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BRIEF REPORT

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Is cytomegalovirus a cause of ureteral stricture in renal transplant recipients?

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Abstract Cytomegalovirus (CMV) is regarded as a predominant infectious agent in solid organ transplants. CMV disease has highly protean clinical manifestations. Nevertheless, urinary tract involvement seems to be very rare during CMV infection. We report two cases of renal transplant recipients in whom ureteral stricture developed in the course of CMV disease. Histologic data were available for them and were consistent with CMV infection. We discuss previous case reports and propose physiopathologic mechanisms.

Key words CMV, ureteral stricture, renal transplantation · Ureteral stricture, CMV, renal transplantation · Renal transplantation, CMV, ureteral stricture

Introduction

Cytomegalovirus (CMV) is regarded as a predominant infectious agent in solid organ transplants. CMV disease has highly protean clinical manifestations such as interstitial pneumonitis, hepatitis, gastrointestinal involvement, pancreatitis, myocarditis, chorioretinitis, and disseminated disease [10]. Nevertheless, urinary tract involvement has been rarely reported during CMV disease. To our knowledge, only one case of ureteritis with symptomatic ureteral stricture has been documented in a renal transplant recipient [5]. We describe two cases of renal allograft recipients who experienced simultaneous CMV disease and ureteral stenosis.

Case reports

Case 1

A 42-year-old woman suffered from end-stage renal failure due to interstitial nephritis. She received a cadaveric kidney transplant in September 1995. The transplanted kidney had one artery, and the surgical procedure, including the vascular anastomosis, was uneventful. The ureter was implanted according to Gregoire's method. The patient was positive for CMV as determined by indirect ELISA, and the donor was positive too. The patient was treated with induction of polyclonal antithymocyte antibodies for 5 days, in combination with prednisone, azathioprine, and cyclosporin. The immediate postoperative period was without complication. On discharge, the serum creatinine concentration was 198 μmol/l.

In October 1995, she presented with fever and suprapubic pain. Physical examination revealed nothing abnormal. Significant laboratory data revealed a white blood cell count of 2600/mm^3, a hamoglobin reading of 9.4 g/dl, a platelet count of 141 000/mm^3, and a serum creatinine concentration of 286 μmol/l. Blood and urine cultures were negative. CMV antigenemia (detection of the pp65 antigen on polymorphonuclear leukocytes [1]) was highly positive (2%), and gancyclovir therapy was started. A renal ultrasonography revealed hydronephrosis. An intravenous pyelography identified a ureteral stricture. The creatinine serum concentration rose to 435 μmol/l. The anastomosis was surgically repaired. A ureteral biopsy showed edema, mononuclear infiltrate, and necrosis. This feature was considered proof of acute rejection, and the patient was treated with high-dose steroids. In situ hybridization revealed CMV genoma in ureteral sections. Ganciclovir therapy was maintained for 14 days, and the patient was discharged on day 30. The serum creatinine concentration was 345 μmol/l.

Case 2

A 50-year-old man suffered from IgA nephropathy. He had been treated by peritoneal dialysis since November 1995. He received a cadaveric kidney in June 1996. The transplanted kidney had one ar-

tery, and the surgical procedure, including the vascular anastomosis, was uneventful. The ureter was implanted according to Gregoire's method. He had previously been positive for CMV, whereas the donor was negative. Immunosuppressive therapy comprised induction of polyclonal antithymocyte antibodies for 5 days, prednisone, azathioprine, and mycophenolate mofetil. The immediate postoperative course was without complication, and the patient was discharged on day 15 after the transplantation. The serum creatinine concentration was 98 μmol/l. He was admitted 10 days later because of fever, severe suprapubic pain, and leucopenia. Laboratory tests showed a serum creatinine level of 150 μmol/l and a white blood cell count of 2000/mm^3. Other results were within the normal range. Both blood and urine cultures were negative. CMV antigenemia was strongly positive (1 %), and ganciclovir therapy was begun. Renal ultrasonography and intravenous pyelography showed hydonephrosis and a very tight ureteral stenosis. The part of the transplant with the ureteral stricture was resected, and the ureter was reimplanted. A histologic study of ureteral sections revealed extensive inflammation, necrosis without any sign of rejection, and one cell exhibiting CMV inclusion. CMV was detected in ureteral cells by means of of monoclonal antibody staining that was specific for the virus. A simultaneous kidney allograft biopsy showed no evidence of rejection, but revealed one cell exhibiting an inclusion consistent with CMV infection. The patient was discharged 12 days later. The serum creatinine concentration was 111 μmol/l.

Discussion

Urinary tract involvement has rarely been reported during CMV disease. Some cases of CMV cystitis in human immunodeficiency virus (HIV)-infected patients and in bone marrow transplant recipients have been described [3, 10], but CMV ureteritis seems to be a very rare occurence in the course of CMV disease. Mueller and al. [6] described one case of CMV ureteritis in a child infected with the HIV. To our knowledge, only one case of ureteral involvement due to CMV infection has previously been reported in organ transplantation. Lowell and al. [5] described an invasive CMV infection in the ureter of a renal transplant 3 months after a combined pancreas-kidney transplantation. The patient presented with acute renal failure and hydronephrosis with hydroureter. Microscopic examination of the ureter revealed fibrosis and inflammation, as well as cells showing inclusions consistent with CMV infection. Immunoperoxydase staining for CMV was also positive.

CMV involvement may play a causative role in the development of ureteral stenosis. Our two patients had symptomatic CMV disease as it is usually defined. They exhibited positive CMV antigenemia, fever, leukopenia, and no other detectable cause of infection. They presented with suprapubic pain and acute renal failure. In situ hybridization in case 1 and monoclonal antibody staining in case 2 were positive for CMV in ureteral sections. Both monoclonal antibodies and in situ hybridization have shown to be rapid diagnostic tools with high degree of sensitivity and specificity [7, 8]. Moreover, to test the clinical significance of this result, we performed in situ hybridization in three consecutive renal biopsies from transplant recipients with CMV disease and a simultaneous increase in serum creatinine concentration. CMV genoma could not be detected in either of them. In case 2, the donor CMV serology was negative. This fact enhances the positive predictive value of positive monoclonal antibody staining in ureter sections. Moreover, no other cause of ureteral stricture could be found. There were neither stones nor blood clots. We did not find any other infectious diseases associated with ureteral stricture, such as tuberculosis or papillomavirus infection, in our patients. In case 1, microscopic examination of the ureter showed rejection. Alternatively, the distal ureteral stricture may have developed from rejection with secondary infection with CMV. Nevertheless, infection with CMV has been implicated in the development of allograft [4]. Thus, one can suppose that both CMV infection and rejection could have led to ureteral stricture in this patient.

The association between the development of ureteral stenosis and exposure to CMV is undoubtedly multifactorial. Although a role for smooth muscle proliferation in the process leading to ureteral stenosis has not been demonstrated, we postulate that CMV could contribute to the disease process during an abortive infection [9], which is characterized by viral-gene expression limited to immediate early gene products without viral replication. CMV immediate gene products are known to affect the expression of many human cellular genes involved in inflammation and immunologic responses [2]. Immediate gene products can inhibit p53 functions [11] either by blocking the progression of the cell cycle or by initiating apoptosis. Alternatively, tissue damage during permissive infection could lead to ureteral stenosis.

In conclusion, we hypothetize that CMV ureteritis could be a rare, but possibly unrecognized, complication of CMV disease in renal transplantation. CMV infection should be considered a possible cause of ureteral stricture in renal transplant recipients. Other studies are required to confirm this preliminary report.

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