

CASE REPORT

Necrotizing enterocolitis in the setting of milk allergy after pediatric living donor liver transplantation

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Abstract

NEC is an idiopathic intestinal mucosal injury that may progress to transmural bowel necrosis without mesenteric ischemia. NEC usually affects 7- to 10-day-old neonates following enteral feeding. A 10-month-old girl with no history of laparotomy underwent LDLT for acute liver failure. After starting enteral feeding on postoperative day 5, she developed abdominal distention. Diffuse PVG and PI were detected by radiologic modalities. Exploratory laparotomy revealed patchy necrosis of the intestine without perforation. The microscopic findings of a resected specimen revealed transmural coagulative necrosis with multiple small thromboses compatible with neonatal NEC features, and eosinophil infiltration was also observed. Subsequently, after the resumption of enteral feeding with cow's milk, she developed severe diarrhea, the symptoms of which were eliminated after the administration of cow's milk was stopped. These clinical and pathological findings support the speculation that NEC might have been induced by a CMA. Food allergies, which can be induced by immunosuppressive agents, should be considered as a potential cause of NEC in the setting of pediatric liver transplantation.

KEYWORDS

food allergy, necrotizing enterocolitis, pneumatosis intestinalis, portal venous gas

1 | INTRODUCTION

NEC is an idiopathic intestinal mucosal injury that may progress to transmural bowel necrosis without mesenteric ischemia. NEC primarily occurs in low-birth-weight neonates at 7–10 days old.¹ NEC typically develops as abdominal distention shortly after starting enteral feeding formula. The overall incidence of NEC is 3.7% in neonates.² PVG or PI is seen in 33% of the affected neonates. Consequently, 20%–40% of NEC infants require surgical intervention.³

The development of a food allergy is an increasingly recognized morbidity after solid organ transplant, ranging from mild and localized symptoms to anaphylaxis or death.⁴ Food allergies are most commonly observed after LT, with reported frequencies ranging from 5.6%–38%.^{5,6} Of note, the prevalence of food allergies is 6%–8% at 1 year of age with a subsequent decline in the general population,⁷ and CMA is the most common form of food allergy in young children, affecting approximately 2% of children under 4 years of age.⁸ We herein present a case of intestinal necrosis, possibly induced by CMA, after pediatric LDLT.

Abbreviations: CHDF, continuous hemodiafiltration; CMA, cow's milk allergy; CT, computed tomography; D-US, Doppler ultrasonography; FPIES, food protein-induced enterocolitis syndrome; LDLT, living donor liver transplantation; LT, liver transplantation. NEC, necrotizing enterocolitis; PI, pneumatosis intestinalis; POD, postoperative day; PVG, portal venous gas; RAST, radioallergen sorbent test.

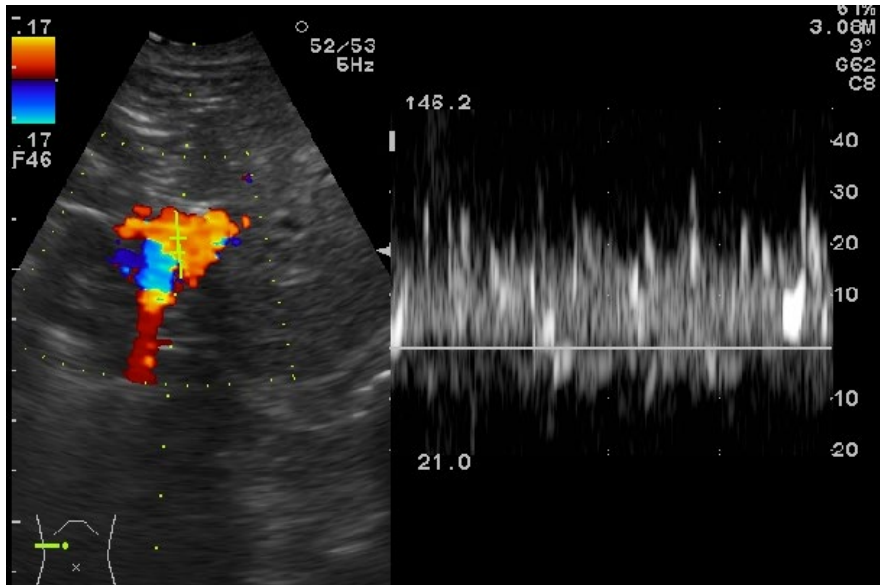


FIGURE 1 D-US showing high echoic particles flowing through the portal vein



FIGURE 2 Contrast-enhanced CT showing PVG and PI. The affected lesions appear to be related to the location of the enteral feeding tube

2 | CASE PRESENTATION

A 10-month-old girl with no remarkable medical history had developed acute liver failure. She received 4-day intensive medical treatment including plasmapheresis for coagulopathy, and CHDF for encephalopathy. In the end, she underwent LDLT by receiving a left lateral segment graft from her ABO-identical mother.

The etiology of acute liver failure could not be determined, despite a thorough examination. LDLT was performed in the standard manner using Roux-en-Y hepatico-jejunostomy for biliary reconstruction. Tacrolimus administration was initiated on the first POD with low-dose steroids, the standard regimen of our pediatric LT program, as has been described elsewhere.⁹

Her postoperative course was uneventful and did not need any vaso-pressors or hemodialysis. She started to receive enteral feeding formula

on POD 5 with a glutamate containing beverage. Milk was administered from POD 6. The next morning, she developed abdominal distention, and her general condition deteriorated within a few hours into shock. Suction fluid from the enteral feeding tube showed milk with a small amount of fresh blood. D-US showed hyperechoic spots flowing in the portal vein and high echoic particles scattered in the liver parenchyma (Figure 1). Contrast-enhanced CT showed PVG and PI; however, it did not show any exact evidence of intestinal necrosis or perforation (Figure 2).

We started medical treatment with a diagnosis of enteritis using wide-spectrum antibiotics, endotoxin absorption therapy with polymyxin B-immobilized fiber column direct hemoperfusion (Toray Medical Co., Tokyo, Japan), and CHDF while we waited for the opportunity to perform surgical intervention. Blood culture and drained ascites did not reveal any signs of bacterial infection. Tacrolimus trough level was 9.2 ng/mL at the onset. We stopped tacrolimus administration and converted the immunosuppressant to cyclosporine A. Repeated CT on POD 13 showed ischemic changes of the affected intestine, and laparotomy was indicated. On exploratory laparotomy, segmental necrotic lesions of intestine, located adjacent to the ligament of Treitz extending 10 cm to the anal side of the jejunio-jejunostomy, were resected (Figure 3). These necrotic lesions appeared to be related to the location of the enteral feeding tube, and mechanical obstruction, especially strangulated ileus, was not proven as a cause of the necrosis.

A month later, enteral feeding of cow's milk was resumed, and she immediately suffered from frequent diarrhea; nevertheless, she took both milk and solids before occurrence of acute liver failure.

A stool examination revealed sheets of eosinophils, and a milk allergy was suspected, although she had not had an allergy to cow's milk before LDLT. RAST for cow's milk, soy, and rice was negative at this point. After the content of enteral feeding was changed to the elemental formula (free of milk protein), her gastrointestinal discomfort was eliminated during 6 months of follow-up after LDLT. She is now doing well with a good graft function.

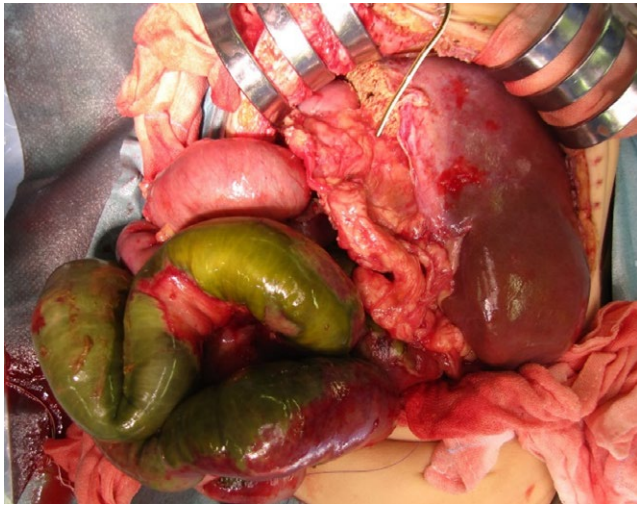


FIGURE 3 Patchy necrosis was observed as discolored intestine

A pathological examination revealed that the opposite side of the mesentery was dominantly affected (Figure 4A). The microscopically viable part of the intestine showed neutrophil infiltration with submucosal edema and hemorrhaging (Figure 4B). Eosinophil infiltration was also observed on the viable parts (Figure 4C). On the necrotic parts, mucosal defects and ischemic changes with multiple fibrin thromboses were observed as coagulative necrosis (Figure 4D).

3 | DISCUSSION

NEC primarily occurs in preterm infants weighing less than 1500 g at birth. Affected infants experience abdominal distention and bloody stool after starting formula feeding, usually at 7–10 days after birth.¹ A randomized controlled trial showed that breast milk feeding decreased the NEC frequency in preterm neonates.¹⁰ Therefore, formula feeding

is suspected as an influential pathogenic factor as well as other potentially contributing factors, such as bowel prematurity and changes in the intestinal bacterial flora.

The present case is not a classic NEC, which occurs in preterm infants, but the clinical symptoms such as feeding intolerance, abdominal distention, pneumatosis, and necrosis of intestine were compatible with Bell's stage 3.¹ Hence, we referred to pediatric LT as unknown conditions to develop NEC in infant. The mechanism of intestinal injury by formula milk remains unclear.¹¹ However, a potential cause of NEC in the present case is CMA, which presents as a wide range of clinical symptoms due to immunological responses to cow's milk proteins.¹² Our patient presented with necrotizing enteritis immediately after starting to consume cow's milk through an enteral feeding tube, and its resumption induced severe diarrhea, which was eliminated by changing the formula. Furthermore, eosinophil infiltration in the viable intestine was observed on the resected specimens. Those clinical and pathological findings support the hypothesis that NEC was induced by CMA. Although the cause of NEC is likely multifactorial, as a consequence of the synergy of potential risk factors, the direct contribution of cow's milk protein in the pathogenesis of NEC was reported in a previous study.¹³

Potential mechanisms for the development of food allergies after solid organ transplantation have been proposed, as follows: (I) the passive transfer of donor allergen-specific immunoglobulin (Ig) E, (II) the transfer of donor allergen-specific B or T cells, (III) immunosuppressive agent-related immune responses, and (IV) the immature gastrointestinal tract and immature immune system of children.⁴ Immunosuppressive agents, such as tacrolimus, prevent rejection by blocking interleukin-2, part of the Th1 cell response; however, in the process of suppressing Th1 cell response, they also prevent the negative feedback mechanism by which the Th1 response inhibits the Th2 response. Thus, the immune system shifts to a Th2 response, which predisposes the patient to allergic disease.¹⁴ Tacrolimus has been implicated particularly strongly in the development of allergies after

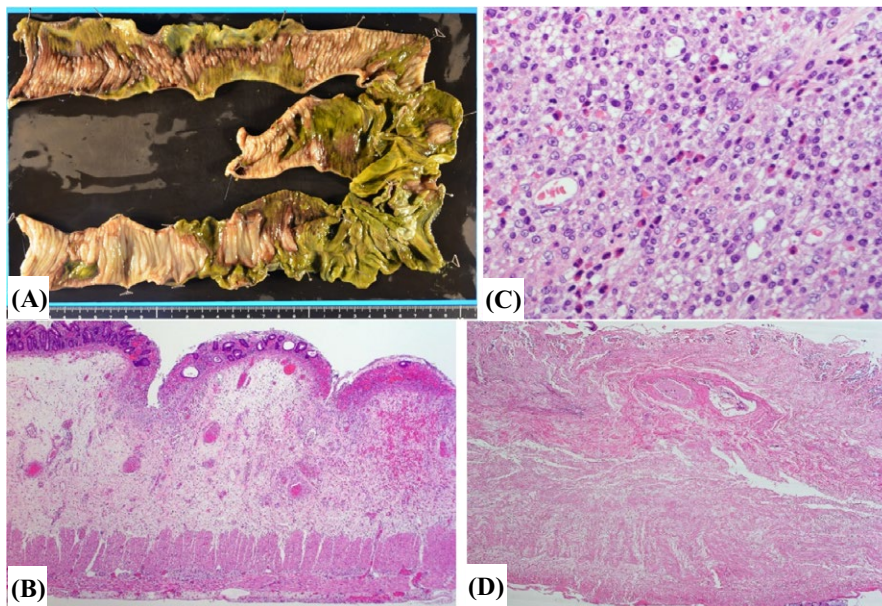


FIGURE 4 The opposite side of the mesentery was dominantly affected by NEC (A). Neutrophil infiltration with submucosal edema and hemorrhaging (B) and eosinophil infiltration (C) were observed on the viable parts. Coagulative necrosis with multiple fibrin thromboses was observed on the necrotic parts (D)

organ transplantation, and switching from tacrolimus to cyclosporine appears to be effective in relieving symptoms.¹⁵ Immediately after LT, various surgical insults may influence the intestinal permeability, thus exposing the body to more allergens, in addition to the immaturity of the gastrointestinal tract in children. Those factors are also considered to have caused the allergic reactions in the present case. On the other hand, food protein-induced intestinal hypersensitivity in infants, called FPIES does not need IgE stimulation.¹⁶ When FPIES is considered as a cause of vomiting or diarrhea, the definitive diagnosis needs to confirm the symptom improvement by avoidance of possible causal food and the provocation of symptoms by oral food challenge. Although tacrolimus administration might have played a certain role to provoke enteral hypersensitivity, we also speculate that symptom reproducibility by readministration of milk and RAST showing negative result for milk proteins were consistent with FPIES as a possible diagnosis of the present case. We only referred to milk proteins as causative agents for intestinal hypersensitivity and left room for interpretation of the immunological mechanisms for allergic reaction to milk proteins.

The pathognomonic imaging findings of NEC are PVG and PI, which are generally associated with varying degrees of bowel injury. In mild cases, children's conditions improve significantly with several days of bowel rest.¹ In severe cases, however, despite medical treatment, dilated bowel loops persist, and the clinical condition deteriorates. Surgical intervention is indicated in 20%-40% of affected infants.³ The indications for surgical intervention include clinical deterioration or radiographic findings consistent with bowel perforation or necrosis. CT is usually essential for diagnosing intestinal necrosis. In the present case, no necrotic signs were noted in the intestine at the onset of PVG, instead appearing only after the disappearance of pneumatosis on a follow-up CT scan. This suggests that intestinal necrosis might have been a consequence of circumferential transmural pneumatosis. The pathological findings of the necrosis occurring at the opposite side of the mesentery support this speculation. The extent of PI might therefore be related to the severity of intestinal ischemia.

The detection of PVG at the onset of symptom aids in the early diagnosis of NEC, but the presence of PVG itself might not be associated with the clinical severity.² PVG following LT has been reported as a common (frequency of 18%) and clinically insignificant sign in the early postoperative period.^{17,18} There have been reports that PVG can be caused by several clinically significant diseases, such as enteritis, graft failure, ileus, and post-transplantation lymphoproliferative disorder.^{17,19,20} At our institute, we experienced 12 PVG cases of 414 pediatric LT cases (2.9%). One was associated with intestinal anastomotic leakage and underwent surgical intervention. One had PVG on POD 3 before starting enteral feeding and did not require any therapeutic changes. The remaining 10 cases had PVG after enteral feeding, including the present case. They all recovered with several days' bowel rest, except for the present case.

In conclusion, NEC can occur after pediatric LT, even in infants. Food allergies, which can be induced by immunosuppressive agents, should be considered as a potential cause of NEC following pediatric

LT. PVG has not been seriously reported after LT. However, our experience suggests that the appearance of PVG is an alarming finding indicating serious gastrointestinal complications.

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