Clinical features and treatment outcome of idiopathic membranous nephropathy in Chinese patients

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Summary

We retrospectively studied the clinical course and levels of proteinuria and serum creatinine in 38 Chinese patients (25 male, 13 female, age 51.6 ± 14.6 years, follow-up duration 58.2 ± 51.1 months) who presented over a 10-year review period. Eight never received any form of specific treatment (group I), seven received oral corticosteroid alone for 6–9 months (group II), 17 were given corticosteroid plus cyclophosphamide for 6–12 months (group III), and six were treated with methylprednisolone alternating with chlorambucil every other month for 6 months (group IV). No untoward effect from drugs sufficient to alter the dosage used was recorded. After 6 months of treatment, over 50% of patients went into remission: a significant reduction in proteinuria (p = 0.01, 0.01, 0.02) with a corresponding rise in serum albumin levels (p = 0.01, 0.01, 0.04) was observed in groups II, III, and IV, respectively, but not in group I.

Introduction

Idiopathic membranous nephropathy (IMN) is the most common form of glomerular disease causing nephrotic syndrome in adults. While many patients have a spontaneous remission of the disease and reduction of proteinuria with time, a significant proportion develop severe and persistent proteinuria, and progress to chronic renal failure or end-stage renal disease. Reports of the natural history of the disease have yielded different results owing to variations in patient population, geographical location, method of patient monitoring, and duration of follow-up. Though the optimal treatment of IMN remains uncertain, Couchoud et al. have shown in a meta-analysis that immunosuppression is useful in inducing complete or partial disappearance of nephrotic syndrome.

Specific treatment with immunosuppressive agents, however, is not without morbidity and potential mortality, and not all patients respond. Moreover, as most of the published data are derived from the Caucasian population, little is known about the clinical course and treatment outcome of IMN amongst Chinese patients in the Far East. To shed light on the natural course of the disease and the influence of different forms of therapy, we retrospectively reviewed the outcome of all patients with a diagnosis of IMN presenting over a 10-year period amongst ethnic Chinese in Hong Kong.
Methods

All patients with histologically-proven membranous glomerulonephritis presenting to Queen Mary Hospital, University of Hong Kong in the 10 years leading up to June 1996 were included in this retrospective analysis. Patients with systemic lupus erythematosus were excluded. Potential secondary causes were carefully sought after and excluded by clinical history, particularly with regard to the use of drugs, and by serological tests for infectious and connective tissue diseases. Screening for occult malignancy was routinely carried out in all patients over the age of 50 by obtaining complete blood count, serum carcinoembryonic antigen and alpha fetoprotein levels, chest radiograph, faecal occult blood and other appropriate tests as required.

Patients who satisfied the criteria for a diagnosis of IMN were analysed as four subgroups based on the treatment given. There was no difference in the pre-treatment duration of proteinuria (data not shown). Where treatment was implemented, data were collected on renal function, urinary protein excretion and serum albumin at the start of treatment and at specific time points thereafter. Hypertensive subjects, defined as those with blood pressure over 140/90 mmHg on three successive occasions, were treated with enalapril (5–20 mg/day) either singly or in combination with a calcium-channel antagonist (in most cases, nifedipine was used).

Group I comprised eight patients who received supportive treatment alone and never received any specific (immunosuppressive) therapy. Group II comprised seven patients who received oral corticosteroid alone, given in the form of prednisolone starting at 0.5 mg/kg/day and tapered over a period of 6–9 months (median 7 months) according to response to therapy. Group III comprised 17 patients who received corticosteroid plus cyclophosphamide. Corticosteroid was given orally as in group II. Cyclophosphamide was given orally at 1 mg/kg/day and stopped after 6–12 months (median 6 months) regardless of response. None of the patients in this group received either drug intravenously. Group IV comprised six patients who received corticosteroid and chlorambucil alternately for 6 months according to a protocol designed by Ponticelli et al. Briefly, 500 mg of methylprednisolone was infused intravenously daily for 3 days followed by oral prednisolone 0.5 mg/kg/day for 27 days at months 1, 3, and 5, alternating with chlorambucil 0.2 mg/kg/day for 30 days at months 2, 4, and 6.

All patients were monitored at 1–3-monthly intervals depending on individual need and disease severity. During each visit, plasma creatinine and serum albumin, complete blood count, urinary protein excretion either in the form of dipstick testing or collection of 24-h urine specimen for protein and creatinine, blood pressure alongside other clinical data were recorded. The end-point for analysis of treatment outcome was June 1997, so that all recruits would have been followed for at least 12 months or more.

For simplicity in gauging clinical outcome, complete remission was arbitrarily defined as a reduction of proteinuria to 0.2 g/24 h or below, partial remission as a reduction of proteinuria to 2 g/24 h or below in the presence of stable renal function. Where proteinuria remained >2 g/24 h, it was classified as persistent disease. Any increase in serum creatinine of more than 50% over the baseline creatinine at presentation was taken as significant renal function deterioration.

Statistics

In two-group comparisons, Student’s t test was used. A univariate approach was used to evaluate different covariates on renal function deterioration. *p* values of <0.05 were considered significant.

Results

Over a 10-year period, 59 patients presented with biopsy-proven membranous glomerulonephritis. Eight had hepatitis B surface antigenaemia, two had malignant conditions within 18 months of diagnosis, two had rheumatoid arthritis, one died of acute myocardial infarction shortly after diagnosis, two lived in old-age homes and could not be followed regularly, one chose to take Chinese herbal medicine and defaulted follow-up, one was a drug addict with doubtful compliance, while two of four patients who were already near end-stage renal failure at presentation received a renal transplant in less than 6 months from diagnosis. All these patients were excluded from the study. The epidemiological and clinical characteristics of the remaining 38 patients with IMN are summarized in Table 1.

As the patients were recruited over a 10-year study period, two different time points were chosen to reflect their short-term (after 6 months of therapy) and long-term (after 5 years of diagnosis) clinical outcomes. At 6 months, two patients (25%) were in complete remission and one (14%) in partial remission in group I, but the degree of proteinuria and serum albumin levels as a group were not significantly altered. Five patients (71%) in group II were in remission, complete in two (29%) and partial in three (42%). In group III, 11 patients (65%) remitted; complete remission was observed in four (24%), and partial remission in seven patients (41%). In group IV, complete remission was present in one (17%), and
Table 1  Demographic features and clinical characteristics at presentation

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Group I (Supportive treatment)</th>
<th>Group II (Steroid only)</th>
<th>Group III (Steroids + Cyclophosphamide)</th>
<th>Group IV (Ponticelli’s regimen)</th>
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<tbody>
<tr>
<td>n</td>
<td>38</td>
<td>8</td>
<td>7</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>Age (years)</td>
<td>51 ± 14.6</td>
<td>47 ± 12</td>
<td>58 ± 16.9</td>
<td>52 ± 16.6</td>
<td>48 ± 6.2</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.26 ± 0.42</td>
<td>1.23 ± 0.36</td>
<td>1.23 ± 0.40</td>
<td>1.14 ± 0.43</td>
<td>1.33 ± 0.36</td>
</tr>
<tr>
<td>Serum albumin (g/dl)</td>
<td>2.58 ± 0.7</td>
<td>3.4 ± 0.5</td>
<td>2.83 ± 0.36</td>
<td>2.1 ± 0.35</td>
<td>2.4 ± 0.85</td>
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<tr>
<td>Proteinuria (g/24 h)</td>
<td>5.9 ± 3.3</td>
<td>3.2 ± 2.9</td>
<td>7 ± 5</td>
<td>6.3 ± 2.1</td>
<td>7.2 ± 2.5</td>
</tr>
<tr>
<td>Required antihypertensive(s)</td>
<td>14</td>
<td>2</td>
<td>3</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Follow-up duration (months)</td>
<td>45.7 ± 36.8</td>
<td>58.2 ± 51.1</td>
<td>59.1 ± 32.2</td>
<td>37.5 ± 31.7</td>
<td>36.6 ± 32.9</td>
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</tbody>
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Values are means ± SD.

partial remission in two patients (33%). In groups II through IV, there was a significant reduction in proteinuria, with a corresponding rise in serum albumin compared with baseline levels (Figures 1 and 2).

To eliminate bias as a result of a difference in the length of follow-up, we analysed the long-term outcome at 5 years among those patients who had been followed for this period of time or longer. As only three group II and two group IV patients had been followed for over 5 years, they were excluded for this evaluation. Among six group I (median follow-up 64 months) and eight group III (median follow-up 81 months) patients who had been followed for at least 5 years, the serum creatinine almost remained unchanged in both groups (Figure 3), but there was a progressive reduction in the amount of proteinuria in group III patients over the follow-up period. This improvement was not observed in group I (Figure 4). However, due to the relatively small patient numbers and the high standard deviation, this difference was only just significant ($p = 0.048$).

Renal function deterioration occurred in one patient in each of group I (13%), group III (6%) and group IV (17%) during the follow-up period. In group II, two (29%) had renal function deterioration, of whom one required renal replacement therapy 2 years after presentation (Figure 5). To assess the impact of different factors on renal function deterioration, the following variables were taken into account: sex, age, presenting plasma creatinine levels, proteinuria, blood pressure, tubulointerstitial scarring on renal biopsy. Univariate survival analysis showed that an elevated presenting plasma creatinine level ($p < 0.05$) was the single most important factor in predicting renal function deterioration, while other factors did not correlate significantly with subsequent changes in plasma creatinine.

No significant complication was recorded among patients of groups I and II. In group III, one patient with persistent nephrotic syndrome died of myocardial infarction 14 months after presentation, one patient with renal insufficiency had a cerebrovascular accident 30 months after presentation, and another patient developed carcinoma of the colon requiring a right hemicolectomy 5 years after presentation while in partial remission. One group IV patient had a severe episode of pneumonia 6 years after presentation, requiring intensive care. In particular, none of the patients in all the three treatment groups had their medications reduced or terminated because of drug-related side-effects, although one patient reported mild gastrointestinal upset in the second cycle of chlorambucil. Apart from the patient who died from myocardial infarction, none of the patients in all groups had any thrombotic episodes, noting that over 40% still had a daily urinary protein excretion of more than 2 g at 12 months.

Discussion

The aim of this retrospective study was to give an overview on the clinical course, and treatment outcome of idiopathic membranous nephropathy amongst Chinese patients, on whom such data, to our knowledge, are lacking in the literature.

While drugs, systemic lupus erythematosus, and rheumatoid arthritis are the conditions most frequently associated with membranous glomerulonephritis in Western society, hepatitis B surface
antigenaemia remains the strongest association in the locality of Hong Kong, where 10% of its population of 6 million people are carriers of the virus. Though a direct causal relationship between the virus and membranous nephropathy may be difficult to establish, it was reflected by the higher prevalence of the carrier state among membranous nephropathy patients in this series (13.6%) compared to the general population (10%) in Hong Kong and southern China.

Because of the length of time over which patients were included in the present analysis, the treatment regimen reflected our views at different times. In general, a policy of treating only those patients with heavy proteinuria applied. This explains the difference in the presenting proteinuria and serum albumin levels between the untreated (group I) and the treated (groups II, III, IV) patients. There was no difference in the creatinine values in the four groups of patients.

Overall, our results show that IMN runs a benign course for most patients in the locality of Hong Kong. While 13% (5/38) of patients developed renal function deterioration over a period of 60 months, only 2.6% (1/38) went into end-stage renal failure requiring dialysis. Given the risks associated with immunosuppression, it is justifiable to elect only those patients with severe persistent nephrotic syndrome or significant progressive renal failure for treatment. This could explain the relative lack of
trols in a randomized fashion. Nevertheless, our results are in sharp contrast to those obtained from Caucasians, in whom corticosteroid alone for 6 months failed to achieve any difference between treatment and control groups in terms of creatinine clearance and 24-h urinary protein excretion. Although in our series steroid alone induced remission in up to 71% of patients, it did not offer as much renal function protection as the other form of treatment, as reflected by the fact that 6% in group III vs. 29% in group II had developed renal function deterioration, noting that both groups had a comparable degree of proteinuria and serum creatinine at presentation.

Although a number of factors have consistently correlated with progression to chronic renal insufficiency in idiopathic membranous nephropathy, they appear late, are not quantitative in nature and have not been validated. Initial serum creatinine levels, singled out as an important prognosticator in subsequent renal function deterioration, thus have potential implications in guiding the form of treatment any individual patient should receive. This concept of stratifying patients on presentation as to their risk of developing renal failure has been alluded to in a recent review.

Although most patients were severely nephrotic at presentation (Table 1), none developed renal vein thrombosis, a common complication of the nephrotic syndrome, despite the absence of anticoagulant prophylaxis that would otherwise have been given in Caucasians, reflecting the fact that Chinese are in general less prone to venous thrombosis. This is in line with the observation that Chinese patients with prosthetic heart valves require smaller doses of warfarin and a lower target of international normalized ratio (INR) than their Caucasian counterparts as a prophylaxis against thromboembolic complications. While leukopaenia and gastrointestinal upset are frequent causes of interrupting chlorambucil in Caucasian patients, they are uncommon in Chinese patients, although the number of patients receiving chlorambucil was comparatively small in our series.

This study has highlighted the categorical differences in clinical features and treatment outcomes between Caucasian and Hong Kong Chinese patients with IMN. The form of treatment that gives the best results in the former may not apply in the latter. Whether Chinese patients are ‘more sensitive’ to immunosuppressives and hence require less immunosuppression to achieve and sustain remission of IMN has yet to be investigated by a randomized and controlled prospective study.

### References

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