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CLINICAL STUDY

The Role of Pure Diffuse Mesangial Hypercellularity in Patients with Proteinuria

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Background. Pure diffuse mesangial hypercellulality (DMH), in its primary form, is a relatively rare histological finding, and scant data exist in the literature regarding its clinical course and prognosis in nephrotic adults with this diagnosis. *Methods*. We retrospectively analyzed the clinical and histological data of 8 out of 41 patients with the above diagnosis in regard to response to the treatment, outcome and prognostic indicators. *Results*. Six patients received oral prednisolone as initial therapy, five of whom receiving it as monotherapy at first. The two other patients did not receive anything at all. Three out of the above six patients received prednisolone either with cyclophosphamide or with cyclosporine (CyA). Three patients responded with complete remission, two showed partial remission, and one did not respond at all. During follow-up, none of the patients with complete response appeared to have relapse. The two patients with initial partial response to steroids received CyA in combination with low dose of oral prednisolone. The other patient who did not respond at all from the beginning did not receive anything more due to his bad general condition. Plasma creatinine remained stable in those with complete or partial response to treatment. None of the clinical characteristics was found to be predictive of the degree of renal function impairment at the time of renal biopsy. The three patients with partial or no response were characterized by the severity of mesangial hypercellularity. Patients with complete or partial response to therapy did not differ with regard to age, plasma creatinine, and severity of proteinouria at biopsy. Presence of mesangial IgM was not associated with poor or satisfactory response. In general, no clinical feature at the time of biopsy was predictive of a response to therapy. *Conclusions*. At present, it seems that adult patients with DMH and proteinuria represent a heterogeneous group with different clinical courses despite a similar morphological appearance in initial biopsies. We conclude that serial biopsies taken at regular intervals coupled with a longer follow-up may provide answers concerning the real intentity of DMH.

Keywords diffuse mesangial hypercellulality, IgM, prednisolone, cyclophosphamide, cyclosporine, proteinuria

INTRODUCTION

Diffuse mesangial hypercellularity (DMH) in idiopathic nephrotic syndrome (NS) was originally described by Churg et al.[1] and White et al.[2] in 1970. This histopathological pattern is relatively uncommon in Europe and North America, where it is thought to account for 2–10% of all patients with NS.[1,3] DMH has been described in some patients with minimal change (MCD) nephrotic syndrome (MCNS) who are either steroid-resistant or steroid-dependent.[4] DMH in idiopathic NS has also been seen in association with focal segmental glomerulosclerosis (FSGS) or the deposition of mesangial IgM.[5] The relationship between DMH, MCNS, and FSGS remains unclear. Some authors separate DMH and MCNS,[6] while others consider them the same entity.[6,7] Other authors believe that these entities represent a continuum, and that over time, DMH may convert to normal, MCNS, or FSGS.[7] The same consideration refers also to IgM deposits: IgM nephropathy either is or is not a separate clinicopathological entity.[7–9]

The insufficient data concerning clinical course and pathological findings of adult patients with this rare condition prompted us to analyze retrospectively patients with proteinuria in whom a diagnosis of DMH was made.

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PATIENTS AND METHODS

From a study period of 36 months, clinical and histological data of adult patients with NS and renal biopsies showing DMH were reviewed. The diagnosis of DMH was based on the following criteria[10]:

- the presence of three or more cells per mesangial region in a thin, 2–3 μm section away from the vascular pole;
- a lesion involving >80% of the glomeruli in the specimen;
- the absence of double contours or spikes of the glomerular capillary walls visible by silver impregnation;
- the absence of dense deposits in the basement membranes visible with the trichrome stain; and
- no clinical or histological evidence of associated disease such as IgA nephropathy, lupus, vasculitis, HIV and hepatic disease.

All biopsies in our study contained >10 glomeruli. The diagnosis of FSGS required even the presence of a single glomerulus with segmental hyalinosis or scar. Grading of the cellularity was done on the basis of the number of mesangial cells per peripheral mesangial area according to criteria adopted by WHO Committee on Clasification and Nomenclature of Renal Diseases.[11] One or two mesangial cells per area were accepted as normal, whereas three cells were indicative of mild mesangial hypercellularity, 4–5 cells represented moderate hypercellularity, and >5 cells were graded as severe hypercellularity. Based on these criteria, a total of eight patients out of 41 were indentified. Clinical and laboratory information for each patient was available both at the time of biopsy and throughout their follow-up.

All biopsies were taken using a standard Trucut needle, before instituting treatment. In each case, four stains were available for review by light microscopy: haematoxylin, mason trichrome, periodic acid-Schiff, and silver methenamine period acid-Schiff (Jones). Immunofluorence studies were done using labeled antisera against IgG, IgA, IgM, C3, C4, and fibrinogen. Lesions with sole or dominant IgM deposits in the mesangium were categorized in the IgM-positive group. In addition to establishing the diagnosis, the following features were recorded: mesangial sclerosis, epithelial cell proliferation, synechiae with Bowman's capsule, and diffuse mesangial deposits of IgM and C3. Furthermore, the severity of tubular atrophy and interstitial fibrosis, the extent of inflammatory tubulointerstitial infiltrate, and the presence of arteriosclerosis were also evaluated and graded on a scale from 0 to 3.

RESULTS

A review of 41 renal biopsies performed for a period of 36 months revealed eight patients (19.51%) with idiopathic DMH associated proteinuria. Clinical and demographic data of the patients are presented in Table 1. Histological data of the patients are presented in Table 2. The immunofluorescent microscopic study showed a prominent positive reaction for IgM with or without C3 in 5 patients (62.5%) as a diffuse mesangial pattern. In two patients, traces of mesangial IgG and IgA were also indentified. Complement components other than C3 were observed in two cases (C1q).

Table 1
Clinical data of eight patients with DMH

Male/female	5/3
Age	55.5 ± 16.31
Plasma creatinine (mg/dl)	1.65 ± 1.01
Proteinuria	3.78 ± 2.94
Hematuria	5 (62.5%)

Table 2
Histological findings in eight patients with DMH

Mesangial hypercellularity	5 (62.5%)
Mesangial sclerosis	4 (50%)
Synechiae	3 (37.5%)
Tubular atrophy	3 (37.5%)
Interstitial fibrosis	4 (50%)
Arteriosclerosis	4 (50%)

Six patients received oral prednisolone as initial therapy, five of whom were receiving it as monotherapy at first. The two other patients did not receive anything at all (the first patient appeared to have advanced renal failure with enxtended sclerosis, and the second one had mild proteinouria with generally good histological findings). Three out of the above six patients received prednisolone either with cyclophosphamide or with cyclosporine (CyA). Three patients responded with complete remission, two showed partial remission, and one did not respond at all. The time of remission (complete or partial) ranged from two weeks to four months, with most patients responding within three months. During follow-up, none of the patients with complete response appeared to have relapse. The two patients with initial partial response to steroids received CyA in combination with low dose of oral prednisolone. Complete remission was achieved in four weeks. The other patient who did not respond at all from the beginning did not receive anything more due to his bad general condition. Plasma creatinine remained stable in those with complete or partial response to treatment.

None of the clinical characteristics was found to be predictive of the degree of renal function impairment at the time of renal biopsy. The three patients with partial or no response characterized by the severity of mesangial

hypercellularity. Patients with complete or partial response to therapy did not differ with regard to age, plasma creatinine, and severity of proteinouria at biopsy. Presence of mesangial IgM was not associated with poor or satisfactory response. In general, no clinical feature at the time of biopsy was predictive of a response to therapy.

DISCUSSION

DMH, an uncommon biopsy pattern, has been described as more resistant to steroids than MCD but usually resolved whether treated or not.[12] There have been significant variations among studies in the reported frequency and resistance to therapy of DMH, possibly because of the criteria used to establish the diagnosis.[12,13]

Our study population is small, but indicative of the general response of patients with DMH. Three of the total of six patients that received therapy showed remission after taking a combination of steroids plus cyclophosphamide or CyA. The poorer response obtained in our study is similar to that reported in children in the Southwest Pediatric Nephrology Study Group (SPNSG)[14] and the International Study of Kidney Disease in Children (ISKDC).[15] Considering our patients as a small group DMH in adults with proteinouria, must be clearly differentiated from MCD and should be regarded as a distict entity. On the contrary with the results of the SPNSG and the ISKDG, our observations suggest that treatment with cytotoxic drugs is probably warranted in patients with DMH that are unresponsive to steroids. CyA has been used in a few patients with DMH,[16] but at present, no conclusion can be drawn regarding its efficacy because, even outside of our study, only a small number of patients have been treated so far. Two of our patients who received CyA went into complete remission after treatment with CyA. We suggest, therefore, that CyA at a low dose for a prolonged period of time is safe and may be considered as an alternative treatment for patients with partial or no response to steroids.

We noticed that the response to the treatment is the most important clinical factor that determines the final outcome. Renal function remained stable in all patients that responded completely or partially to the treatment. From our analysis, it was found that no clinical feature that we measured at the time of biopsy was predictive of response to treatment. Two non-responders were much younger, but otherwise did not differ with regard to the severity of DMH, the prevalence of haematuria, or the degree of proteinuria. The reason why younger adult patients with this lesion are more often resistant to steroids is not clear.[7] Perhaps different pathogenetic mechanisms may operate at different stages of life in producing the same lesion, some of which are steroid sensitive.

Our analysis was carried out to determine if any of the histological parameters had an influence on the response to treatment, only the presence of mesangial hypercellularity seemed to had an independent predictive value. It was more common finding in non-steroid responders. The same group of patients were also IgM-positive. These results, according to recent data, indicate that the presence of mesangial IgM deposits in association with DMH increases the likehood of resistance to therapy and reflects a more severe course of clinical disease. However, it lacks specificity. Thus, despite different opinions, our observations support the view that DMH with IgM mesangial deposits is not a distinct clinicipathological entity, and the presence of mesangial IgM deposition correlates frequently, but not always, with a poorer response to treatment and worse outcome.[17,19]

At present, it seems that adult patients with DMH and proteinuria represent a heterogeneous group with different clinical courses despite similar morphological appearance in initial biopsies.[20] Many items concerning therapy and clinicopathological features remain controversial. The group of patients that respond to therapy with a combination of drugs have IgM deposition and appear to have mesangial hypercellularity. We conclude that serial biopsies taken at regular intervals coupled with a longer follow-up may provide answers concerning the real intentity of DMH.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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