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Case Report

Congenital Podocytopathy with Podocyte Loss and Glomerular Crescents: A Case Report in a Preterm Newborn

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Abstract

Podocytes, also known as glomerular visceral epithelial cells, are highly renal specialized cells leaving between them slit diaphragms that ensure the integrity of the renal basement membrane, playing a major role in establishing a size-selective barrier to protein loss. The reduction in podocyte number represents an important determinant of progressive impairment of the glomerular function that leads to the development of massive proteinuria and ultimately to renal scarring. Podocytopathies are generally considered typical of childhood and adulthood. Here we report a case of podocyte loss presenting in a newborn, prospecting the hypothesis that podocytopathies could start in the perinatal period or, putatively, in the intrauterine life.

INTRODUCTION

Podocytes, also known as glomerular visceral epithelial cells, are highly renal specialized cells characterized by a complex cell structure, with primary processes, secondary processes, and finally foot processes [1]. The foot processes of neighboring podocytes interdigitate, leaving between them filtration slits that are bridged by slit diaphragms [2]. Slit diaphragms ensure the integrity of the renal basement membrane, playing a major role in establishing size-selective barrier to protein loss [3]. Podocytes synthesize matrix molecules to the glomerular basement membrane, including type IV collagen, laminin, entactin, and agrin [4]. In human pathology, the role of podocyte damage has been increasing in recent years, leading to a podocentric view of kidney diseases [5]. Recent studies in humans have provided evidence that podocytes are functionally and structurally injured very early in the natural history of diabetic nephropathy [6]. Decreased podocyte number and/or density as a result of apoptosis or detachment, and a reduction in nephrin protein in the slit diaphragm with podocyte foot process effacement, all comprise the principal features of diabetic podocytopathy that clinically manifests as albuminuria and proteinuria [7]. Podocyte depletion has been also reported to be linked to glomerulosclerosis [8]. The reduction in podocyte number has been shown to represent an important determinant of progressive impairment of the glomerular perselectivity that leads to the development of massive proteinuria and ultimately to renal scarring [9].

Since podocytopathies are generally considered typical of childhood and adulthood, this study was aimed at reporting a case of podocyte loss presenting in a newborn, prospecting the hypothesis that podocytopathies could start in the perinatal period or, putatively, in the intrauterine life.

CASE PRESENTATION

Clinical data

A 630g male neonate (second born of a healthy 5 years - old sister) was born prematurely at 23 weeks of gestation by vaginal delivery. No relevant data were obtained by maternal anamnesis. The APGAR score was 1, 2, 4 at 1, 5, 10 minutes respectively: after cardiopulmonary resuscitation and administration of surfactant in the delivery room, he was moved in the NICU where mechanical ventilation was started and another dose of surfactant was given. The respiratory distress syndrome evolved in a severe Chronic Lung Disease treated with non invasive (or invasive if needed) ventilation, diuretics (furosemide at start for 7 days, hydrochlorothiazide and spironolactone afterwards). A central venous catheter was left for 60 days.

An acute renal failure developed in the first days of life with oliguria and creatinine values of 2.68, 1,97, 1,59 respectively on day 3, 6, 8 of life. Normal creatinine values were obtained

al 8 days of life along with a recovery of dieresis. Although diuresis values had stabilized about 2-3 ml/Kg/h oliguria and water retention occurred frequently in the weeks following. Since day 10 of life persistent proteinuria (until 100 mg/dl) was documented. Ipokaliemia was present since day 36 of life persistently requiring KCl supplementation. No abnormality of renal structure at US was found till the first 2.5 months of life when a fungal disease were suspected and treated with lipid-based amphotericin B for 3 weeks.

Besides antifungal therapy, different nephrotoxic antibiotics were administered during child's lifetime because of flogosis indexes positivity. Particularly, gentamicin and amikacin were given, the former in the first 3 days before the onset of acute renal failure and the latter in different cycles for a total of 33 days. On day 7 of life and for 7 days a topic therapy with gentamicin ointment was given for a cutaneous ulcer subsequently diagnosed as mycotic lesion.

At the age of 3,5 months, after 3 ibuprofen cycles (at 15, 45, 90 days respectively), surgical closure of the patent ductus arteriosus was performed. During the 1st ibuprofen cycle antibiotic therapy with amikacina was ongoing; the 2nd cycle started when amphotericin B treatment was just finished.

At the age of 1.5 months a cytomegalovirus infection was diagnosed with thrombocytopenia and cholestatic hepatopathy. Therapy with intravenous ganciclovir was administered for 30 days, followed by oral valganciclovir for 60 days.

Death occurred at 6 month of life in the context of a chronic liver disease with portal hypertension.

Pathological findings

The renal architecture appeared well preserved and compatible with the gestational age of the newborn. The most relevant pathological changes were found inside developing glomeruli. Glomerular changes were focal and patchy, with the majority of developing glomeruli appearing normal (Figure 1a). In affected glomeruli, lesions were predominantly segmental, affecting only one or two quadrants. Podocyte loss was the main pathological elementary lesion detected in developing glomeruli. Different degrees of podocyte loss were observed in different glomerular tufts: in some renal corpuscles, podocyte loss was mild, affecting few capillaries (Figure 1b); in other glomeruli, disappearance of podocyte precursor nuclei was moderate and diffuse to multiple zones of the glomerular tuft (Figure 1c); in some glomerula bodies, loss of podocytes appeared diffuse to the majority of glomerular capillaries, offering images of "naked" glomeruli (Figure 1d).

Podocyte pathological changes were paralleled by changes in the Bowman's capsule epithelial cells. Whereas in normal glomeruli parietal cells appeared inconspicuous, characterized by a thin nucleus bordering the renal capsule (Figure 1a), in affected glomeruli we observed a sequence of progressive pathological changes, reflecting the participation of parietal epithelium to the pathological process. Cell and nuclear swelling (Figure 1b), Nuclear prominence towards the urinary space (Figure 1c), and initial cell proliferation (Figure 1d) were the sequential pathological modifications more frequently detected in affected glomeruli. Finally, in some glomeruli, parietal cell proliferation ended with crescent formation, encircling retracted glomeruli (Figure 1e). Interestingly, no significant parietal cell changes was detected in glomeruli characterized by the absence of significant podocyte loss.

DISCUSSION

Podocytes play a key role in maintaining the blood-urine barrier for high-molecular-weight proteins. They are considered to be terminally differentiated renal cells and, as a consequence, podocyte death cannot be compensated by regenerative proliferation. Various diseases leading to podocyte damage and loss, resulting in proteinuria and nephrotic syndrome, have been recently grouped under the definition of podocytopathies [10]. Podocytopathies represent a spectrum of renal diseases, including acquired and genetic nephropathies. Hereditary podocytopathies have increasingly been recognized to be involved in the development of steroid-resistant nephrotic syndrome. Mutations in podocyte genes alter the development and structural architecture of podocytes, including interdigitating foot processes and the slit diaphragms which are an essential part of the glomerular filtration barrier [11]. Acquired podocytopathies, including idiopathic Focal Segmental Glomerulosclerosis (FSGS) and minimal change disease are historically considered as immunological diseases [12]. Other renal diseases included among podocytopathies are diffuse mesangial sclerosis, collapsing glomerulopathy, and diabetic nephropathy [6]. Recently, a major role in the progression of podocytopathies towards end stage kidney disease has been attributed to the upregulation of Transforming Growth Factor-β (TGF-β) by injured podocytes. According with this hypothesis, TGF-β activity in podocytes might lead to thickening of the glomerular basement membrane, modifying its architecture and function. Moreover, upregulation of TGF-β could also lead to podocyte apoptosis and detachment from the GBM, or alternatively to Epithelial-Mesenchymal Transition (EMT) of podocytes, initiating the development of glomerulosclerosis [13]. Until now, at the best of our knowledge, podocyte loss leading to a podocytopathy has been described in childhood and, in particular, in kidney diseases of adulthood. Here we show that podocyte loss may occur even in the perinatal period and most probably it could begin during the intrauterine life. In our patient, developing glomeruli, normally chacterized by voluminous podocyte precursors with a large roundish nucleus with dense chromatin, encircling the glomerular tuft, showed "naked" glomerular segments, due to the loss of podocyte precursor cells. In the newborn kidney, podocyte loss was focal, affecting scattered glomeruli. Moreover, in the affected glomeruli, podocyte precursor loss appeared segmental, affecting only some areas inside the glomerular body. These pathological findings show striking similarities with FSGS, a podocytopathy normally diagnosed in childhood and adults. The finding of severe podocyte loss in a neonatal kidney suggests that podocyte loss may originate much earlier than previously considered, occurring in the intrauterine life and/or immediately after birth and progressing for years till the clinical presentation in childhood or in adulthood.

The case here reported confirms at histological level previous recent data on the increased urinary excretion of podocytes in

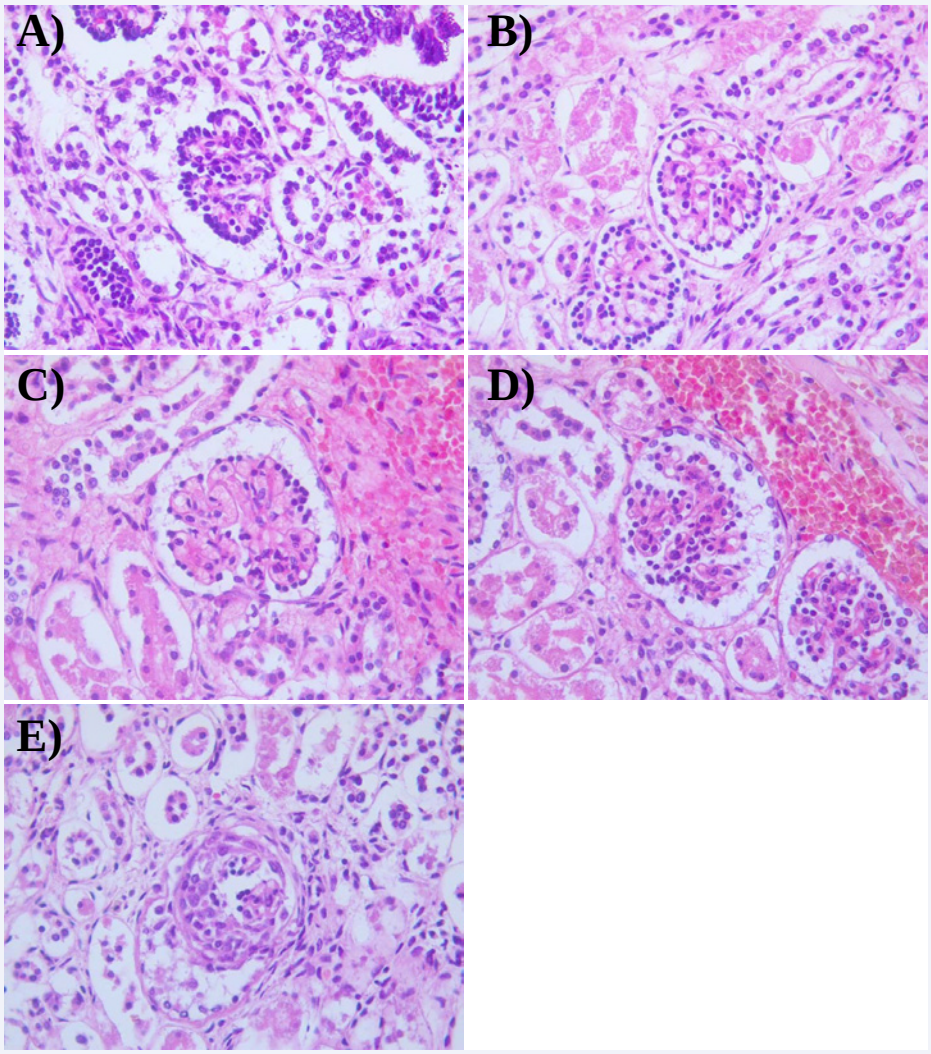

Figure 1 **A)** A normal number of glomerular podocytes surrounding the renal matrix. HE. **B)** A gradual decrease in number of renal podocytes. Capillaries and mesangium are more evident at higher power. OMx400. **C)** A major decrease of podocytes with larger capillaries are detected. OMx400. **D)** A loss of podocytes following an increase in deposition of the mesangial matrix are observed. The epithelium of the parietal Bowman's capsule present initial signs of swelling. **E)** A cellular crescent occupies the vast majority of the glomerula. A total loss of podocytes is observed.

premature infants following indomethacin treatment [14] and lays stress on the necessity for perinatal pathologists to better analyze the podocyte burden in neonatal kidneys, podocytopathies being not restricted to the adult age.

In conclusion, the finding of a severe podocyte damage in a newborn kidney adds a new brick to the complex chapter of podocytopathies, suggesting that, in order to reach a more complete understanding of podocyte diseases, the renal pathologist and the nephrologist should communicate more effectively with the neonatologist and the perinatal pathologist. A dialogue between nephrologists and neonatologists will help the nephrologist provide more accurate diagnostic and prognostic information, in order to select the optimal therapy for these complex and problematic kidney diseases. Moreover, since the developmental origins of health and disease hypothesis is now strongly supported by multiple animal and human evidences [15], neonatologists need to consider the impact that the in utero and early post-natal environment can have on podocyte development, podocyte burden and on podocytopathy insurgence later in life.

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