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Hereditary multiple intestinal atresias: 2 new cases and review of the literature

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Abstract Intestinal atresias are a common cause of newborn bowel obstruction (Dalla Vecchia LK, Grosfeld JL, West KW, et al, Intestinal atresia and stenosis: a 25-year experience with 277 cases. Arch Surg 1998; 133[5]:490-496). Hereditary multiple intestinal atresias, first reported by Guttman et al in 1973, is the rarest form of multiple atresias (Guttman FM, Braun P, Garance PH, et al, Multiple atresias and a new syndrome of hereditary multiple atresias involving the gastrointestinal tract from stomach to rectum. J Pediatr Surg 1973;8:633-640; Bass J, Pyloric atresia associated with multiple intestinal atresias and immune deficiency. J Pediatr Surg 2002;37:941-942.). It has been proposed to be autosomal recessive, to involve atresias in a variable combination of sites from stomach to rectum, and to be universally fatal (Bilodeau A, Prasil P, Cloutier R, et al, Hereditary multiple intestinal atresia: thirty years later. J Pediatr Surg 2004;39:726-730; Moreno LA, Gottrand F, Turck D, et al, Severe combined immunodeficiency syndrome associated with autosomal recessive familial multiple gastrointestinal atresias: study of a family. Am J Med Genet 1990;37:143-146). Patients have significant intestinal dysfunction and unrelenting sepsis stemming from a poorly defined, severe immunologic defect. Our case report presents 2 full siblings to nonconsanguineous parents with pyloric atresia, multiple small bowel and colonic atresias, and severe immune dysfunction. Care was withdrawn within 3 months of life on both siblings after multiple bouts of sepsis. Data suggest that the immune defect may not be primary, but in fact be secondary to intestinal dysfunction. Although the subjects in this article ultimately had fatal outcomes, a comprehensive immunologic/physiologic picture is presented in hopes of furthering the understanding of this grave disease.

1. Case reports

1.1. Patient 1

A male infant born at 37 2/7 weeks estimated gestational age to a 20-year-old Hispanic gravida 3 para 2 mother presented at 1 day of age with abdominal distension. Plain radiographs revealed a dilated stomach with no distal air and no calcifications. Simultaneous barium fluoroscopic evaluations (upper gastrointestinal [GI] series and barium enema) showed pyloric atresia and obstruction at the level of the sigmoid colon. With these findings, the patient underwent a laparotomy. Operative findings included microgastria with antral and pyloric atresia; atretic distal ileum, cecum, and right colon; a small but patent transverse colon; an atretic, string-like left colon; foreshortened mesentery; and a patent

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distal rectum. An end ileostomy, gastrojejunostomy, and resection of distal ileum, cecum, and right colon were performed. Pathology of the small and large bowel revealed focally thinned muscularis propria with the lumen being nearly occlusive at points and with other areas being filled with reactive dense fibrous material along with histiocytes and neutrophils. The Georgia state screen showed an elevated Immunoreactive trypsinogen level (normal cystic fibrosis transmembrane conductance regulator gene) and a below-normal acylcarnitine level. No other direct immunologic workup was performed. Postoperatively, this infant had profound GI dysfunction with dependence on total parenteral nutrition (TPN) and bouts of polybacterial and fungal septicemia. Care was withdrawn at 3 months of age because of uncontrolled sepsis.

1.2. Patient 2

A full female sibling of patient 1 was born at 2562 g and 36 weeks estimated gestational age after a pregnancy complicated by polyhydramnios. Fluoroscopic examination during a barium swallow demonstrated filling of the stomach; however, no contrast passed beyond. No calcifications were noted on plain abdominal radiographs. In the operating room, membranous pyloric atresia was confirmed with dilated, peristalsing small bowel. The fluid contained within the distended small bowel was very thin, milky, and yellow-brown, not the expected thick, tarry green meconium. An ileal web was found 8 cm proximal to the ileocecal valve. The distal end of the cecum was atretic. The entire colon had a "beads on a string" appearance, with small patent segments of a few millimeters in length interspersed with completely atretic segments (Fig. 1A, B). The patent segments contained thick white material, devoid of any bile staining. Retrograde examination revealed a patent distal colon, rectum, and anus. A pyloroplasty, subtotal colectomy, ileocectomy, and end ileostomy were performed. Initial pathology showed significant enterocolitis, submucosal fibrosis, and ulceration within the distal ileum and cecum. There was fibrous obliteration of the appendix and colonic stenosis with extensive necrotizing colitis, ulceration, and inspissated luminal contents throughout the entire colon. Ganglion cells were noted throughout all bowel specimens submitted.

The baby did poorly postoperatively. She was never fed because of high GI fluid and protein losses; ileostomy output was approximately 300 mL/(kg d) despite receiving flagyl and Coly-Mycin M per os and octreotide up to 2 μg/(kg h) intravenously. All state screening metabolic tests were within normal limits except for an elevated immunoreactive trypsinogen; no abnormalities were noted within the cystic fibrosis transmembrane conductance regulator gene. At 4 weeks, a small bowel follow-through showed a relatively featureless proximal small bowel with thickened folds distally and very little proximal peristaltic motion (Fig. 2). Immunologic evaluation showed an acute postoperative immunoglobulin (Ig) decrease, with baseline IgG of approximately 80 mg/dL and IgM consistently measuring less than 5 mg/dL. Despite attempts at reconstitution with Ig transfusions, the infant's levels would improve initially only to return to baseline within days. Lymphopenia was exhibited with decreased T lymphocytes (total CD3+ = 43%; reference range [rr] = 53%-84%), helper T cells (CD3+, CD4+ = 548; rr = 1600-4000 cells per microliter), suppressor T cells (CD3+, CD8+ = 79; rr = 560-1700 cells per microliter), and NK cells (CD3−, CD56+, CD16+ = 124; rr = 170-1100); B cell numbers were elevated (CD19+ = 45%; rr-6-32%). Despite persistent lymphopenia, cultured lymphocytes preserved T-cell function in response to pokeweed mitogen, *Candida*, and phytohemagglutinin, with little response to concanavalin. This pattern was not consistent with most known forms of autosomal recessive severe combined immunodeficiency (SCID).

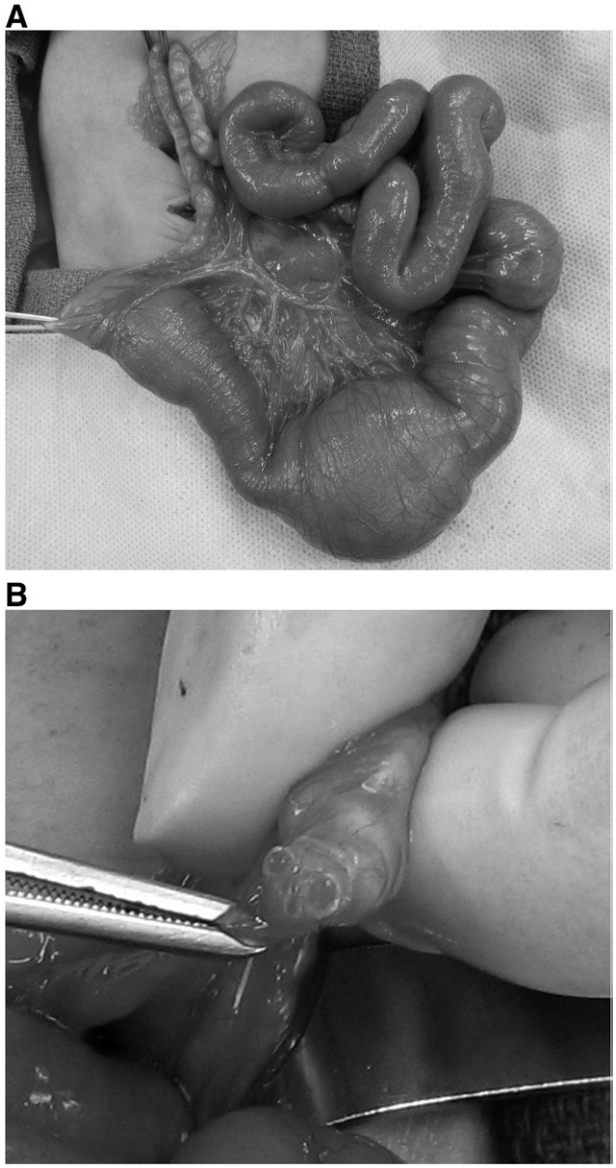

Fig. 1 A, Small bowel dilation and atresia with intact mesentery. Colon exhibiting "beads on a string" atresias throughout. B, Cut end of colon showing "sieve-like" lumen.

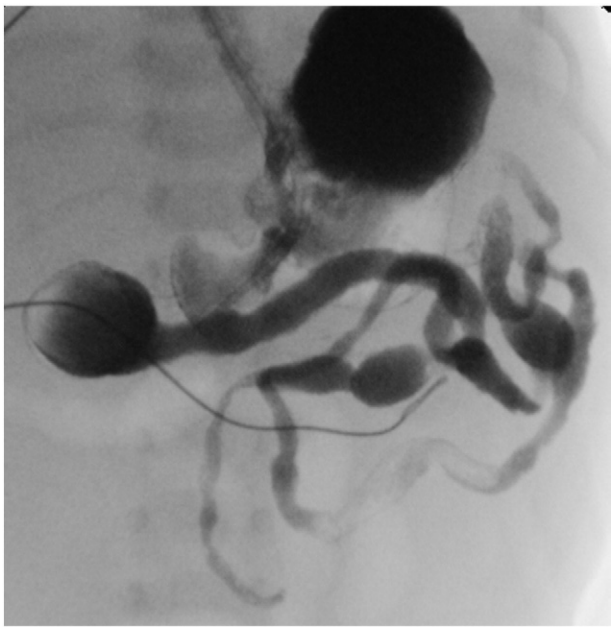

Fig. 2 Upper GI with small bowel follow-through at 4 weeks of age. Featureless bowel proximally with thickened folds distally. Poor peristaltic activity noted during this examination.

Persistent, unexplained inflammation in the GI tract led to continued high GI fluid output. α-1 antitrypsin from stool samples was elevated (1.00; rr = 0.00-0.62 mg/g). *Clostridium difficile* toxin was negative. Fecal calprotectin was also elevated at 391 (rr = 51-120 μg/g). Electron microscopy of endoscopic biopsies obtained at 7 weeks of age revealed degenerative changes in the epithelium and structural irregularities of the microvilli consistent with an ongoing, acute ulcerative process; and inflammatory changes were observed by light microscopy.

A genetics consult was obtained, but no further testing was suggested or performed. The first stages of liver dysfunction secondary to TPN were seen at 6 weeks of age with elevated total and direct bilirubin and still no oral feeds being tolerated. With the significant constellation of problems (bowel dysfunction, dependency on TPN, liver dysfunction, and immune dysfunction) and at an age precluding small bowel transplant was not yet an option, the family withdrew care; and the baby died at approximately 2 months of age.

3. Discussion

Hereditary multiple intestinal atresia (HMIA), from all reported cases, is a rare condition with a fatal outcome [1]. Autosomal recessive inheritance is probable, although the candidate gene has not been identified to date [2]. This family had 4 children in total. We have no details on 1 child. The first male born was treated for pyloric stenosis as an infant but has been otherwise healthy. Etiology is still a topic of debate, with early primary vascular accident, inflammatory processes, volvulus, and failure of recanalization all proposed possibilities [2-4]. None of these explanations adequately explains the multiplicity of atresias without mesenteric defects while adhering to what is currently known of fetal bowel development. Although some suggest that the histopathologic finding of variable stages of inflammation within a single specimen indicates that the inflammation is most likely secondary rather than a cause for obstruction, we believe that an inflammatory state is the foundation of the disease process [5]. Both presented patients, at the initial operation, evidenced the well-described "sieve-like" intestinal lumens suggesting an in utero inflammatory process [2,3]. Patient 2 had a persistent and significant acute inflammatory state evidenced by stool markers, routine histopathology, and electron microscopic evaluation throughout her life. Although both patients retained the majority of their small bowel, high output losses at all times precluded oral feedings. We suggest that, in patients with HMIA, such continued/uncontrolled inflammatory states may be the cause of feeding intolerance rather than "short gut syndrome" (from loss of length) [6-8]. We believe that this poorly functioning intestinal system is directly related to the observed immunodeficiencies as well.

Multiple cases document immunoglobulin defects and/or lymphocyte abnormalities; but in all but a few reports, no systematic approach has been undertaken to definitively diagnose the true immunologic defect. Moreno et al [9] postulated that the immunologic defect was SCID when graft-versus-host disease and delayed hypersensitivity skin tests were noted. However, other patients with HMIA have had normal T-cell numbers with decreased B-cell populations and also suffered from graft-versus-host disease [10]. Little immunologic investigations were performed in our first case; however, in-depth immunology workup ensued with the presentation of the sibling. Although lymphopenia (T cells) was present, the cells functioned in vitro, thus making SCID a less likely diagnosis.

Researchers have become aware of the complex interplay between a well-functioning immune system and a well-functioning GI system [11]. Regulatory T cells (Tregs) have been shown to help maintain intestinal homeostasis and are the targets for many inflammatory bowel disease therapies [11]. Animals that are deficient in Tregs develop an inflammatory bowel disease–like gut inflammation that can be reversed by adoptive transfer of Tregs [12]. Designated adhesion molecules and chemokines must also be present to recruit lymphocytes in the gut associated lymphoid tissue, lamina propria (small bowel), and intraepithelial compartment (colon); without them, cytokine release occurs and leads to Treg interactions that subsequently increase inflammatory states [13,14]. Although our second patient's present peripheral white blood cells functioned well in in vitro testing, tissue specificity may also play an important role. Reports have shown that although Tregs may function

normally to control inflammatory states in the skin, the same cells may be dysfunctional in the intestines [12]. We believe that the persistent inflammatory state results in an altered bowel microenvironment leading to the significant secretory diarrhea and an inability to feed, ultimately weakening the immune function and setting up an environment in which these babies are prone to sepsis.

Hereditary multiple intestinal atresia has been described for more 30 years, but the basic initiating insult remains unclear. It does not appear as though the immune dysfunction fits any recognized form of SCID (at least in our described patients). It does, however, appear plausible that an inflammatory state present in utero initially causes the multiplicity of atresias and continues after birth leading to significant GI losses that are unable to be modulated by current known therapies. Presumably, these large-volume on-going losses then lead to immune dysfunction (losses of lymphocytes) and liver dysfunction (secondary to use of hyperalimentation). Although the immunologic workup on our second patient was significantly more extensive than investigations on the older sibling, questions remained unanswered because of her early death; antienterocyte and anti-islet cell autoantibodies, etc, may have helped to define this disease process further.

A high index of suspicion for HMIA should be given to any vomiting newborn with multiple intestinal atresias that include the pylorus/antrum, small bowel, and colon. When future cases are encountered, early investigations should be made to define each patient's defects both immunologically and pathologically. Although this is currently a rare disease with a bleak outcome, each case can present us with an opportunity to learn more about the true pathophysiology. Further investigations are necessary to answer questions regarding feasibility of small bowel transplant or bone marrow transplant as plausible treatment options. Until then, palliative care for affected infants and genetic counseling for their parents should continue to be important components of care.

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