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Post-transplant neutrophilic interstitial nephritis – an important cause of graft dysfunction

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Abstract Post-transplant neutrophilic interstitial nephritis (NIN) is characterized by an interstitial infiltrate consisting of polymorphonuclear cells that leads frequently to acute graft dysfunction. In 220 graft biopsies performed because of renal dysfunction over 2 years in our unit, 11 (5%) diagnoses of NIN were made. Only two patients had chronic pyelonephritis as original disease. Four patients had urological problems before transplantation. After transplantation, five patients had urinary tract infection, one had urethral stenosis, two had vesicourethral reflux and one patient had a perinephritic abscess. Seven patients had fever (63%). Only in six patients did urine culture lead to microorganism isolation. After 6 months, only two patients had a serum creatinine level < 1.4 mg/dl, five patients had abnormal function, three had lost their grafts, and one patient had died with sepsis. We conclude that 5% of the biopsies performed in our center disclosed NIN, an entity that causes graft dysfunction and progresses frequently to chronic renal failure. In some cases, no infectious etiology could be detected.

Key words Kidney transplantation · Nephritis · Polymorphonuclear cells

Introduction

We can define neutrophilic interstitial nephritis (NIN) as a histopathological entity characterized by the presence of renal interstitial infiltration basically composed of neutrophils and associated with interstitial edema. Eventually, clusters of polymorphonuclear cells (PMN) obliterating the tubular lumen can be seen. NIN in transplanted kidneys frequently leads to major acute renal dysfunction that is not always reversible with treatment. Differential diagnosis with acute rejection is often very difficult to establish. This picture can be found along with infections of the upper urinary tract (UTI), but it may also be seen during the initial phases of rejection, mainly those accompanied by major vascular impairment. The aims of this study were to evaluate the incidence of post-transplant NIN and to define the clinical features of this pathology that presents special characteristics among transplanted patients.

Patients and methods

We reviewed 220 graft biopsies obtained from 95 transplanted patients over a period of 2 years in our center. All biopsies were obtained because of tailed or failing renal function. In 82% of these cases, serum creatinine was higher than 1.4 mg/dl. Routine baseline biopsies were excluded. NIN was defined as the presence of an infiltrate in the graft, basically composed of PMN. We analyzed the results in terms of the time the diagnosis was made, the presence of urinary tract disease and/or infection, the clinical picture, treatment and outcome of the disease.

Results

Of the 220 graft biopsies, 11 (5%) showed signs of post-transplant NIN. The histopathological characteristics can be seen in Fig. 1. All these diagnoses were performed before 6 months after grafting. Six patients were females. This sex distribution was different from that usu-

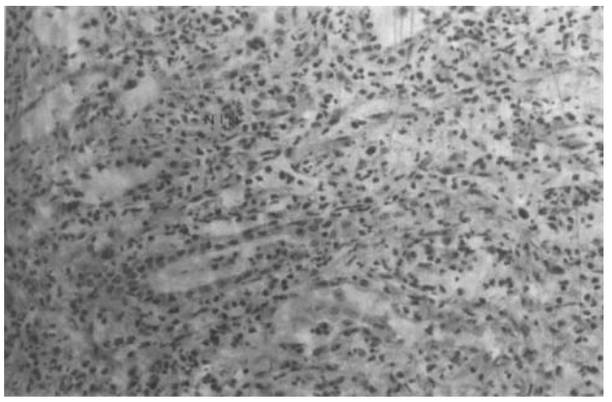

Fig. 1 Neutrophilic interstitial nephritis (H&E × 40)

ally found in transplant patients; more women seemed to be affected than men. Seven of the patients had received cadaveric donor kidneys, two living-related and two nonrelated. Eight patients received triple therapy (azathioprine, prednisone and cyclosporin A). Original disease was chronic glomerulonephritis in seven patients, chronic pyelonephritis in two, and diabetic nephropathy in two. Four patients suffered with urological problems before transplantation, three with vesicourethral reflux and one with UTI (33%). Eight patients did not show any urological pathology before grafting. Five patients showed UTI after transplantation, two with frequent relapses. One patient showed urethral stenosis and was using a double-J catheter at the time of diagnosis. Three patients showed vesicourethral reflux to the graft and one patient showed a perinephritic abscess.

The clinical presentation of these patients was characterized basically by fever, which occurred in seven patients, and renal dysfunction. Graft pain and oliguria rarely occurred. A microorganism could be isolated from the urine from only five patients. Organisms found were *Escherichia coli* (three), *Staphylococcus aureus* (three), *Streptococcus faecalis*, *Acinetobacter*, *Proteus mirabilis* and *Staph. epidermis*. Among the six patients with negative blood and urine cultures, three had an infectious focus outside the graft, and three had no detectable infectious disease. Treatment frequently instituted before the histopathological results were known included antibiotics in two patients, methylprednisolone in four, antibiotics and methylprednisolone in four, antibiotics and antilymphocytic globulin in one, and none in one. At the end, seven patients had received antibiotics. After treatment, the outcomes were normalization of renal function in three patients, all treated by antibiotics, persistence of abnormal renal function in five (45.5%), graft loss in three (27.3%), and death of one patient caused by sepsis. Histologic analysis of these lost grafts detected one case chronic pyelonephritis and two of acute vascular rejection.

Discussion

NIN is not a rare clinical problem in transplantation medicine and, in this setting, shows some peculiar characteristics. Its differentiation from rejection is very difficult, since functional impairment is its more frequent clinical presentation. Fever is also a common finding. This picture certainly leads to undue rejection treatment in our center, as previously reported by Huang et al. [1] and Thomalla et al. [10].

UTI is a frequent occurrence after renal transplantation. Of all transplanted patients, 80% have at least one occurrence of UTI, and 25% of these patients die from infection and 40% of these deaths occur as a result of infection or infection associated with rejection. This high incidence of infection might certainly be influenced by the strong impairment of the immune system, by the common presence of vesical dysfunction and by the mandatory instrumentation of the urinary tract. However, UTI after transplantation has some unique characteristics, quite different from those of UTI that occurs in native kidney. For example, the UTI is frequently associated with cellular rejection or tubulopathy. Histopathologic differential diagnosis may be difficult [12]. Neutrophils may occur in the presence of acute tubular necrosis caused by ischemic injury or associated with a rejection process. The quantity of neutrophils found in a transplanted kidney may also be lower than in a native kidney, even during a clear infection process, because of steroid use.

Negative immunofluorescence studies for antibodies and immune deposits reported by Neilson [5] have shown the histopathologic features of NIN to comprise neutrophil infiltration, interstitial edema, tubular basement membrane disruption and, in severe cases, normal interstitial architecture dissolution.

Mahon et al. [3] have reported that 28% of transplant patients evolve with UTI, 72% of them in the first month. Of these, only 43% were infections caused by *E. coli*. Rubin et al. [9] reported a prevalence of 40% UTI in 47 transplant patients, 63% of whom were women, and 60% of whom had impaired renal function. In this study, all patients had a positive antibody-coated bacterial assay and showed a high rate of relapse, an increased risk of bacteraemia and renal dysfunction more frequently. These authors suggest that prolonged antimicrobial therapy of early post-transplant infections can decrease the occurrence of both bacteremia and relapsing UTI. Palmer et al. [6] have reported five patients in whom fine needle aspirative cytology (FNAC) was performed as part of an evaluation of acute renal dysfunction. Bacteria were detected in the aspirates, and in other cases yeasts have been seen invading the renal parenchyma, with urine culture positive for *Candida albicans* [7]. Treatment with amphotericin B did not prevent septicemia and death. These authors suggested the

use of FNAC to differentiate asymptomatic leukocytouria from invasive infection.

Leigh et al. [2] have reviewed the prevalence of UTI after transplantation and found that it occurs in 65% of patients, mainly in those with chronic pyelonephritis, and more frequently in women. An association of this pathology with positive urine culture or urinary pathology does not always exist, and for this reason diagnosis is frequently wrong. Probably because of inadequate treatment, many of these patients show permanent impairment of renal function, suggesting that a chronic inflammation has become established in these kidneys. Pearson et al. [8] has observed that when treatment of post-transplant infections is correct and immediate, the percentage of complications is low. Another characteristic of post-transplant NIN is the presence of infection caused by unusual organisms. This has been reported by Michigan [4] and Wise et al. [11], who confirmed the importance of renal fungal infections in transplant mortality.

When we deal with a functional loss in a transplanted kidney we should always exclude the possibility of a urinary infection through analysis of the urinary sediment and culture before considering treatment with high doses of immunosuppressive drugs. We should also remember that in the first 6 months after transplantation, infection frequently starts along with bacteraemia, impairment of renal function and parenchymal damage. These events are rare after 6 months after grafting.

We conclude that NIN is a cause of acute renal failure after transplantation, since it was found in 5% of the biopsies performed at our center and occurs more frequently in women. This disease is frequently associated with fever, but not always can an infection process be found. This graft dysfunction is difficult to differentiate from acute rejection, and sometimes progresses to chronic renal failure. Unusual infecting organisms must always be sought. NIN is sometimes associated with UTI, but in some cases, an infection is never found. We should always differentiate NIN from acute cellular rejection so as to consider the right and quick treatment.

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