AETIOLOGY AND PROGNOSIS OF DE NOVO GRAFT MEMBRANOUS NEPHROPATHY

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Summary

In order to investigate the aetiology and prognosis of de novo graft membranous nephropathy (DNGMN), we review 25 such cases observed among 1258 grafts. Coexistence of chronic rejection lesions and their parallel progression with DNGMN suggest that DNGMN may be part of the rejection process. DNGMN developed in 12 per cent of HLA-identical living donor recipients vs only two per cent of both haplo-identical and cadaver donor recipients; in the latter group, all DNGMN patients had ≤2 HLA-AB mismatches. Graft survival after diagnosis of DNGMN is only 49 per cent at five years. We conclude that DNGMN is associated with chronic rejection, develops preferentially in well-matched grafts and carries a rather poor prognosis.

Introduction

De novo graft membranous nephropathy (DNGMN) is an increasingly recognised distinct clinical entity. In 1982 we described nine cases of DNGMN [1]. In a French collaborative study analysing 19 other cases, a review of the literature recorded 42 published cases [2].

In none of these reports was the aetiology of DNGMN elucidated. The prognosis appeared to be poor in our limited previous study [1], while others indicated that DNGMN did not adversely affect graft function [2] and survival [3].

In order to assess the aetiology and prognosis of DNGMN, we review 25 such cases observed in our centre.

Methods

Between 1963 and December 31st, 1983, we performed 1258 renal grafts. Detailed histocompatibility data are available since 1973. Since 1976, all graft specimens were routinely processed for light and immunofluorescence microscopy
using standard fluorescent antisera; electron microscopy is performed only in selected cases. The present study is based on the 450 grafts subjected to pathological examination (biopsy or transplant nephrectomy) from 1976 to July 31st, 1984. Our indications for biopsy are acute rejection resistant to therapy, unexplained graft dysfunction and persistent proteinuria.

Patients were treated with a conventional immunosuppressive regimen (azathioprine and steroids) except for a few receiving cyclosporine; most of the patients transplanted in the last seven years were also given antilymphocyte or antithymocyte serum.

The criteria for the diagnosis of membranous graft nephropathy are detailed in our previous report [1]. The diagnosis of DNGMN is certain when sufficient clinical and/or pathological data allow the exclusion of membranous nephropathy as the cause of the original renal disease. DNGMN is stated to be probable when available pre-transplant clinical data indicate a diagnosis other than membranous nephropathy without definitive histological proof.

The patients’ notes were reviewed up to July 31st, 1984. Nephrotic syndrome is defined by proteinuria >5g/L or >3g/24hr or proteinuria with albuminaemia <3g/dl; improvement of nephrotic syndrome by a regression of proteinuria <1g/24hr; remission by reduction of proteinuria <350mg/24hr or absence on morning urine sample. Deterioration of graft function is defined as a doubling of the serum creatinine.

Results

DNGMN was observed in 25 patients: de novo characteristics were certain in 18 cases and probable in the seven others. There were 14 men and 11 women, aged from seven to 45 (mean: 28) years at the time of transplantation. In 18 of them, quantifiable proteinuria was noted three to 48 (mean: 13) months after transplantation and was the main indication for biopsy demonstrating DNGMN 3 to 30 (mean: 13) months later; in five cases, DNGMN was discovered on a biopsy specimen performed six to 54 (mean: 24) months after transplantation to elucidate graft dysfunction; in the last two cases, DNGMN was found in a graft removed 24 to 39 months after transplantation and was associated with other glomerular lesions. All patients were on conventional immunosuppressive regimens.

The overall incidence of DNGMN is two per cent (25/1258) in the whole population and 5.6 per cent (25/450) among histologically documented grafts.

Mild to severe chronic rejection lesions are present together with DNGMN in all patients. Serial histological data are available in six patients. In three of them appearance of DNGMN, absent on a previous biopsy 12 to 31 months earlier, was associated with progression of chronic rejection lesions. In the three others a subsequent pathological examination two to 46 months after the discovery of DNGMN showed a parallel progression of DNGMN and chronic rejection lesions.

If we restrict the analysis to grafts performed since 1973, it appears that incidence of DNGMN is significantly higher in HLA-identical living donor groups (2/17) compared to that of the HLA-haploidentical living donor group.
(3/141) and cadaver group (18/847) (p<0.05). This is not due to more frequent pathological examination in the first group since only 5/17 grafts were histologically documented in this group, vs 55/141 in the second and 377/847 in the third group respectively. In the 18 cadaver graft recipients with DNGMN, histocompatibility was particularly good: five had none, five had only one, and eight had two HLA-A,B mismatches with their donors.

Among the 23 patients in whom DNGMN was discovered on biopsy, graft survival was 91, 86, 79, 63 and 49 per cent respectively 1, 2, 3, 4 and 5 years after diagnosis. The clinical course was assessed in 19 patients with a potential follow-up of at least one year after demonstration of DNGMN (range: 5–85, mean: 38 months). One patient with minimal proteinuria at the time of diagnosis has normal graft function and no proteinuria 46 months later. Two patients with proteinuria <3g/L at the time of diagnosis are in remission with good graft function 60 to 85 months later. In one patient, the nephrotic syndrome is markedly improved and renal function remains normal 66 months after diagnosis. In five patients, proteinuria remains unchanged with stable graft function, 25 to 48 months after diagnosis. In the last 10 patients, proteinuria did not remit and graft function deteriorated two to 40 months after diagnosis, leading to return to haemodialysis in seven of them five to 50 months after diagnosis. Deterioration of graft function was more frequent (although not significantly) in cadaver grafts (10/16) than in living donor grafts (0/3), when serum creatinine was above 1.7mg/dl (4/5) rather than below this level (6/14) and when nephrotic syndrome was present (7/11) rather than absent (3/8) at the time of biopsy.

Two patients received a second graft: recurrence of the DNGMN leading to graft loss was observed in one patient previously reported [4], while the other has normal graft function and no proteinuria nine months after the second graft.

Discussion

DNGMN is more frequent than previously assumed. Its occurrence in our population is at least two per cent. If we restrict the analysis to histologically documented grafts, the prevalence of DNGMN reaches 5.8 per cent, compared to a two per cent rate reported by others [2,5]: variable incidence among series might simply reflect differences in indications for graft biopsy. Thus, Cheigh [6] found DNGMN in 7.8 per cent of grafts which developed nephrotic syndrome.

Pathogenesis of DNGMN and particularly identification of offending antigen(s) are not yet elucidated. Various exogenous antigens such as hepatitis B virus and antilymphocyte globulins have been suspected but never demonstrated as responsible [1]. Another possible source of antigen is the graft itself: histoincompatible alloantigens might elicit antibody production leading to immune complex glomerulonephritis. In other words, DNGMN could in some way be part of the rejection process. Some of our observations suggest this hypothesis. DNGMN coexists with chronic rejection lesions of variable degree in all of our patients. In two of them DNGMN was superimposed upon other severe and complex lesions of transplant glomerulopathy found in graft nephrectomy specimens. Repeated pathological examinations in six cases show a striking
parallelism between the appearance or evolution of DNGMN lesions and those of chronic rejection. Association of DNGMN and chronic rejection damage has already been described by us [1] and by Dische [7] and can also be found by reviewing pathological data provided in other reports [2,5,8].

If alloantigens are responsible for the development of DNGMN it might seem paradoxical that in our series the disease appears in well-matched grafts and is even more frequent among HLA-identical living donor grafts than in cadaver grafts. It must be added that three other cases of DNGMN occurring in HLA-identical living donor grafts were reported [1,5,8]. In fact, Thoene's experimental studies support the suggestion that the development of DNGMN is enhanced by a good histocompatibility: in the rat, immune complex glomerulonephritis develops in grafts coming from MHC-identical donors and is thought to result from immunisation against minor renal alloantigens independent of MHC [9]. Other factors that may play a role include the immunosuppressive treatment, as discussed elsewhere [1] and individual susceptibility, as suggested by our case of DNGMN recurrence [4].

In our limited previous report, the prognosis of DNGMN appeared poorer than that of idiopathic membranous nephropathy [1]. This is confirmed by the present study, now extended to 25 patients: five year graft survival is only 49 per cent, compared to a five year kidney survival of 88 per cent in a large series of untreated idiopathic membranous nephropathy [10]. Others have claimed that DNGMN has a benign course [6] and does not adversely affect graft function [2] and survival [3]; however two of these reports involve only three [6] and 6 [3] patients. The discrepancy between our results and those of Charpentier [2] may be explained by a greater proportion of DNGMN patients with abnormal renal function and nephrotic syndrome at the time of diagnosis in our series, perhaps resulting from a more severe form or a more advanced stage of the disease. Extended follow-up of such patients in large series will give a more precise assessment of their long-term course.

References

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8 Case records of the Massachusetts General Hospital (Case 45-1979). N Engl J Med 1979; 301: 1052
9 Thoenes GH. Transplant Proc 1981; 13: 1197
Open Discussion

CAMERON (LONDON) May I make one comment on your very nice presentation and ask a question. The comment is that it is interesting that different units in different areas seem to be finding very differing incidences. For example, out of 1,200 grafts we have just one case and we biopsy every nephrotic patient and very many others. When I was looking at the literature, before the publication of your series, I noticed that there seemed to be a deficit of patients with other forms of glomerulonephritis as an aetiology of the renal failure in patients who developed subsequently de novo membranous. Clearly if the initial disease is membranous and they develop a membranous lesion in the graft it is considered a recurrence. It is striking that in the reported cases there is cystinosis, reflux nephropathy, and very curiously three cases of secondary amyloid, which was a grossly distorted pattern. Did you also see this absence of other forms of primary glomerulonephritis in these patients?

PIRSON The cause of the initial renal disease leading to de novo graft nephropathy in 18 cases where the diagnosis was certain were, five cases of glomerulonephritis, one focal glomerulosclerosis, one extracapillary glomerulonephritis, one membranous glomerulonephritis and two other cases which could not be specified but with sufficient data allowing the exclusion of membranous glomerulonephritis and eight chronic interstitial nephritis, two haemolytic uraemic syndrome, two polycystic renal disease, and one oxalosis. There were no cases of amyloidosis. I would add that this prevalence is more than five per cent if we add all the histology we documented.