

Case Report

Hypertension, Chronic Kidney Disease, and Renal Pathology in a Child with Hermansky-Pudlak Syndrome

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We report a child with Hermansky-Pudlak Syndrome (HPS) and chronic kidney disease (stage II) with histological diagnosis of focal segmental glomerulosclerosis (FSGS). A 15-year-old male of Puerto Rico ancestry with history of HPS, hypertension (HTN), asthma, obesity, and chronic kidney disease (CKD) stage II presented with new-onset proteinuria without edema. His blood pressure had been controlled, serum creatinine had been 0.9–1.4 mg/dL, and first morning urine protein/creatinine ratio (UPC) ranged from 0.2 to 0.38. Due to persistent nonorthostatic proteinuria with CKD, renal biopsy was performed and FSGS (not otherwise specified) with chronic diffuse tubulopathy (tubular cytoplasmic droplets) and acute tubular injury was reported. Ceroid-like material is known to infiltrate tissues (i.e., lungs, colon, and kidney) in HPS, but the reason for the renal insufficiency is unknown. Nonspecific kidney disease and in one adult case IgA nephropathy with ANCA-positive glomerulonephritis have previously been reported in patients with Hermansky-Pudlak syndrome. To our knowledge, we report the first pediatric renal pathology case of HPS associated with CKD. This paper discusses presentation and management of renal disease in HPS.

1. Introduction

Hermansky and Pudlak reported in 1959 two cases of unrelated albinos with lifelong bleeding tendency and peculiar pigmented reticular cells in the bone marrow as well as in lymph nodes and liver biopsies. One albino was female and the other was male, both were 33 years old. The female had renal insufficiency. After her death, autopsy revealed horseshoe kidney with large amount of pigment in reticuloendothelial cells and in the walls of small blood vessels [1]. Hermansky-Pudlak syndrome (HPS) is an autosomal recessive disorder that is caused by different genetic mutations [2]. This syndrome is characterized by oculocutaneous albinism, platelets storage-pool deficiency, and lysosomal accumulation of ceroid lipofuscin [2]. These patients have decreased skin and hair pigmentation and transillumination of the iris with markedly decreased visual acuity. Patients

with HPS have easy bruisability, secondary to the absence of platelet dense bodies, which trigger platelet aggregation [2]. Ceroid lipofuscin is an amorphous lipid protein complex, and its accumulation in tissues is believed to be responsible for pulmonary fibrosis and granulomatous colitis [3]. This ceroid lipofuscin also accumulates in the kidney, giving it a dark appearance when examined during an autopsy or kidney biopsy [4, 5]. Although no specific renal disease has been attributed to HPS, compromised renal function in these patients has been reported [1, 4]. Renal insufficiency has been thought to occur due to the ceroid lipofuscin deposition in the kidney. Gahl et al. reported a series of 49 patients with HSP, of which 9 had CKD; however, no kidney biopsies were performed and there is no information about the proteinuria and hypertension in any of the above reports [2].

To our knowledge, we report the first pediatric renal pathology case of HPS associated with CKD, tubular pathology,

focal segmental glomerulosclerosis (FSGS), and hypertension.

2. Case Report

The patient is a 15-year-old male born in Puerto Rico to nonconsanguineous parents of Puerto Rican descent. He moved to the USA when he was 2 years old at which time the diagnosis of HPS was made by hematologist who saw him because of easy bruisability and prolonged bleeding time. Genetic testing was done, and he was found to be homozygous for the 16 bp duplication in the HPS1 gene, which is denoted c.1472.87dup 16 on the cDNA level. The 3.9 kb deletion in the HPS3 gene was not present. He had no known family history in parents, grandparents, and immediate relatives of renal failure, albinism, or known HPS, although paternal grandmother had hypertension.

Our service was consulted secondary to persistent hypertension detected during a hospitalization for asthma-like symptoms, when he was 8 years old. He had no history of obstructive sleep apnea with negative sleep study. Physical examination at that time showed an active child, with global developmental delay, albino, obese (with body mass index >95th for age) with normal cardiovascular and respiratory exam. He had horizontal nystagmus; rest of neurological exam was within normal limits. He had no fever, heart rate was 96 beats per minute, and blood pressure in the right arm was 149/93 mmHg, left arm 127/78 mmHg, right leg 154/64 mmHg, and left leg 151/77 mmHg in sitting position. Serum chemistries showed sodium of 135 mg/dL, potassium of 3.8 mg/dL, blood urea nitrogen of 16 mg/dL, and creatinine of 1 mg/dL. Urine analysis showed no protein or blood at that time. Echocardiogram (ECHO) showed mild left ventricular hypertrophy (LVH). Renal ultrasound showed both kidneys to be normal in position and without evidence of hydronephrosis. The right kidney measured 8.4 cm, and left kidney measured 9.7 cm. Doppler examination demonstrated patency of renal veins, with resistance indices 0.5 (right renal artery) and 0.6 (left renal artery). His hypertension workup included normal serum/urine catecholamines, thyroid function tests, and normal brain imaging (MRI head). To control hypertension, a long-acting calcium channel blocker was started. Since then, patient's blood pressure was <90 percentile for age, gender, and height. LVH subsequently resolved as documented on follow-up ECHO at age of 9 years.

At 12 years of age, calcium channel blocker was stopped, secondary to gingival hyperplasia, and an angiotensin receptor blocker (ARB) was started. At that time, patient did not have proteinuria. His blood pressure continued to be well controlled while on ARB. His serum creatinine remained stable (ranged from 1 to 1.3 mg/dL), and serum potassium ranged from 3.8 to 4.6 mg/dL. In this time period, his BMI increased from 31 to 34. Due to chronic abdominal pain, he had a gastric, duodenum, and colonic biopsies done, which showed mild acute-chronic inflammation (there were no bleeding complications).

During his routine follow-up visit at age 14 years, 30 mg/dL of protein without hematuria was noted on the

dipstick, but measured urine protein/creatinine ratio (UPC) of this sample was 0.2. He was seen in the renal clinic every 3–6 months, and since then his first morning UPC ranged from 0.2 to 0.38. A reliable 24-hour urine collection was not possible to obtain due to his developmental delay.

When he was 15 years old, his blood pressure was still controlled with ARB, his serum creatinine was elevated at 1.4 mg/dL, and proteinuria became fixed, that is, 1st morning UPC was 0.38 and 0.5. First morning urinalysis showed pH of 6, yellow color, specific gravity 1.020, 100 mg/dL protein, no blood, and no glucose, and microscopic examination showed 0–3 red blood cells per high-power field and 0–5 white blood cells per high-power field, without casts, indicative of functional renal concentrating and acidifying abilities. He had no edema and no hematuria, and his serum albumin was 4.2 g/dL. Total cholesterol was 138 mg/dL. His BMI was 35. His serologies for hepatitis B/C and lupus; complement 3 and 4, antinuclear antibodies, and vasculitis; antineutrophil cytoplasmic antibodies (ANCA) were all negative. Kidney biopsy was performed due to persistent proteinuria and compromised renal function, with estimated GFR 70 mL/min/1.73 m² by Schwartz formula [6]. The hematology service was consulted prior to biopsy and coagulation studies: prothrombin time (PT) was 10.5 seconds (normal 9.5–12 seconds) and partial thromboplastin time was 26.9 seconds (normal 26.2–33.8 seconds). Immediately after the kidney biopsy, a small perinephric hematoma was observed by ultrasonographic evaluation but no gross hematuria was seen and there were no other complications during and after the procedure. Patient went home the same day.

3. Pathology

On gross pathologic examination, kidney tissue was dark brown. Tissue for light microscopy was evaluated at 10 section levels with H&E, PAS, and trichrome staining. There were total 19 glomeruli in two renal biopsy cores of tan-red cylindrical tissue each core up to 1.2 cm and 1.9 cm. There were three sclerotic glomeruli, including one with segmental hyalinosis; one of the four additional enlarged glomeruli per level of section had perihilar segmental sclerosis. No glomerular hypercellularity, no necrosis, and no crescents were present. Mild interstitial fibrosis with associated tubular atrophy, and no significant interstitial inflammation was present. Acute tubular injury with variable tubular ectasia, variable hypertrophic tubular epithelial cells with marked cytoplasmic vacuolization, fuchsinophilic and PAS-negative waxy dull brown-yellow spherule cytoplasmic inclusions were present. Tubular epithelial simplification and individual cell dropout with luminal granular casts were present. Injured tubules had scattered nuclei with marginated nuclear chromatin and central clearing. No arteriosclerosis was present, and no vascular inflammatory lesions were present, Figures 1(a)–1(c). On immunofluorescent examination, up to 3 enlarged glomeruli per level of section had irregular coarse granular capillary wall and mesangial staining with antisera specific for C3. The glomeruli had no staining with antisera specific for IgG, IgA, IgM, C1q, kappa light chains,

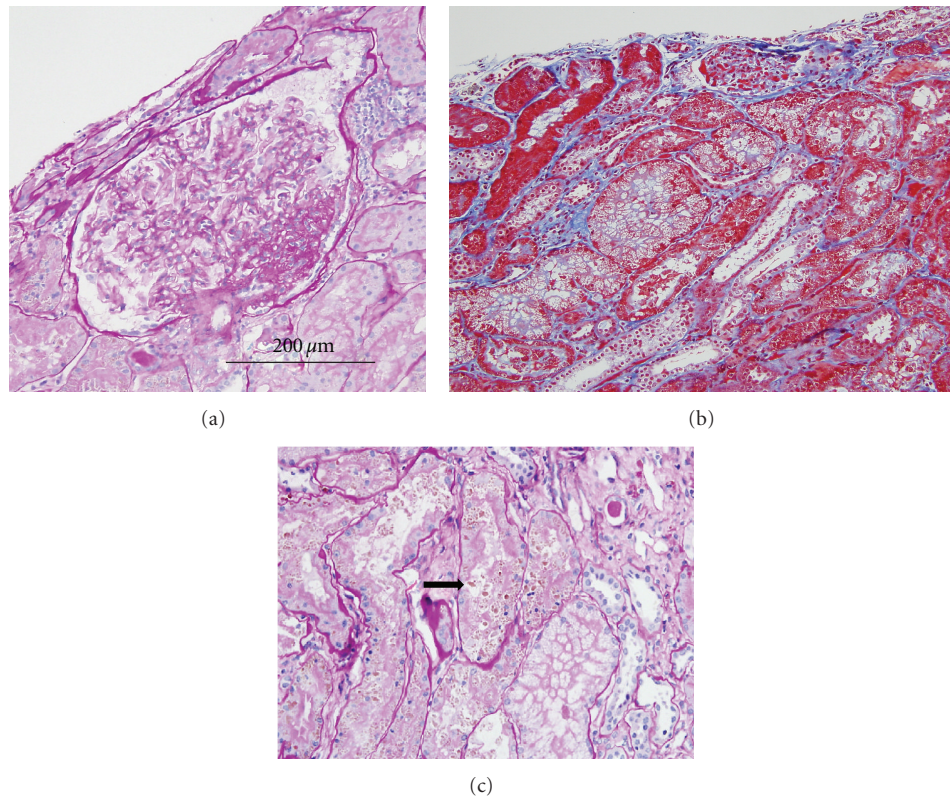


FIGURE 1: (a) Perihilar segmental sclerosis (PAS, original magnification 20x). (b) Diffuse tubulopathy: variably size tubular profiles, hypertrophic tubular epithelial cells, cytoplasmic vacuolization, and coarse fuchsinophilic cytoplasmic accumulations (trichrome, original magnification 20x). (c) Diffuse tubulopathy: tubular epithelial cell cytoplasmic irregular waxy brown-yellow ceroid-lipofuscin—like pigment accumulations (black arrow) (PAS, original magnification 40x).

or lambda light chains. No significant extraglomerular staining was present. Diffuse tubular cytoplasmic droplets were present. Oil red O stain was negative for tubular lipid.

Electron microscopy (Figure 2) revealed no capillary wall or mesangial immune complex-type electron-dense deposits. Infrequent, visceral epithelial foot process effacement was present. No endothelial tubuloreticular inclusions were identified.

4. Discussion

Although original description of HPS originated in Prague, the majority of literature reports describing this syndrome have come from Puerto Rico [2]. When Hermansky and Pudlak reported for the first time in 1959 [1] two cases of albinism and prolonged bleeding time, renal insufficiency was described in one patient with horseshoe kidney. Tagboto et al. [4] reported a patient with HPS with IgA nephropathy and ANCA-positive glomerulonephritis. The kidney tissue showed a dark-brown pigmentation, and the tubular injury was similar to what we found in our case. Ceroid-like lipofuscin material has been found in the urine of HPS patients with renal involvement [7], and the deposition of this material in other tissues (lungs, colon) has been blamed for cellular dysfunction and subsequently fibrosis, although,

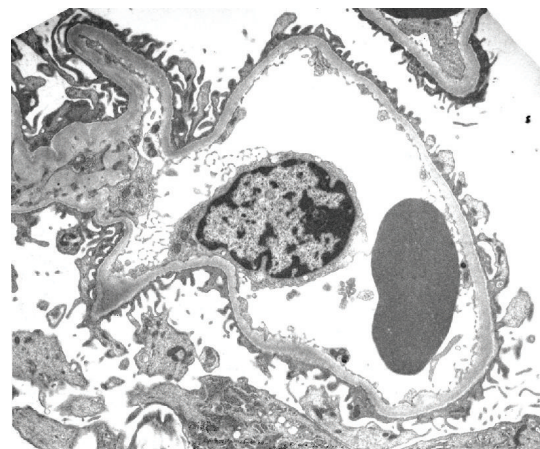


FIGURE 2: Fenestrated endothelium, intact glomerular basement membranes, and infrequent podocyte foot process effacement (transmission electron microscopy, original magnification 6000x).

if this is the cause, the exact mechanism has not been described. The mechanism of injury of renal tubular cells by lipofuscin accumulation is not completely understood.

HPS is a rare, autosomal recessive disorder which affects multiple cytoplasmic organelles: melanosomes, platelet

dense granules, and lysosomes. HPS can be caused by mutation in several genes: HPS1 (common among population of the Northwestern part of Puerto Rico) [8], HPS3 [9], HPS4 [10], HPS5 [11], and HPS6 [12]. HPS2 [13], which includes immunodeficiency in its phenotype, is caused by a mutation in the AP3B1 gene [14]. HPS7 is caused by a mutation in the DTNBP1 gene [15]. HPS8 is caused by a mutation in the BLOC1S3 gene [16]. HPS is characterized by defect in the coat-protein complexes resulting in abnormal function of lysosomes, melanosomes, and platelet dense granules as HPS-gene products are part of distinct protein complexes: the adaptor complex AP-3 and various BLOCs (biogenesis of lysosome-related organelles complex) [14–16]. Although there is no data to support it, it is plausible to hypothesize that podocytes of HPS subjects may demonstrate molecular defects in proteins analogous to dysbindin (part of BLOC-1, found in axonal synapses) involved in lysosomal trafficking.

The HPS phenotype is heterogenic, and it was reported that HPS observed in an isolated Swiss Alps village [17, 18] usually shows a relatively mild clinical course with normal life expectancy and the lack of clinical manifestations of ceroid storage. Our patient presents yet another phenotype with HTN and constellation of renal lesions that include evidence of tubular injury and FSGS.

Patients with HPS have mild prolonged bleeding time secondary to functionally impaired platelets, but platelet numbers are normal. Our patient had had a gastric and colonic biopsy in the past, as well as a tooth removal without significant bleeding. We had not observed significant complications during and after the kidney biopsy. Slow rise in serum creatinine from 1 mg/dL at age 8 y to 1.4 mg/dL at age 16 y might be clinically important in our case description, indicative of slow progression despite multiple risk factors: obesity, HTN, FSGS, and presence of tubular fuchsinophilic cytoplasmic inclusions with mild interstitial fibrosis on renal biopsy.

To the best of our knowledge, there are no previous reports of pediatric HPS patients with described renal pathology. The animal model of HPS is the Fawn-Hooded rat (FH) and pale ear mouse [19, 20]. The FH rat has an inherited platelet storage-pool deficiency and a widespread impairment of serotonin storage, susceptibility to systemic and pulmonary hypertension, but does not have mutations in the gene homologous to HPS1. The FH rat has a genetic predisposition to develop chronic renal failure, FSGS, HTN, and proteinuria [19]. The progression of sclerosis results in premature death from end-stage kidney disease in these rats. But the precise cause of the spontaneous development of systemic hypertension in FH rats is not well understood [19]. HPS1 is homologous with the “pale ear” mouse (ep mutation). In that mouse, there is lysosomal accumulation of beta-galactosidase and EM showed large multilamellar granules in proximal tubules with the accumulation of lipofuscin material in the tubules [20].

In the last decade, there has been an increased incidence of FSGS associated with obesity [21]. Verani [22] reported 14 biopsies of obese adults with FSGS. In that report, glomerulomegaly was reported in patients with FSGS associated with obesity, as well as lack or hyperplasia of glomerular

epithelial cells. In that report, patients with FSGS associated with obesity had higher cholesterol and atherosclerosis. Our patient had normal cholesterol and no atherosclerosis on biopsy. Kambham et al. reported that only 10% of their patients with idiopathic FSGS had glomerulomegaly [21]. No tubular lesions, as in the case of our patient, had been reported in FSGS associated with obesity. In a previous case of HPS, tubular atrophy and accumulation of a ceroid-like material in tubular epithelial cells were reported [4]. Obesity has not been a part of phenotypic description of HPS. Our patient had increased BMI and hypertension with LVH since initial presentation at age 8 years. We can speculate that HTN was secondary to obesity at 8 years of age but it would be uncommon clinical scenario to encounter the child at this age with HTN significant enough to cause LVH due to obesity alone. He had no history of obstructive sleep apnea. Our patient did not have evidence of renal artery stenosis or endocrine causes of hypertension, and his blood pressure was controlled with monotherapy. The effects on the kidney secondary to obesity in animals and humans include structural and functional changes, such as increased GFR, increased renal blood flow, and renal hypertrophy [21, 22]. Some of the changes in the renal tissue of our patient might be consistent with FSGS associated with obesity, and the tubular changes may contribute to the renal insufficiency. Although it is not our intention to draw any association between HPS and FSGS, we can speculate that obese patients with HPS and hypertension may be at risk of unrecognized FSGS. However, it is possible that the sclerosis of the glomeruli observed in our case is secondary to the tubular damage.

To the best of our knowledge, this is the first pediatric case of HPS associated with CKD and defined renal pathology. Further studies are needed to determine the cause of renal insufficiency in patients with HPS.

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