Alagille Syndrome and Colonic Polyposis:
A True Connection?

by Suneal Agarwal, Leon Kundrotas, Swapna Gupta

Alagille syndrome is a rare autosomal dominant disorder that results in multiple comorbidities. Due to recent advances in medicine, surgery and nutrition, patients with Alagille syndrome are living longer and new pathologies resulting from the underlying JAG2/NOTCH receptor mutation are being discovered. Our current understanding of Alagille Syndrome is chronic cholestasis and an increased risk of developing cirrhosis and hepatocellular carcinoma due to malformation of ductal system during embryonic development. What is new in this report is an expanding discussion of Alagille Syndrome including nutritional management, hepatic complications with review of current literature and a polyposis-like syndrome.

This case report describes a 35 year-old patient with Alagille syndrome who initially presented with rectal bleeding and microcytic anemia. Colonoscopy revealed numerous polyps throughout the colon and biopsies of certain lesions revealed colorectal adenocarcinoma. This case report will review the comorbidities commonly associated with this syndrome.

CASE PRESENTATION

A 35 year-old white female with a known history of Alagille syndrome presented with a 3 day history of rectal bleeding. Three episodes of bloody diarrhea were followed by gradually formed stool streaked with blood. She denied abdominal pain, nausea, emesis, weight loss, history of non-steroidal anti-inflammatory (NSAID) use or prior history of rectal bleeding. She reported a history of heavy menses, controlled by oral contraceptives, but denied any other bleeding. There was no family history of colorectal cancer.

The diagnosis of Alagille syndrome was given shortly after birth as she was found to have neonatal jaundice secondary to intrahepatic biliary atresia; this later required biliary diversion. Her patent ductus arteriosus and ventral septal defects were repaired surgically after birth and she underwent pulmonary valvotomy for pulmonic stenosis within her first year of life. Just three months prior to her current presentation she had an ileal resection with ileocolonic anastomosis for refractory pruritus. She never had a colonscopy prior to surgery.

Physical examination revealed features of Alagille syndrome, including a “triangular” face, deep-set eyes and narrow palpebral fissures. Cardiovascular examination revealed a 3/6 systolic murmur. She exhibited no tenderness on abdominal exam. Rectal

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exam revealed no hemorrhoids or palpable masses; however, gross blood was visualized. Her laboratory results were significant for microcytic anemia with hemoglobin of 8.7 g/dL and a mean corpuscular volume of 55 fl. Her iron studies revealed a total iron of 14 mcg/dl, total iron binding capacity of 458 mcg/dl, transferrin saturation of 3% and ferritin of 6 ng/ml.

An upper endoscopy was unremarkable. Colonoscopy revealed more than 50 polyps throughout the entire colon (Figure 1). There were 3 pedunculated polyps that were actively bleeding (Figure 2); each was biopsied and found to be adenocarcinoma (Figure 3). The patient subsequently underwent a total colectomy; lymph node dissection did not show lymphatic involvement. Hereditary nonpolyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP) genetic testing were performed but found to be negative for the mutations.

**DISCUSSION**

Alagille syndrome is a rare autosomal dominant genetic disorder with an incidence that has been reported from 1 in 70,000 births to 1 in 100,000 births. The pathophysiology of Alagille syndrome is linked to involvement of the JAG1 and NOTCH2 genes. The JAG1 gene is found on chromosome 20, and 90% of patients with Alagille syndrome display a microdeletion of 20p12 found within the JAG1 gene. Eight percent of patients have the entire deletion of JAG1. The rest are thought to have mutations in NOTCH2. Both JAG1 and NOTCH2 are involved in the NOTCH signaling pathway that leads to cell differentiation during embryonic development.

Alagille syndrome usually has nearly complete penetrance; however, the expression is extremely variable. The diagnosis is usually suspected after birth as patients often present with persistent jaundice. They often also exhibit involvement of organs other than those of the gastrointestinal system, including cardiac, pulmonary, ophthalmologic, neurologic, skeletal and renal.

Among the gastrointestinal abnormalities, the main organs involved, as described in previous literature, have been the liver and pancreas. Pancreatic exocrine deficiency is usually present, although the pathophysiology is not well understood. Hepatic involvement is thought to be linked to ductal malformation and up to 96% of patients present with chronic cholestasis. These patients have high levels of conjugated bilirubin, attributed to lack of development of interlobular bile ducts. Histopathologically, there is evidence of bile duct paucity, with an increased portal tract-to-bile duct ratio. The prevalence of colonic polyps in this syndrome may have been underreported since the clinical manifestations of colonic polyps are silent until anemia develops. Often patients with Alagille syndrome die from other fatal disorders associated with this condition prior to the completion of the adenosomatous polyp-to-colon cancer sequence.

There is some debate about surgical and/or medical management of the cholestasis. A recent study suggests that performing surgeries like the Kasai procedure might be associated with inferior outcomes. Often, the hyperbilirubinemia resolves naturally as the liver develops during infancy. Medical management of chronic cholestasis includes ursodexocholic acid, which have been used with marginal success, cholestyramine, rifampin and naltrexone. However, the pruritus is often extreme and partial external biliary diversion is unavoidable.

Nutrition is also important when addressing patients with Alagille syndrome. With reduced bile flow into the intestine, there is poor digestion of dietary fat. Essential fats and triglycerides are necessary for proper development; hence infant formulas containing high levels of medium-chain triglycerides are usually substituted for conventional formulas. Because of the poor absorption of fat-soluble vitamins, these patients are often deficient and will need either large oral doses
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ConClusion
As further medical, nutritional and surgical advances are made, patients with Alagille Syndrome are living longer lives, and new pathology is being identified. Alagille syndrome is known for its nearly complete penetrance and variable phenotypic expression, allowing for multiple varying organ involvement within the same individual. Our current understanding of Alagille Syndrome with gastroenterology pathology is centered on the increased risk of these patients to develop cirrhosis and hepatocellular carcinoma, owing to malformation of ductal system during embryonic development and chronic cholestasis. This report further adds evidence to the possible association of the underlying condition that afflicts this population, a mutation in the JAG1/NOTCH receptor, with the development of colorectal cancer.

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References


