CASE REPORT

Case reports: necrotizing enterocolitis

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Abstract

Necrotizing enterocolitis (NEC) is the most common gastrointestinal emergency and cause of significant morbidity and mortality in preterm infants. The typical presentation is that of a preterm infant beyond first week of age on substantial enteral feeding who suddenly presents with gastrointestinal symptoms. The diagnosis of NEC is confirmed by abdominal x-ray findings. The precise mechanism for initiation of the inflammatory cascade in NEC is still unknown; two major risk factors are prematurity and advancing enteral feeds. Less commonly it can occur in term or preterm infants, without being fed, who have suffered a hypoxic ischemic injury to the intestine. In either case, there is intestinal wall inflammation with necrosis and sub-mucosal gas formation. The severity of inflammation and extent of bowel involvement is variable resulting in a spectrum from medically managed NEC to surgical NEC or profoundly unstable, metabolic acidosis and death. Early recognition, bowel rest, antimicrobial therapy, periodic radiological evaluation, supportive therapy of fluids, electrolytes and nutrition are the mainstays of management. We present 3 cases of NEC in preterm infants with varying degree of severity and different outcomes.

Key words

Pneumatosis intestinalis, Gastrointestinal inflammation, Preterm infants, Intestinal necrosis

1 Introduction

Despite many advances in the field of neonatology, necrotizing enterocolitis (NEC) continues to be a cause of significant morbidity and mortality. It is the most common gastrointestinal emergency in preterm infants and the incidence is inversely related to the gestational age at birth, highest in those whose birthweight is less than 1,500 g [1, 2]. Although NEC is more common in the preterm infant after initiation of feeds, it can also occur in the term infant or preterm infant who may or may not have had intestinal bacterial colonization [3, 4]. NEC has been broadly characterized as primary or secondary NEC. Primary NEC is the more common variety that occurs after the first week of life in a relatively stable preterm infant on enteral feeds, with no recognizable inciting event. Secondary NEC occurs in preterm or term infants who may or may not have been fed, usually having a recognizable trigger [5]. Once NEC sets in, both primary and secondary types behave similarly and may present with a constellation of gastrointestinal and systemic signs. Gastrointestinal signs include feeding intolerance with emesis, abdominal distention with tenderness, hematochezia and abdominal wall discoloration [5]. Nonspecific systemic signs may include metabolic acidosis, hematologic and metabolic abnormalities, temperature instability, lethargy, apnea/bradycardia, respiratory failure, and hemodynamic instability. Radiographic findings consistent with NEC are pneumatosis intestinalis, hepatic portal venous gas (see Figure 1) and free peritoneal air

in the in presence of progressive disease. Depending upon the severity and staging of disease, NEC is treated with medical therapy with or without surgical intervention. Medical therapy consists of bowel rest, gastric decompression, intravenous (IV) antimicrobial therapy, management of hematologic and metabolic abnormalities, serial abdominal exams and radiographic studies. The severity of disease and/or the presence of intestinal perforation as evidenced by free peritoneal air in the abdomen on radiographic evaluation (see Figure 2) or a positive paracentesis determine the necessity for surgical intervention [6]. Without these findings, there is little consensus on the optimal timing of surgical intervention as well as the type of intervention performed [7-9].

Since we can recognize predisposing events in secondary NEC, there are suggested recommendations for preventive strategies [10]. However, primary NEC still eludes the exact mechanism of pathophysiology. We describe three cases of NEC in previously stable premature infants on full enteral feeds with varying degree of severity of NEC. The first and second cases would qualify as primary NEC. The infant in the third case was similar to the first two cases of feeding associated NEC; however also received a blood transfusion within 24 hours of the onset of symptoms which some believe may be an additional cofounder in the development of NEC [11].

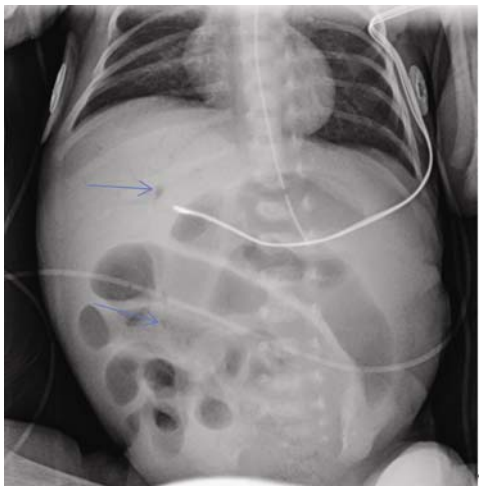

Figure 1. Dilated intestinal loops with portal venous gas and pneumatosis intestinalis (see arrows)

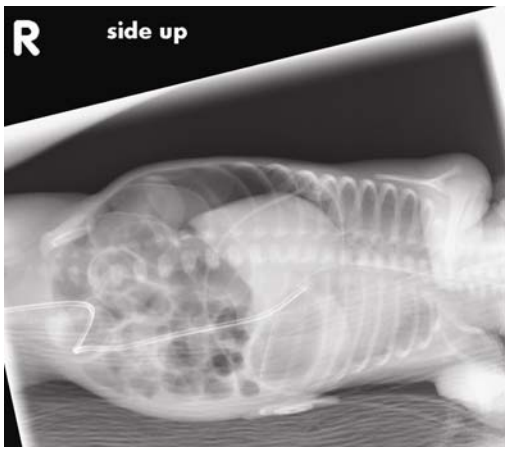

Figure 2. Free peritoneal air indicative of bowel perforation on left lateral decubitus view

2 Case presentation

2.1 Case 1

A preterm male infant born by cesarean section at 30 and 1/7 weeks' gestation weighing 850 grams for maternal HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome, preterm labor and severe intrauterine growth

restriction. Maternal antibiotics and betamethasone were administered prior to delivery. Apgar scores of 8 and 8 were assigned at 1 and 5 minutes of life. Only routine resuscitation was provided in the delivery room. He was started on caffeine and high flow nasal cannula (HFNC) for apnea of prematurity shortly after birth and successfully weaned off respiratory support by DOL 13; he never had an oxygen requirement. He was started on empiric antibiotics (IV ampicillin and gentamicin) which were discontinued after 48 hours and negative blood culture. Enteral feeds were initiated on day of life DOL 2 with breast milk; full enteral feeds were reached by DOL 11 with breast milk fortified to 24 calorie per ounce with human milk fortifier. On DOL 15 he had tachycardia and tachypnea, as well as a mildly elevated temperature to 37.8˚C. At that same time he had a foul smelling bloody stool and an abnormal abdominal exam; firm and tender on palpation. Enteral feeds were held, an oral gastric tube was used for gastric decompression, a blood culture, complete blood count (CBC) and basic metabolic profile were obtained; he was started on IV ampicillin and gentamicin. An abdominal film showed extensive hepatic portal venous gas and pneumatosis, consistent with a diagnosis of NEC. The pediatric surgical team was consulted. Lab results revealed a mild metabolic acidosis (base deficit of -6) and hyponatremia (130 mEq/L). He also had neutropenia, with an absolute neutrophil count (ANC) of 992 and increased bands (19%). Over the next few days he became thrombocytopenic (100,000) and had worsening neutropenia (ANC 360) with eosinophilia (12%) and monocytosis (24%). Metronidazole IV was added to his antibiotic regimen for 48 hours. Serial abdominal films showed pneumatosis intestinalis, bowel wall thickening and progression to left-sided pneumatosis. Blood culture remained negative. He completed a 10 day course of IV ampicillin and gentamicin with bowel rest. Total parenteral nutrition via a peripherally inserted central catheter (PICC) was administered until full feeds were resumed. He was managed medically with resolution of metabolic, electrolyte and hematologic abnormalities; no surgical intervention was necessary. He resumed enteral feeds and tolerated advancement to full enteral feeds; the caloric density was increased for suboptimal growth. He had no additional complications and was discharged at 36 weeks' postmenstrual age weighing 1,960 grams.

2.2 Case 2

A preterm male infant delivered by spontaneous vaginal delivery at 27 and 6/7 weeks' gestation weighing 1,020 grams, pregnancy was complicated by preterm labor, premature rupture of membranes and chorioamnionitis. Maternal antibiotics and betamethasone were given prior to delivery. Baby received positive pressure ventilation (PPV) by bag mask ventilation in the delivery room and APGAR scores assigned were 5 and 8 at 1 and 5 minutes of life. He was transported to the NICU on continuous positive pressure ventilation (CPAP) of 5cm of water on 0.3 FiO_2. He was started on empiric IV ampicillin and gentamicin which were discontinued after 48 hours and a negative blood culture. He was kept on CPAP of 5 cm of water but weaned down to 0.21 FiO_2 and subsequently to HFNC the following day. His symptoms were consistent with mild respiratory distress syndrome and he was weaned off respiratory support by DOL 14. Four days later, DOL 18, he was started back on HFNC 2 liters at 0.21 FiO_2 for apnea and desaturations. Enteral feeds were initiated on DOL 1 with breast milk; full feeds were reached on DOL 13 with breast milk or donor breast milk fortified with human milk fortifier at 24 calories per ounce. On DOL 18 he was increased to 27 calorie and switched to premature infant formula given a lack of maternal breast milk. For the next five days he exhibited intermittent feeding intolerance with emesis, aspirates or increased abdominal girth with repeated normal abdominal exams, stable vital signs and abdominal films showing nonspecific bowel gas pattern with distended loops but no pneumatosis intestinalis. On DOL 23 he had increasing apneic episodes and hyperglycemia; his abdominal girth increased by 3.0 centimeters and the abdomen appeared firm and tender. Abdominal film showed extensive pneumatosis intestinalis and portal venous gas. Enteral feeds were held, gastric decompression with continuous suctioning and a sepsis work up initiated. A complete blood count, metabolic profile, blood gas and blood culture and were drawn, which revealed neutropenia (ANC 1134), anemia (hematocrit 25.9%) and thrombocytopenia (45,000). He was started on IV ampicillin, gentamicin and morphine. He was intubated for respiratory failure and placed on mechanical ventilation; a post intubation blood gas showed a severe mixed metabolic and respiratory acidosis with a pH of 6.86. He was started on dopamine for hypotension. A pediatric surgery consult was called and an exploratory laparotomy was performed given his rapidly progressive clinical decline and concern for possible abdominal compartment syndrome. The surgical team noted pan-intestinal ischemia with areas of dusky tissues interspersed with areas of pallor. Given that there was pan-intestinal involvement with no areas of delineation, no resection was performed.

These findings were consistent with fulminant NEC or NEC totalis. The bowels were placed within the 6.0 centimeter sterile Silo which allowed for abdominal decompression. The infant rapidly deteriorated and support was withdrawn after futility of care was discussed with the parents, only eight hours after diagnosis.

2.3 Case 3

A preterm female born at 27 and 6/7 weeks' gestation weighing 940 grams was admitted to our NICU for prematurity, respiratory distress and concerns for sepsis. The pregnancy was complicated by preterm labor and premature prolonged rupture of membranes (greater than 48 hours). Maternal antibiotics and betamethasone were given prior to delivery. A cesarean section was performed secondary to non-reassuring fetal heart rate and cord prolapse. Apgar scores of 5 and 8 were assigned at 1 and 5 minutes of life and delivery room management included PPV via bag mask with 0.25 FiO_2. She was briefly placed on non-invasive mechanical ventilation (NIMV) and quickly transitioned to CPAP. She was started on empiric antibiotics for preterm labor and prolonged rupture of membranes, treated for 48 hours and discontinued after a negative blood culture. Enteral feeds were initiated on the DOL 1 and full enteral feeds were reached by DOL8. She was receiving premature 24 calorie formula; on DOL 12 this was increased to 27 calorie for suboptimal growth. On DOL 14 she was found to be anemic on routine laboratory testing with a hematocrit of 24.8% and she was given a packed red blood cell transfusion, later that day she was noted to be mildly hypothermic after being held by mom, her abdomen appeared mottled, abdominal girth had increased by 2.0 centimeters and appeared tender to palpation. She was inconsolable and had tachycardia to the 200's. An abdominal film was obtained which showed pneumatosis and extensive hepatic portal venous gas (see Figure 3). Enteral feeds were held with constant gastric decompression via oral gastric tube and she was started on intravenous fluids. Antimicrobial coverage was started with IV ampicillin and gentamicin after blood culture was obtained, serial abdominal exams performed and the pediatric surgical team was consulted. There was severe acidosis and hyperglycemia at initial presentation and she subsequently developed neutropenia (ANC 1320), bandemia (42%), thrombocytopenia (29,000) and hyponatremia (127 mEq/L). On serial abdominal x-rays pneumatosis persisted with interval resolution of hepatic portal venous gas without evidence of free peritoneal air. Eight hours after medical therapy was initiated, she was intubated for increasing apneic episodes and placed on morphine drip for pain. Hemodynamically she became progressively unstable requiring multiple normal saline boluses and dopamine for cardiovascular support. Approximately 24 hours after medical therapy was initiated she continued to decompensate, repeat abdominal films showed no evidence of free peritoneal air. The surgical team re-evaluated the infant and the decision was made to proceed with an exploratory laparotomy given her progressive decline, increasingly abnormal physical exam with progressive distention, tenderness and abdominal wall discoloration and hematologic abnormalities. Laparotomy was performed and intraoperative findings included malodorous and purulent fluid present in abdomen, patchy necrotizing enterocolitis affecting the distal small bowel and ascending colon to the hepatic flexure, visible pneumatosis intestinalis with gas bubbles under the serosa and a perforation in the distal ileum resulting in resection of 60 centimeters of necrotic small bowel, creating a jejunostomy and mucous fistula. The pathology gross description reported that the "serosal surface of all bowel segments was diffusely dusky brown, opened bowel segments revealed friable tan-brown luminal contents and a diffusely eroded mucosal surface with complete loss of the usual velvety surface and folding pattern". Microscopically there were scattered foci of pneumatosis intestinalis present in serosal and submucosal regions; necrotic mucosa admixed with bacteria and regions of transmural necrosis with focal areas of marked transmural inflammation. Peritoneal fluid culture was positive for Enterobacter cloacae and Prevotella bivia, peripheral blood culture was negative. Her antimicrobial therapy was changed to meropenem based on Enterobacter cloacae susceptibilities to complete an additional ten days of IV antibiotics for peritonitis. On post-operative day (POD) 6 the jejunostomy and mucous fistula appeared necrotic and she was taken back to the operating room for further evaluation. Intraoperative findings included frank necrosis of bowel with a leaking perforation, the necrosis spanned the terminal ileum, cecum, ascending colon and a portion of the proximal transverse colon; a hemicolectomy was performed. The jejunostomy and about ten centimeters of small bowel were also necrotic and removed. A primary jejunocolic and jejunojejunal anastomosis was performed. She remained NPO for two weeks at the onset of NEC and received total parenteral nutrition (TPN) via a PICC line. Repeated attempts to feed her when medically stable with small continuous and or bolus enteral feeds were unsuccessful. She remained intubated for eleven days and on a morphine drip for pain for approximately two weeks. Initially she required

vasopressor support with dopamine until she was started on hydrocortisone for adrenal insufficiency which was eventually weaned on DOL 43. Upon completion of antimicrobial therapy and weaning off dopamine, enteral feeds were resumed on DOL 30 with donor human milk. By DOL 60 she continued to have feeding intolerance and had only made small advances in enteral feeds; she had frequent loose stools and suboptimal growth from short bowel syndrome. On DOL 77 she had an upper gastrointestinal study that showed significant gastroesophageal reflux, dysmotility and dilated bowel. A short course of IV metronidazole was started for bacterial overgrowth; the feeds were changed to a hypoallergenic formula. She continued to have persistent feeding intolerance. On DOL 85 a barium enema showed a midsigmoid stricture; on DOL 87 she went to the OR for further bowel resection, lysis of adhesions and had a gastrostomy tube (GT) placed. She had an elevated direct hyperbilirubinemia consistent with cholestasis related to prolonged use of TPN. She was discharged home on DOL 124 at 44 weeks' postmenstrual age weighing 3,230 grams on partial oral and GT feeds and home TPN.

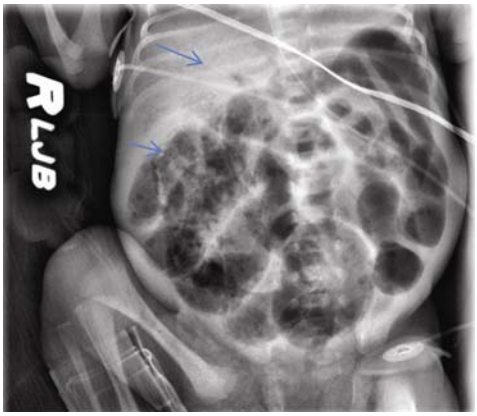

Figure 3. Disseminated pneumatosis intestinalis and diffuse portal venous hydrogen

3 Discussion

We have presented three cases of NEC to illustrate the range of varying intensity of NEC requiring medical and/or surgical intervention. The first case was managed without surgical intervention and resulted in a favorable outcome would be classified as medical NEC. The third case required multiple surgical interventions and prolonged hospital stay due to short-bowel syndrome and poor growth resulting in discharge to home on partial enteral and parenteral nutrition. This case depicts the complications associated with survivors of NEC which can continue even after discharge from NICU. The second case shows how rapidly some of the infants with severe extensive NEC can deteriorate in the initial presentation and that even surgical intervention cannot salvage them. All three infants were on full enteral feeds and relatively stable from a cardiovascular and respiratory standpoint with minimal or no support. These cases demonstrate that NEC continues to be a significant cause of morbidity and mortality in survivors in neonatal intensive care units.

The etiology and pathophysiology of primary NEC remains to be fully elucidated but it is likely multifactorial leading to intestinal mucosal injury [10, 12]. The immaturity of the preterm intestinal mucosa includes decreased immune function, impaired motility, carbohydrate malabsorption and abnormal bacterial colonization [5, 13]. Subsequent bacterial fermentation of undigested carbohydrates leads to the production of gases and short chain fatty acids (SCFA); specifically acetic, butyric, formic, isobutyric, lactic and propionic acid [5]. In animal studies acetic and butyric acids have been shown to induce intestinal mucosal injury similar to NEC pathology in preterm infants [14, 15]. Several groups have investigated the role of cytokines in the development, progression and severity of NEC [16-18]. Others have found that there is an alteration of intestinal bacterial colonization and lack of bacterial diversity in infants with NEC leading to a loss or suppression of healthy bacterial flora [19-21]. There is suggestion that the development of feeding associated or primary NEC may be an inflammatory process related to the presence of undigested carbohydrates in the distal ileum/proximal colon, which is acted upon by the abnormal bacterial flora producing short chain fatty acids at a faster rate than the premature intestine and liver can handle. This results in accumulation of organic acids which may be responsible for initiating injury to the preterm intestinal mucosa, compromising the mucosal barrier, translocation of bacteria and systemic acidosis. These ultimately

lead to an inflammatory response, sub-mucosal gas production, transmural necrosis, perforation and a systemic cytokine surge which is often seen in the initial stages of NEC. Hydrogen gas production by bacteria leads to the radiographic findings of pneumatosis intestinalis and hepatic portal venous gas. A pro-inflammatory response at the site of mucosal injury further propagates intestinal damage and systemic illness [5].

There have been several recommendations for preventative strategies based on the proposed mechanisms of NEC. There have been in vitro and animal studies as well as human clinical trials investigating the benefits of probiotics [22-24]; however larger trials are necessary prior to recommending routine use in preterm infants [12, 25, 26]. There are recommendations for early initiation of enteral feeds and advancement of enteral feeds in accordance with evidence based feeding protocols [10, 12], promoting adequate intestinal motility and prevention of carbohydrate malabsorption. The use of human milk is preferred over the use of formula [10, 27]; allowing for passage of maternal immunoglobulins to the infant and promotion of healthy intestinal flora. There is support for the judicious use of antimicrobial therapy [10] to minimize unnecessary exposure, risk of necrotizing enterocolitis, increased bacterial antibiotic resistance [28] and potential alteration of intestinal flora with selection for alternative bacterial strains including fast fermenters [29]. Both primary and secondary NEC continue to be a significant cause of mortality and morbidity in NICU survivors; avoidance of predisposing factors, early recognition, aggressive treatment and further investigations into potential therapies and preventative measures are needed.

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