INTERSTITIAL FOAM CELLS IN THE NEPHROTIC SYNDROME BELONG TO THE MONOCYTE/MACROPHAGE LINEAGE


Hospital Curry Cabral, Lisbon, Portugal. *Guy's Hospital, London, United Kingdom

Summary

Interstitial foam cells are occasionally seen in patients with the nephrotic syndrome. In a group of patients with the nephrotic syndrome we were able to demonstrate that these cells express markers characteristic of the monocyte/macrophage lineage. Their presence was related to the previous duration of proteinuria, but they had no apparent influence on the subsequent evolution of renal function. The mechanisms leading to their presence are unknown.

Introduction

Lipid-containing cells with a foamy appearance have long been described in the renal interstitium of patients with the nephrotic syndrome [1]. Such cells seem to be more frequent in the nephrotic syndrome due to mesangio-capillary or focal and segmental sclerosing lesions and in certain cases they are also noted in glomeruli.

However, the origin of these interstitial cells is disputed. Some believe they represent tubular cells [2], which have acquired lipids or lipoproteins that have escaped the glomerular filter. Others suggest they represent lipid-containing macrophages [3], similar to those observed in atheroma lesions, in which extensive data suggest their macrophage origin [4]. They have not been correlated with clinical findings or prognosis of the underlying renal disease.

We describe our findings in patients with the nephrotic syndrome of various aetiology, of large lipid-loaded interstitial cells with a foamy appearance, strongly HLA-DR positive and expressing other markers characteristic of cells of the monocyte/macrophage lineage.

Patients and methods

Twenty-nine adult patients with the nephrotic syndrome were studied. Systemic lupus erythematosus syndrome was present in four cases, Henoch-Schönlein
purpura in one, and a membranous nephropathy associated with penicillamine in another patient. The remaining 23 had the idiopathic types of glomerulonephritis (membranous 15, mesangio-capillary 3, focal and segmental sclerosing lesions 2, minimal change 3).

Renal biopsies were performed in 19 patients within six months of apparent onset of the nephrotic syndrome. The remaining biopsies were performed later in the course, two of them being second biopsies obtained at 18 and 69 months from onset respectively because of deteriorating renal function.

Renal tissue was obtained in all cases by percutaneous renal biopsy and processed for conventional optical and immunoperoxidase studies.

A panel of previously well-characterised monoclonal antibodies was applied at appropriate dilutions to sequential cryostat sections, and revealed using an indirect immunoperoxidase method. Sections were counterstained with Mayer’s haemalum. We employed monoclonal antibodies recognising epitopes expressed in all leucocytes (2D1), B cells (TO 15), monocyte/macrophages (FMC 32), natural killer cells (Leu 7), Pan T (UCHT 1), T helper/inducer (Leu 3a) and T cytotoxic/suppressor lymphocytes (UCHT 4), and an anti-C3 b receptor. Anti-HLS-DR monoclonal antibodies were also used, as well as M704 and DH 2. A positive control (tonsil section) was used with each monoclonal antibody, as well as a negative control in each biopsy.

Double staining with immunoperoxidase-lipid (Sudan B) was additionally used in two cases.

Results

In all biopsies studied, HLA-DR was expressed on capillaries (either peritubular or glomerular), on interstitial round or stellate cells, and with a variable intensity on the cytoplasm of epithelial tubular cells. These epithelial cells also reacted with the anti-NK cell antibody (Leu 7), but not with the remaining monoclonal antibodies.

<table>
<thead>
<tr>
<th>Histological diagnosis</th>
<th>Foam cells (HLA DR +)</th>
<th>No foam cells</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Membranous</td>
<td>5</td>
<td>11*</td>
<td>16</td>
</tr>
<tr>
<td>Mesangio-capillary</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Focal and segmental sclerosing lesions</td>
<td>2</td>
<td>–</td>
<td>2</td>
</tr>
<tr>
<td>Minimal change</td>
<td>–</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>SLE: Membranous</td>
<td>1</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Crescentic</td>
<td>–</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Henoch-Schonlein Purpura</td>
<td>–</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>10</strong></td>
<td><strong>19</strong></td>
<td><strong>29</strong></td>
</tr>
</tbody>
</table>

*one patient penicillamine-induced
In 10 biopsies (Table 1) variable numbers of interstitial cells showed a strong and characteristic pattern with the anti-HLA-DR monoclonal antibodies (Figure 1). They were large cells expressing both membrane and cytoplasmic HLA-DR, in the latter case in a reticulated pattern suggesting a foamy appearance. Identical results were obtained with both anti-HLA-DR monoclonal antibodies.

A similar characteristic pattern was consistently obtained with the monoclonal antibodies FMC 32 (Figure 2), recognising respectively epitopes present on monocyte/macrophages and all leucocytes. With the anti-C3b (TO 5) and anti-helper/inducer lymphocyte (Leu 3a) monoclonal antibodies only a faint, weaker reaction was detected. In contrast, no reaction was noted with the remaining monoclonal antibodies.

The use of the double-staining peroxidase-lipid revealed that the positive HLA-DR foamy cells were also strongly Sudan B positive, identifying them as lipid-containing foam cells.

Review of the light microscopy sections in these 10 cases revealed in all of them variable numbers of interstitial foam cells.

Table 1 shows the types of nephrotic syndrome in the patients studied. The interstitial foamy macrophages were noted in 33 per cent of the idiopathic membranous, 66 per cent of the mesangio-capillary and in the two cases with focal and segmental sclerosing lesions.
Figure 2. Immunoperoxidase study of a renal biopsy from a 48-year-old female patient with a long-standing nephrotic syndrome (69 months). This was a second renal biopsy, done because of deteriorating renal function. A large number of interstitial foamy macrophages (JMC 32-positive) are present. Cryostat section counterstained with haematoxylin X 400

TABLE II. Clinical findings in the patients with idiopathic membranous glomerulonephritis, divided according to the presence of HLA-DR foam cells (see text)

<table>
<thead>
<tr>
<th>Foam cells (HLA DR+)</th>
<th>p value</th>
<th>No foam cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=5</td>
<td></td>
<td>n=10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Classical findings when biopsied</th>
<th>Foam cells</th>
<th>p value</th>
<th>No foam cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from apparent onset</td>
<td>32±27*</td>
<td>&lt;0.005</td>
<td>5.4±6.4*</td>
</tr>
<tr>
<td>Range</td>
<td>3-69</td>
<td></td>
<td>0.5-24 months</td>
</tr>
<tr>
<td>Decreased renal function</td>
<td>2/5</td>
<td>NS</td>
<td>2/10</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>6.9±2.7*</td>
<td>NS</td>
<td>8±5.1*</td>
</tr>
</tbody>
</table>

Follow-up

| Deteriorating renal function     | 2/5        | NS      | 5/9           |

(Unpaired student 't' test or \(X^2\) test where appropriate)

*Mean ± SD

Table II compares the clinical findings in the group of patients with idiopathic membranous glomerulonephritis (where enough patients were available for comparison), divided according to the presence or absence of the interstitial
HLA-DR positive foam cells. Only the time from apparent onset of the nephrotic syndrome was significantly increased in the group with foam cells, indicating a relation between their presence and the duration of proteinuria. No relation with subsequent evolution of renal function was observed.

Discussion

Our results using monoclonal antibodies demonstrate that the interstitial lipid-containing foam cells observed in a number of patients with nephrotic syndrome express markers characteristic of cells belonging to the monocyte/macrophage lineage (positivity with monoclonal antibodies 2D1, HLA-DR, FMC 32). They also express a C3b receptor and react with an anti-helper/induced monoclonal antibody, findings described in monocytes or macrophages [5,6]. No reaction was noted with the remaining monoclonal antibodies (UCHT 1, UCHT 4, Leu 7, TO 15), or with the negative controls, excluding any false positive results.

Foamy macrophages have been described in a number of diseases and in sites from vessel walls in atherosclerosis [4] to the spleen in idiopathic thrombocytopenia [7]. In some cases they can be related with increased uptake or metabolism of lipids or lipoproteins (for example in atheroma) [8], while in other cases phagocytosed material (for example damaged platelets in idiopathic thrombocytopenic purpura [7], or bacteria such as M Leprae [9], may contribute to their origin. The finding of foam cells thus seems to be non-specific, possibly indicating only exhaustion of the cell’s capacity to process all the engulfed material [7].

In the kidney, they are observed most often in the interstitium, as we have shown, but are also seen in glomeruli on occasion [10]. The interstitial cells could acquire their lipid inclusions in the tubules, or in the glomeruli, subsequently migrating into the interstitium. Alternatively lipoproteins escaping through the glomerulus in proteinuric states and taken up by tubular cells could subsequently be transferred into phagocytic cells, since monocytes possess receptors for very low-density lipoproteins.

However, it is possible that the lipid inclusions present in the foamy macrophages are unrelated to the lipoproteinuria, being related instead to other factors such as intra-macrophage metabolic changes or increased intra-renal platelet destruction.

Whatever the reason for the appearance of interstitial foam cells, they seem to correlate with the duration of the proteinuria, but not with subsequent changes in renal function; apparently they have no direct prognostic significance, at least in our small series of patients.

Acknowledgment

Monoclonal antibodies FMC 32, 2D1, UCHT 1, UCHT 4, TO 15 were gifts from Doctors H Zola, P Beverley and D Mason respectively.
References

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Open Discussion

CHAIRMAN Thank you very much for this very clear and interesting presentation.

AHLMEN (Gottenburg) I would very much like to hear your opinion on the foam cells in patients with Alport’s syndrome, who most often have mild proteinuria.

CAMERON Well, this comes back to the point that we found no correlation between the amount of proteinuria in these nephrotic patients and the appearance of the foam cells, and we think they are not related to proteinuria. I would have liked to have shown you some pictures from Alport’s syndrome, and we intended to do this, but the problem was that we have used up all our Alport’s material on other studies. Clearly we need to get hold of some biopsies prospectively and do this. I would suspect that they are going to turn out to be the same cells and we will find them later in the course of the Alport’s evolution. Certainly in our own experience of children and adults with Alport’s syndrome they are usually visible in the later course of the disease, especially in uraemic patients. For example, in a five year old with isolated haematuria you virtually never see the foam cells.

BONE (Liverpool) What are the chances of finding foam cells in peripheral blood?

CAMERON We have not looked in this study recently. We were looking very actively at monocytic cells in peripheral blood in our transplant patients and incidentally you might find some foam cells in such patients. You can, of course, see them in the plasma of some lipid storage diseases as well as in the tissues.