Clinicopathologic Features of Hepatic Involvement in Senior-Loken Syndrome: A Case Report and Review of Literature

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Abstract
Senior-Loken syndrome is an autosomal recessive disorder, characterized by the combination of nephronophthisis and retinopathy, the hepatic manifestations of which have not been well characterized. We describe here a case of a 14-year-old girl with Senior-Loken syndrome who presented with persistent elevation of liver enzymes. Histological examination of liver biopsy specimen revealed remarkable portal expansion featured by portal fibrosis and minute ductile duplication, consistent with the malformation of interlobular bile ducts. The liver parenchyma and lobular architecture were relatively preserved with minimal inflammation. The clinical and morphologic features for the triad of nephronophthisis, retinopathy, and congenital hepatic fibrosis were reviewed and compared with other cases available in the literature. We presented a case of Senior-Loken syndrome with severe nephronophthisis and mild retinal degeneration in association with congenital hepatic fibrosis. The liver involvement poses a big challenge to the clinical interventions after renal transplantation.

ABBRévIATIONS
ALP: Alkaline Phosphatase; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase

INTRODUCTION
Senior-Loken syndrome is a rare autosomal recessive disorder, characterized by the combination of nephronophthisis and retinopathy, which usually presents in the first two decades of life. The estimated prevalence is about 1 in 1 million people worldwide. It was first described in 1961, separately by Senior et al., and Loken et al. [1,2], and has also been referred to as hereditary renal-retinal syndrome, juvenile nephronophthisis with leberamaurosis, and renal dysplasia with retinal aplasia. Hepatic manifestations of Senior-Loken syndrome have been mentioned in a small number of reports.

Nephronophthisis presents initially with polyuria and polydipsia and progressing insidiously to end-stage renal disease by the second decade. The main histological findings are tubular atrophy, interstitial fibrosis, and thickening and lamellation of the tubular basement membrane [3,4]. It is the most common genetic cause of end stage renal disease in the first three decades, presenting alone or in combination with another multisystem disorder, and Senior-Loken syndrome accounts for about 10-15% of cases [5-7].

The retinal lesions in the Senior-Loken syndrome are variable, ranging from Leber’samaurosis to retinitis pigmentosa. This condition causes vision problems, including an increased sensitivity to light (photophobia), involuntary movements of the eyes (nystagmus), and extreme farsightedness (hyperopia). Retinitis pigmentosa is characterized by bone spicule pigmentation of the retina and presents initially with night blindness which slowly progress to daytime blindness. Leber’samaurosis is a severe form of retinal dystrophy which leads to blindness nystagmus and a diffuse atypical retinal pigmentation and pallor of the optic disc [7]. Other ocular findings that have been reported in this syndrome include cataract, Coat’s disease and keratoconus [8,9].

Liver involvement in Senior-Loken syndrome has been reported rarely, but the clinicopathologic features are not well characterized. The present case reports was aimed at describing the clinical and morphologic features in a recent case of Senior-Loken syndrome and, in conjunction with prior reports, summarizes the known features of liver involvement in this syndrome.

CASE PRESENTATION
A 14-year-old female patient was referred to the pediatric hepatology division for the evaluation of persistent elevation of liver enzymes with intermittent itching in the soles of the feet.
Her past medical history was significant for end-stage renal disease secondary to nephronophthisis, and decreased night vision due to retinitis pigmentosa, with a diagnosis of Senior-Loken syndrome type 1, with NPHP1 gene mutation, rendered in 2014. She subsequently underwent hemodialysis followed by peritoneal dialysis, and cadaveric renal transplantation in July 2015.

She was asymptomatic overall, denying jaundice, icterus, dark urine, fatigue, and malaise. Her family history was non-contributory. She was progressing normally in school. In early 2014 when she first presented for end-stage renal disease at 12 years of age, an ultrasound at that time was interpreted as cirrhosis, and a liver biopsy was performed. She was then noted to have abnormal liver enzymes and alkaline phosphatase (ALP), with alanine aminotransferase (ALT) and aspartate

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age at diagnosis (years)</th>
<th>Retinal lesions</th>
<th>Hepatomegaly</th>
<th>Liver function tests</th>
<th>Liver biopsy</th>
<th>Other</th>
<th>Follow-up</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>12</td>
<td>Tapetoretinal degeneration</td>
<td>Y</td>
<td>Mild elevation ALP: normal</td>
<td>Diffuse peri-lobular fibrosis, small bile duct proliferation</td>
<td>Mental retardation</td>
<td>Died of uremia at age 13</td>
<td>[6]</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>12</td>
<td>Tapetoretinal degeneration (since birth)</td>
<td>Y</td>
<td>Minimal elevation</td>
<td>Portal fibrosis</td>
<td>Mental retardation, psychomotor retardation</td>
<td>Died of uremia at age 19</td>
<td>[23]</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>4.5</td>
<td>Not able to follow light and blindness within 4 years of age</td>
<td>Y</td>
<td>Normal</td>
<td>Portal fibrosis, ductal proliferation</td>
<td>Growth retardation, polydactyly and cerebral abnormalities</td>
<td>Died of uremia at age 5</td>
<td>[25]</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>5.5</td>
<td>Not able to follow light and blindness within 4 years of age</td>
<td>Y</td>
<td>AST 54 ALT 65 ALP 240</td>
<td>Portal fibrosis, ductal proliferation, centri-lobular congestion</td>
<td>Growth retardation, thymic atrophy, phtosis</td>
<td>Died of uremia at age 5.75</td>
<td>[25]</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>15</td>
<td>Pigmentary retinopathy</td>
<td>Y</td>
<td>ALT 70 ALP 300</td>
<td>Liver fibrosis (not biopsy-proven)</td>
<td></td>
<td>Liver failure 2 years later after kidney transplantation and cyclophosphamide therapy</td>
<td>[24]</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>13</td>
<td>Pigmentary retinopathy (night blindness)</td>
<td>Y</td>
<td>ALT 53 ALP 222 the rest: normal</td>
<td>Fibrosis, portal infiltration, proliferation of bile ducts</td>
<td></td>
<td>A minor increase in liver enzymes in 4-year follow-up</td>
<td>[24]</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>12.5</td>
<td>Retinitis pigmentosa</td>
<td>Y</td>
<td>NA</td>
<td>Portal fibrosis</td>
<td>Mental retardation, coloboma, skeletal anomalies, and cerebellar ataxia</td>
<td>NA</td>
<td>[5]</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>13</td>
<td>Retinitis pigmentosa</td>
<td>NA</td>
<td>NA</td>
<td>Liver fibrosis (not biopsy-proven)</td>
<td>Mental retardation, kyphoscoliosis, short metatarsale IV, cerebellar ataxia, pulmonary emphysema</td>
<td>NA</td>
<td>[5]</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>12</td>
<td>Retinitis pigmentosa (decreased night vision)</td>
<td>Hepatosplenomegaly</td>
<td>ALT:144-770 AST: 37-300 ALP: 97-851</td>
<td>Ductal proliferation, portal fibrosis</td>
<td></td>
<td>Current</td>
<td>This report</td>
</tr>
</tbody>
</table>

Notes: Case 2, mother had abnormal ERG; Cases 3 and 4 were monozygotic twins; Cases 5 and 6 were sisters from one family; NA, not available.

Abbreviations: ALT: Alanine Transaminase; AST: Aspartate Transaminase; ALP: Alkaline Phosphatase
aminotransferase (AST) being elevated to 1.5 to 2 times the upper limit of normal in late 2014. Her liver enzymes fluctuated between normal to slightly elevated until early 2016 when enzymes surged, with ALT of approximately 500 U/L, AST 200 U/L, and ALP 800 U/L. Her serum bilirubin and albumin had remained normal throughout the course.

On examination, she was found to have short stature and underweight (<5th percentile for age) before renal transplantation in 2015 but had gained weight normally since, achieving normal ranges in August 2016. Her eye examination showed no icterus or nystagmus and negative pupillary reflexes. She was also found to have hepatomegaly and splenomegaly. There were no stigmata of portal hypertension, and upper endoscopy showed no varices.

Her laboratory studies were remarkable for pancytopenia, particularly low platelet count, which were largely ascribed to hypersplenism after bone marrow biopsy to rule out hematological disorders in January 2014. Her transplanted renal function was within normal range, with creatinine of 0.54 mg/dl and blood urea nitrogen of 17 mg/dl in July 2016. Tests for anti-nuclear, anti-mitochondrial, anti-liver-kidney microsomal, anti-myeloperoxidase, and anti-serine protease 3 antibodies were negative; however, anti-smooth muscle antibody was detected positive three times (31.6, 38.4 and 42.4, normal: not detectable). Serological tests for the viral hepatitis, including hepatitis A, hepatitis B, and hepatitis C, were negative. The liver ultrasonography in July 2016 revealed coarsened hepatic echo texture with nodular contour consistent with cirrhosis.

A liver core needle biopsy was performed (Figures 1-3). The portal tracts were enlarged, expanded primarily by fibrosis. Within the fibrous portal stroma numerous bile duct profiles could be seen, representing bile duct reduplication. There was no significant inflammation in the portal tracts. There was no duct dilation, bile plugs, cholangitis, or ductular proliferation. The lobular histology was essentially unremarkable, with no evidence of cholestasis, any sinusoidal dilation, and normal reticulin framework. PAS and iron stains were negative. Central veins had a normal appearance, no dilation or pericentral fibrosis.

DISCUSSION

In its classical form, Senior-Loken syndrome consists of nephronophthisis and retinopathy. Also reported are several variants, including some with short stature, kyphoscoliosis, small hands (short metacarpals), madarosis, dysmorphic features of face and hands, pancreatitis, and hepatic fibrosis [5,10-13]. Cases in which there is hepatic involvement are rare and the clinicopathologic features in such cases therefore not well characterized.

Senior-Loken syndrome, like nephronophthisis disorders generally, is considered one of the “ciliopathies,” multisystem developmental disorders stemming from defects in genes encoding ciliary proteins [4,14]. Mutations in NPHP2 and NPHP3 genes in particular, although only accounting for 1% of all cases of nephronophthisis overall, are prevalent among patients with liver involvement [4,15,16]. The NPHP2-encoded protein inversin interacts with nephrocystin-1, the product of NPHP1, and together these co-localize to cilia within the developing nephron [16]. NPHP3 encodes nephrocystin-3, which interacts with nephrocystin-1 and inversin and can inhibit canonical wnt signaling [17,18].

The nephronophthisis disorders are genetically heterogeneous, originating from a variety of mutations in a small number of pleiotropic genes [19]. Molecular diagnosis may utilize genetic markers, homozygosity mapping with single nucleotide polymorphism microarrays [16,17,19], linkage analysis, and microsatellite markers, in addition to the traditional positional cloning. A novel approach involving the step-wise Sanger sequencing and targeted exome sequencing is recently proposed for studying patients with nephronophthisis [20].

The clinicopathologic features of hepatic dysfunction in the case described above are consistent with congenital hepatic fibrosis, a disorder that results from failure of the ductal plate to properly mature during embryogenesis. It primarily affects the small interlobular bile ducts [5,10]. Congenital hepatic fibrosis may arise sporadically or as part of an autosomal recessive inherited disease. Pathologically, it is defined by a variable degree of perportal fibrosis, irregularly shaped reduplicating bile ducts, cystic ductal malformations, and abnormalities of portal veins [6,10]. It has a variable clinical course, ranging from minimally symptomatic disease to cirrhosis. The most common manifestation is portal hypertension, frequently presenting...
with variceal bleeding or findings attributable to hypersplenism [10,21].

The clinicopathologic findings presented a challenging differential diagnosis. Congenital hepatic fibrosis must be distinguished from biliary cirrhosis, the latter demonstrating a contrasting picture of regenerative nodules, periportal edema, and ductular reaction not seen in this case. Caroli’s disease is characterized by the findings of congenital hepatic fibrosis with the additional features of cholangitis, marked cholestasis, and portal inflammation. Lastly, extrahepatic biliary obstruction presents with cholestasis and a histologic picture including ductular proliferation, rather than duct reduplication, with periportal edema and inflammation.

Congenital hepatic fibrosis, with its varied clinical manifestations, was recognized first by Kerr in 1961 [22]. Since then, it was found to be associated with polycystic kidney disease and nephronophthisis. Congenital hepatic fibrosis in association with nephronophthisis was first described by Boichis and coworkers in 1973 in a family where parents were first cousins [23]. The triad of nephronophthisis, retinal degeneration, and congenital hepatic fibrosis was first mentioned in 1975 [4], and named Senior-Boichis syndrome thereafter [24]. A total of 9 cases were reported so far according to literature search using multiple keyword combinations (Table 1); several other cases that were presented in meeting abstract were not included in the comparison [3,24-26]. All these cases presented with typical features of severe nephronophthisis leading to dialysis, renal transplantation, or death due to uremia [6,26]. The retinal manifestations varied from decreased night vision in the first decade of life (as in the present case) to blindness by the age of 4 years. All cases showed mild elevation of liver enzymes, normal or slight elevation of alkaline phosphatase, and hepatomegaly with or without splenomegaly. The eight biopsy-proven cases demonstrated portal or peri-portal fibrosis and multiple ductile duplications secondary to either minute ductal proliferation or ductile malformation. In contrast to typical congenital hepatic fibrosis, dilatation of bile ducts and portal vein abnormalities were not observed; likewise, we did not observe this feature in our case. These biopsy findings were confirmed subsequently in three autopsies [6,26]. Two cases developed worsening liver function after renal transplantation and immunosuppressive
therapy (including the current case) [25], suggesting increased susceptibility to the toxic reagents in the presence of congenital hepatic fibrosis. Follow-up studies were very limited, and one out of the two cases showed signs of liver failure two years later after renal transplantation and the use of immunosuppressive drugs [25].

In summary, we presented a case of Senior-Loken syndrome with severe nephronophthisis, mild retinal degeneration, and congenital hepatic fibrosis. The clinical presentation and histopathology were described. It is worth nothing that liver involvement poses a big challenge in this patient after renal transplantation.

REFERENCES


