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BRIEF REPORT

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Nephrogenic adenoma associated with cytomegalovirus infection of the ureter in a renal transplant patient: presentation as ureteral obstruction

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Abstract Nephrogenic adenoma (NA), a rare benign lesion of the urinary tract, is widely accepted to be a metaplastic reaction due to urothelial injury. It mainly occurs in the urinary bladder and rarely in the ureter. Renal transplant recipients are prone to the development of NA. However in those patients, NA was diagnosed exclusively in the bladder. Herein, we present the – to our knowledge – first case of NA involving a transplanted ureter. A 42-year-old female kidney transplant recipient suffered hematuria, oliguria, and acute renal failure and presented with ureteral obstruction and hydronephrosis of the renal transplant. To our surprise, evidence of cytomegalovirus (CMV) infection of the NA was demonstrated using special immunohistochemical staining. The findings in this case raise the possibility that CMV infection, as an irritant of the ureteral epithelium, may be an etiological factor of NA.

Keywords Cytomegalovirus · Nephrogenic adenoma · Renal transplantation · Ureter

Abbrevations *CMV* Cytomegalovirus · *NA* Nephrogenic adenoma

Introduction

Nephrogenic adenoma (NA), a rare lesion of the urinary tract, is now widely accepted to be an immature metaplastic reaction to urothelial injury [5, 7, 8]. It was initially described by Davis in 1949 as an unusual hamartomatous formation of the urinary bladder [5]. In 1950, Friedman and Kuhlenbech reported eight cases and coined the term "nephrogenic adenoma" because of the lesion's resemblance to the tubular and cystic structures of the nephron [5]. Since then, about 400 cases have been reported [5, 7, 8]. It has been called adenomatous metaplasia, bladder hamartoma, and nephrogenic metaplasia. The lesion is currently considered to be benign with a recurrence rate of 36–60%. In the reported cases, patient age has ranged from 3 weeks to 94 years, with a male predominance of about 2:1. The most frequent presentation is hematuria. NA may develop anywhere in the urinary tract, from the renal pelvis to the urethra, with the most frequent location being the urinary bladder (55–72%). Only about 4–8% of the lesions occur in the ureter.

Many conditions have been considered to be the predisposing factors to NA, including surgery or trauma, infection, chronic inflammation, calculus, carcinoma, transplantation, immunosuppression, congenital anomaly, and long-term hemodialysis [5, 7]. The incidence of NA among renal transplant recipients is believed to be higher than that within the general population [1, 9]. However, the reason for the increased prevalence in this group remains unclear. NA has been reported for at least 58 renal transplant recipients [1, 4, 9, 10]. All of these cases were with adult recipients, and all of them developed in the urinary bladder. Herein, we report a case of NA involving a transplanted ureter. To our knowledge, this is the first reported case of NA involving a transplanted ureter, as well as the first case involving a ureter with cytomegalovirus (CMV) infection.

Case report

A 42-year-old woman underwent cadaveric renal transplantation for end-stage renal disease due to suspicious chronic interstitial nephritis. The donor and recipient were both CMV seropositive. A stricture at the ureterovesical junction of the graft was found shortly after the operation. She then received double-J catheterization. Her serum creatinine level stabilized at around 1.4 mg/dl. Immunosuppression with cyclosporine, prednisolone, and azathioprine was prescribed. The initial dosage of cyclosporine was 125 mg twice daily (7.2 mg/kg per day) with blood trough levels (fluorescence polarization immunoassay) around 300 ng/ml. One month later, she had two consecutive episodes of urinary tract infections, the first involving *Salmonella*, the second, *Candida*. After removal of the double-J catheter and adequate antibiotic treatments, her creatinine level stabilized at around 1.5 mg/dl. Unfortunately, 3 months after transplantation, the patient suffered an episode of painless gross hematuria. Anorexia and oliguria developed since then. She was admitted to the hospital 1 week later. The physical examinations revealed elevated blood pressure and bilateral pedal edemas. Marked deterioration of renal function, as indicated by an increase in serum creatinine to 6.3 mg/dl, was found. With a cyclosporine dosage of 100 mg twice daily (5.7 mg/kg per day), a blood trough level of 244 ng/ml was obtained. A sonogram of the renal transplant showed moderate hydronephrosis and the presence of a cystic structure measuring about 4 cm in size just inferior to the allograft. An antegrade pyelogram evidenced total obstruction of the upper third of the ureter with a polypoid-filling defect within the ureter (Fig. 1). The cystic lesion simultaneously proved to be a lymphocele without communication to the collecting system. Double-J catheterization was attempted, but was blocked by the polypoid lesion. The cystoscopy revealed a normal appearance of the urinary bladder.

Four months after transplantation, she received surgical intervention with ureterolysis and pyeloplasty. A yellowish polypoid lesion, measuring approximately 15 × 5 × 3 mm in size, within the upper third of the ureter and associated with severe fibrosis and complete obstruction was disclosed. The postoperative condition was smooth, and the serum creatinine level returned to 1.8 mg/dl. The polypoid lesion, composed of densely packed tubular and glandular structures and lined by cuboidal and flat cells, proved to be a nephrogenic adenoma (Fig. 2). Some tubular epithelial cells showed the formation of intranuclear and intracytoplasmic inclusions. Immunohistochemical staining with monoclonal antibody (DAKO) revealed a nuclear and cytoplasmic staining pattern consistent with CMV early antigen. Cytokeratin staining confirmed that only the tubular epithelial cells contained CMV. Because of the diagnosis of CMV ureteritis, the patient received a course of intravenous ganciclovir for 2 weeks. Azathioprine was withdrawn simultaneously.

Six months after the transplantation, a renal biopsy revealed chronic vascular rejection with mild transplantation glomerulopathy and no evidence of viral inclusions. Hydronephrosis or hematuria did not recur after the operation during a 15-month follow-up period. The serum creatinine level remained around 3.0 mg/dl at 15 months of follow-up.

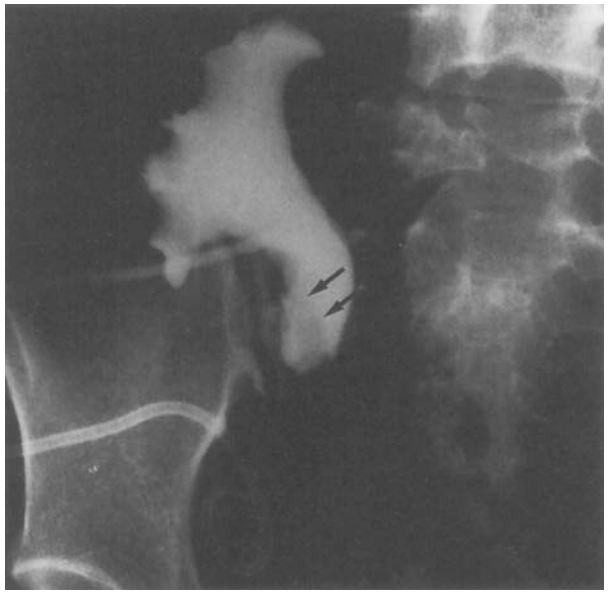

Fig. 1 Antegrade pyelogram showing hydronephrosis and dilatation of the upper third of the ureter of the renal transplantation. *Arrows* indicate a polypoid-filling defect within the ureter

Discussion

Ureterovesical anastomosis and/or immunosuppressive therapy have been thought to be the main causes of NA in renal transplantation recipients [2, 3]. However, in the recent renal transplantation studies of Tse et al. [10] and Fournier et al. [4], the NA lesions did not always occur on the same side as the ureterovesical anastomosis. Thus, the surgical procedure of ureter implantation cannot solely explain the high incidence of NA in renal transplantation patients. Beaudry et al. [2] reported a case with partial regression of NA after the discontinuation of azathioprine and in which immunosuppression was considered to be the cause of NA. However, other studies reported conflicting results. A case of recurrence of NA after cessation of azathioprine therapy has been reported [4]. The presence of intravesical bacille Calmette-Guerin, an immune stimulant, was also shown to be a predisposing condition of NA [10]. Furthermore, only renal transplantation patients had NA, although recipients of other organs also received immunosuppressive therapy [4, 10]. These results suggest that the role of immunosuppression, if any, is likely to be indirect.

Frequent urinary tract infections and repeated surgical injuries (instrumentation, resection, and biopsy) are known to be strong causative factors of NA in renal transplantation recipients [1, 4, 10]. Banyai-Falger et al. [1] demonstrated that in seven cases of bladder NA among renal transplantation recipients, six cases (86%) were related to recurrent bacterial infections. In a review of 22 patients with bladder NA, Tse et al. [10] showed that 13 patients (59%) had a history of surgical traumas other than ureterovesical anastomosis, and 10 patients (45%) had recurrent urinary tract infections. Both infection and surgical injury act as irritants to the

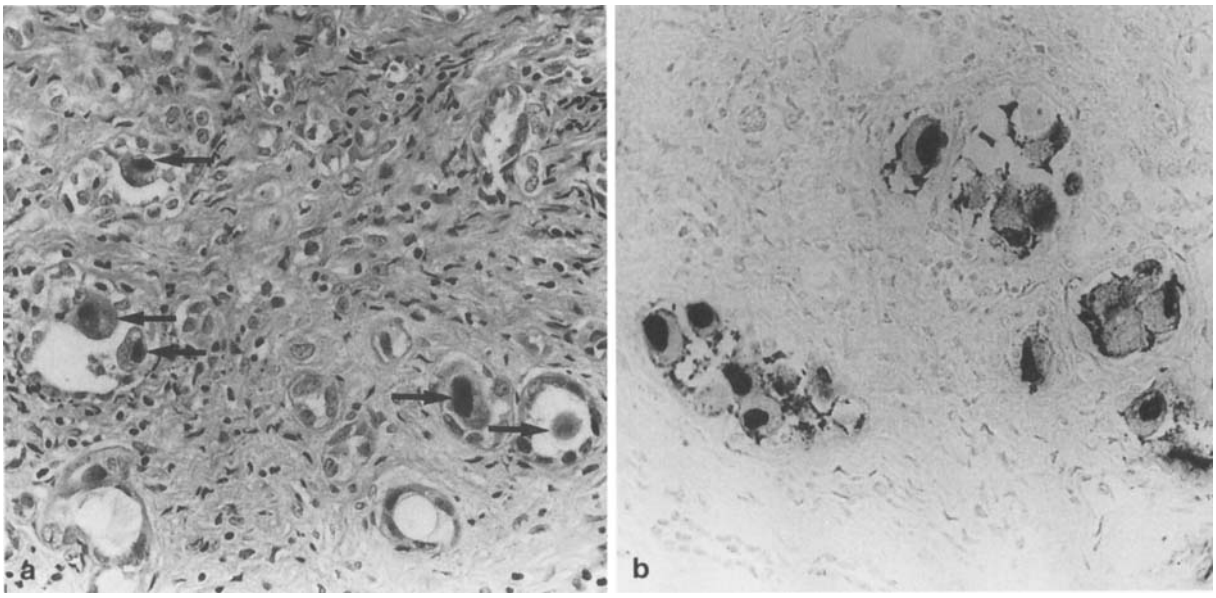

Fig. 2a Characteristic tubular structure of nephrogenic adenoma, with flat to cuboidal cells lining the tubules and focal inflammatory cell infiltration. Some tubular epithelial cells containing intranuclear or intracytoplasmic inclusions (*arrows*) (H & E, × 200). **b** Immunohistochemical staining with monoclonal antibody showing positive for CMV early antigen (× 200)

urothelium of both the bladder and the ureter. It therefore seems reasonable to expect an association between the development of NA in the ureter as well as in the urinary bladder in renal transplantation recipients. Nevertheless, no previous case of ureter NA in a renal transplantation patient has been reported. The reasons for the lack of reports may include lower clinical suspicion and fewer routine orders for retrograde ureterography or intravenous pyelography in renal transplantation recipients. In the present case, repeated urothelial injuries due to instrumentation (percutaneous nephrostomy, double-J catheterizations) and infections (*Salmonella*, *Candida*, and CMV) were considered to be the causes of NA development.

Only three cases of CMV ureteritis have been reported previously [6]. Among them, two cases involved renal transplantation recipients. Both cases lacked typically systemic symptoms of CMV infection and presented with ureteral obstruction, hydronephrosis, and allograft dysfunction. However, no evidence of NA was noted in these two cases. CMV infection has been referred to as an etiological factor in two previously reported cases of bladder NA [2, 3], based on the demonstration of CMV inclusions within the tubular epithelial cells of NA. But the recent studies of Fournier et al. [4] and Banyai-Falger et al. [1] involving nine and seven cases of NA, respectively in the bladder of renal transplantation recipients suggested that NA is not related to CMV disease. However, the former study used only light microscopy to detect CMV inclusions, and three patients in the latter study received ganciclovir therapy before transplantationation. There is convincing evidence that preemptive ganciclovir prophylaxis may reduce the risk of CMV-related disorders. Furthermore, the patient numbers in both studies were relatively small. Thus, the possibility of CMV infection in the promotion of NA development cannot be excluded completely. The present case reported herein, without ganciclovir prophylaxis, demonstrating CMV within the tubular epithelial cells of NA exclusively by specific immunohistochemical staining, raises the possibility that CMV infection is an etiological factor of NA, even in the transplantationed ureter. Therefore, preemptive ganciclovir therapy may be indicated for renal transplantation patients to prevent CMV infection and the development of NA.

An association between NA and bladder carcinoma in renal transplantation recipients has recently been demonstrated [1, 10]. Because of the high rate of recurrence and possible association with bladder carcinoma, periodic follow-up of NA is now widely suggested [1, 4, 9, 10]. Since both frequent instrumentation and repeated biopsy are possible risk factors for the development of NA, periodic urinary cytology follow-up every 3 months (as opposed to cystoscopy) has been suggested for renal transplantation recipients with bladder NA [1, 10]. In cases of ureter NA, the addition of periodic sonography for early recognition of ureteral obstruction and hydronephrosis may be indicated.

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