Transplant Int (1992) 5 [Suppl 1]: S23–S25

TRANSPLANT
International

Monoclonal immunoglobulins in patients with renal transplants: characterization, evolution and risk factors

C. Chakalarovski, Ph. Lang, Cl. Buisson, B. Bourgeon, L. Intrator, L. Deforge, A. Benmaadi, G. Fruchaud, G. Rostoker, Ph. Remy, D. Belghiti and B. Weil

Department of Nephrology and INSERM U 139, Hopital Henri Mondor, Créteil 94010, France

Abstract. Gammopathies were found to be present in 25 (13%) of 192 HIV-negative renal transplant recipients with more than 30 months follow-up prospectively investigated for monoclonal or oligoclonal immunoglobulins (mIg) by agarose gel electrophoresis and immunofixation. Eleven patients had only one monoclonal band, whereas 14 had two or more bands. Of these bands, 60% were IgG kappa, 29% IgG lambda and 11% IgM lambda or kappa, and 90% did not exceed 2 g/l. Most gammopathies occurred early post-transplant (median 5 months) and they were always transient. Some predisposing factors for mIg emergence could be identified: 1. age, but only in women, 2. duration of dialysis, 3. occurrence of prior cytomegalovirus infection, and 4. immunosuppressive regimen including cyclosporine. Serological evidence for active EBV infection was obtained in ten patients, but in six cases infection occurred subsequent to the finding of mIg. In eight patients, the clinical course was characterised by severe infection or tumours (one Kaposi's sarcoma, one B-cell brain lymphoma). The present findings and experimental studies support the view that the development of mIg in renal transplant patients is associated with a failure of regulatory T-cell function. This T-B-cell imbalance requires a careful follow-up in these patients.

Key words: Renal transplantation – Gammopathies

Organ transplantation is associated with an increased risk of developing monoclonal or oligoclonal B-cell lymphomas [2, 10], and a high incidence of monoclonal immunoglobulins (mIg) has recently been described in renal transplant patients [7, 18, 22]. It is unclear whether these mIg are predisposing factors for the development of B-cell malignancies, and they are classifed by Kyle as monoclonal gammopathies of undetermined significance [14, 15]. The present study was performed to evaluate the incidence, the characteristics and the natural history of these gammopathies. We also tried to determine the risk factors for the occurrence of these mIg.

Offprint requests to: Dr. Ph. Lang, Department of Nephrology, Hopital Henri Mondor, Créteil 94010, France

Patients and methods

HIV-negative renal transplant recipients (n = 192) with a functional kidney at 3 months were prospectively investigated for monoclonal or oligoclonal immunoglobulins by agarose gel electrophoresis and by the immunofixation method of Ritchie and Smith [20]. The tests were performed every 3–6 months. All the patients had a follow-up of at least 30 months since transplantation. They received anti-lymphocyte globulins (Mérieux) prophylactically for 2 weeks in association with steroids and azathioprine. Thereafter, patients with low panel reactive antibodies were randomized to receive or not to receive a triple-drug therapy including cyclosporine (CsA). The dose of CsA never exceeded 8 mg/kg per day. Secondary transplant patients and highly sensitized patients were systematically treated with a triple-drug therapy. Finally, the present study included 116 patients treated with a triple-drug therapy and 76 patients treated without CsA.

Statistical analysis was carried out using the chi-squared test or Mann-Whitney U test where appropriate.

Results

Of the study group, 25 (13%) had a monoclonal or multiclonal gammopathy. Of these, 14 (56%) had multiple bands: 12 had two bands, one had three bands and one had four bands. The classification of these mIg showed 22 IgG kappa (60%), 11 IgG lambda (29%) three IgM lambda (9%) and one IgM kappa. The concentration of the mIg was always below 2 g/l except for four bands (3 g/l, 6 g/l, 7 g/l, 15 g/l).

The gammopathies appeared within 2–27 months after transplantation (median, 5 months; mean, 8 ± 6.4 months). In 24 patients there was a period exceeding 2 years since the first detection of the mIg. The bands were always transient. Resolution occured within 12 months in 15 patients, within 12–18 months in five patients and after 18 months in four patients, the longest time being 42 months.

There was no direct correlation between the development of mIg and the sex of the patient. Males represented 64% of the patients with mIg and 68% of those without mIg. Age had an effect on the development of gammopathy, but the higher frequency of mIg in older patients was only observed in women (48.5 ± 7.4 vs 39 ± 10.5 years, $P = 0.006$). No significant difference was observed in men with or without mIg (40 ± 10.2 vs 39.4 ± 9.5 years, respectively).

The duration of haemodialysis prior to transplant was a risk factor for the occurrence of mIg. The mean duration of haemodialysis was 45.7 ± 43 months in patients with mIg compared with 23.7 ± 2 months in patients without mIg ($P < 0.05$).

Continuous prospective virological surveillance of these patients showed that cytomegalovirus (CMV) infection occurred more frequently in patients with mIg than in patients without (22/25 vs 98/167, respectively; $P = 0.01$). Although it was not a significant risk factor, primary CMV infection was more frequent in patients with mIg (10/22, 45%) than in patients without (28/98, 29%). In six patients the switch from IgM to IgG anti-CMV antibodies was unusually delayed, occurring after 18 months. HBs antigen was detected in only 2/25 patients and hepatitis-C virus antibodies were confirmed by a recombinant immunoblot assay (RIBA) in 5/20 (25%) patients. This high percentage is identical to the prevalence found in our transplant population. Significant modification of the serological response to EBV-specific antigens was observed in ten renal transplant recipients. It must be noted that in six patients, these modifications occurred subsequent to the finding of mIg.

The immunosuppresive regimen seemed to have an effect on the development of gammopathy. In the triple-drug therapy group, 16% of the patients had a mIg compared to 8% in those treated without CsA. However, this difference did not reach statistical significance. We found no correlation between the number of rejection episodes per patient and the presence or absence of serum mIg (1.2 ± 0.8 and 1.0 ± 0.7 rejection episodes, respectively).

The number of circulating $CD4^+$ lymphocytes was determined in six patients in parallel with the finding of mIg. The number of $CD4^+$ cells was either less than 150 mm^3 or, if higher, the $CD4^+/CD8^+$ ratio was less than 0.5.

In eight patients, the mIg were associated with the development of severe infections (major wound infection, severe CMV colitis, HSV hepatitis, listeriosis septicaemia, pulmonary aspergillosis, visceral leishmaniasis), or tumours (Kaposis' sarcoma, brain lymphoma).

Discussion

In our study, the incidence of monoclonal and multiclonal gammopathies was 13%. In previous reports using the same sensitive detection method, a similar incidence of mIg has been found after renal transplantation [19, 22].

Gammopathies belonged to either the IgG or the IgM class. IgA was not detected. In B-cell malignancies and in B-cell benign neoplasias, the distribution of mIgG, mIgA and mIgM approximates the frequency of plasma cells producing these heavy chains in bone marrow of healthy adults, i.e. 10% IgM-, 50% IgG-, and 40% IgA-containing cells. The absence or low frequency of mIgA seems to be typical for this category of gammopathy. With respect to the light chain distribution, the kappa/lambda ratio was not altered, in agreement with some reports [18, 19] but not all [22].

The detection of multiple bands has been described in all the categories of gammopathies, but they are found with an unusually high incidence in organ and bone marrow tranplantation [14]. Monoclonal and multiclonal gammopathies had the same outcome, most of them disappearing within 12 months. In the absence of idiotypic study, and although most of the multiple bands had a different light chain, it remains uncertain whether they are produced by a single or by several B-cell clones. The finding of multiple bands or high mIg concentrations did not influence the clinical outcome.

The triggering mechanisms for mIg development remain largely unknown. It is likely that the association of immunosuppressive therapy, chronic antigenic stimulation (the allograft itself) and infection, particularly viral episodes, influence their appearance in genetically susceptible individuals. The depressed humoral and cellular immunity observed in chronic renal failure [1, 13] might also be a risk factor for the emergence of mIg after transplantation, as suggested by this study which shows a high incidence of mIg in patients who have been on dialysis for many years.

It is well known that there is an age-related increase in mIg ascribed to decreased T-cell control of B-cell function [4], but conflicting data have been reported in transplant patients [17, 18, 19, 22]. In the present study, age also had an effect on the development of gammopathies, but this age-related increase was only observed in the women. In other words, the development of mIg in renal transplantation was more frequent in young men than in young women. This observation remains unexplained, but in the general population, B-cell lymphoid proliferations are more frequent in men than in women, possibly indicating that women require the age-cofactor for the emergence of mIg.

Patients treated with the triple-drug therapy had an increased incidence of mIg compared with recipients treated with azathioprine and steroids alone. This may reflect the influence of the intensity of immunosuppressive therapy, but a specific effect of CsA cannot be excluded. This drug can induce autoimmunity [21], increases serum immunoglobulins [11], and promotes B-cell lymphomas experimentally and in humans [11]. Alteration of the cytokine network by CsA might be involved in the pathogenesis of these gammopathies. CsA enhances IL-1 receptor expression [6] and IL-6 gene transcription [24]. However, the link between these in vitro finding and in vivo B-cell stimulation still remains unclear [12].

Other factors may have contributed to the emergence of mIg such as infections, especially from cytomegalovirus which is known to be able to activate B cells and to depress cell-mediated immunity [23]. A recent CMV infection was found in almost 90% of patients developing mIg. Experimentally, CMV-induced immunosuppression is re-

lated to genetic factors [8] and this might explain in part why only a relatively small proportion of CMV-infected patients developed mIg.

Reflecting the alteration of cell-mediated immunity, the serological profile of CMV infection in patients who developed mIg was often characterized by the long-term persistence of IgM anti-CMV antibodies. B-cell lymphomas observed in transplant patients are generally associated with EBV infection [16], but the triggering role of EBV infection for mIg development remains uncertain. Because of its inherent ability to transform the host cell, EBV infection might appear as the main triggering factor for mIg emergence, but in the present study, evidence for EBV infection was found only in 40% of the patients with mIg. However, serological determination of EBV infection is not very reliable in immunosuppressed patients and it remains possible that most mIg in transplant patients are due to an inefficient elimination of EBV-infected cells by cytotoxic T lymphocytes [3]. In our transplant population, only one patient developed a B-cell lymphoma. This patient had two mIg 1 month after a CMV infection, but frequent EBV serological surveys showed that EBV infection occurred only 4 months later in association with the brain lymphoma. This observation suggests that EBV infection was the triggering event for the development of lymphoma, but not for the emergence of the mIg.

Whatever is the triggering event for mIg, their presence imply an insufficient control of B-cell proliferation by relevant T cells. Their detection should be associated with a regular follow-up of the EBV serological profile. The occurrence of an EBV infection in association with a mIg should probably lead to a decrease in immunosuppressive therapy and it could be useful to initiate treatment with acyclovir [9].

Acknowledgements. This study was supported by grants from AURA.

References

1. Cappel R, Van Beers D, Liesnard C, Dratwa M (1983) Impaired humoral and cell mediated immune response in dialysed patients after influenza vaccination. Nephro 33: 21–25
2. Cleary ML, Sklar J (1984) Lympho-proliferative disorders in cardiac transplant recipients are multiclonal lymphomas. Lancet 2: 489–493
3. Crawford DH, Edwards JM Sweny P, Hoffbrand AV, Janossy G (1981) Studies on long term T-cell mediated immunity to Epstein-Barr virus in immunosuppressed renal allograft recipients. Int J Cancer 28: 705–709
4. Crawford J, Eye MK, Cohen HJ (1987) Evaluation of monoclonal gammapathies in the 'well' elderly. Am J Med 82: 39–45
5. Creyssel R, Gibaud A, Cordier JF, Boissel JP (1975) The frequency distribution of heavy chain classes and light chain types of 1000 monoclonal immunoglobulins. Biomedicine 22: 41–48
6. Degiannis D, Stein S, Czarnecki M, Raskova J, Raska K (1990) Cyclosporine induced enhancement of interleukin 1 receptor expression by PHA-stimulated lymphocytes. Transplantation 50: 1074–1076
7. Deteix P, Chapuis-Cellier C, Ghais Z, Lefrançois N, Brusa M, Touraine JL, Traeger J (1985) Systematic survey of immunoglobulin abnormalities; frequency and evolution in organ transplant recipients. Transplant Proc 17: 2651–2654
8. Grundy JE, Mackenzie JS, Stanley NF (1981) Influence of H2 and non-H2 genes on resistance to murine-cytomegalovirus infection. Infect Immun 32: 277–286
9. Hanto DW, Frizzera G, Gajl-Peczalska KJ, Sakamoto K, Purtilo D, Balfour H, Simmons R, Najarian JS (1982) Epstein Barr virus-induced B-cell lymphoma after renal transplantation. Acyclovir therapy and transition from polyclonal to monoclonal B-cell proliferation. N Engl J Med 306: 913–918
10. Hanto DW, Simmons RL (1984) Lymphoproliferative diseases in immunosuppressed patients. In: Morris PJ, Tilney N (eds) Progress in transplantation, vol 1. Churchill Livingstone, Edinburgh, pp 186–208
11. Hattori A, Kunz H, Gill TJ, Shinozuka (1987) Thymic and lymphoid changes and serum immunoglobulin abnormalities in mice receiving cyclosporine. Am J Pathol 128: 111–120
12. Kunzendorf U, Brockmöller J, Bickel U, Jochimsen F, Walz G, Roots I, Offermann G (1991) Promotion of B-cell stimulation in graft recipients through a mechanism distinct from interleukin-6 gene superinduction. Transplantation 51: 1312–1315
13. Kurtz P, Kohler H, Meuer S, Hutteroth T, Meyer Z, Buschenfelde KH (1986) Impaired cellular immune response in chronic renal failure: Evidence for a T cell defect. Kidney Int 29: 1209–1214
14. Kyle RA (1978) Monoclonal gammapathy of undetermined significance – Natural history in 241 cases. Am J Med 64: 814–826
15. Kyle RA (1984) 'Benign' monoclonal gammopathy – misnomer? JAMA 251: 1849–1854
16. List A, Greco A, Vogler L (1987) Lymphoproliferative diseases in immunocompromised hosts: the role of Epstein-Barr virus. J Clin Oncol 5: 1673–1689
17. Peest D, Schaper B, Nashan B, Wonigeit K, Raude E, Pichlmayr R, Haverich A, Deicher H (1988) High incidence of monoclonal immunoglobulins in patients after liver or heart transplantation. Transplantation 46: 389–393
18. Radl J, Valentijn RM, Haaijman JJ, Paul LC (1985) Monoclonal gammapathies in patients undergoin immunosuppressive treatment after renal transplantation. Clin Immunol Immunopathol 37: 98–102
19. Renoux E, Bertrand F, Kessler M (1988) Monoclonal gammapathies in HBs Ag positive patients with renal transplants (letter). N Engl J Med 318: 1205
20. Ritchie RF, Smith R (1976) Immunofixation. III. Application to the study of monoclonal proteins. Clin Chem 22: 1982–1985
21. Sorokin R, Kimura K, Schroder D, Wilson DH, Wilson DB (1986) Cyclosporin-induced autoimmunity. Conditions for expressing disease, requirement for intact thymus and potency estimates of autoimmune lymphocytes in drug-treated rats. J Exp Med 164: 1615–1623
22. Stanko CK, Jeffery JR, Rush DN (1989) Monoclonal and multiclonal gammopathies after renal transplantation. Transplant Proc 21: 3330–3332
23. Van Son WJ, The TH (1989) Cytomegalovirus infection after organ transplantation: an update with special emphasis on renal transplantation. Transplant Int 2: 147–164
24. Walz G, Zanker B, Melton LB, Suthanthiran M, Strom TB (1991) Possible association of immunosuppressive and B-cell lymphoma-promoting properties of cyclosporine. Transplantation 49: 191–194