

Dear Editor

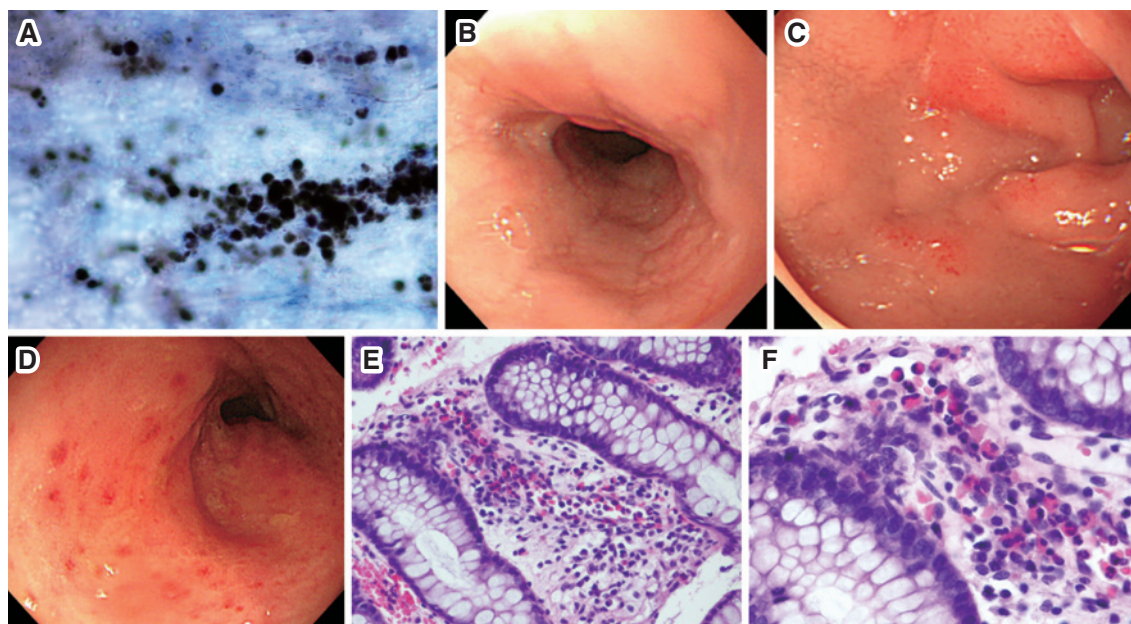
**Food Allergy after Cord Blood Stem Cell Transplantation with Tacrolimus Therapy in Two Patients Who Developed Veno-Occlusive Disease**

An increased prevalence of food allergy (FA) was noted in tacrolimus-immunosuppressed young pediatric liver transplant recipients.<sup>1</sup> However, there have so far been few cases of FA described after other types of solid organ transplantation such as the kidney<sup>2</sup> or heart.<sup>3</sup> In addition, to the best of our knowledge, there has been no report of FA that developed after cord blood stem cell transplantation (CBSCT) and tacrolimus administration. We herein report 2 patients who developed FA-related gastrointestinal symptoms after CBSCT using tacrolimus. Because switching immunosuppressive drug therapy from tacrolimus to Cyclosporin A (CsA) decreased the serum levels of IgE in both cases, we believe that FA was caused by the same mechanisms, as has been previously reported in liver transplantation recipients treated with tacrolimus.<sup>1,4</sup> Interestingly, both of our patients developed veno-occlusive disease (VOD) after CBSCT.

**CASE REPORT 1**

A 2-month-old Japanese male developed hemophagocytic lymphohistiocytosis and was diagnosed with fa-

miliar hemophagocytic lymphohistiocytosis (FHL) type 2. At 6 months of age, CBSCT was performed. (Donor HLA genotype was A\*02: 07: 26: 01, B\*15: 01: 46: 01, C\*01: 02: 04: 01, DRB1\*04: 03: 08: 03. Recipient HLA genotype was A\*02: 07: 26: 01, B\*15: 01: 46: 01, C\*01: 02: 03: 03, DRB1\*04: 05: 08: 03.) Graft-versus-host disease (GVHD) prophylaxis consisted of tacrolimus and short-term methotrexate. On day 9, the patient developed VOD, which resolved following the infusion of fresh frozen plasma and the administration of corticosteroids. GVHD in the acute phase was seen only in the skin (grade I). Our patient ate a regular diet with cow's milk after the transplantation and gradually avoided drinking milk. At 9 months of age, he developed prolonged diarrhea accompanied by poor weight gain. Infections were ruled out based on laboratory tests. He continued his regular diet, but gradually developed dehydration and malnutrition due to severe prolonged diarrhea and appetite loss. This led to the institution of tube feeding. When he was 24 months old, his height was 80.5 cm (-1.9 SD) and his body weight was 9 kg (BMI z-score -1.8). A blood test revealed eosinophilia and high levels of total serum IgE (1713 IU/ml). A serum analysis revealed specific IgE antibody to egg white, milk, and soybean, but not to aeroallergens. A stool smear showed increased levels of eosinophils (Fig. 1A). The diarrhea resolved after eliminating eggs, milk and soybean from his diet. A food challenge test with fresh cow's milk caused diarrhea and increased the number of eosinophils in his stool. Consequently, he



**Fig. 1** Gastrointestinal eosinophilic inflammation. (A) Cluster of eosinophils in stool mucous. ( $\times 400$ , Hansel's stain). (B) Pan-edema of esophageal wall in case 2. (C) Erythema on duodenal wall in case 2. (D) Erythema and erosion on colon wall in case 2. (E-F) Dense eosinophilic infiltration of colon wall in case 2 ( $\times 100$  &  $\times 400$ ).

was diagnosed to have having milk allergy. Because he had been hospitalized for almost 1 year due to prolonged diarrhea, his guardians did not want us to perform any challenge tests for other foods, which would extend the hospitalization. He did not show any symptoms due to food hypersensitivity after starting the elimination diet, but his total serum IgE concentration gradually increased to 6515 IU/ml when he was 30 months old. In addition, specific IgE to food allergens, which was undetectable at 24 months of age, became positive for rice and wheat. This led us to diagnose him as having tacrolimus-induced hypersensitivity to multiple food allergens, a condition that has previously been reported in liver transplantation.<sup>1,4</sup> We therefore switched the immunosuppressive drug from tacrolimus to CsA. Following this, his total serum IgE decreased to 1152 IU/ml and specific IgE to rice or wheat also decreased within a month, thus suggesting that tacrolimus contributed to producing specific IgE to these food allergens.

## CASE REPORT 2

Another 2-month-old Japanese male developed hemophagocytic lymphohistiocytosis and was diagnosed with FHL type 3. At 7 months of age, CBSCT was performed with a similar regimen and the same GVHD prophylaxis. (Donor HLA genotype was A\*02: 01: 26: 01, B\*35: 01N, C\*03: 03N, DRB1\*04: 10: 09: 01. The recipient HLA genotype was A\*02: 01: 26: 01, B\*35: 01: 15: 11, C\*03: 03N, DRB1\*04: 10: 12: 01.) He also developed VOD on day 6 after CBSCT. By age 15 months, he occasionally experienced vomiting and frequent diarrhea. He also demonstrated appetite loss leading to a poor weight gain. He especially avoided eating all foods containing eggs. At 18 months of age, his height was 74.8 cm (-2 SD) and his body weight was 9 kg (BMI z-score 0). He was found to have high total and allergen-specific serum IgE levels, as well as a stool smear that showed increased levels of eosinophils. A food challenge test with dried whole egg caused severe hives. Consequently, we diagnosed him to have egg allergy. His guardians did not want us to perform challenge tests for other foods because the hives that developed after the egg challenge test had been severe. His diarrhea improved within 1 month after eliminating eggs, milk and soybeans from his diet. However, his loss of appetite did not improve. The serum total IgE level increased to 4461 IU/ml when he was 23 months old. Gastrointestinal endoscopy showed edema of the entire esophageal wall and erythema with dense eosinophilic infiltration in the walls of the stomach, duodenum and colon (Fig. 1B-F). After switching his immunosuppressive drug from tacrolimus to CsA and treating him with prednisolone, he rapidly responded with an improved appetite, and his total serum IgE level decreased to 408 IU/ml, thus suggesting that the eosinophilic inflammation leading to appetite loss may be related to

tacrolimus. However, the specific food allergens causing eosinophilic inflammation were unclear.

## DISCUSSION

These are the first reported cases of FA after CBSCT with tacrolimus treatment. Previous studies reported that FA developed in approximately 20% of the patients in whom liver transplantation was performed using tacrolimus,<sup>1,5</sup> while food allergy rarely occurred after kidney transplantation using tacrolimus.<sup>2</sup> In addition, a recent report showed that changing the immunosuppressive drug from tacrolimus to CsA improved the symptoms associated with FA.<sup>4</sup> These observations strongly suggest that these types of transplantation-associated FA are transplant organ- and tacrolimus-related. Tacrolimus is thought to promote the development of FA because (i) it increases the permeability of the small bowel,<sup>6</sup> which may cause an increased absorption of food proteins, and (ii) it suppresses Th1 cells more strongly than CsA,<sup>7</sup> thus leading to Th2-skewing.<sup>8</sup> Similar mechanisms may have been involved in our cases.

FHL is a rare autosomal recessive disorder of immune dysregulation associated with uncontrolled T cell and macrophage activation and hypercytokinemia. FHL is fatal unless a hematopoietic stem cell transplant is performed in infancy, when FA usually develops. Both of our cases underwent CBSCT in infancy, and this treatment modality was thought to have increased their risk of developing FA.

VOD, another common feature in our patients, is a syndrome characterized by rapid weight gain, ascites, hepatomegaly, and jaundice. The pathogenesis of VOD is thought to be due to damage to liver sinusoidal endothelial cells (LSECs) and subsequent damage to hepatocytes.<sup>9</sup> As tacrolimus-related food allergy mainly occurs after liver transplantation but rarely after other types of solid organ transplantation, we suppose that liver damages due to VOD might contribute to the development of FA in our cases. In the liver, hepatic sinusoids are lined by LSECs and naïve T cells recirculating within the sinusoids can be in direct contact with Kupffer cells or LSECs located within the lumen of the sinusoids.<sup>10</sup> It has been shown that Kupffer cells, LSECs and liver dendritic cells uptake and present gut-derived antigens, including food allergens, to naïve T cells, thus resulting in immune tolerance both in CD8<sup>+</sup> T cells and CD4<sup>+</sup> T cells.<sup>10</sup> Therefore, it is possible that VOD-associated damages to the liver, especially to these cells that can induce immune tolerance, might have suppressed oral tolerance to food allergens and promoted the development of FA in our patients.

Because we could not check for sensitization in the CBSCT donors due to the establishment of privacy restrictions imposed by the Japanese cord blood bank network, we cannot rule out the possibility that the transferred immune cells themselves may have led to

the development of the FA observed in our cases. However, the time from transplantation to the development of FA would most likely have been shorter if the transferred food allergen-specific immune cells caused the disease.

Our cases strongly suggested that FA needs to be considered after SCT, as well as in liver transplantation, in which tacrolimus is used to suppress GVHD. Moreover, further investigation of the mechanisms that lead to the development of FA after liver transplantation or severe liver damage might provide helpful clues to elucidate precisely how oral tolerance becomes established and how it can be abrogated.

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