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Interleukin-8 serum and urine concentrations after kidney transplantation

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Abstract We conducted a prospective study of 12 patients undergoing kidney transplantation. In these patients, we monitored interleukin-8 (IL-8) in both serum and urine before and after kidney transplantation. Levels of IL-8 were analyzed by a solid-phase double ligand ELISA method. Three patients with an uneventful recovery after transplantation showed IL-8 serum levels below the detection limit, whereas some small amounts were detected in the urine of these patients. IL-8 serum levels markedly increased with acute graft rejection and infection. Increments in serum and urine preceded clinical complications in all patients. Highest levels were observed in bacterial infection and lowest in acute rejection. Although nonspecific, IL-8 can be considered as an indicator molecule of inflammatory processes occurring during kidney transplantation.

Key words Interleukin-8 · Kidney transplantation · Rejection Infection

Introduction

Neutrophil accumulation in the transplanted kidney represents a common feature during acute cellular rejection and bacterial or viral infection. The accumulation of neutrophils is mediated by the local production of chemoattractant factors that regulate the migration of polymorphonuclear leukocytes from the vascular compartment to the tissues. Interleukin-8 (IL-8) is a chemotactic cytokine that was initially isolated from lipopolysaccharide stimulated human peripheral blood monocytes [1]. In addition to being a neutrophil chemotaxin, IL-8 also activates neutrophils [2] and has been shown to be chemotactic for T lymphocytes [3]. IL-8 is secreted mainly by macrophages [1], and in addition, nonimmune cells such as fibroblasts [4], endothelial cells [5], and kidney epithelial cells [6] can generate IL-8 in response to macrophage-derived cytokines, IL-1, and TNFa. IL-8 by virtue of its capacity to attract inflammatory cells is a prime candidate to explain the recruitment of inflammatory cells into the graft during rejection or infection. The aim of this study was to investigate endogenous IL-8 production and its relation to allo-immune and infectious complications.

Materials and methods

Patient selection

A total of 12 patients undergoing kidney transplantation from living-related donors were studied. The mean age was 41 years (range 19–58). Nine patients were male and three were female. All patients received prophylactic immunosuppression with cyclosporin, azathioprine, and methyl prednisolone. Rejection episodes were treated with 1 g doses of methylprednisolone. For rejection treatment, some patients required antilymphocyte globulin (ALG).

Samples

Serum and urine samples were collected daily for the first 3 weeks after transplantation. Thereafter, samples were obtained 3 time a week until discharge from hospital.

IL-8 ELISA assay

Antigenic IL-8 was quantitated by a solid phase double-ligand method using an ELISA assay kit purchased from R&D Inc., System (Minn., USA). The detection limit of this method is about 18 pg/ml. All samples were tested undiluted.

Rejection

Clinical rejection was defined by an increase in serum creatinine. Acute rejection was proved histologically in all cases.

Infection

Bacterial infection was diagnosed clinically and by cultures from blood, sputum, and urine. CMV infection was suspected by typical clinical symptoms such as unexplained fever, cytopenia, renal dysfunction, and interstitial pneumonitis, and confirmed by serological evidence of infection (a positive IgM or four-fold increase in anti-CMV IgG).

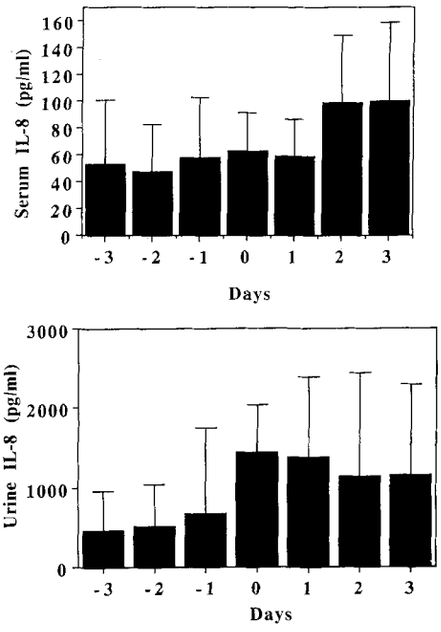

Fig. 1 Serum and urine IL-8 levels in eight patients with acute cellular rejection after kidney transplantation (mean ± SD). Day 0 is defined as the day on which antirejection therapy was started

Results

A total of 480 samples were analyzed for IL-8. In the case of a complication, day 0 was defined as the day on which clinical diagnosis was established and specific therapy initiated.

Stable grafts

In three patients, transplantation was successful and showed an uneventful recovery. In these patients serum levels were below the detection limit of normal healthy volunteers (less than 18 pg/ml). Urine levels in these patients (50 ± 43 pg/ml) were comparable with those of normal volunteers (47 ± 38.9, $n = 26$).

Rejection

Eight episodes of acute cellular rejection were observed. In these patients, IL-8 serum levels had risen 2 days prior to clinical diagnosis (47 ± 35 pg/ml). Levels on day 0 were in the same range (62 ± 28 pg/ml) and increased further (99 ± 49 pg/ml on day 2). IL-8 urine levels prior to clinical symptoms were far higher than those stable patients or normal healthy volunteers (505 ± 532 pg/ml on day − 2). Levels on day 0 increased further (1444 ± 1719 pg/ml) and remained in the same range on days 1, 2, and 3 (Fig. 1).

Bacterial infection

Two patients presented with bacterial gram-negative pneumonia. In these two patients, serum levels of IL-8 were elevated on day − 2 (200 ± 39 pg/ml), increased further on day 0 (350 ± 40 pg/ml), and reached a peak on day 2 (470 ± 56 pg/ml), and decreased with the clinical recovery from infection. Urine IL-8 levels showed the same pattern. Serum and urine IL-8 levels measured in bacterial infection were significantly higher than those observed during rejection ($P < 0.01$).

Viral infection

Two patients had CMV infection. In these patients, serum and urine IL-8 were elevated 8 to 10 days prior to initial clinical presentation and increased further with a peak on day 16. One patient had viral hepatitis with significant hepatic cytolysis. In this patient, the most elevated levels of serum (more 1200 pg/ml) and urine (more than 8000 pg/ml) were observed.

Discussion

In this study, we found that serum and urine concentrations of IL-8 were elevated in kidney allograft recipients during acute rejection, bacterial infection, and viral infection. However, increments were most pronounced in the case of viral hepatitis, and bacterial infection, and were less in acute rejection and CMV infection. These finding suggested that IL-8 production is dependent on the initial stimulus. Bacterial products stimulate IL-8 production more efficiently than alloreactivity or CMV infection. Cytokines of major importance in alloreactivity such as IL-2 and interferons were not able to induce IL-8 in vitro (personal unpublished data). The increase in urine IL-8 was concomitant with the clinical onset of acute rejection (day 0) whereas serum IL-8 reached significant levels onyl on day 2. Therefore, measuring urine IL-8, which is secreted by both graft-infiltrating cells and activated resident endothelial and kidney cells, may accurately reflect the cytokine production within the graft. Inflammatory complications after kidney transplantation are associated with elevated levels of serum and urine IL-8. However, monitoring of IL-8 does not permit clinical complications to be specified.

References

1. Yoshimura T, Matsushima K, Oppenheim JJ, Leonard EJ (1987) Neutrophil chemotactic factor produced by lipopolysaccharide (LPS)-stimulated human blood mononuclear leukocytes. Partial characterization and separation from interleukin-1 (IL-1). J. Immunol 139:788–793
2. Bagglioni M, Walz A, Kunkel SL (1989) Neutrophil-activating peptide-1/interleukin-8, a novel cytokine that activates neutrophils. J Clin Invest 84:1045–1047
3. Larsen CG, Anderson AO, Appella E, Oppenheim JJ, Matsushima K (1989) The neutrophil-activating peptide (NAP-1) is also chemotactic for lymphocytes. Science 243:1464–1466
4. Strieter RM, Phan SH, Showell HJ, Remick DR, Lynch JP, Genord M, Raiford C, Eskandari M, Marks RM, Kunkel SL (1989) Monokine-induced neutrophil chemotactic factor gene expression in human fibroblast. J Biol Chem 264:10621–10626
5. Strieter RM, Kunkel SL, Showell HJ, Remick DG, Phan SH, Ward PA, Marks RM (1989) Endothelial cells gene expression of neutrophil chemotactic factor by TNFa, LPS and IL-1β. Science 243:1467–1469
6. Shmouder RL, Strieter RM, Wiggins RC, Chensue SW, Kunkel SL (1992) In vitro and in vivo interleukin-8 production in human renal cortical epithelia. Kidney Int 41:191–198