

**APOPTOTIC ENTEROPATHY IN A NEONATE WITH ALLERGIC
ENTEROCOLITIS**

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Abstract

Apoptosis is a histopathologic feature of a few distinct enteropathies including graft versus host disease and autoimmune enteropathy. We describe an unusual case of a neonate who presented on day 1 of life with rectal bleeding and was found to have severe ulceration on colonoscopy with prominent apoptosis on histopathology. The subsequent clinical course was consistent with allergic enterocolitis.

Apoptosis is a distinct feature of a few enteropathies, most prominently, graft-versus-host disease of the gut, and autoimmune enteropathy. It can also be seen in inflammatory bowel disease, and certain viral infections of the colon such as cytomegalovirus. Herein we describe an unusual case of a neonate with allergic gastroenteritis with severe ulceration of the rectosigmoid and prominent apoptosis who responded well to elemental formula.

A 2-month-old full term infant, born by vaginal delivery following normal pregnancy, presented on day 4 of life with hematochezia. His diet was limited to a commercial cow milk-based infant formula. He was noted to have bright red blood in his stool since day 1, initially attributed to bleeding from his circumcision wound but later noted to be rectal bleeding, accompanied by occasional non-bloody, non-bilious emesis. His weight was down 0.2kg from his birth weight of 3.24kg (6% weight loss). Family history was negative for food allergies, atopy or inflammatory bowel disease.

On exam, his weight was 3.08kg (z score: -1.2), length 50cm (z score: -0.2), weight-for-length 18 percentile (z score: -0.9). He was afebrile with normal vital signs. He had mild scleral icterus. His abdomen was soft, with normal bowel sounds and no hepatosplenomegaly. Anal inspection was normal, and rectal exam was notable for normal anal tone and a small amount of bloodstained stool that was guaiac positive. Lab studies yielded a normal CBC with white blood cell count of 15,000/ μ L, hematocrit 42/ μ L, and platelets 331,000/ μ L. Eosinophil count was initially elevated at 15% but subsequently normalized to 4% on the second day. Coagulation parameters, chemistries and liver enzymes were normal. Indirect bilirubin was 12.6 mg/dL, direct bilirubin 0.6 mg/dL, albumin 3.6 g/dL and total protein 5.4 g/dL. CRP was mildly elevated at 0.63 mg/dL. KUB showed a normal bowel gas pattern.

On presentation, he was switched to an amino-acid based formula for presumed milk protein allergy. Due to persistently bloody stools, and irritability, an ultrasound of the abdomen performed on day 7 of life was normal, with no evidence of intussusception. A flexible sigmoidoscopy done on day 9 revealed diffuse erythema and rectal mucosal ulcerations. Biopsy showed severely active colitis with prominent epithelial apoptosis in intact crypts (Figure 1A) with no increase in eosinophils, and immunostains for CMV, adenovirus and HSV were negative.

He continued to have bloody stools, with irritability and intermittent emesis. An UGI with small bowel series performed on day 10 showed markedly delayed gastric transit with a narrow and irregular antrum. The duodenojejunal junction was appropriately located. The entire small bowel was irregular, featureless and thickened. Given the findings on UGI, continued rectal bleeding and ill appearance, he was made NPO. An EGD and repeat flexible sigmoidoscopy were performed on day 11. The stomach and duodenum appeared severely erythematous with punctate ulceration. The rectosigmoid colon was erythematous with prominent ulcers (Figure 2). Histology was notable for marked increase in eosinophils in the lamina propria of the antrum and corpus of the stomach (Figure 3), and focal active colitis was noted in the sigmoid with fibropurulent material next to an ulcer (Figure 1B). Remarkably, no apoptotic bodies or eosinophils were found. Viral culture and CMV shell vial sent from tissue from colon and stomach were negative. An immunological work up revealed mildly low IgG at 577mg/dL (normal range: 700-1200mg/dL). Other immunoglobulin titers were normal. T and B cell subtypes were within normal range. Specific IgE to milk and soy were negative.

The amino-acid based formula was resumed following the endoscopy, day 12 of life, and he improved rapidly with complete resolution of blood in stool over the next few days. He was discharged on day 15, and, on follow up evaluation 2 weeks later, was noted to be tolerating the same infant formula, with good weight gain, and continued absence of blood, both grossly and microscopically, from the stool. He was still well on a dairy free diet at follow up at a year of age when dairy was reintroduced uneventfully.

DISCUSSION

This case is notable for the unusual presentation of presumed allergic enterocolitis with very early onset of rectal bleeding, severe ulceration of the rectosigmoid and prominent epithelial apoptosis on colonic biopsy. Allergic enterocolitis is a common entity in infants with an estimated prevalence of 0.16%¹. It is the most common cause of rectal bleeding in otherwise asymptomatic, healthy infants. While it typically presents at 2-8 weeks, rectal bleeding as early as even the first day of life has been described². Early presentation is presumed to be due to sensitization to cow milk protein in utero.

Erythema, increased friability, punctuate hemorrhages, and aphthous ulcers are the most common endoscopic features of allergic enterocolitis^{3,4}. Larger ulcers are uncommon and may represent severe mucosal injury. Histologically, the most common features are patchy infiltration by inflammatory cells, predominantly eosinophils, with normal mucosal architecture^{3,5}. Apoptosis has been rarely reported as a feature of this entity. Kumugai et al⁶, reported a case series of infants with presumed allergic proctocolitis; the endoscopic findings included mucosal congestion, erosion and aphthoid ulceration, but none of the infants had severe mucosal ulceration as was seen in our patient.

The differential diagnosis of apoptotic bodies in colon biopsies includes autoimmune enteropathy, graft versus host disease (GVHD), and inflammatory bowel disease (IBD)⁷. Apoptotic bodies can also be seen in viral infections of the colon, particularly CMV⁸. Colonic epithelial cells are recycled by apoptosis and phagocytosis. Hence it is thought that apoptotic bodies are a feature of increased epithelial cell turnover, such as in conditions of severe mucosal injury⁶. The clinical course of the infant described here is consistent with allergic enterocolitis.

Conclusion: This is an unusual case of presumed allergic enterocolitis in a newborn baby with a very early presentation, with severe ulceration on colonoscopy, and with prominent apoptosis on histology. Although apoptosis is more commonly described in autoimmune enteritis, GVHD, IBD and viral infections, it has been rarely described in allergic enterocolitis of infancy.

References:

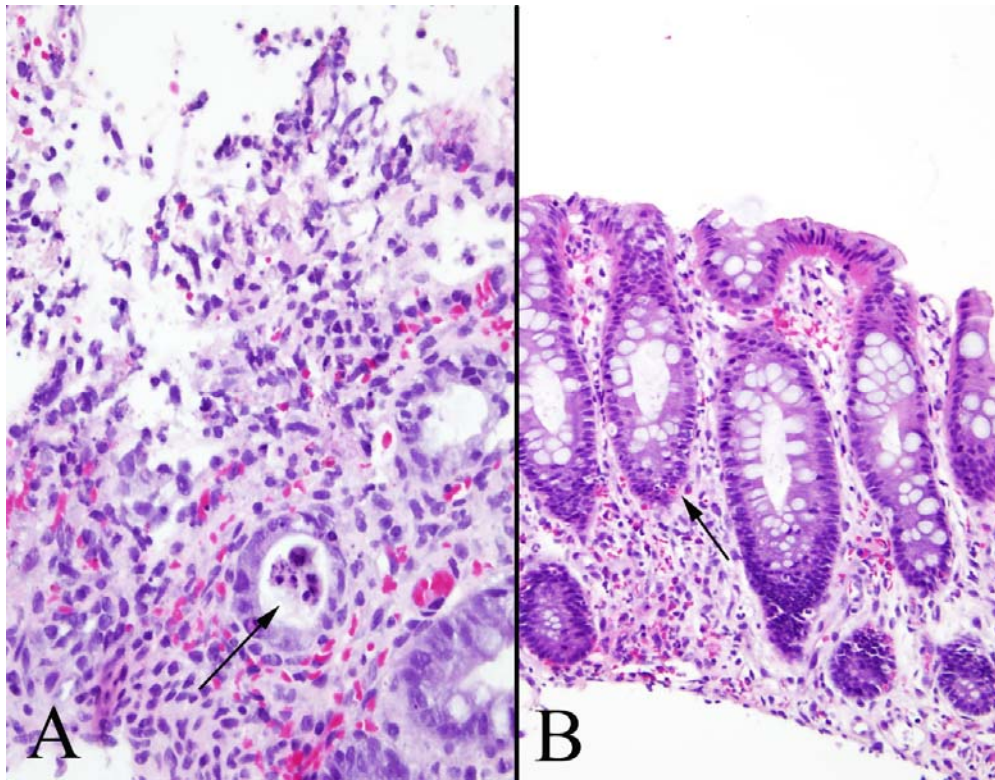
1. Elizur A, Cohen M, Goldberg MR, et al. Cow's milk associated rectal bleeding: a population based prospective study. *Pediatr Allergy Immunol* 2012;23:766-70.
2. Wilson NW, Self TW, Hamburger RN. Severe cow's milk induced colitis in an exclusively breast-fed neonate. Case report and clinical review of cow's milk allergy. *Clin Pediatr (Phila)* 1990;29:77-80.
3. Mori M, Ohtsuka Y, Ishida A, et al. Outcome of infants presenting rectal bleeding: A retrospective study in a single institution. *Pediatrics international : official journal of the Japan Pediatric Society* 2014.
4. Arvola T, Ruuska T, Keranen J, Hyoty H, Salminen S, Isolauri E. Rectal bleeding in infancy: clinical, allergological, and microbiological examination. *Pediatrics* 2006;117:e760-8.
5. Machida HM, Catto Smith AG, Gall DG, Trevenen C, Scott RB. Allergic colitis in infancy: clinical and pathologic aspects. *Journal of pediatric gastroenterology and nutrition* 1994;19:22-6.
6. Kumagai H, Masuda T, Maisawa S, Chida S. Apoptotic epithelial cells in biopsy specimens from infants with streaked rectal bleeding. *Journal of pediatric gastroenterology and nutrition* 2001;32:428-33.
7. Di Sabatino A, Ciccocioppo R, Luinetti O, et al. Increased enterocyte apoptosis in inflamed areas of Crohn's disease. *Diseases of the colon and rectum* 2003;46:1498-507.
8. Tzankov A, Stifter G, Tschorner I, Gastl G, Mikuz G. Detection of apoptoses in gastro-intestinal graft-versus-host disease and cytomegalovirus colitis by a commercially available antibody against caspase-3. *Pathology, research and practice* 2003;199:337-40.

Figure legends:

Figure 1: Panel A: Rectal biopsy with numerous apoptotic figures (arrow) and erosion. No increase in eosinophils. Panel B: Follow up rectal biopsy with mild acute inflammation (arrow) (H&E, 400x).

Figure 2. Endoscopic picture of sigmoid colon showing severe ulceration

Figure 3: Marked eosinophilic infiltrate in lamina propria of stomach biopsies. Mild neutrophilic gastritis is present; an immunostain for *Helicobacter* was negative (H&E 400x).





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