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ARPC1B Mutation Manifesting as Recurrent Hematemesis With Metaplasia

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Abstract: *ARPC1B* is important in the maintenance and assembly of the ARP2/3 complex. Loss of this complex due to *ARPC1B* mutation results in impairment of actin polymerization and subsequent defects in chemotaxis, cell migration, and DNA repair. Individuals with this rare mutation present in infancy and have abnormal innate and adaptive immune responses. They develop immune-mediated inflammatory disease with associated platelet defects, eosinophilia, rashes, and bowel disease. Recurrent gastrointestinal hemorrhage has been described in known cases. Here, we report a case with endoscopic and histologic findings in a patient with this rare mutation.

Keywords: ARPC1B, genetic mutation, metaplasia, gastrointestinal hemorrhage, immunodeficiency, congenital, hemorrhagic gastritis

INTRODUCTION

Mutations in the *ARPC1B* gene cause a syndrome of combined immunodeficiency, allergy, and autoimmunity. Clinical manifestations include skin findings, infections, food allergies, and gastrointestinal (GI) bleeding (1). The pathophysiology of the disease is due to a defect in actin polymerization. Variable endoscopic and histologic findings are reported in this disorder. We present a case of gastric metaplasia discovered in an infant who presented with failure to thrive and recurrent GI bleeding associated with *ARPC1B* mutation.

CASE REPORT

A full-term male Kenyan infant presented to our center at 4 months of age with persistent upper GI bleeding. He had hematochezia and a pustular rash beginning at 2 weeks of age and was diagnosed with milk protein allergy following flexible sigmoidoscopy demonstrating nodular hyperplasia. Parents were consanguineous, and family history revealed a deceased sibling who presented with similar symptoms. At 4 months of age, the patient began to develop recurrent hematemesis, persisting despite bowel rest and use of total parenteral nutrition. Upper endoscopy demonstrated severe hemorrhagic gastritis and was treated by argon plasma coagulation. Biopsies revealed squamous metaplasia of the gastric mucosa, with the proliferation of thin vessels and vascular prominence in the lamina propria. He was transferred to our center due to persistent hematemesis. He had no evidence of thrombocytopenia, anemia, or coagulopathy. His weight was below the first percentile, with Z score of –4.51.

Repeat upper endoscopy revealed diffusely hemorrhagic gastric mucosa, again treated with argon plasma coagulation. Histology showed severe chronic inflammation, granulation tissue, ulceration,

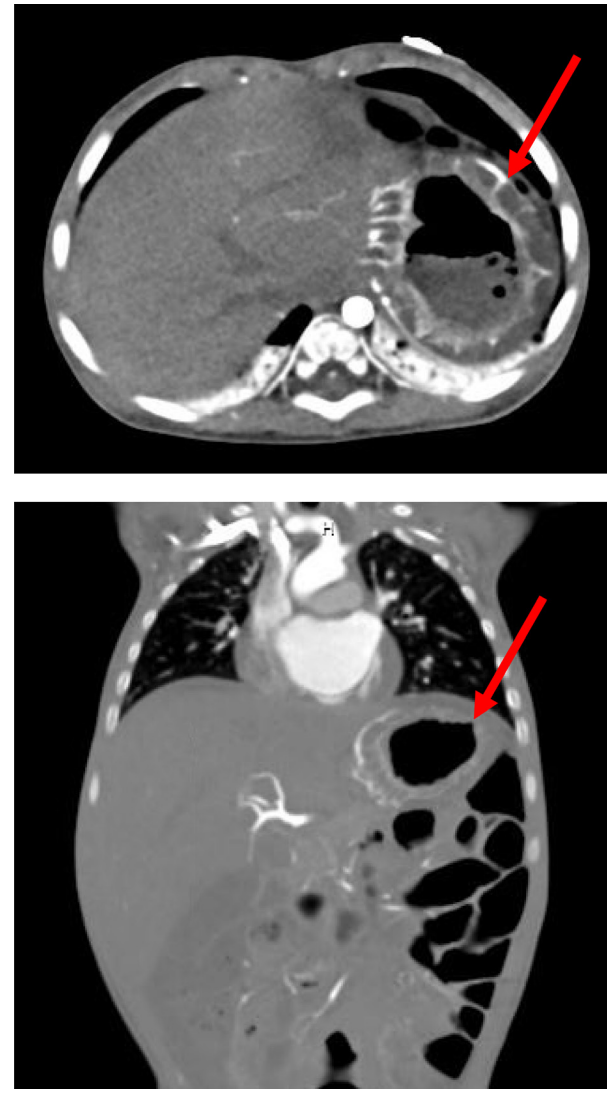

FIGURE 1. Sagittal and coronal views of Computed tomography abdomen with arrows marking diffuse gastric wall thickening.

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and intestinal epithelial metaplasia. Computed tomography scan of the abdomen demonstrated diffuse gastric wall thickening (Fig. 1). Computed tomography angiography showed enlargement of the gastric arteries with diffusely prominent gastric wall arterial branches and early venous drainage diffusely from the stomach with prominent vascular arcades of the serosal and mucosal surfaces. The diffuse gastric wall thickening, hyperemia, and prominent gastric arteries were determined to be compatible with gastritis and not a manifestation of a vascular lesion like angiodyplasia.

Attempts to introduce oral or nasogastric feeds resulted in hematemesis, requiring support with total parenteral nutrition. Repeat endoscopy 1 month later indicated visible improvement in gastric hemorrhage. Histology showed focal ulceration with acutely inflamed granulation tissue and fibroconnective tissue with chronic inflammation and squamous and intestinal metaplasia (Fig. 2). Evaluation for Wiskott-Aldrich syndrome, autoimmune polyendocrinopathy candidiasis ectodermal dystrophy, autoimmune lymphoproliferative syndrome, autoimmune enteropathy, and very early onset inflammatory bowel disease was negative. Given known consanguinity between parents and a similarly affected deceased sibling, genetic abnormalities were suspected. Whole exome sequencing revealed a pathogenic homozygous splice site mutation in the *ARPC1B* gene. Parents and a living sibling were tested and found to be healthy carriers of this *ARPC1B* mutation. The patient has not had recurrence of GI bleeding on postpyloric feeding with elemental formula and has demonstrated appropriate weight gain with improvement in weight to the 15th percentile with Z score of –1.37. An allogeneic stem cell transplant has been performed without complications and with good prognosis.

DISCUSSION

ARPC1B is an important protein for the maintenance and assembly of the Arp2/3 complex. Loss of the Arp2/3 complex results in impairment of actin polymerization and subsequent defects in chemotaxis, cell migration and proliferation, and DNA repair.

This has important hematologic and immunologic ramifications. Studies on T cells from *ARPC1B*-deficient patients demonstrate impaired the formation of the immune synapse between T cells and antigen-presenting cells and decreased expression of TCR and CD8, resulting in decreased signaling and proliferation with antigen stimulation (2). *ARPC1B* deficiency results in microthrombocytes and impaired platelet spreading (3). It has been described as having a similar phenotype to Wiskott-Aldrich Syndrome.

Patients with *ARPC1B* deficiency commonly present in infancy or early childhood with immune-mediated inflammatory disease, platelet defects, eczema and food allergies, cutaneous vasculitis, and GI bleeding (1,2).

Hemorrhagic gastritis is infrequently encountered in children, and reported cases have documented a variety of etiologies including viral infections, oncologic infiltrates, non-steroidal anti-inflammatory drug use and hypergastrinemia, and cow's milk protein allergy (4–6). In a study of 19 children with chronic renal failure who underwent endoscopy and measurement of serum gastrin levels, hemorrhagic gastritis was the most common abnormal endoscopic finding, seen in 31.5% (6). The mucosal changes in these patients were attributed to hypergastrinemia from chronic renal failure. Hemorrhagic gastritis secondary to cow's milk protein allergy, treated with milk protein exclusion, has been described (5); its pathophysiology is most similar to that of *ARPC1B* mutation in our patient. Treatment for hemorrhagic gastritis is variable and includes medical therapy with acid suppression and steroids and endoscopic therapies like bipolar cautery or argon plasma coagulation (4,5,7). Our patient was successfully treated with simultaneous nutritional and endoscopic therapy.

Volpi et al, in the largest case series of patients with *ARPC1B* deficiency, reported that infections and bleeding were the most common clinical manifestations, occurring in 100% and 79% of patients, respectively (1). They reported that of 14 patients, 7 had at least 1 episode of upper or lower GI bleeding. Five cases had GI biopsies with variable histologic abnormalities, including 2 patients with eosinophilic inflammation in the colon, 2 with nonspecific chronic

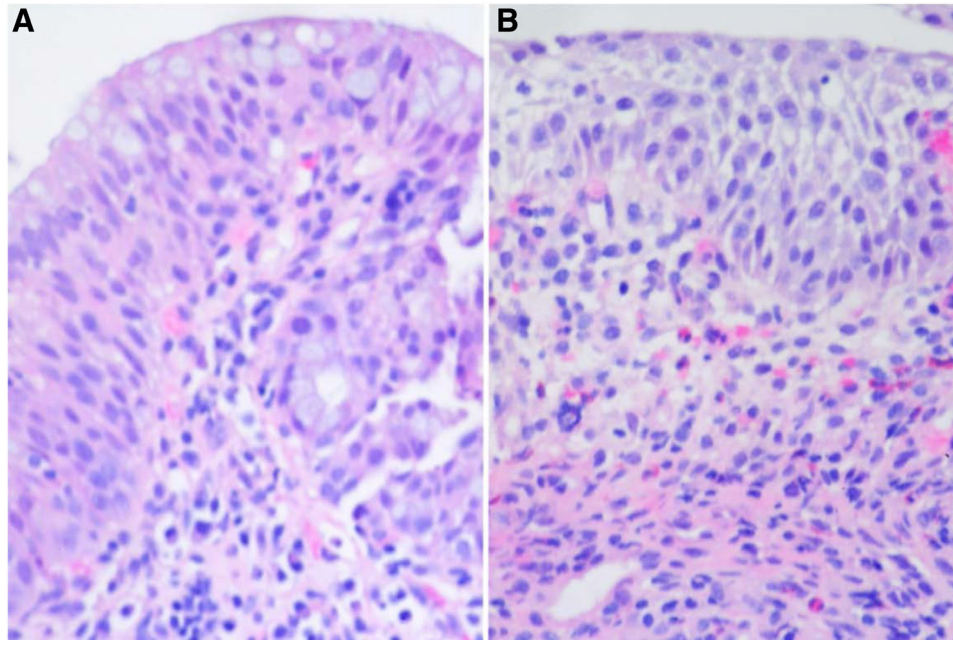

FIGURE 2. Histology showing metaplasia from the first gastric biopsy at our center. A) Intestinal (goblet cells) and transitional-type metaplasia in the surface epithelium. B) Squamous epithelial metaplasia in a different area of the same biopsy. Both images show prominent mixed inflammation in the lamina propria. Both images: H&E stain, original magnification = 200×.

inflammation in unspecified locations, and 1 with normal colonic biopsies (1). None had metaplasia.

The variability in reported histologic abnormalities suggests that GI bleeding in these patients is unlikely to be attributable to a single entity such as infection or allergic gastroenteritis. The histologic abnormalities seen in ARPC1B deficiency are likely the unfortunate combination of multiple risk factors including increased susceptibility to infections, dysfunctional hemostasis, and defects in cell trafficking. Our case is one of the first to describe gastric metaplasia associated with *ARPC1B* deficiency.

Metaplasia is an adaptive response of tissue to mucosal injury. Our patient had both intestinal and squamous metaplasia, which was likely the result of multiple factors including immune dysregulation and potentially repeat endoscopic management of bleeding. Gastric intestinal metaplasia is a well-described consequence of chronic gastritis often related to *Helicobacter pylori* infection or reactive gastropathy. While more common in adults, gastric intestinal metaplasia has been reported in the pediatric population. In contrast, gastric squamous metaplasia (GSM) rarely occurs, even in the adult population. Tolia et al reported a 13-year old with GSM who presented with pernicious anemia and ulcerative colitis (8). The remainder of GSM in the literature occurred in patients 39–90 years of age (9). These are the earliest reported pediatric cases of squamous metaplasia of the stomach. No clear guidelines have been published regarding the frequency of surveillance endoscopy for gastric metaplasia in pediatric patients, but the potential for dysplastic changes and malignant transformation exists. Given the high frequency of GI mucosal disease, this should be considered in the long-term management of patients with *ARPC1B* deficiency.

Our patient's clinical presentation with disease onset in infancy, rash, and recurrent GI hemorrhage is phenotypically consistent with that described in *ARPC1B* homozygous mutations. Given the rarity of this disorder, reported treatment is variable and ranges from steroids and immunosuppressive therapy to curative stem cell transplant. Although rare, immune-mediated inflammatory disease should be considered in the differential diagnosis of recurrent hemorrhagic gastritis without clear etiology. Long-term endoscopic follow-up is essential to evaluate the development of gastric metaplasia and its consequences.

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REFERENCES

1. Volpi S, Cicalese MP, Tuijnenburg P, et al. A combined immunodeficiency with severe infections, inflammation, and allergy caused by *ARPC1B* deficiency. *J Allergy Clin Immunol*. 2019;143:2296–2299.
2. Randzavola LO, Strege K, Juzans M, et al. Loss of *ARPC1B* impairs cytotoxic T lymphocyte maintenance and cytolytic activity. *J Clin Invest*. 2019;129:5600–5614.
3. Kahr WH, Pluthero FG, Elkadri A, et al. Loss of the Arp2/3 complex component *ARPC1B* causes platelet abnormalities and predisposes to inflammatory disease. *Nat Commun*. 2017;8:14816.
4. Friedlander J, Shehab S, Harrison M, et al. Severe erosive hemorrhagic gastritis in a pediatric patient. *J Pediatr Gastroenterol Nutr*. 2012;55:119.
5. Machado RS, Kawakami E, Goshima S, et al. [Hemorrhagic gastritis due to cow's milk allergy: report of two cases]. *J Pediatr (Rio J)*. 2003;79:363–368.
6. Urganci N, Ozcelik G, Kalyoncu D, et al. Serum gastrin levels and gastroduodenal lesions in children with chronic renal failure on continuous ambulatory peritoneal dialysis: a single-center experience. *Eur J Gastroenterol Hepatol*. 2012;24:924–928.
7. Zhang L, Xie XY, Wang Y, et al. Treatment of radiation-induced hemorrhagic gastritis with prednisolone: a case report. *World J Gastroenterol*. 2012;18:7402–7404.
8. Tolia V, Chang CH, Emami A. Juvenile onset pernicious anemia, partial intestinal villous atrophy, ulcerative colitis, and squamous metaplasia of the stomach. *Am J Gastroenterol*. 1986;81:803–807.
9. Oide T, Kan M, Masunaga A, et al. Histopathology of immature (ongoing) squamous metaplasia of the stomach. *Pathol Int*. 2018;68:318–320.