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ORIGINAL ARTICLE

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Acquired glomerulocystic kidney disease following hemolytic uremic syndrome

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Abstract Glomerulocystic kidney disease (GCKD) is a rare congenital condition that is usually reported in infants and young children. Only five cases of acquired GCKD after an acquired renal disease have been reported. Among these, two patients have developed cystic glomerular lesions following hemolytic uremic syndrome (HUS). We report a third case in a 2-year-old patient with this association. Common features between these three cases include atypical HUS, development of GCKD after prolonged peritoneal dialysis treatment, severe hypertension, and normal-sized kidneys without development of macroscopic cysts. Pathology findings in our patient include heavy expression of epidermal growth factor receptor in proximal tubules and evidence of obstruction of the glomerular outflow. We speculate that cystic dilatation of the Bowman's capsule may be secondary to ischemic lesions leading to proximal tubular obstruction.

Keywords Hemolytic uremic syndrome · Glomerulocystic kidney disease

Introduction

Glomerulocystic kidney disease (GCKD) is a rare condition characterized by cystic dilatation of the Bowman's capsule and collapse of the glomerular tuft. In most congenital cases, dysplastic elements in the renal medulla are reported, suggesting early development of the disease during renal morphogenesis [1].

Despite common pathological findings, the term GCKD encompasses different clinical entities. These have been classified into: (1) GCKD associated with malformation syndromes, (2) GCKD associated with renal dysplasia, or (3) primary GCKD [1]. The latter has been reported in familial or sporadic cases and includes dominant GCKD in adults, familial hypoplastic GCKD, sporadic non-syndromal GCKD, and autosomal dominant polycystic kidney disease, which may be associated with predominant glomerulocystic changes in young patients [1]. In addition, rare cases of non-congenital GCKD, developing after inflammatory or vascular renal diseases, have been reported in the literature [2, 3, 4, 5, 6].

We describe a case of GCKD in a 2-year-old girl following hemolytic uremic syndrome (HUS). This child is the third and youngest patient that has been reported with this association.

Case report

The patient had unremarkable prenatal and perinatal history. A prenatal ultrasound scan had documented kidneys of normal appearance during late pregnancy. She first presented at 5 months of age with anorexia. During the following weeks, she developed vomiting, mild fever, and epistaxis. The initial evaluation tests demonstrated anemia (hemoglobin 8 g/dl) without thrombocytopenia, normal renal function, and mild hemoglobinuria. Two months later she became pale and was admitted to her local hospital with vomiting, fever, periorbital edema, and mild hypertension. No episodes of diarrhea were reported. She was then rapidly referred to our institution with moderate renal failure, thrombocytopenia, and severe anemia. Her initial laboratory evaluation confirmed the diagnosis of HUS, demonstrating hemolytic anemia (hemoglobin 5.5 g/dl, reticulocyte count 9 %, direct bilirubin 3.0 mg/dl, haptoglobin <1 mg/dl, numerous schizocytes on the blood smear), worsening thrombocytopenia (55,000/mm^3), and renal failure (blood urea nitrogen 48 mg/dl, serum creatinine 1.4 mg/dl). Serum and stool analysis failed to demonstrate a verocytotoxin-producing *Escherichia coli* infection. By renal ultrasonography, both kidneys were of normal size but were diffusely hyperechogenic. These findings were consistent with HUS. Four days later, peritoneal dialysis was initiated to treat non-oliguric renal failure. During

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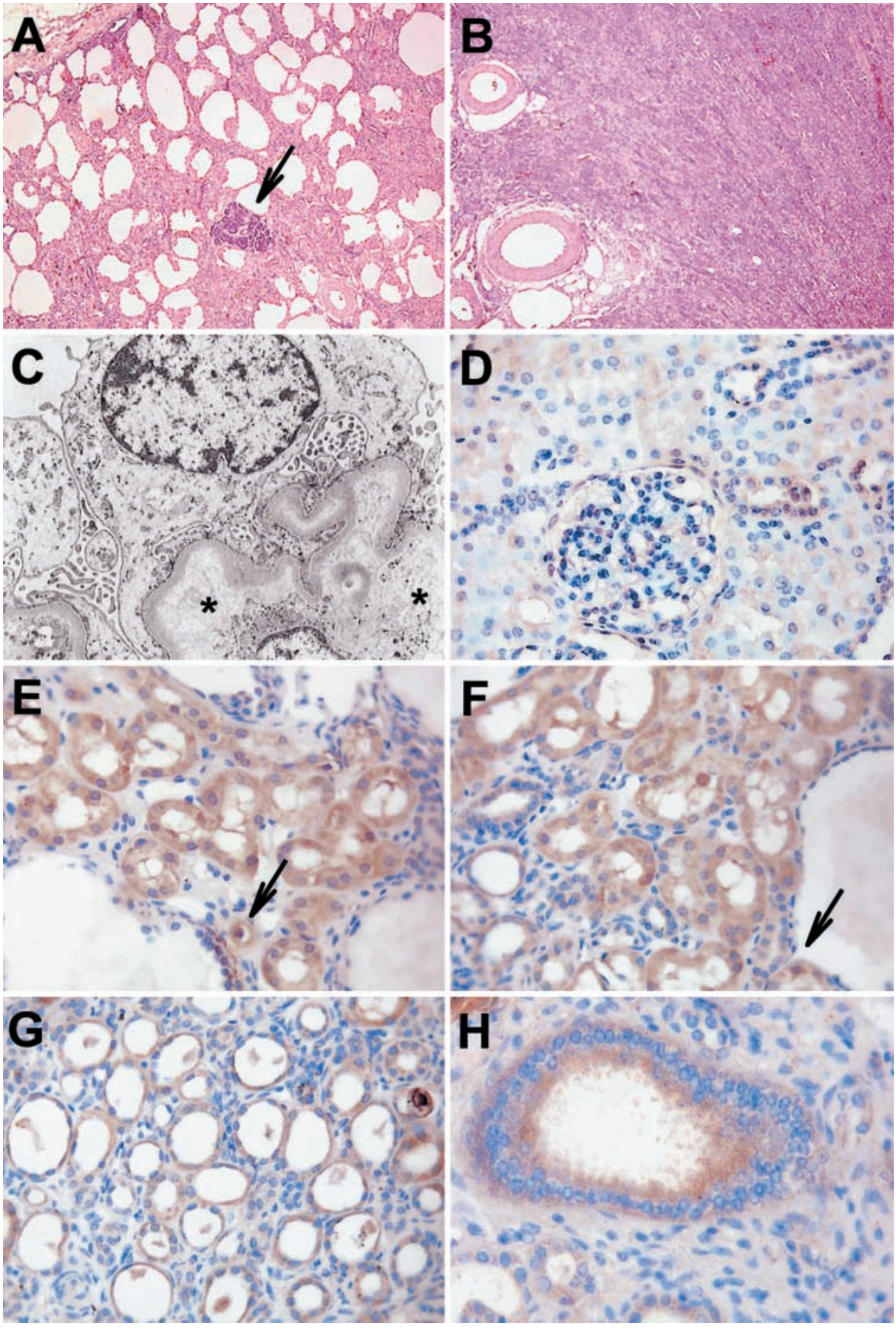
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◀ **Fig. 1A, B** Low magnification views showing (**A**) numerous glomerular cysts with retracted glomerular tufts within the renal cortex and (**B**) well-developed renal medulla and papilla with vascular and tubular bundles (hematoxylin and eosin staining). The *arrow* indicates a focal area of immature tubular structures. **C** Electron micrograph of a collapsed tuft within a glomerular cyst. A podocyte cell overlays a diffusely enlarged glomerular basement membrane with particularly expanded lamina rara interna. In the subendothelial space, large deposits of amorphous and fibrillary material are present (*asterisks*). **D–H** Immunocytochemical detection of epidermal growth factor receptor (EGFR). Staining is markedly enhanced in cortical (**E** and **F**) and medullary (**G**) tubules compared with normal kidney (**D**). Little staining is present in the Bowman's capsules. Most tubules are irregularly shaped and some appear extremely narrowed (**E** *arrow*). The tubulo-glomerular junctions of several glomeruli also appear extremely narrowed (**F** *arrow*). Occasional cystic tubules, lined by multiple loose layers of epithelial cells with prominent apical EGFR expression, are noticed at the cortico-medullary junction (**H**)

the following 3 months the patient demonstrated several episodes of relapsing hemolytic anemia with thrombocytopenia, requiring 13 blood transfusions. She was treated with four plasma exchanges without significant benefits. Thereafter, she became severely hypertensive (diastolic blood pressure constantly higher than 100 mmHg) without response to aggressive ultrafiltration and combined therapy with calcium and angiotensin converting enzyme inhibitors. For this reason, she underwent a left kidney nephrectomy at the age of 2 years, which resulted in a substantial improvement of her blood pressure control. After 2.5 years of chronic peritoneal dialysis, she has recently received a renal allograft and has normal renal function at her 6 months' follow-up. During the transplantation procedure, the remaining kidney was also removed.

Renal pathology

Both native kidneys had normal size and demonstrated marked glomerular cystic changes. The left kidney measured 7×4.5×3.2 cm. By light microscopy, the renal parenchyma was characterized by cystic dilatation of the Bowman's capsules, containing collapsed glomerular tufts (Fig. 1A). The overall architecture of the medulla and papilla was well preserved, without evidence of dysplasia and with normal organization of the vasa recta (Fig. 1B). Large arterioles showed focal and segmental areas of intimal hyperplasia, while afferent arteries presented diffuse hypertrophy of the media with obliteration of the vascular lumen. In addition, several areas containing immature tubular structures could be identified in the renal cortex (Fig. 1A). At higher resolution, proximal tubules appeared irregularly shaped (Fig. 1E and F). Several narrowed or obliterated tubules were also noticed (Fig. 1E). In a few glomerular cysts that had been sectioned through the urinary pole, the tubulo-glomerular junction appeared extremely narrowed (Fig. 1F). Other findings included occasional cystic tubular structures, lined by loose epithelial cells and lacking a regular monolayer organization, primarily located at the corticomedullary junction (Fig. 1H). Electron microscopy showed characteristic HUS changes, including thickening of the glomerular basement membrane and subendothelial deposits of fibrillary and amorphous material (Fig. 1C).

Heavy staining for epidermal growth factor receptor 1 (EGFR)[1] was apparent in cortical and, to a lesser extent, medullary tubular cells (Fig. 1F and G) compared with a control normal kidney specimen (Fig. 1D). Overexpression of EGFR was also apparent in the cystic tubular structures described above, with prominent apical staining (Fig. 1H). No expression of EGFR was noticed in the Bowman's capsule epithelium of glomerular cysts. The right kidney demonstrated similar changes to the left kidney.

[1] Immunocytochemical detection of EGFR was performed with specific rabbit polyclonal antibodies (Oncogene Science, Tarrytown, N.Y., USA) and streptavidin/biotin-labeled secondary antibodies (DAKO, Carpinteria, Calif., USA). Working dilutions for both antibodies were 1:50. Peroxidase activity was revealed with hydrogen peroxide/diaminobenzidine solution (Ortho Diagnostic Systems, Raritan, N.J., USA)

Discussion

GCKD is a rare condition that presents as a primary isolated disease or in association with malformation syndromes or renal dysplasia [1]. In a few cases, however, glomerulocystic lesions appear to develop after an unrelated glomerular disease. This small group of cystic glomerular lesions includes single case reports of GCKD associated with mesangial glomerulonephritis [4], Wegener's granulomatosis [3], progressive systemic sclerosis [6], and two reports of GCKD developing after HUS in one adolescent and one adult patient [2, 5]. In these two patients, no glomerular cysts were observed in the first renal biopsy performed at the onset of HUS. Given the very young age and characteristic HUS symptoms of our patient, we did not perform an initial renal biopsy. However, contrary to most infantile cases of GCKD [7, 8], the kidneys were not enlarged and lacked macroscopic cysts by renal ultrasonography. The prenatal ultrasound scan was also carefully reviewed and showed kidneys of normal appearance during late pregnancy. Moreover, the renal pathology demonstrated normally developed medullary pyramids, in contrast to the abnormal architecture of the papilla and renal medulla that is generally reported in congenital GCKD [1]. Thus, we believe this patient is the third and youngest reported case of secondary GCKD following HUS.

All three patients share several characteristics [2, 5]. In particular, they all had atypical HUS, with permanent renal failure. GCKD was always diagnosed after several years of peritoneal dialysis, when nephrectomy was performed for severe hypertension. In all patients, the kidneys were not enlarged and lacked macroscopic cysts by renal ultrasonography. In at least two cases, patients had relapsing episodes of hemolytic anemia, indicating long-lasting active microangiopathy during the months following initiation of dialysis.

It is also remarkable that all reported cases of secondary GCKD have developed in patients with inflammatory or thrombotic renal vascular lesions. Two patients have developed GCKD after systemic sclerosis or Wegener granulomatosis [3, 6], which are characterized by severe inflammatory narrowing or occlusion of renal arterioles. Marked arteriolar changes have also been described in one patient that has developed glomerulocystic lesions after mesangial glomerulonephritis [4].

Moderate expansion of the urinary space is known to occur after HUS [9]. These changes have been attributed to ischemic events secondary to vascular lesions [9].

On these bases, it has been proposed that ischemic damage to the outlet of the Bowman's capsule or the adjacent proximal tubule during HUS may cause glomer-

ular outflow obstruction leading to cystic formation [5]. Our findings of abnormal tubular glomerular junctions and narrowed proximal tubules further support this hypothesis. Similar findings have also been reported in one other case of GCKD, using serial sections throughout the urinary pole of cystic glomeruli [10].

To further investigate the etiology of secondary GCKD, we studied the expression of EGFR. A whole body of evidence has accumulated in the past decade showing that EGF and transforming growth factor-α play a major role in the development of renal tubular cysts through their action on EGFR [11, 12]. In particular, EGFR is overexpressed and mislocated to the apical membrane in clinical and experimental models of polycystic kidney disease [13]. In our patient, we failed to demonstrate expression of EGFR in the cystic Bowman's capsule epithelium, but found heavy expression in cortical tubular cells. It is well known that EGF and EGFR are upregulated during renal embryogenesis and that EGF can promote cell regeneration after acute renal injury [12]. Thus, EGFR overexpression in this case may reflect regeneration of tubular elements in a chronically ischemic parenchyma. Whether enhanced EGFR expression is involved in the creation of tubular obstruction remains unclear. Focal areas containing immature tubular structures are probably part of this same regeneration process, as frequently described in end-stage kidneys [13].

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LITERATURE ABSTRACT

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Glomerulosclerosis in mice transgenic for human insulin-like growth factor-binding protein-1

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Background The growth hormone (GH)/insulin-like growth factor (IGF) system is thought to participate in the glomerulosclerosis process. Because IGF-binding proteins (IGFBPs) modulate IGF actions and hence GH secretion, this study assessed whether mice transgenic for human IGFBP-1 have altered susceptibility to glomerulosclerosis.

Methods A line of transgenic mice that express human IGFBP-1 mRNA in the liver under the control of the alpha1-antitrypsin promoter has been obtained, and morphological changes in the kidney tissue were assessed. Glomerulosclerosis was identified using light microscopy, light microscopic morphometry, and electron microscopy. Extracellular matrix components were analyzed by immunohistochemistry.

Results There was a marked increase in mesangial extracellular matrix area in homozygous transgenic mice at three months of age as compared with heterozygous transgenic mice and nontransgenic littermates. These changes were not associated with alterations in glomerular volume or cellularity. The expansion of extracellular matrix area was related to a marked increase in laminin and type IV collagen and to the appearance of type I collagen.

Conclusions These observations indicate that the enhanced expression of IGFBP-1 may result in the development of glomerulosclerosis without glomerular hypertrophy. The changes are potentially related to a decrease in IGF-I availability and/or to an IGF-I-independent role of IGFBP-1.