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Aggressive gastrointestinal food allergy in neonates and its possible relationship to necrotizing enterocolitis

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ABSTRACT

INTRODUCTION: The incidence of gastrointestinal food allergy (FA) in neonates is increasing. Despite this, cases of patients with gastrointestinal FA who develop necrotizing enterocolitis (NEC) requiring laparotomy are extremely rare.

PRESENTATION OF CASE: We describe two cases that presented with bloody stool with a probable diagnosis of FA as eosinophils were positive in the stool at onset. Both cases failed conservative treatment. Jejunostomy and ileostomy were performed in both cases due to secondary NEC with underlying acute FA. Post-surgery, raised peripheral blood eosinophil count, presence of cow's milk-specific IgE antibody and positive allergen-specific lymphocyte stimulation test were found. Stoma closure were performed 3 and 1 months later in both cases. Postoperative recovery was uneventful.

DISCUSSION: A few reports have not identified risk factors for NEC secondary to FA. Thrombocytopenia and rise in C-reactive protein (CRP) levels 2 days after the development of FA may be suggestive of FA with NEC. Methicillin-resistant *Staphylococcus aureus* (MRSA) was detected in the fecal culture of both patients at the time of the onset of NEC. The toxic antigen produced by MRSA may cause activation of milk-protein-primed T cells and exacerbate FA.

CONCLUSION: The decrease of platelet levels and rise in CRP may indicate the development of secondary NEC in patients with FA. Additionally, MRSA detected in the fecal culture also may be a risk factor for NEC through the activation of cellular immunity reaction pathways.

1. Introduction

Gastrointestinal food allergy (FA) in children tends to occur in the first 1–6 months of their life [1–3]. The incidence of FA in neonates is increasing; although, it is still a relatively rare condition. Progressive FA in the neonatal period may need to be clinically differentiated, especially in those with mechanical bowel obstruction [2]. Reports of FA in neonates who subsequently develop necrotizing enterocolitis (NEC) is extremely rare [1,3–5]. Furthermore, common risk factors for the development of NEC secondary to FA are unknown. Targeted treatment for FA in patients cannot be started until a definite diagnosis is made, with repeated detailed clinical inspection and conservative treatment being a reasonable initial strategy. However, a decision should be made for laparotomy if a patient develops NEC. Therefore, a combination of both conditions presents difficult clinical problem. We report 2 neonates with FA who required laparotomy due to secondary NEC. We reviewed previous reports (in English) on patients with this condition. Here, we attempt to determine risk factors for the development of NEC in patients diagnosed with FA based on the clinical features of our 2 patients. Our report is in accordance with the SCARE criteria [6].

2. Presentation of case

2.1. Case 1

A preterm boy born at 28th week of gestation with a birth weight of 1133 g suddenly presented with abdominal distension and bloody stool on day 25 at the neonatal intensive care unit (NICU) while being fed on both breast milk and infant formula. The development of FA was suspected as stool examination was positive for eosinophilic inflitration. However, abdominal X-ray imaging showed pneumatosis intestinalis soon after the development of FA. Abdominal distention worsened progressively and another abdominal X-ray image showed diffusely dilated intestine (Fig. 1a) within a couple of hours after the initial X-ray. An emergent laparotomy was performed based on the diagnosis of NEC. During surgery, the colon was noted to be discolored, dark red and spotty, with the presence of pneumatosis intestinalis,

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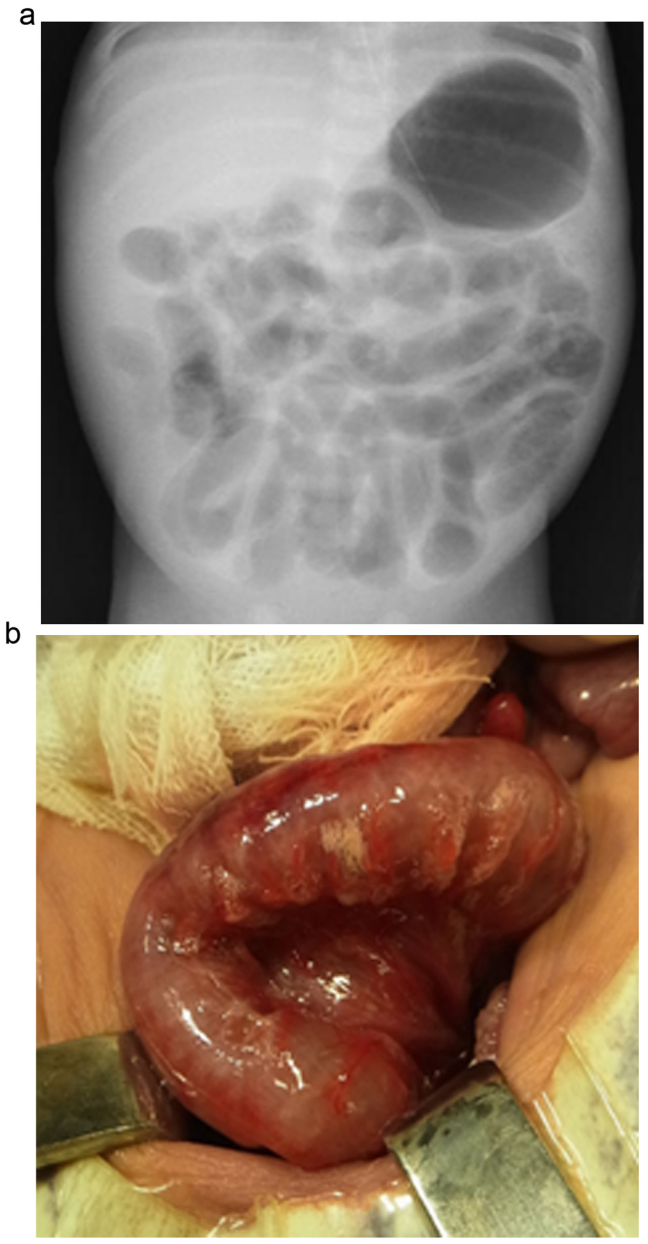

Fig. 1. (a) The abdominal X-ray shows pneumatosis intestinalis and diffusely dilated intestine. (b) Pneumatosis intestinalis is seen in the transverse colon at laparotomy.

a characteristic feature of NEC (Fig. 1b). Thankfully, no intestinal perforation was found. Ileostomy was performed. After 2 days from the onset of FA, C-reactive protein (CRP) levels were noted to have risen from 0.57 mg/dL to 12.22 mg/dL, and the platelet count dropped from $35 \times 10^4/\mu L$ to $15 \times 10^4/\mu L$. Post-operatively, peripheral blood eosinophil count reached 22%, from 4% preoperativelyand cow's milk-specific IgE antibody and allergen-specific lymphocyte stimulation test (ALST) to lactoferrin were positive. This supports the diagnosis of FA complicated by NEC. In addition, methicillin-resistant *Staphylococcus aureus* (MRSA) was detected in the fecal culture at the time of the onset. The patient recovered without MRSA sensitive antibiotics. Ileostomy closure was performed 3 months later with concurrent sigmoidectomy and descending colectomy due to severe stenosis. Postoperative recovery was uneventful.

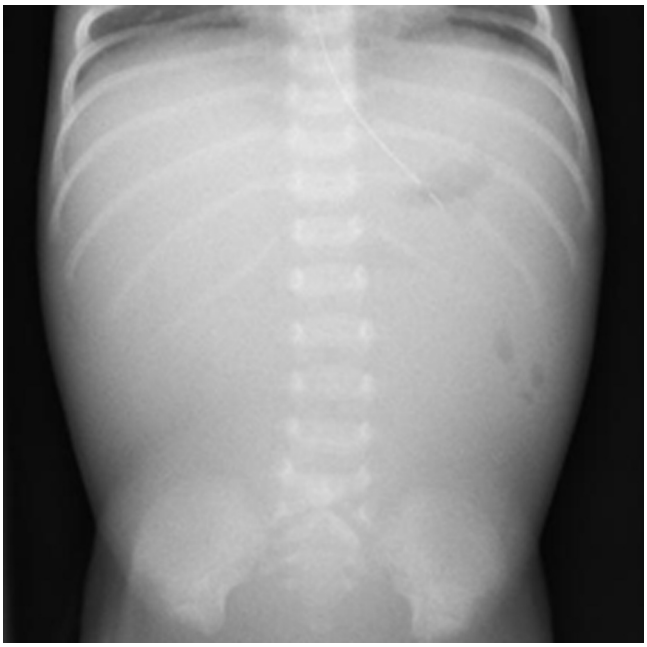

Fig. 2. Gasless abdomen is seen on abdominal X-ray.

2.2. Case 2

A full-term boy born at 38th week of gestation with a birth weight of 1980 g was transferred to NICU because of the sudden presentation of bilious vomiting and bloody stool on day 6 while being fed breast milk. Stool examination revealed eosinophilic infiltration. Development of FA was suspected. Conservative treatment was continued as mechanical intestinal obstruction was ruled out with abdominal ultrasonography and upper gastrointestinal series. However, he soon became unresponsive. An abdominal X-ray image showed gasless abdomen 2 days after the onset of symptoms (Fig. 2), and ascites was detected on abdominal ultrasonography. Two days after the onset of symptoms, CRP levels rose from 0.11 mg/dL to 14.0 mg/dL, and the platelet count decreased from $23 \times 10^4/\mu L$ to $4.0 \times 10^4/\mu L$. He was diagnosed with NEC and an emergent laparotomy was performed as conservative treatment was unlikely to succeed. Proximal jejunostomy was performed since almost the whole intestine and some parts of the colon showed extensive and severe inflammation, evidenced by marked swelling and a pale appearance. MRSA was detected in the fecal culture at the time of the onset. However, the patient also recovered without an MRSA sensitive antibiotics. The intestinal biopsy specimen taken during surgery showed irreversible necrotic change (Fig. 3a) and more than 20 eosinophils per field at x400 magnification (Fig. 3b). Phagocytosed MRSA were not identified in the biopsy specimen. After the surgery, peripheral blood eosinophil count reached 16% with positive ALST to lactoferrin. These findings support the diagnosis of FA complicated by NEC. Jejunostomy closure was performed a month later. Postoperative recovery was uneventful.

3. Discussion

Reports on neonates with FA who develop secondary NEC are extremely rare [1,3–5]. It is necessary to be cognizant of this condition as the incidence of FA in neonates is increasing. Therefore, it is critical to investigate the difference between patients with FA who recover with conservative treatment and those who require laparotomy. In this series, we performed laparotomy to decompress the distended intestine with resection of necrotic intestine as res-

Table 1
Clinical findings reported in the English literature on gastrointestinal food allergy in neonates complicated with necrotizing enterocolitis.

	Author	Gestational age (weeks)	Birth weights (g)	Symptoms	Image findings	Concurrent disease
1	Eggertsen [1]	39	2900	Emesis, AD	PI	–
2	Walther [4]	Unknown	4150	Lethargy	PI → PP	–
3	Our case 1	28	1133	BV, Emesis	PI	RDS
4	Our case 2	38	1980	BV, Emesis, AD	Gasless	–

*AD: abdominal distension; BV: bilious vomit; PI: pneumatosis intestinalis; PP: pneumoperitoneum; RDS: respiratory distress syndrome.

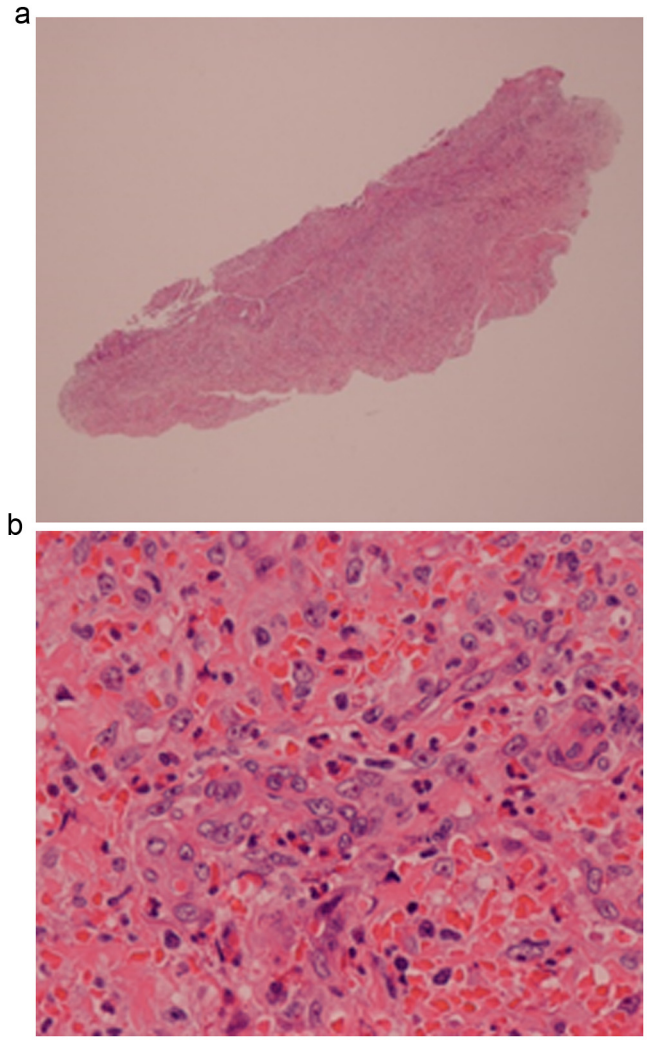

Fig. 3. (a) The intestinal structure shows irreversible necrotic change (Hematoxylin and Eosin stain ×100). (b) Counts of more than 20 eosinophils per high power field demonstrate eosinophilic infiltration. (Hematoxylin and Eosin stain ×400).

piratory distress due to abdominal distension and thrombopenia were present for both cases. There are no risk factors for FA except for empirical evidence that patients with low birth weight may be more susceptible, while the risk factors for NEC have been consistently identified as prematurity, intestinal ischemia, umbilical artery catheterization, and bacterial infection [2]. We show clinical features of our two patients and those with similar condition reported in the literature in Table 1. There were no typical risk factors for secondary NEC in each case with no deviation in their birth weights. Furthermore, both cases presented atypically for NEC as the patent ductus arteriosus had closed. Furthermore, they did not present with congenital heart disease or severe respiratory distress, which are the usual causes of systemic circulatory failure resulting in relative intestinal ischemia during NEC.

The blood tests for allergy in our patients were in line with described FA diagnostic criteria. A significant decrease in platelet level and a rise of CRP level 2 days after development of FA in both patients indicate severe inflammation, which cannot be explained by uncomplicated FA. These findings suggest the progression to NEC. A report by Feuille et al. [7]. supports our opinion that increased platelet count is normally observed as an acute reaction in FA. Thus, these findings may be considered as characteristics of FA with secondary NEC as they were not found in neonatal patients with FA who recovered with conservative treatment in our institution.

One patient presented with pneumatosis intestinalis on abdominal X-ray imaging. The other one presented with a gasless abdomen on the abdominal X-ray and ascites on abdominal ultrasonography. A few authors have previously described pneumatosis intestinalis in FA, although it is also a specific characteristic of NEC [2]. In addition, gasless abdomen is usually seen in FA. Thus, it is difficult to distinguish both conditions based on imaging.

The guidelines on the diagnosis and treatment of FA in Japan indicate that during the histopathological inspection of the intestinal specimen, eosinophil count of more than 20 per field at 400X magnification might be detected [8]. There are no prior case reports on histopathological findings for the diagnosis of FA in patients with NEC. This decisive finding was critical in confirming the coexistence of both conditions. When patients with progressive FA need laparotomy, we recommend taking biopsy to support the diagnosis.

MRSA was detected on fecal culture of both patients at the time of the onset of FA. This finding was not found in neonates with FA who recovered with conservative treatment in our institution. Infectious enteritis due to MRSA is unlikely as both patients recovered without MRSA sensitive antibiotics and no phagocytosed MRSA was identified in the specimen for case 2. There are some supportive reports to explain the etiology in our patients. MRSA may produce δ-toxin and toxic shock syndrome toxin 1 (TSST-1) that causes intestinal ulceration and NEC [9,10] Omata et al. [11] also described that TSST-1 produced by MRSA may function as a superantigen, resulting in the activation of milk-protein-primed T cells and exacerbation of FA. This may be the underlying mechanism in our cases. In addition, Mino et al. [12] described that toxic antigen produced by MRSA may contribute to the induction of cell death in organs in animal experiments. Therefore, we hypothesize that in our patients, there was an exacerbation of allergic reaction due to a breakdown of the intestinal mucous barrier caused by toxic antigen.

4. Conclusion

A persistent decrease of platelet levels and rise of CRP levels were observed that may indicate secondary development of NEC. MRSA detected on fecal culture also may be a risk factor for NEC through the activation of cellular immunity reaction. Whether expression of the MRSA antigen toxin in intestinal specimen correlates with the severity of intestinal mucous injury in patients with FA requires further study.

Conflicts of interest

The authors declare having no conflicts of interest for this article.

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Ethical approval

Written informed consent for publication of their clinical details and/or clinical images was obtained from the parent of the patient.

Consent

Written informed consent for publication of their clinical details and/or clinical images was obtained from the parent of the patient.

Author contribution

Kazuto Suda: study design, data collection, writing the paper.
Toshihiro Yanai: He reviewed the paper.
Miki Toma: She reviewed the paper.
Tsubasa Aiyoshi: data collection.
Takato Sasaki: data collection.
Toshihiro Muraji: He reviewed the paper.

Guarantor

Kazuto Suda.

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