

CASE REPORTS OF THE UNIVERSITY OF PUERTO RICO
SCHOOL OF MEDICINE HOSPITALS



Renohepaticopancreatic Dysplasia: Diagnostic Dilemma

ALICIA FERNÁNDEZ-SEIN, MD*; MARÍA S. CORREA-RIVAS, MD†; KEILA PRATTS, MD*;
HUMBERTO LUGO-VICENTE, MD‡

We present the case of an eighteen day old baby boy hospitalized with an abdominal mass, renal insufficiency and jaundice. Multiple radiographic, radionuclear and surgical interventions were required to diagnose renohepaticopancreatic dysplasia, also known as Ivemark II syndrome. In spite of aggressive

intensive care support, the patient developed multisystemic organ failure and died. Clinical presentation and autopsy findings are presented.

Key words: Cysts, Dysplasia, Ivemark, Renohepaticopancreatic, Syndrome

In spite of modern technological advances, the evaluation of a newborn presenting an abdominal mass continues to be a medical challenge. There are situations where performing various radiological and/or nuclear studies do not bring forward the correct diagnosis but rather confuse the clinician. Tissue biopsies and lastly an autopsy, often produce the definitive diagnosis. This case report focuses in the difficulty in diagnosing renohepaticopancreatic dysplasia, (also known as Ivemark II syndrome), a rare and complex condition during the neonatal period, different from Ivemark I syndrome related to bilaterality/asplenia syndromes, and associated to cardiac anomalies. A team approach is essential in the evaluation and management of such patients.

Case report

An eighteen day old baby boy presented with postprandial vomiting, jaundice and abdominal distention since three days prior to hospitalization. Marked hepatomegaly and a left lower quadrant lobulated soft

mass were palpable. The patient also exhibited bilateral simian creases. Initial laboratory results showed metabolic acidosis (HCO_3^- : 12), renal insufficiency (BUN: 42 mg/dl, creatinine: 1.7 mg/dl), elevated hepatic enzymes (AST: 207 U/L, ALT: 123 U/L), direct hyperbilirubinemia (total bilirubin: 8.1 mg/dl, direct bilirubin: 4.8 mg/dl), hyperammonemia (ammonia: 278 mcg/dl), and hypoglycemia.

Abdominal magnetic resonance imaging (MRI) showed dilatation of intra and extrahepatic biliary ducts. An abdominal ultrasound suggested renal parenchymal disease and a choledochal cyst type 4a associated to Caroli's disease. Hepatobiliary scan (HIDA scan) failed to show transit of radiolabeled bile into the cystic area ruling out a choledochal cyst. Ultrasound guided diagnostic fine needle aspiration of the cystic area was performed and the fluid obtained for analysis suggested a pancreatic origin (amylase: 571 U/L, lipase >850 U/L, and pH: 8.0). In view of the presence of multiple cystic lesions on pancreas, liver and kidneys, a presumptive diagnosis of Ivemark II syndrome was entertained. There was no family history of hepatic, renal or pancreatic anomalies and there was no consanguinity.

Exploratory laparotomy had to be delayed for three days because the patient developed septic shock and acute respiratory distress syndrome. Mechanical ventilation and inotropic support were required. At laparotomy, hepatomegaly with fibrosis, multiple hepatic cysts and

From the *Departments of Pediatrics, †Pathology and ‡Surgery, Medical Sciences Campus, University of Puerto Rico, San Juan, Puerto Rico.

Address correspondence to: Alicia Fernández-Sein, MD, Department of Pediatrics, Medical Sciences Campus, University of Puerto Rico. PO Box 365067 San Juan, Puerto Rico 00936-5067. E-mail: afernandez@rcm.upr.edu

ductal dilatation, mild ascites and a large epigastric pancreatic cyst were found. Intra-operative cholangiogram showed a patent common biliary duct. (See Figure 1). Liver

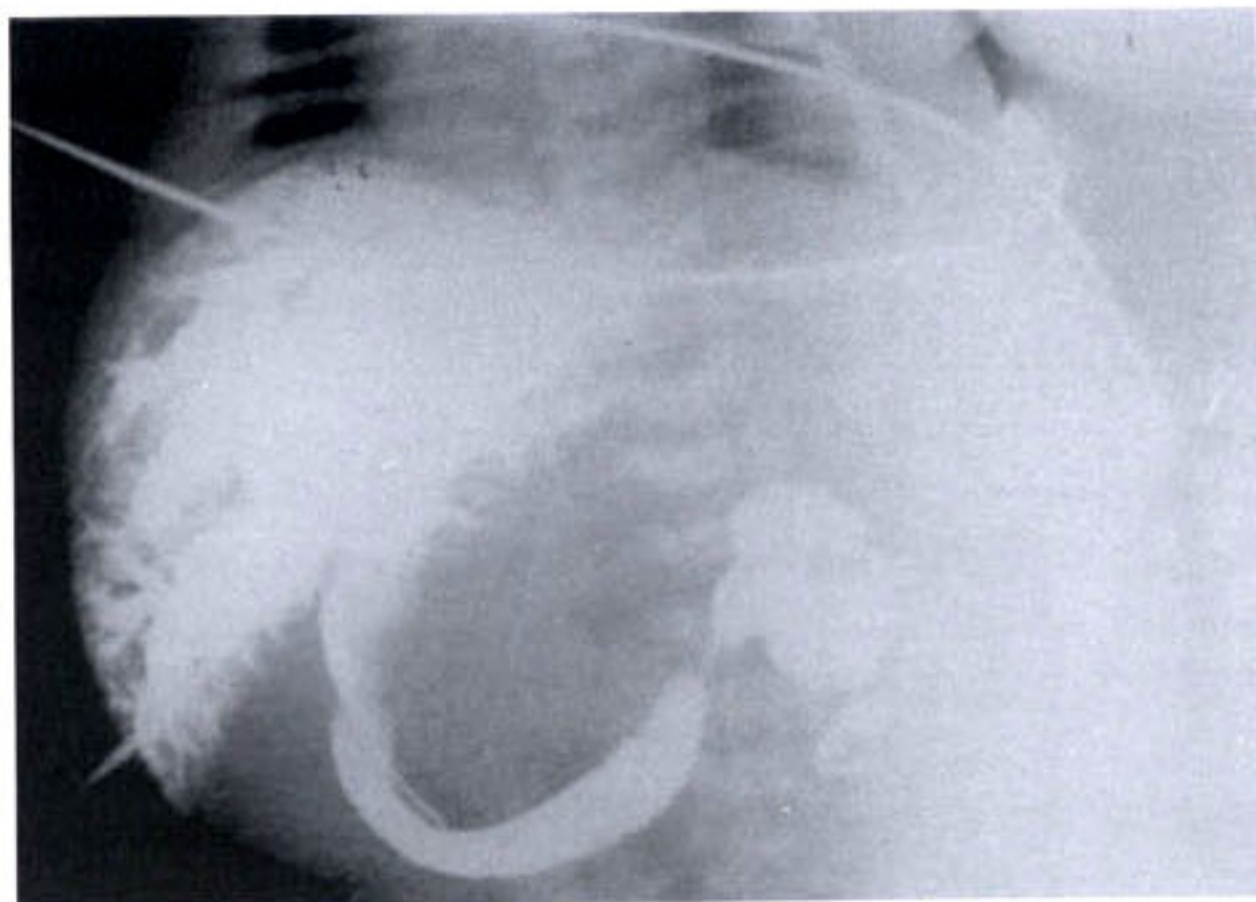


Figure 1. Intraoperative cholangiogram showing massive bilious ductal ectasia. Ballooning of the duodenal sweep is caused by the pancreatic cyst.

wedge biopsy and Roux in Y cystojejunostomy were performed. The liver biopsy showed bile duct proliferation, duct dilatation, bile plugs, and marked intracanalicular and intracellular cholestasis, all compatible with obstructive cholangiopathy. The patient's condition continued to deteriorate, developing renal failure, anasarca and hyperkalemia. Ventilatory and inotropic support had to be maintained. Prolonged PT and PTT parameters required multiple fresh frozen plasma transfusions and vitamin K administration. On the other hand, hepatic enzymes and bilirubin levels decreased progressively. Enteral feedings were unsuccessfully attempted on multiple occasions and parenteral nutrition was given continuously. Anasarca and renal failure worsened. Ventilation parameters had to be increased and therapeutic decompression paracentesis was performed in an attempt to improve renal perfusion. Despite all these measures, the patient developed multisystemic organ failure and died at 46 days of age, 28 days after admission.

Autopsy findings

Autopsy revealed a well developed, slightly icteric and markedly edematous baby boy weighing 6300 gm. External examination showed low set ears, cyanosis of the lips and nailbeds, bilateral simian creases and a markedly globose abdomen. There was a recent transverse surgical incision, 11.5cm long, at the mid abdomen, and a peritoneal catheter in the left upper abdominal quadrant. The liver was palpable 5 cm below the right costal border at the midclavicular

line. On internal examination, the subcutaneous tissues were markedly edematous, with bilateral serosanguinolent pleural effusions (6 ml in each cavity) and 10 ml of yellow serous ascitic fluid. The peritoneum was opaque, fibrotic and the intestinal loops markedly adhered. The organs presented normal anatomical relations with enlarged kidneys and an enlarged liver that extended 9 cm below the right costal border at the midclavicular line. The spleen was not seen anteriorly. Inspection of the kidneys, liver and pancreas revealed the presence of cysts as have been described in *renohepaticopancreatic dysplasia* also known as *Ivemark II syndrome*.

The kidneys were symmetric, reniform, markedly enlarged and cystic, with a combined weight of 120 gm, when the expected weight is 34 ± 9 gm. On section, they presented multiple round cysts throughout, (0.2cm on average), and the pelvicalyceal system was small but patent. Microscopically, the kidneys presented diffuse cystic renal dysplasia. There was a disorganized renal architecture with round cysts of varying sizes, increased interstitial fibrosis, islands of cartilage, and immature tubules surrounded by mesenchymal collarettes. Focal interstitial hemorrhages were also seen.

The liver was enlarged and weighed 420gm, expected 140 ± 40 gm. Externally, it presented normal shape with a slightly nodular opaque surface. On section, the cut surface was firm, and green with foci of fibrosis. The ducts were markedly dilated imparting a cystic appearance



Figure 2. Liver. Note cystic appearance due to marked ductal dilatation.

(Figure 2). Microscopically, there was portal expansion by fibrosis with porto-porto fibrosis and proliferation and tortuosity of bile ductules at the periphery of the portal areas (biliary dysgenesis) and marked duct dilatation. Extramedullary hematopoiesis and marked intracellular and intracanalicular cholestasis were also noted. The

pancreas also presented multiple cysts ranging in size from 0.2 to 0.6 cm. Microscopically, they were lined by low cuboidal epithelium while others had no apparent lining and contained blood and polymorphonuclear cells. There was marked interstitial fibrosis with sprinkle of lymphocytes and scattered islands of pancreatic tissue (Figure 3). Other autopsy findings included marked

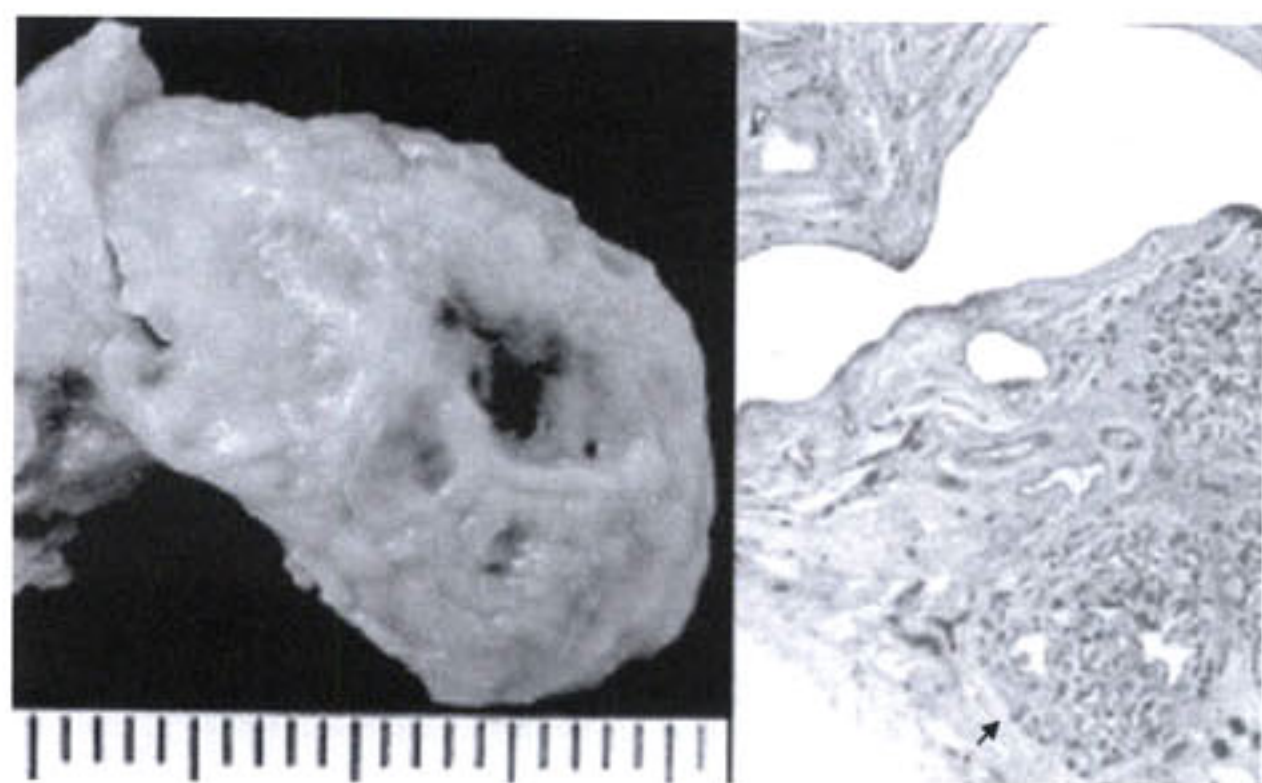


Figure 3. Pancreas. Note several residual pancreatic cysts, after cystectomy. Cysts are lined by simple cuboidal epithelium. Islands of pancreatic tissue are seen within fibrous tissue (*).

involutional changes of the thymus and perithymic hemorrhages, focal acute inflammation of the colonic serosa and a bilateral acute bronchopneumonia with extensive pulmonary hemorrhages; this last finding representing the immediate cause of death in this patient with multiorgan failure.

Discussion

Renohepaticopancreatic dysplasia (RHPD) or Ivemark II syndrome was first described by Ivemark, Oldfelt, and Zetterstrom in 1959 in two siblings that died from renal failure several weeks after birth (1). This is distinct from Ivemark I syndrome, which is related to bilaterality/asplenia syndromes and cardiac malformations. Ivemark II syndrome is probably inherited as an autosomic recessive disease, with a male predisposition. Sporadic cases have been reported and it is extremely rare and uniformly fatal (2). Bernstein et al. described in 1987 five patients with similar findings: a) renal cystic dysplasia with abnormally differentiated ducts, deficient nephron differentiation and glomerular cysts, b) hepatic abnormality consisting of enlarged portal areas containing numerous elongated biliary ducts, with a tendency to perlobular fibrosis, and c) pancreatic abnormality consisting of fibrosis and cysts, with a diminution of parenchymal tissue (3).

It is difficult to differentiate antemortem Ivemark II syndrome from Caroli's disease because of the intrahepatic

ductal dilatation. Initially, we entertained the impression of a choledochal cyst until the HIDA failed to show communication into the cystic area. The cyst aspiration yielded material compatible with pancreatic secretions.

There are two reported cases of children with Ivemark II syndrome that survived the neonatal period but died early in infancy of renal insufficiency, chronic jaundice and insulin dependent diabetes mellitus (3). There are no reported survivors over one year of age. This raises an ethical dilemma that has to be discussed with the parents; how aggressive we should be in view of such poor prognosis. In our case, this was the first born of a young couple that wanted to save their baby against all odds. Initial renal and hepatic insufficiency rapidly lead to anasarca and massive visceromegaly impairing adequate ventilation. Fluid restriction, diuretics and colloid infusions failed to control progressive ascites and edema formation. Finally, renal and hepatic failure lead to multiple complications and multisystemic organ failure supervened. Autopsy confirmed the diagnosis of renohepaticopancreatic dysplasia (RHPD). It also demonstrated extensive organ involvement incompatible with prolonged life, even with intensive medical support.

Although there are cases, such as ours, of sporadic Ivemark II Syndrome (2,3,4), there is a tendency of the condition to recur in families. Tora et al. proposed an autosomal recessive pattern of inheritance (5). Therefore, genetic counseling should be offered since there might be a risk of 25% recurrence of the syndrome in future pregnancies. Prenatal ultrasonography may show renal dysplasia as early as the sixteenth week of gestation, progressing in severity from then on (6). Therefore, ultrasonography should be performed on all mothers with history of a previously affected baby. Other conditions that present with RHPD are Goldston and Zellweger syndromes, several chondrodysplasias, some chromosomal aberrations, such as trisomy 9 and 13, and glutaric aciduria type II. But in most of these syndromes there are ocular, genital, cardiac or some involvement of the central nervous system, which our patient did not exhibit. He did present with polydactyly and simian creases. As Tora et al. suggests, RHPD could be a non-specific final common pathway of response of the affected organs to a variety of developmental disturbances caused by mutations in different genes (5).

The evaluation of an abdominal mass in a neonate is an energy-consuming event that requires a team approach of highly qualified specialists to reach the proper diagnosis. Although rare, renohepaticopancreatic dysplasia, (Ivemark II syndrome) should be considered in patients with hepatic, renal and pancreatic involvement, as it carries a very poor prognosis.

Resumen

Se presenta el caso de un bebé de dieciocho días de nacido con insuficiencia renal, masa abdominal e ictericia. Requiere múltiples evaluaciones radiográficas, radionucleares y cirugía para confirmar el diagnóstico de displasia renohepaticopancreática o síndrome de Ivemark II. A pesar de un manejo intenso, el paciente desarrolla fallo multiorgánico y fallece. Los resultados de la autopsia discutidos son compatibles con la impresión clínica.

References

1. Ivemark BI, Oldfelt V, Zetterström R. Familial dysplasia of

kidneys, liver and pancreas: a probably genetically determined syndrome. *Acta Paediatr Scand* 1959;48:1-11.

2. Larson RS, Rudloff MA, Liapis H, et al. The Ivemark syndrome: prenatal diagnosis of an uncommon cystic renal lesion with heterogeneous associations. *Pediatr Nephrol* 1995;9:594-598.
 3. Bernstein J, Chandra M, Creswell J, et al. Renal-hepatic-pancreatic dysplasia: a syndrome reconsidered. *Am J Med Genet* 1987;26:391-403.
 4. Strayer D, Kissane J. Dysplasia of the kidneys, liver, and pancreas: report of a variant of Ivemark's syndrome. *Hum Pathol* 1979;10:228-234.
 5. Torra R, Alos L, Ramos J, Estivill X. Renal-hepatic-pancreatic dysplasia: an autosomal recessive malformation. *J Med Genet* 1996;33:409-412.
 6. Abbi R, Daum F, Kahn E. Ontogeny of renal dysplasia in Ivemark syndrome: light and immunohistochemical characterization. *Ann Clin Lab Sc* 1999;29:9-17.
-