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Severity of primary MPGN, rather than MPGN type, determines renal survival and post-transplantation recurrence risk

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Previous studies suggested that membranoproliferative glomerulonephritis (MPGN) type II has a worse renal survival and an unacceptable risk of recurrence post transplantation. We hypothesised that other factors may determine this risk. We analysed all cases ($n=70$) of MPGN diagnosed by renal biopsy in Ireland from 1972 to 1995. We used Cox regression analysis to determine factors that were independently predictive of renal failure. MPGN II had more crescent formation and mesangial proliferation ($P<0.05$). Mean follow-up duration was 13.8 years, during which time 41 (58.6%) developed end-stage renal failure (ESRF). The median time to ESRF was 8.3 years (95% confidence interval 5.7–10.9) and 5-, 10-, and 20-year probabilities of ESRF were 32, 54, and 70%, respectively. Multivariate analysis revealed that severity of interstitial fibrosis ($P<0.05$), crescent formation ($P<0.01$) and mesangial proliferation ($P<0.05$) were independently associated with ESRF. Decade of diagnosis, age, MPGN type, and creatinine or complement level at baseline did not predict renal survival in this model. In 21 (49%) of the 43 renal transplants, MPGN recurred. Younger age at initial diagnosis ($P<0.01$) and the presence of crescents on the original biopsy ($P<0.005$) were independently associated with recurrence on multivariate analysis. MPGN type was not associated with recurrence in this model. Contrary to previous reports, after controlling for crescent formation, MPGN II was not associated with more ESRF or recurrence in the allograft. It is therefore the more aggressive glomerular changes associated with MPGN II, rather than the disease type *per se*, that determine outcome.

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Membranoproliferative glomerulonephritis (MPGN) is an uncommon cause of chronic glomerulonephritis in the developed world.[1–3] It typically affects children and young adults with a mean age at onset ranging from 8 to 30 years.[4] MPGN is a disease that lacks any unique serological markers and has no pathognomonic clinical features, but rather is a histologically defined entity characterised by global and diffuse mesangial cell proliferation with migration of mesangium into the glomerular capillary walls, producing an apparent split or double-contoured appearance. It is seen in association with a variety of infections and other systemic diseases. In particular, it has become apparent that, in many parts of the world, hepatitis C virus (HCV), with or without associated cryoglobulinaemia, is an important aetiological factor for MPGN type I.[5,6] Several longitudinal outcome studies have been performed, most of which were published in the early 1990s. Of note, most of these studies were performed before the aetiological importance of HCV was appreciated. Therefore, we do not have accurate knowledge of the natural history in the idiopathic (non-HCV associated) form of this disease.

MPGN is classified into three subtypes on the basis of pathological features identified by light, immunofluorescence and electron microscopy. Type I MPGN is characterised by subendothelial deposits in the capillary wall. In type II MPGN, elongated electron dense densities are seen within the glomerular, tubular and Bowman's capsular basement membrane; hence, it is also referred to as 'linear dense deposit disease'. Previous studies have indicated a recurrence rate of 90% following renal transplantation for this type of MPGN.[7] Type III MPGN is a variant of type I in which there are many subepithelial as well as subendothelial deposits.[8,9]

Of note, we have previously reported that familial MPGN III may occur and is linked to a locus on chromosome 1,[8,9] an area that encompasses the regulators of complement cluster, suggesting a role for disordered complement regulation in the pathogenesis of this disease.

Because of the rarity of MPGN, guidance for physicians is based on case series performed mainly before 1990. The majority of these were published before the importance of HCV was known. In addition, factors potentially predictive of end-stage renal failure (ESRF) or recurrence of primary

disease in a transplant were frequently considered in isolation from each other. We were interested in what factors were independently predictive of outcome (ESRF and recurrence in the renal allograft) when analysed by multivariate analysis. Therefore, we performed a retrospective cohort analysis on a large group of patients with primary MPGN.

RESULTS

Histopathological characteristics at presentation

Of the 70 patients with primary idiopathic MPGN, 30 patients had type I disease (43%), 23 had type II (33%), and 17 had type III (24%). The percentages of cellular crescents, glomerular sclerosis, interstitial fibrosis and degree of mesangial proliferation are summarised in Figure 1. The light microscopic changes were very similar for types I and III. There was a significant increase in the percentage of fresh crescents ($P<0.05$) and degree of mesangial proliferation ($P<0.05$) in type II MPGN.

Clinical characteristics at presentation

The clinical characteristics at presentation are summarised in Table 1. Mean age was 24.9 years (range 3–76) and 41 (59%) were male. Type II patients were younger ($P=0.001$) and exhibited a female preponderance ($P<0.05$), which contrasts with a slight male preponderance among those with type I or III disease. All type III patients had nephrotic-range proteinuria at presentation compared to two-thirds of those with type I or II disease ($P<0.05$). There was no significant difference in the prevalence of hypocomplementaemia at presentation.

Renal survival

Univariate analysis. During the period of follow-up, 41 patients (58.6%) became dialysis dependent. Univariate analyses of factors associated with this outcome measure are summarised in Table 2. There were 11 deaths (16%) during the period of follow-up, all of which occurred after the development of ESRF. Figure 2 depicts the unadjusted probability of developing ESRF over time. The overall median time to ESRF from diagnosis was 8.3 years (95% confidence interval (CI) 4.4–12.3) and 5-, 10-, and 20-year probabilities of ESRF were 32, 54, and 70%, respectively. Using life table survival analysis, the presence of nephrotic-range proteinuria ($P<0.01$), cellular crescents on biopsy at diagnosis ($P<0.005$), degree of mesangial proliferation ($P<0.005$) and degree of interstitial fibrosis ($P<0.01$) were associated with a higher propensity to ESRF (Figure 3). Interestingly, neither MPGN type ($P=0.6$; Figure 3), treatment modality ($P=0.5$) nor complement profile at presentation ($P=0.9$) was associated with ESRF. There was no cohort effect, with the same probability of ESRF observed in the three cohorts ($P=0.3$). Renal survival probability was the same in patients with accurate treatment data ($n=59$) and those without ($n=11$, $P=0.5$).

We evaluated a predictive scoring system for two groups of patients. Firstly, in those patients with no cellular crescents, $<20\%$ interstitial fibrosis and $\leqslant +2$ mesangial proliferation ($n=16$), median renal survival was 13.8 years and 10-year probability of ESRF was 12%. This compared to a median renal survival of 6.4 years and 10-year ESRF probability of 69% in those without this triad ($n=54$; hazard ratio 0.21, 95% CI 0.15–0.70, $P<0.005$). Secondly, nephrotic patients with at least one cellular crescent ($n=18$) exhibited a median renal survival of 4.5 years and 10-year ESRF probability of 92%. This compared to a median renal survival of 11.9 years and 10-year ESRF probability of 41% in those without the combination of nephrotic syndrome and crescentic nephritis ($n=52$; hazard ratio 3.0, 95% CI 2.0–11.9, $P<0.0005$).

Multivariate analysis. Using multivariate Cox regression analysis, the degree of interstitial fibrosis ($P<0.05$), degree of mesangial proliferation ($P<0.05$) and the presence of at least one cellular crescent at diagnosis ($P<0.01$) were independently associated with ESRF (Table 3).

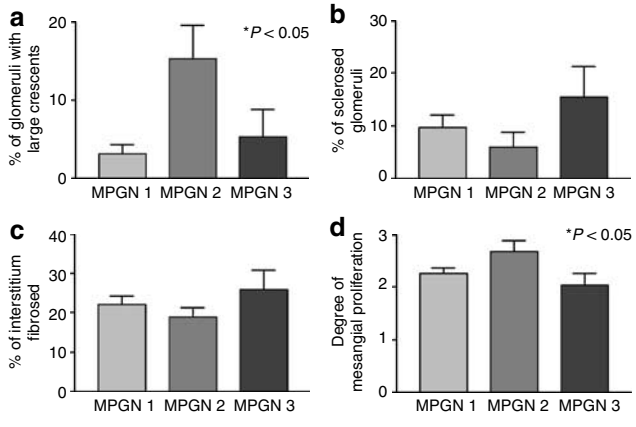

Figure 1 | Histopathological characteristics at diagnosis. (**a**) Mean cellular crescent fraction was 3.1 ± 1.2, 15.3 ± 4.3 and $5.3\pm3.5\%$ for types I, II and III, respectively. (**b**) Respective values for percentage of glomeruli sclerosed were 9.7 ± 2.4, 5.9 ± 2.9 and $15.4\pm5.9\%$, for percentage of interstitium fibrosed (**c**) 21.9 ± 2.3, 18.9 ± 2.1 and $25.7\pm5.0\%$ and for degree of mesangial proliferation (**d**) 2.3 ± 0.1, 2.7 ± 0.2 and 2.0 ± 0.2. The bars represent the mean $\pm$ s.e.m. *$P<0.05$.

Table 1 | Clinical characteristics of the patients at presentation according to MPGN type

	Type I	Type II	Type III	*P*-value
Age (years) (mean, range)	33.2 (5–76)	13.7 (4–34)	26 (3–66)	0.001
Male (*n*, %)	22 (73)	8 (34)	11 (64)	0.02
Creatinine (mg/dl) (median, IQR)	0.9 (0.6–1.9)	0.8 (0.6–1.3)	0.8 (0.7–1.4)	0.23
Nephrotic at presentation (*n*, %)[a]	18 (64)	15 (65)	15 (100)	0.03
Low C3 at presentation (*n*, %)[b]	12 (46)	5 (29)	7 (58)	0.28

IQR=interquartile range.
[a]*n*=66.
[b]*n*=55.