Glomerulomegaly and Proteinuria in a Patient with Idiopathic Pulmonary Hypertension

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Abstract. Glomerulomegaly is a histologic finding present in idiopathic pulmonary hypertension, congenital cyanotic heart disease, morbid obesity associated with sleep apnea syndrome, sickle cell disease, and polycythemic states. This study examines the case of a 34-yr-old woman with idiopathic pulmonary artery hypertension who presented with nephrotic-range proteinuria. Kidney biopsy revealed enlarged glomeruli with mesangial-proliferative glomerulonephritis. A review of the pertinent literature and a discussion of the proposed pathophysiologic mechanisms leading to glomerulomegaly are presented. (J Am Soc Nephrol 8: 1966–1970, 1997)

Case Presentation
A 34-yr-old woman diagnosed with pulmonary hypertension 2 yr earlier was admitted with shortness of breath, dyspnea on exertion, and edema of the lower extremities. Physical examination revealed an overweight patient (weight, 158 lb; height, 5 feet) with blood pressure 130/90 mmHg; heart rate 100 beats/min; respiratory rate 16/min, and temperature 36.8 C. Neck examination revealed mild jugular venous distention; lungs were clear. Heart examination showed a split S2 sound with a gallop rhythm. Abdomen was obese with no masses or organomegaly, lower extremities had 2+ pitting edema, and neurological examination was normal.

Chest x-ray showed clear lung fields and enlarged central pulmonary arteries; electrocardiogram revealed right axis deviation and right ventricular hypertrophy. Workup for collagen vascular disease and for a hypercoagulable state was negative. A hepatitis profile was negative. Sodium was 141 mmol/L, potassium 3.9 mmol/L, bicarbonate 26 mmol/L, chloride 108 mmol/L, blood urea nitrogen 6.8 mmol/L, creatinine 106.4 \( \mu \)mol/L, cholesterol 6.76 mmol/L, uric acid 400 \( \mu \)mol/L, calcium 2.2 mmol/L, phosphorus 1.4 mmol/L, total protein 5.4 g/dl, with albumin 2.6 g/dl. Liver function tests were within normal limits. Prothrombin time and partial thromboplastin time were normal. Other laboratory data were as follows: hemoglobin 17.4 g/L, hematocrit 51.2%, platelet 197,000/mm\(^3\), and white blood cell count 5,500/mm\(^3\) with a normal differential. The urine analysis showed specific gravity of 1.018, pH 6.5, and 4+ proteinuria. Urine sediment showed four red blood cells per high-powered field; no casts were seen. A 24-h urine collection showed 5 g of protein, and creatinine clearance was 70 ml/min. Renal ultrasound showed no obstruction, normal kidney size, and echogenicity. Echocardiogram revealed mild right atrial and ventricular enlargement with depressed right ventricular function, as well as paradoxical septal wall motion consistent with right ventricular pressure overload. Estimated pulmonary artery systolic pressure was >74 mmHg.

Pathologic Data
On light microscopy, 12 glomeruli were available for examination. Most of the glomeruli were markedly enlarged, and there was mild diffuse global mesangial hypercellularity, as well as mesangial sclerosis (Figure 1). There was no evidence of basement membrane thickening on periodic acid-Schiff-stained sections, and no segmental necrotizing or sclerotic lesions were noted. Moderate-to-severe focal tubular atrophy with associated interstitial fibrosis and patchy interstitial inflammation composed predominantly of mononuclear inflammatory cells was also present. There were no glomeruli available in the tissue submitted for immunofluorescent examination. The thick sections for electron microscopy showed a glomerulus with mesangial hypercellularity and increased mesangial matrix, as well as moderate focal tubular atrophy and minimal fibrointimal hyperplasia of the small arteries. There were no electron-dense deposits identified within the mesangium, paramesangial region, or glomerular capillary basement membrane. Visceral epithelial cells showed focal effacement of the foot processes (Figure 2).

To demonstrate the glomerulomegaly in the patient’s biopsy, morphometry parameters were obtained and compared with those found in normal kidney of an age- and weight-matched control subject (Table 1). Both the mean and the largest value of the glomerular surface area for the kidney biopsy were significantly higher than those of the control subject. In contrast, the mean tubular diameters were comparable.
Glomerulomegaly in Pulmonary Hypertension

Figure 1. (A) Patient's biopsy. A glomerulus sectioned through the vascular pole shows moderate hypercellularity and marked enlargement (surface area = 0.7486 mm²). (B) Control biopsy from an age- and weight-matched patient who died of head trauma shows a glomerulus sectioned through the vascular pole, which is significantly smaller than the one in A (surface area = 0.2578 mm²). The tubules in the renal biopsy and the control display no significant differences in size (hematoxylin and eosin stain for both panels, ×1000).

Figure 2. Electron microscopic study shows mesangial sclerosis (M). There is focal fusion of the foot processes, but electron dense deposits are not seen. Some cells with swollen cytoplasm are seen (C) and probably represent endothelial cells. Lu, lumen. Magnification, × 12,000.

Discussion

Glomerular enlargement in congenital cyanotic heart disease was first described in 1953 (1) and later confirmed by others (2). Initially, glomerular enlargement was described on the basis of visual inspection, but subsequent semiquantitative morphometric studies confirmed the increased glomerular size (3). The first extensive study of the morphology of the kidney in congenital cyanotic heart disease was done by Meesen and Litton (1). The main lesions were found in the glomeruli, with capillary congestion and ectasia, thickening or splitting of the capillary wall, focal and diffuse hypercellularity, and segmental or global sclerosis. Moreover, mesangial hypercellularity and thickening was frequently encountered (Table 2). In congenital heart disease and cor pulmonale, it has been postulated that chronic hypoxia and increased carbon dioxide, as well as passive congestion of the systemic circulation, lead to those changes. The glomerulomegaly was thought to underlie the increase in the surface area that is available for filtration and that was reported to correlate with the degree of cyanosis and patient age. Later, Marinozzi (4) observed that the glomerular enlargement was dependent primarily on an increase in the number of capillary loops, but not their diameter, and was
attributed to polycythemia. In addition, a component of endothelial and mesangial hypercellularity with matrix expansion was thought to contribute to the glomerular enlargement, especially in patients with cyanotic heart disease and pulmonary hypertension (5,6). In addition, impaired oxygen transport and/or hypoxemia results in hypertrophy and hyperplasia of erythropoietin-producing cells (7).

Although some authors reported a correlation between polycythemia and enlargement of the glomeruli in cyanotic heart disease (5,6,8), the relationship between the two may be an epiphenomenon rather than causative. The glomerular lesions in congenital cyanotic heart disease cannot always be correlated with the degree of oxygen desaturation or polycythemia (2). Furthermore, mesangial proliferation, capillary dilatation, and enlargement of the glomeruli have been described in patients with primary pulmonary hypertension and congenital heart disease, in the absence of polycythemia or cyanosis (2,9). Glomerular enlargement and changes in the mesangium have been found in cor pulmonale, right-sided heart failure, and in secondary forms of pulmonary hypertension, suggesting elevation of right heart pressure as an etiologic factor (10).

The mechanism by which increased pressure in the right side of the heart induces glomerular changes remains unknown. Increased hydrostatic pressure might be a factor, but it may not be the only one. Elevated right-sided pressures found in congestive heart failure, renal vein thrombosis, and constrictive pericarditis are frequently associated with proteinuria, and it is postulated that increased right-sided pressure may be transmitted to the renal veins, resulting in mesangial lesions. Consistent with that, examination of postmortem records of 1391 randomly selected cases showed that the most common condition associated with diffuse enlargement of the kidneys was chronic cor pulmonale. Histologic material, which was available for six of these cases, showed a striking and consistent increase in the glomerular diameter (11).

Nephrotic-range proteinuria is a recognized complication in individuals with massive obesity and sleep apnea syndrome. These patients have hypoxia, hypercapnia, and, frequently, pulmonary and systemic hypertension. These individuals have glomerular capillary hypertension secondary to increased intravascular volume, hyperdynamic circulation, and renal vasodilatation. Renal insufficiency has been well documented in massively obese individuals with sleep apnea syndrome, and renal biopsies often show glomerulomegaly and focal segmental glomerulosclerosis (12). In addition, it is suggested that hyperlipidemia and hypercholesterolemia may act as aggravating factors (13). Glomerulomegaly has also been described in patients with sickle cell anemia (14). The mean glomerular diameter of Bowman’s capsule in sickle cell disease is markedly increased compared with healthy control subjects or patients with idiopathic focal glomerulosclerosis. Young persons with sickle cell anemia have increased renal plasma and blood flow, and frequently have elevated GFR (15,16). Renal cortical hyperperfusion probably accounts for the glomerular enlargement described in these patients, because glomerulomegaly was shown to correlate with increases in GFR, glomerular plasma flow, and glomerular pressure in a variety of experimental models (17,18). These renal hemodynamic and histopathologic alterations can be prevented by lowering glomerular pressure, suggesting a causal relationship between glomerular flow and pressure with glomerulomegaly (17,19).

The occurrence of glomerulomegaly in alcoholics with hepatic steatosis (20) and lipid disorders supports the notion that glomerular hypertension, together with lipid metabolic abnormalities, may play a synergistic role in the development of this entity. Tables 3 and 4 summarize the mechanisms responsible for the development of glomerulomegaly and the clinical conditions associated with it.

Glomerulomegaly has been considered a benign condition. However, in a study by Fogo et al. (21), the presence of
**Table 3. Proposed mechanisms for the development of glomerulomegaly**

<table>
<thead>
<tr>
<th>Initiating Abnormalities</th>
<th>Possible Direct Causes</th>
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<tbody>
<tr>
<td>Increased metabolic demands (e.g., obesity)</td>
<td>Glomerular capillary hypertension secondary to increased intravascular volume, hyperdynamic circulation, and renal vasodilation</td>
</tr>
<tr>
<td>Impaired oxygen transport and/or hypoxemia</td>
<td>Hypertrophy/hyperplasia of erythropoietin-producing cells</td>
</tr>
<tr>
<td>Polycythemia vera and secondary forms</td>
<td>Increased intravascular volume, increased blood viscosity</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>Elevated GFR, renal cortical hypertension</td>
</tr>
<tr>
<td>Increased systemic venous pressure (e.g., cor pulmonale, congenital heart disease)</td>
<td>Passive congestion of systemic circulation</td>
</tr>
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**Table 4. Conditions associated with glomerulomegaly**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Physiologic Abnormalities</th>
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<tbody>
<tr>
<td>Congenital cyanotic heart disease</td>
<td>Impaired oxygen transport and/or hypoxemia and secondary polycythemia</td>
</tr>
<tr>
<td>Cor pulmonale</td>
<td>Hypoxemia, hypercapnia, secondary polycythemia</td>
</tr>
<tr>
<td>Obesity and sleep apnea syndrome</td>
<td>Hypoxemia, hypercapnia, polycythemia, hyperdynamic circulation, and lipid abnormalities</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>Impaired oxygen transport and increased viscosity</td>
</tr>
<tr>
<td>Polycythemia vera</td>
<td>Hyperviscosity</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>Liver disease-associated abnormalities</td>
</tr>
<tr>
<td>Hepatic steatosis</td>
<td>Hyperdynamic circulation and lipid abnormalities</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Hypoxemia and lipid abnormalities</td>
</tr>
</tbody>
</table>

glomerulomegaly in biopsies of patients with minimal change disease suggested an increased risk for progression to focal segmental glomerulosclerosis. Proteinuria has been described as the most frequently observed abnormality of renal function in several case reports (22,23), and it occurred in 60% of 17 patients studied by Spear (24), with azotemia and hematuria encountered less frequently. Deterioration of renal function has been described in a patient with congenital cyanotic heart disease, and the decline in creatinine clearance was attributed to progressive glomerular sclerosis (25).

In summary, the mechanisms causing glomerulomegaly remain controversial. However, it is likely that glomerular hemodynamic changes resulting from increased intravascular volume, glomerular capillary hypertension, increased blood viscosity, and passive congestion of systemic circulation associated with lipid metabolic abnormalities play a major role in its development.

**Acknowledgment**

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**References**

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**Renal Section Training Program at Baylor College of Medicine, Houston, Texas**

The program trains fellows in the practice of clinical nephrology and prepares future faculty members for careers in academic medicine by encouraging the pursuit of scientific endeavors at both clinical and basic science levels. Members of the division are currently pursuing questions of calcium and divalent cation metabolism in relevant tissues (i.e., smooth muscle cells, bone, and kidney cells), using state-of-the-art molecular biology techniques with the hope that knowledge gained from these studies will provide insight into hypertension and bone disease in renal failure. Additionally, the Section is investigating issues of gene regulation pertinent to the adaptation of kidney cells to osmotic stress, as well as central nervous system complications of dysnatremias. The Renal Pathology Laboratory is conducting studies related to abnormalities of the cell cycle in relation to renal disease, using a well characterized murine model of chronic obstructive uropathy. Clinical studies on human subjects, currently being conducted, involve medications and side-effects in renal failure; dialyzer membrane biocompatibility; and the effects of uremic toxins on myocyte function.

To encourage individuals’ pursuit of knowledge, to stimulate interest, and to broaden exposure to new topics and information, the training program presents several weekly conferences (see below). Research trainees are required to spend at least 80% of their time conducting original research. They are actively involved in study design, methodology, organization, evaluation, and assimilation of data for their respective projects. Teaching responsibilities include periodic presentation by trainees at molecular biology and clinical conferences, as well as participation in weekly research conferences (see below).

**Renal Section Weekly Conferences:**

- Molecular Biology Conference: Presentation by faculty and trainees on concepts and principles of recombinant DNA technology.
- Clinical Conference: Presentations by faculty and trainees covering case studies and renal pathology.
- Physiology Conference: Presentations by faculty covering various aspects of renal physiology.
- Research Conference: Presentation by faculty and trainees in the Renal Section who are engaged in research. These meetings provide intensive interaction between various members of the Renal Section and critical review of everyone's data.
- Clinical Nephrology Conference: Presentations by faculty on dialysis, renal transplantation, problems of chronic renal failure, and other topics. In addition, visiting scientists present seminars on a regular basis on various aspects of clinical and renal research.
- Other Seminars and Workshops: Other departments at Baylor and adjacent institutions also conduct vigorous seminar programs open to the scientific community. Prominent meetings of this type are listed on our department calendar.