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Tubulointerstitial nephritis caused by the antiviral agent foscarnet

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Abstract. The antiviral agent foscarnet has long been used in our unit to treat cytomegalovirus (CMV) infections in renal transplant patients. The clinical effect has been convincing and, apart from changes in serum calcium levels, very few side effects have been noted. We have, however, observed a nephrotoxic reaction in a series of patients with initially good renal function who therefore received high doses of foscarnet. Transplant biopsies performed in five of those patients revealed degenerative changes in the tubular epithelial cells as well as tubular calcium deposits and an infiltration of the interstitium by mixed mononuclear and polymorphonuclear leucocytes. Renal insufficiency was accompanied by high fever. After withdrawal of the drug, the temperature rapidly normalized, whereas serum creatinine continued to rise for about 3 days and then fell back towards previous levels. We conclude that transplant biopsies are of great value in distinguishing between a foscarnet nephrotoxic effect and CMV nephritis, various forms of rejection, and other causes of impaired renal function.

Key words: Foscarnet, in kidney transplantation – Cytomegalovirus infection, foscarnet in – Antiviral drug, foscarnet, in kidney transplantation – Nephrotoxicity, foscarnet and – Renal transplantation, foscarnet in.

Since 1982 foscarnet (phosphonoformate), an inhibitor of viral DNA polymerase, has been used in more than a hundred organ transplant patients in our unit to treat cytomegalovirus (CMV) infections. Our general experience has been that the drug is capable of reducing the duration and the severity of the infection without causing serious side effects [1, 13]. The most frequent adverse effects have been hyper- or hypocalcemia. Favorable results have also been reported in AIDS patients with CMV pneumonitis [7]. In contrast, however, several centers have noted a high incidence of renal insufficiency during foscarnet treatment of various viral infections in nontransplanted patients [3, 5, 8, 9].

Initially, the maximum dose of foscarnet used was 0.1 mg/kg body weight per minute, given by constant infusion for 7 days, followed by b. i. d. administration of the same dose for another 7 days. Since the drug is eliminated mainly by glomerular filtration, the dose was reduced according to renal function. This was necessary in most of the renal transplant patients. Due to recurrence of CMV infection in some cases and based on frequent determinations of serum concentrations of foscarnet [13] as well as in vitro studies of the inhibitory effect of the drug on CMV virus replication, the recommended dosage was later increased to 0.178 mg/kg body weight per minute for patients with normal renal function, aiming at a plasma concentration of 200 mg/l. During the last year we have observed a number of adverse reactions characterized by severe renal functional impairment and fever. Transplant biopsies were performed in five patients with this reaction.

Subjects

Five renal transplant patients received foscarnet due to clinical suspicion of CMV infection. Four were females and one was male. Their ages ranged from 35 to 62 years. The main symptoms of CMV infection were fever accompanied by leucopenia and/or rise in serum aminotransferase levels, but one case (BB) had localized pulmonary infiltrates. Two patients had primary CMV infections with seroconversion 2 and 19 months after the transplantation (cases BB and CJ, respectively). Three patients

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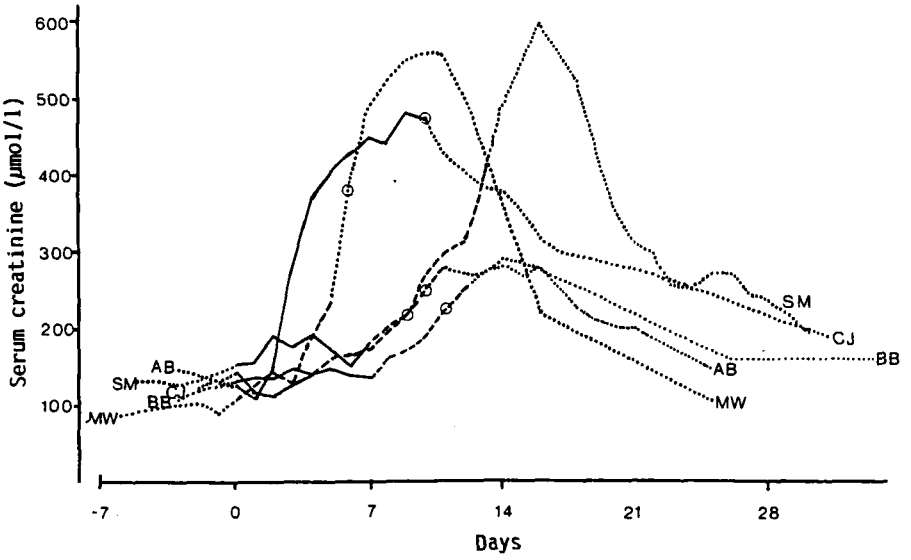

Fig. 1. Serum creatinine levels in five renal transplant patients before, during, and after foscarnet treatment. *Circles* indicate time of biopsy. —, Continuous infusion; ---, b.i.d. treatment; . . ., no treatment

had reactivated CMV infections with increased titers of IgG antibodies, appearance of IgM antibodies, and/or presence of CMV in the urine (the only finding in case MW). All patients received maintenance immunosuppressive therapy with a combination of cyclosporin A, prednisolone, and azathioprine.

Initial serum creatinine values ranged from 103 to 151 µmol/l. Foscarnet treatment was initiated with doses ranging from 0.111 to 0.178 mg/kg body weight per minute.

Results

Clinical course

During foscarnet treatment, most of the symptoms of CMV infection were overcome. The temperature was normalized within 4 days in three cases and fell in the fourth from 40 °C to values fluctuating between 36.8 ° and 38.3 °C. Pulmonary infiltrates in case BB progressed for 3 days and then gradually resolved. Leucocyte counts increased in all patients and the transaminase levels were normalized except in patient MW, who also maintained the same temperature as before treatment.

Figure 1 shows the patients' low serum creatinine levels before foscarnet administration, the rise that occurred in all patients during treatment, and the drop that followed upon withdrawal. With some delay, the foscarnet dosage was adjusted to renal function, but the reduction could not prevent further increase in serum creatinine. The serum concentration of foscarnet was obtained in one patient only (case BB). On the day of withdrawal, the trough concentration during b.i.d. treatment was 565 mg/l (target level 200 mg/l). Serum creatinine continued to increase in most patients for about 3 days after foscarnet was stopped and then gradually fell back towards normal for 3 or more weeks.

In addition to the serum creatinine rise, all patients again showed increasing body temperature to 37.8 °–38.9 °C. The temperature was normalized in all patients within 2–3 days after discontinuation of the drug. Three patients developed hypocalcemia, which was severe in one.

Because acute rejection was suspected, two patients received antirejection therapy with methylprednisolone and antithymocyte globulin, respectively, for 4–5 days during treatment with foscarnet. Four patients received netilmycin at different stages in relation to foscarnet: two in the 1st week and two in the 2nd week of treatment, and for 2–8 days. Two patients received cotrimoxazole from 4 days before until 2 days past foscarnet treatment and from day 2 to day 7 of foscarnet treatment, respectively.

Histopathology

Tissue was obtained from all grafts by percutaneous needle biopsy or by a surgical wedge procedure on the days indicated in Fig. 1. The specimens were processed by standard histochemical methods for light and electron microscopy and, when sufficient in amount, also for immunofluorescence.

By light microscopy all five biopsies demonstrated a rather complex picture of an acute tubulointerstitial disease. Despite differences in extent and quality of the inflammatory process between single specimens, they had the following characteristics in common:

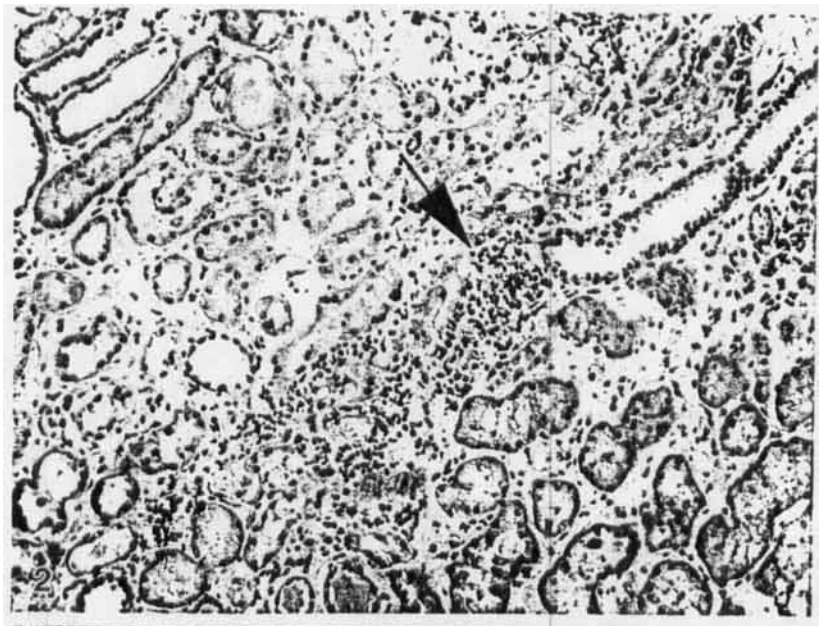

Fig. 2. Renal biopsy of patient MW. Deep cortical area with small infiltrate of inflammatory cells, mixed composition with presence of neutrophils, close to damaged tubular profile with severe degenerative changes in epithelium (*arrow*). (H & E, x 120)

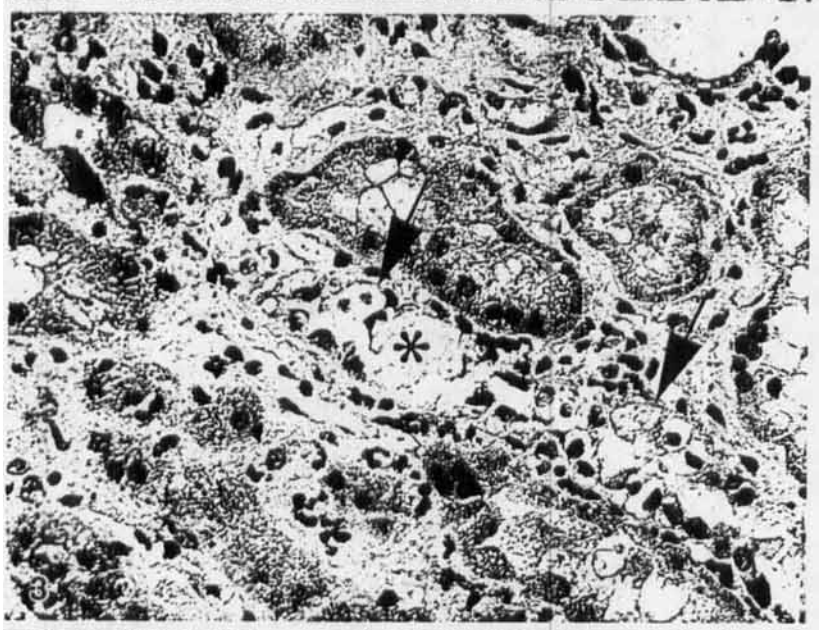

Fig. 3. Renal biopsy of patient MW. Tubular lesion with small calcification (*asterisk*) within area with damaged epithelium showing vacuolization and pyknosis (*arrows*). (H & E, x 315)

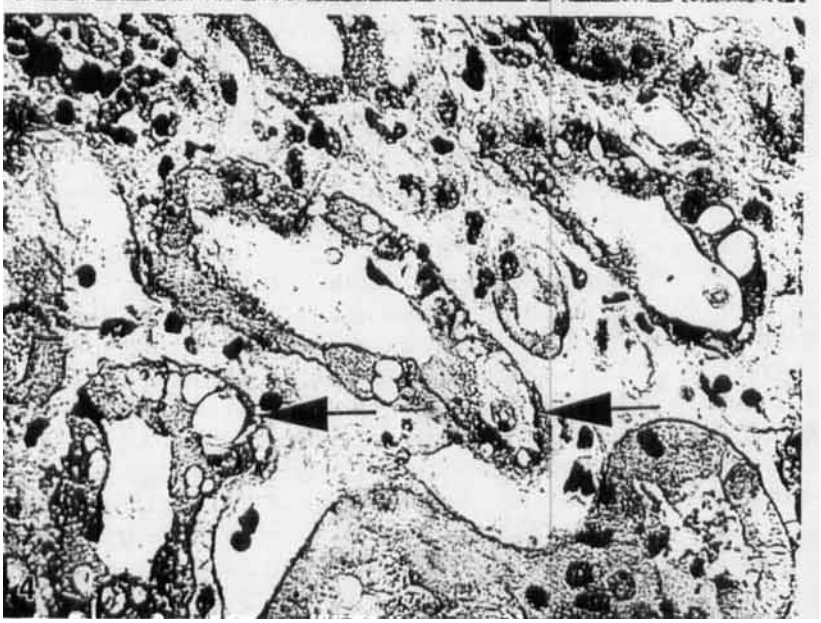

Fig. 4. Renal biopsy of patient BB. Higher magnification to demonstrate tubular epithelial cell degeneration with prominent vacuolization of anisometric type including very large vacuoles (*arrows*). (H & E, x 500)

1. Focal epithelial cell degeneration in the straight part of proximal tubules
2. Prominent anisometric vacuolization of affected cells and single cell necrosis
3. Desquamation with formation of casts containing epithelial cell fragments
4. Deposition of calcium salts in areas of destruction
5. Severe inflammatory cell response of mixed composition but always with a dominance of neutrophilic polymorphonuclear cells.

These changes are illustrated in Figs. 2–4. No CMV inclusions were observed in either epithelial or endothelial cells in any biopsy.

Four cases (BB, CJ, MW, AB) were studied by electron microscopy. All specimens demonstrated severe damage to the epithelial cell structure. However, the picture was complex, with several compartments of organelles affected, and therefore rather unspecific as regards the pathogenesis.

Sufficient tissue for immunofluorescence was obtained from one patient only (AB). No specific deposits of immunoglobulins, complement, or fibrin were detected.

Energy dispersive X-ray analysis (EDAX) was carried out on a specimen from case BB using a scanning electron microscope. This analysis gives a spectrum that reveals the relative proportions of elements in the field area. Focused on a tubule containing precipitates, the highest peaks recorded were phosphorous and calcium, followed by silicon and sulphur, which are constituents of the glass on which the tissue was mounted. The P/Si ratio was 2.5 and the Ca/Si ratio was 1.5. In contrast, EDAX analysis of the adjacent interstitium showed the highest peaks for silicon and sulphur. The P/Si ratio was 0.5 and the Ca/Si ratio was 0.3.

A follow-up transplant biopsy during excellent graft function was performed in case AB after 8 months. This showed restoration of tubular structure, disappearance of tubular precipitates, and only minimal cellular infiltrates in the interstitium.

Discussion

Histopathological evaluation of a biopsy from a malfunctioning renal transplant is often difficult. This is partly because several tissue-destructive processes may have been, or are in fact, simultaneously present in the transplant. A process of allograft rejection, if not arrested, will sooner or later damage the interstitium, vessels, and tubules of the graft. Likewise, ischemic, toxic/allergic, and infectious/septic processes all threaten the structural integrity of the transplant. In the five cases studied here, the selective destruction of epithelial cells, with widespread degenerative alterations at the subcellular level, as well as the type of inflammatory reaction, with PMNs dominating in the cellular infiltrates, all point to a pathogenesis other than rejection.

The histopathological changes and also the clinical features that these five cases share strongly suggest that foscarnet was causative, although other factors might also have played a role. Cotrimoxazole may cause impairment of renal function and tubulointerstitial nephritis [10, 15], and this effect is reinforced by concomitant treatment with cyclosporin A [12, 15].

CMV infection might cause transplant nephritis [14], but it seems unlikely that this would develop during foscarnet treatment, when other symptoms of CMV infection have receded, and then resolve upon cessation of the drug. Furthermore, the typical histopathological changes seen in CMV transplant nephritis are endothelial cell hypertrophy and necrosis in the glomeruli [14] and thus differ from those observed in our patients.

The severe inflammatory cell infiltration and febrile reaction are suggestive of an immune mechanism, which would then have occurred despite the rather heavy immunosuppressive therapy given to these patients. This interpretation would not be contradicted by the reported correlation between foscarnet serum concentration and rise in serum creatinine, including cases of improved renal function despite continued foscarnet administration at a lower dosage [8, 9, 16]. Autoimmune side effects may also be dose-dependent, as for instance with hydralazine and captopril [4, 11].

The number of patients and transplants reported here is too low to demonstrate HLA susceptibility markers, but the fact that four patients had HLA B15 and four grafts had DR4 may be significant.

These five cases of foscarnet nephrotoxicity appeared unexpectedly after several years of uncomplicated experience with this drug. One reason for this may have been the higher dosage used during the last few years, very high daily doses being given to patients with normal renal function. A high serum concentration was verified in one patient. In the unfortunate absence of serum concentration data in the others, it can only be speculated whether the nephrotoxicity was the result of overdosage of the drug or whether it occurred with serum concentrations in the targeted, therapeutic range.

Another possible cause of the unexpected appearance of renal failure during foscarnet treatment is the fact that the diagnosis can easily be overlooked

in the often complex clinical situation. Cases SM and CJ were recognized only in retrospect and after the recognition of this entity in cases BB and MW, in whom the rapid rise in serum creatinine observed during foscarnet treatment was unexpected because several months had elapsed after the transplantation, and rejection or cyclosporin toxicity were not likely to occur. In the last case, presenting with the same clinical picture, foscarnet toxicity was suspected early and confirmed by transplant biopsy and by resolution of fever and renal functional impairment upon discontinuation of the drug.

Foscarnet is a potent inhibitor of proximal tubular reabsorption of inorganic phosphate and has a phosphaturic effect in humans [17]. The demonstration of high proportions of calcium and phosphorous by EDAX suggests that the tubular precipitates may consist of calcium phosphate. This would explain why proper hydration of the patient may prevent nephrotoxicity [6].

Obviously, close attention to the dosage of the drug is mandatory, with immediate dose correction upon any change in renal function, and, if possible, monitoring of the foscarnet serum concentration. As is the case for acyclovir, bolus doses may prove more harmful than continuous infusion [2].

The occurrence of fever and deteriorating renal function in the special clinical setting in which the use of this drug is usually indicated may cause serious diagnostic and therapeutic problems. However, this tubulointerstitial nephritis is reversible upon withdrawal of the drug, possibly also on dose reduction only. The mere recognition of the entity and a transplant biopsy will suffice for proper diagnosis.

In our experience, foscarnet is a most useful mode of treatment for CMV infections in organ transplant recipients, and it will remain so despite its nephrotoxic properties.

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