Fundus changes in mesangiocapillary glomerulonephritis type II: clinical and fluorescein angiographic findings

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Summary

Previously we have demonstrated a deposit in Bruch's membrane in a single case of mesangiocapillary glomerulonephritis type II. We studied a group of patients with this disease and described extensive clinical and fluorescein angiographic abnormalities, which were in marked contrast to the findings in a group of patients with other forms of glomerulonephritis. This finding contributes to our understanding of the pathophysiology of the complex of the retinal pigment epithelium, Bruch’s membrane, and choriocapillaris.

A comparison can be made between the anatomy of the glomerulus and the choriocapillaris-Bruch's membrane-retinal pigment epithelium complex, in which the choriocapillaris is likened to the glomerular tuft, Bruch’s membrane to the glomerular basement membrane, and the retinal pigment epithelium to the glomerular epithelium.1

In a previous case report of a patient with type II mesangiocapillary glomerulonephritis (MCGN) we have demonstrated the occurrence of deposits in the choriocapillaris and Bruch’s membrane which have the clinical appearance of drusen but the histopathological characteristics of deposits in the glomerulus.2 In type II MCGN, which is frequently associated with partial lipodystrophy (PLD), deposits of electron dense material, often with a ribbon like appearance, are found within the glomerular basement membrane.3 This is in contrast to the discrete deposits found in (a) membranous nephropathy, where the material lies initially between the basement membrane and the epithelium; (b) in type I MCGN, where the deposit is predominantly subendothelial between the basement membrane and the endothelium; and (c) in mesangial proliferative glomerulonephritis, where the majority of the deposits are in the mesangium4 (Fig. 1).

We have therefore examined clinically the eyes of patients with a variety of glomerular disorders, including further cases of type II MCGN and partial lipodystrophy (PLD), and report our findings.

Methods and patients

From the diagnostic index at the Manchester Royal Infirmary Renal Unit we selected for ophthalmic investigation 17 patients with biopsy proved glomerular disease and two further patients with PLD but who had never had a renal biopsy. The histological diagnosis was withheld from the ophthalmologists who examined the patients by routine clinical methods, fundus photography, and fundus fluorescein angiography. All the patients were normotensive and had been so for some months, though many had had a period of hypertension earlier in the course of their illness. Patients 4, 7, and 13 had reached end stage renal failure and had had successful renal transplantation at the time of the study. No patient was receiving dialysis.

Details of the patients are given in Tables 1, 2, and 3.

Results

None of the patients had ocular symptoms. All the anterior segments appeared normal and no hypertensive retinopathy was detected.
Fig. 1  Predominant sites of deposition of immunoreactive and electron-dense material in various glomerulopathies.

Of the 12 patients without PLD six had type I MCGN, one had minimal change disease (a term used by renal pathologists to describe a nephritis in which there is no evidence of disease on light microscopy), and five had membranous nephropathy.

Table 1  Clinical details of cases with PLD

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Glomerular disease</th>
<th>Time since diagnosis (yr)</th>
<th>Blood pressure (mm Hg)</th>
<th>Current medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>43</td>
<td>M</td>
<td>MCGN I</td>
<td>0-6</td>
<td>140/90</td>
<td>Tenoretic, Nifedipine, Hydralazine.</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>F</td>
<td>MCGN (type unknown)</td>
<td>27</td>
<td>135/90</td>
<td>Atenolol, Methyldopa, Bendrofluazide.</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>F</td>
<td>MCGN II</td>
<td>24</td>
<td>130/80</td>
<td>Cyclosporin, Atenolol.</td>
</tr>
<tr>
<td>4</td>
<td>36</td>
<td>M</td>
<td>MCGN II</td>
<td>2-2</td>
<td>150/85</td>
<td>Allopurinol, Captopril, Frusemide, Cyclosporin, Prednisolone, Atenolol.</td>
</tr>
<tr>
<td>6</td>
<td>43</td>
<td>F</td>
<td>MCGN II</td>
<td>31</td>
<td>110/70</td>
<td>Tenoretic.</td>
</tr>
</tbody>
</table>

Tenoretic = atenolol 100 mg and chlorthalidone 25 mg.

Ophthalmoscopic examination of these eyes revealed a few drusen (Fig. 2), but with no difference in

Table 2  Clinical details of cases without PLD

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Glomerular disease</th>
<th>Time since Diagnosis (yr)</th>
<th>Blood pressure (mm Hg)</th>
<th>Current medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>51</td>
<td>M</td>
<td>Membranous</td>
<td>2</td>
<td>180/100</td>
<td>Prednisolone, Atenolol, Nifedipine.</td>
</tr>
<tr>
<td>9</td>
<td>31</td>
<td>M</td>
<td>MCGN I</td>
<td>6</td>
<td>140/90</td>
<td>Nil.</td>
</tr>
<tr>
<td>10</td>
<td>43</td>
<td>F</td>
<td>MCGN I</td>
<td>9</td>
<td>140/85</td>
<td>Azathioprine, Prednisolone, Atenolol.</td>
</tr>
<tr>
<td>11</td>
<td>44</td>
<td>F</td>
<td>MCGN I</td>
<td>6</td>
<td>160/90</td>
<td>Nil.</td>
</tr>
<tr>
<td>12</td>
<td>73</td>
<td>M</td>
<td>Membranous</td>
<td>5</td>
<td>140/70</td>
<td>Prednisolone, Atenolol, Nifedipine.</td>
</tr>
<tr>
<td>13</td>
<td>49</td>
<td>F</td>
<td>MCGN I</td>
<td>1</td>
<td>180/95</td>
<td>Azathioprine, Prednisolone, Atenolol.</td>
</tr>
<tr>
<td>14</td>
<td>39</td>
<td>M</td>
<td>Membranous</td>
<td>6</td>
<td>125/90</td>
<td>Nil.</td>
</tr>
<tr>
<td>15</td>
<td>32</td>
<td>M</td>
<td>Membranous</td>
<td>2</td>
<td>140/90</td>
<td>Azathioprine, Prednisolone, Frusemide, Spironolactone.</td>
</tr>
<tr>
<td>16</td>
<td>25</td>
<td>F</td>
<td>MCGN I</td>
<td>1-5</td>
<td>150/90</td>
<td>Nil.</td>
</tr>
<tr>
<td>17</td>
<td>50</td>
<td>M</td>
<td>MCGN I</td>
<td>13</td>
<td>160/90</td>
<td>Methylpapa, Frusemide, Propranolol.</td>
</tr>
<tr>
<td>18</td>
<td>29</td>
<td>F</td>
<td>Minimal change</td>
<td>3</td>
<td>90/60</td>
<td>Nil.</td>
</tr>
<tr>
<td>19</td>
<td>50</td>
<td>F</td>
<td>Membranous</td>
<td>7</td>
<td>130/80</td>
<td>Nil.</td>
</tr>
</tbody>
</table>
frequency from that expected in normal age matched population. Similarly the fluorescein angiograms showed only a few hyperfluorescent spots corresponding to scattered drusen.

Of the seven patients with PLD (Table 4) five were found to have a very striking abnormality in the fundi (Figs. 3,4,5). There was a regular, bilaterally symmetrical distribution of discrete yellow spots, similar to drusen, more densely present posteriorly but spreading up to and beyond the equator. The lesions were not elevated, but were associated with some ‘irregularity’ of pigmentation. In the same five patients fluorescein angiography showed gross abnormalities correlating with the drusen-like appearance, and similar to that seen in the previous case report, with hyperfluorescence corresponding to the yellow lesions but with no leakage of fluorescein. There was some variation from case to case in the dimensions and distribution of the deposits, but there was symmetry within each case. The visual acuity was unaffected. Four of these five cases had biopsy proved type II MCGN, and the fifth was likely to be in this category on the basis of PLD and nephrotic syndrome, though no biopsy was ever taken.

Two patients with PLD had normal ophthalmoscopic and angiographic appearances. One had unclassified MCGN, and the other had no evidence of glomerular disease.

Table 4  Ophthalmic findings in cases with PLD

<table>
<thead>
<tr>
<th>Case</th>
<th>Visual acuity</th>
<th>Fundus examination</th>
<th>Fluorescein angiography</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6/6</td>
<td>6/9</td>
<td>Massive drusen-like deposits and mottled pigmentation</td>
</tr>
<tr>
<td>2</td>
<td>6/6</td>
<td>6/5</td>
<td>Drusen-like deposits and mottled pigmentation</td>
</tr>
<tr>
<td>3</td>
<td>6/6</td>
<td>6/6</td>
<td>Massive drusen-like deposits and mottled pigmentation</td>
</tr>
<tr>
<td>4</td>
<td>6/9</td>
<td>6/9</td>
<td>Massive drusen-like deposits and mottled pigmentation</td>
</tr>
<tr>
<td>5</td>
<td>6/36</td>
<td>6/24</td>
<td>Massive drusen-like deposits and mottled pigmentation</td>
</tr>
<tr>
<td>6</td>
<td>6/6</td>
<td>6/6</td>
<td>Normal</td>
</tr>
<tr>
<td>7</td>
<td>6/5</td>
<td>6/5</td>
<td>Massive drusen-like deposits and mottled pigmentation</td>
</tr>
</tbody>
</table>

Fig. 2  Fundus photograph of case 18 showing scattered drusen at the posterior pole.

Discussion

We have described for the first time, to our knowledge, in this and in our recent publication an abnormal deposit in the eye at the level of Bruch’s membrane and choriocapillaries in type II mesangio-capillary glomerulonephritis. Our findings in this communication support the hypothesis that the choriocapillaris - Bruch’s membrane - retinal pigment epithelial complex may respond to disease in a similar way to the glomerulus.

The previously reported fundus changes seen in glomerular disease can be broadly divided into those associated with hypertension, those associated with vasculitis causing glomerulonephritis, those resulting from treatment of the renal lesion, and those...
considered to be specifically related to the renal lesion. In systemic hypertension the fundus abnormalities are well recognised, and they are described in renal patients. In accelerated hypertension infarcts of the retinal pigment epithelium, corresponding to failure of lobules of choriocapillaris to be perfused, termed Elschnig's spots, are described, but they differ from the lesions we report in that they are much more widespread and are not associated with the focal pigment clumping seen in Elschnig's spots. In addition there is no history of visual disturbance in any of our patients, whereas if there were such widespread infarction of the retinal pigment epithelium visual symptoms would be expected.

A series of patients with glomerulonephritis with and without hypertension have been studied ophthalmoscopically. None of these showed any fluorescein angiographic abnormality, though the type of glomerulonephritis was not identified.

Vasculitis, such as is seen in systemic lupus erythematosus, may involve the renal circulation as well as the retinal and choroidal circulation, giving rise to cotton-wool spots, haemorrhages, swelling of the optic nerve head, and vascular occlusion. In the cases we have studied no features of vasculitis were present.

Ocular complications of chronic renal disease involve exudative retinal detachment and crystals of cystine in the cornea and retina, and the complications of treatment include cataract, raised intraocular pressure, opportunistic retinitis, and retinal microaneurysms.

A number of familial disorders are described which affect the eye and kidney. Those which involve the retina and choroid include Alström's syndrome, which comprises pigmented retinopathy, obesity, diabetes mellitus, and nerve deafness, often associated with renal insufficiency; Alport's syndrome, which is characterised by lenticonus, spherophakia, sensorineural deafness, and a hereditary nephropathy and sometimes pigmentary...
retinopathy with or without subretinal and Bruch's membrane deposits; and adult polycystic kidney disease. A miscellaneous group of hereditary renal lesions associated with other fundus abnormalities, usually manifest as pigmentary retinopathies, are described. The only previous publications comparing pathology of the kidney and eye refer to patients with diabetes mellitus: microaneurysms have been described in the glomerulus and lesions resembling Kimmelsteil-Wilson nodules were described in the choroid.

Bruch's membrane and the glomerular membrane are structurally homologous in that both are selectively and directionally permeable with a positive

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**Fig. 4** A: Fundus photograph and B. fluorescein angiogram of case 10 showing scattered drusen-like deposits with intense hyperfluorescence.

**Fig. 5** A: Fundus photograph and B. fluorescein angiogram of case 19 showing extensive drusen-like deposits with hyperfluorescence.
charge and a high heparan sulphate content. The two membranes differ in that the collagenous zones of Bruch’s membrane make it much thicker than the glomerular basement membrane. Pathological changes in the renal glomerular basement membrane with similarities to those seen in Bruch’s membrane are identifiable. In aging, the glomerular basement membrane is focally thickened, with the appearance of vesicles in the membrane similar to the aging changes of Bruch’s membrane. In aminoglycoside nephrosis, deposits with an ultrastructural similarity to drusen are present on the epithelial side of the glomerular basement membrane. Aminoglycoside toxicity has been used as an experimental means of creating drusen in the eye. Breaks in the glomerular basement membrane, reminiscent of angioid streaks in Bruch’s membrane, have also been described.

The nature of deposits in different types of glomerulonephritis differs histologically and presumably also pathogenetically. We suggest that, whatever the pathogenesis in MCGN type II, a similar setting pertains in Bruch’s membrane, whereas in the other forms of glomerulonephritis this may not be the case. Recently an early case of MCGN has been studied histopathologically. It is interesting that the early lesion prior to the appearance of the dense deposit is lamellation of the lamina densa of the glomerular basement membranes, very reminiscent of the appearance seen in Alport’s syndrome, which is undisputably associated with a chorioretinal lesion.

Our findings suggest, in patients with type II MCGN and PLD, chorioretinal changes similar may parallel those found in the kidney. Although in all five patients with PLD and fundus changes the ophthalmic findings were very similar, the duration of renal disease ranged from 7 months to 31 years, and sequential observation is necessary to determine whether a lesion is static or variable with time. There is undoubtedly a structural and a pathological comparison to be drawn between the eye and the kidney, and further investigation of patients with glomerular disease may well shed light on the pathophysiological responses of the complex of choriocapillaris, Bruch’s membrane, and retinal pigment epithelial. Similarly, study of the ocular responses may contribute to the understanding of the pathogenesis of the renal lesion.

References


Accepted for publication 4 May 1989.