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BRIEF REPORT

Ulrich Maier
Stefan Madersbacher
Silvia Banyai-Falger
Martin Susani
Thomas Grünberger

Late ureteral obstruction after kidney transplantation

Fibrotic answer to previous rejection?

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U. Maier (✉) · S. Madersbacher
Department of Urology,
University of Vienna,
Währinger Gürtel 18–20,
A-1090 Vienna, Austria
Fax: + 43–1-408 99 66

S. Banyai-Falger
Department of Nephrology,
University of Vienna,
Währinger Gürtel 18–20,
A-1090 Vienna, Austria

M. Susani
Institute of Clinical Pathology,
University of Vienna,
Währinger Gürtel 18–20,
A-1090 Vienna, Austria

T. Grünberger
Department of Surgery,
University of Vienna,
Währinger Gürtel 18–20,
A-1090 Vienna, Austria

Abstract Today, the incidence of urological complications following renal transplantation is 2 %–10 %. Most of these complications occur within the 1st year and affect the distal ureter. We report on two patients who developed very late ureteral obstruction, 14 and 18 years after transplantation. Both patients had rejection episodes 1 and 10 months prior to the ureteral stenosis. Histological examination of one resected ureter revealed findings strongly suggestive of a rejection process. Open surgery with antirefluxive reimplantation into the bladder was successful in both patients, with a postoperative observation time of 20 and 8 months, respectively. We conclude that a percutaneous nephrostomy may be required in patients with rising creatinine and incipient hydronephrosis even long after transplantation has been performed.

Key words Kidney transplantation, ureteral obstruction · Ureteral obstruction, kidney transplantation · Rejection, ureter

Indroduction

Although the rate of urological complications following renal transplantation has sharply decreased over the past years, the literature generally reports an incidence of up to 20 % [1, 3, 5, 10–14, 19, 21]. Complications usually develop within the 1st month after transplantation, the most common one being ureteral stenosis. Publications dealing with late complications following renal transplantation are very rare and cover a postoperative course of at most 5 years [8, 18, 20]. In a recent review, Dreikorn [2] mentions the problem of the distal ureter and differentiates between nonspecific fibrosis and possible rejection as a late urological complication after transplantation.

Patients and results

We report on two patients who required surgery because of ureteral stenosis after 14 and 18 years respectively, following renal transplantation. Both had undergone transplantation at the De-

partment of Surgery of the University of Vienna, where they received cadaveric kidney transplants via a simple anastomosis of the graft ureter to the bladder (no antirefluxive implantation). Follow-up was carried out at the Department of Nephrology, which finally referred them to the Department of Urology because of incipient hydronephrosis with a concomitant rise in creatinine (2.8 mg% and 3.4 mg%). Since transplantation, neither patient had had any other urological complications. A percutaneous nephrostomy was performed, and the subsequent improvement in renal function indicated an underlying ureteral obstruction, which was confirmed with antegrade pyelography and measurement of renal pelvis pressure (Whitaker's test).

Patient 1

A 29-year-old woman received a renal allograft because of glomerulonephritis in March 1979. Immunosuppressive treatment consisted of azathioprine (50–75 ml/day) and prednisolone (5–7.5 mg/day). In November 1991, at the age of 41, she received a 100 mg bolus of dexamethasone for 3 days to treat a rejection episode, which subsequently resolved. A biopsy of the transplant, obtained in May 1992 because of renewed deterioration of renal function, showed recurrence of disease. Therefore, the patient was treated with 200 mg dexamethasone for another 3 days. In March 1993, a ureteral prevesical stenosis was diagnosed sonographically and clinically (rising creatinine levels up to 2.8 mg%); this was treated surgically by resection and ureterocystoneostomy with antireflux plasty. Twenty months after surgery, serum creatinine levels are now in the normal range (1.1 mg%) and ultrasonography shows no signs of obstruction.

Patient 2

A today 54-years-old man received a renal transplant in March 1976 because of bilateral shrinking kidneys of unknown etiology. As immunosuppressive therapy, the patient received prednisolone (20 mg/day) and azathioprine (100 mg/day). In 1989 and again in February 1994, rejection episodes were treated with high-dose dexamethasone (300 mg). In March 1994, a typical prevesical ureteral stenosis developed with hydronephrosis and increasing creatinine levels (3.4 mg%; Fig. 1). Surgery revealed a marked ureteral fibrosis over a distance of 3.5 cm. As in patient 1, surgical treatment consisted of ureteral reimplantation with antireflux plasty after resection of the stenosis.

The patient's postoperative course has been uneventful for 8 months (creatinine 1.3 mg%). Histological examination (Fig. 2) of the resected ureter shows a thickened wall due to an increase in fibrotic tissue in the muscle layer and an edema of the lamina propria. The periureteral tissue is also fibrotic. There is a slight inflammatory infiltrate consisting mainly of small lymphocytes, which are sometimes also seen in-between the epithelium. Circumscribed areas of the mucosa show erosions with a defect of the urothelium. The small vessels in the lamina propria are dilated. Often granulocytes and lymphocytes are observed sticking to the endothelial cells and are found in the intima in a subendothelial location. The larger arteries in the periureteral tissue exhibit a strong concentric intimal fibrosis (Fig. 2E). The histological findings of concentric intimal fibrosis of arteries, endothelialitis of small vessels, and the predominance of small lymphocytes within the inflammatory infiltrate are strongly suggestive of a smoul-dering rejection process. Histologically, we were only able to demonstrate ureteral rejection in patient 2, as we obtained no ureteral specimen for histological examination in patient 1.

Fig. 1 Antegrade pyelography: prevesical ureteral obstruction 18 years after renal transplantation in patient 2

Discussion

The incidence of urological complications following renal transplantation is currently 2 %–10 % [15]. In approximately three of four cases, the distal ureter is then affected. Most complications occur within the first 4 postoperative weeks and are managed by the transplant surgeon. In most cases, these early complications represent either ureteral necroses (which may be total, partial, short, or long) or leaking anastomoses. The second-most frequent urological complication is obstruction by kinking (if the ureter has been left too long) or by a lymphocele. Late complications include predominantly ureteral fibroses or fibroses of periureteral tissue compressing the ureter. During an observation period of 18 years, 2048 kidney transplantations were performed at the Department of Surgery of the University of Vienna. Since all late complications were treated at the Department of Urology, the incidence of these very late ureteral fibroses based on this patient population is 0.009 %.

Just how a stenosis of the transplanted ureter can develop even after many years remains controversial.

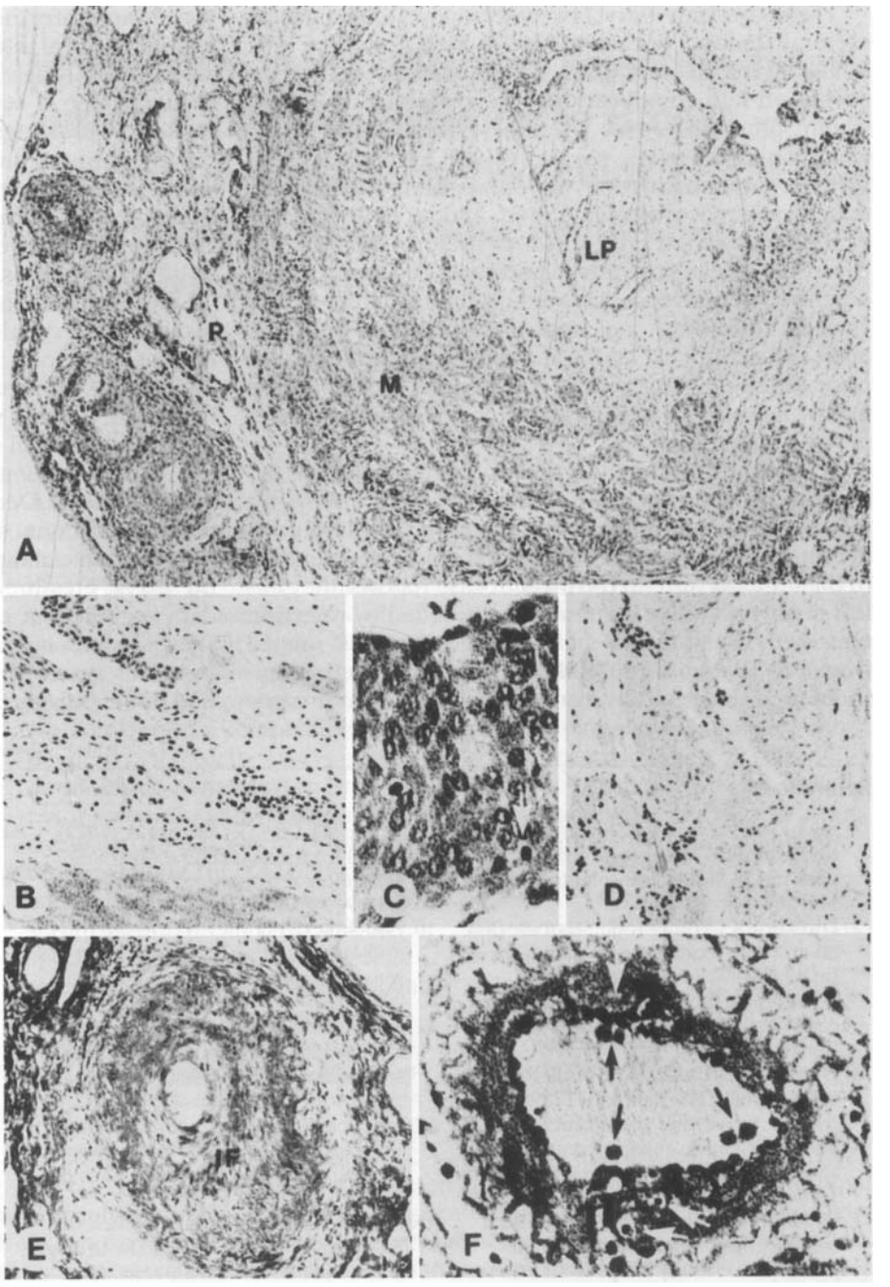

Fig. 2 A–F Histology of the resected ureter of patient 2: **A** thickened wall of the ureter (HE × 40); **B, C, D** small lymphocytes **B** infiltrating the lamina propria (HE × 100); **C** within the epithelium (HE × 400); and **D** in the muscle layer (HE × 200); **E** artery in periureteral location with strong concentric intimal fibrosis (HE × 200); **F** small vessel from the lamina propria showing lymphocytes sticking to the endothelium and in the subendothelial space (HE × 600) (*LP*, lamina propria; *M*, muscle layer; *P*, periureteral connective tissue; *IF*, intimal fibrosis)

A decreased blood supply due to careless removal of the donor organ can be ruled out since this would result in early ureteral necrosis. Another theory, first introduced by Haber and Putong [6] in 1965, states that the ureter – as a part of the allograft – might also be subjected to rejection, resulting in ureteral fibrosis. This theory was confirmed by Robertshaw et al. [15] and Katz et al. [7], who demonstrated alterations in renal parenchyma and the ureter during rejection (histologically, these are very similar, both at the cellular and vascular levels). These rejection episodes might cause ischemic attacks with subsequent "immunologically" induced fibrotic reactions. Loss of ureteral elasticity might then lead to stenosis but also to reflux. Reflux therapy is supported by studies by Dreikorn [4], who established a significant correlation between the number of rejection episodes and the incidence of reflux.

There are only very few case reports dealing with ureteral stenoses occurring after a long period of time following transplantation [9, 17]. Thomalla et al. [20] reported on late complications in eight patients, four of whom presented with ureteral fibrosis after 2, 5, 6 months and 4 years, respectively. Kirkman et al. [8] saw ureteral obstruction in four patients after more than 5 years post-transplantation, and recently Shoskes et al. [18] reported on a series of ureteral obstructions 4 h to 400 weeks post-transplantation. The two patients described in our report showed ureteral stenosis 14 and 18 years following renal transplantation, and both had been successfully treated for clinical rejection episodes prior to the development of the stenosis. Both patients received prednisolone and azathioprine as immunosuppressive therapy.

It is certainly difficult to say why ureteral stenosis occurs after so many years. Essentially, there are only two possible causes: alterations in the periureteral tissue under immunosuppression or rejection episodes extending to the ureteral wall. In the present case reports, the clinical manifestation of stenosis was preceded by rejection episodes. The intervals between these events ranged from 1 to 10 months. In both patients, the rejection episodes were successfully controlled by high-dose cortisone. Therefore, the subsequent ureteral stenoses necessitating surgical intervention might have been due to the rejection episodes. In one case, affection of the ureteral tissue due to a severe rejection episode was demonstrated by histological findings. Due to the small number of patients and the varying observation periods, there is no way to determine whether a relationship exists between specific immunosuppressive regimens (neither patient received cyclosporin) and the development of ureteral stenosis.

We conclude that not only graft rejection but also ureteral stenosis should be considered when creatinine levels rise, even long after successful renal transplantation and even if ultrasonography shows only a slight hydronephrosis. In cases where rejection is excluded by biopsy or by unsuccessful (ex juvantibus) cortisone bolus therapy, a percutaneous nephrostomy should by all means be performed. Decreasing creatinine levels prove the presence of a stenosis. The definite indication for surgical intervention can then be further supported by measuring the pelvic pressure (Whitaker's test). Our retrospective data suggest that endoscopic interventions (e.g., inner stenting) are not indicated, as the stenoses resulting from this type of fibrosis are marked and render resection of the fibrotic ureteral segment mandatory.

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