary tract. Ann Intern Med 93: 249–252
11. Hauser AC, Derfler K, Stockenhuber F, Balcke P (1990) Post-transplantation malignant disease in patients with analgesic nephropathy. Lancet 1: 335
12. Hruby W von, Stellamor K, Zinner G, Marberger M (1983) Der Nierenbekkentumor im Sonogramm. Fortschr Roentgenstr 138: 469–472
13. Hultengren N, Lagergren C, Lungqvist A (1965) Carcinoma of the renal pelvis in renal papillary necrosis. Acta Chir Scand 130: 314–320
14. Leistenschneider W, Nagel R (1979) Lavage-Zytologie bei pathologischen Veränderungen in Nierenbecken und Harnleiter. Akt Urol 10: 35–43
15. Lornoy W, Morelle V, Becaus I, Fonteyne E, Vrouwziekenhus OL (1979) Analgesic nephropathy. N Engl J Med 300: 319–320
16. McCredie M, Ford JM, Taylor JS, Stewart JH (1982) Analgesics and cancer of the renal pelvis in New South Wales. Cancer 49: 2617–2625
17. McCredie M, Stewart JH, Ford JM, McLennan RA (1983) Phenacetin containing analgesics and cancer of the bladder or renal pelvis in women. Br J Urol 55: 220–224
18. Mihatsch MJ, Knüsli C (1982) Phenacetin abuse and malignant tumors: an autopsy study covering 25 years (1953–1977). Klin Wochenschr 60: 1339–1349
19. Milestone B, Friedman AC, Seidmon EJ, Radecke PD, Leff-Toave AS, Caroline DF (1990) Staging of ureteral transitional cell carcinoma by CT and MRI. Urology 36: 346–349
20. Nanra RS (1983) Renal effects of antipyretic analgesics. Am J Med 75: 70–81
21. Netto NR, Almeida Claro JF (1990) CT scanning in the diagnosis of pelvicalyceal filling defects. Arch Exp Urol 43: 683–685
22. Penn I (1991) Post-transplant kidney cancers and skin cancers (including Kaposi's sarcoma). In: Schmähl D, Penn I (eds) Cancer in organ transplant recipients. Part I. Springer, Berlin Heidelberg New York London Paris Tokyo Hong Kong Barcelona Budapest, pp 46–53
23. Penn I (1995) Primary kidney tumors before and after renal transplantation. Transplantation 59: 480–484
24. Schwarz A, Offermann G, Keller F (1992) Analgesic nephropathy and renal transplantation. Nephrol Dial Transplant 7: 427–432
25. Valderrábano F, Jones EHP, Mallick NP (1995) Report on management of renal failure in Europe, XXIV, 1993. Nephrol Dial Transplant 10 [Suppl 5]:1–25
26. Vogt P, Frei U, Repp H, Bunzendahl H, Oldhafer K, Pichlmayr R (1990) Malignant tumours in renal transplant recipients receiving cyclosporin: survey of 598 first-kidney transplantations. Nephrol Dial Transplant 5: 282–288
27. Ward JN, Pitts WR Jr, Bard RH (1992) The dangerous ureter. Urology 39: 322–326