PRETEXT III disease, with P2 and V3 (Case No. 8). The POST-TEXT staging after 2 cycles of CITA was III, and P1 and V3. POST-TEXT staging at the time of initial operation was III, and P1 and V2 after an additional 2 cycles of CITA, and the patient underwent trisegmentectomy. Acute liver dysfunction due to obstruction of the right hepatic vein occurred after left trisegmentectomy. Living donor related liver transplantation was performed 7 days after left trisegmentectomy. Both of the 2 cases that underwent rescue liver transplantation showed P2 or V3 positive in POST-TEXT staging after 2 cycles of CITA.

There were some surgical complications among the 11 cases that underwent liver resections. Both of the 2 cases with mesohepatectomies had bile leak complications, and only one of 6 trisegmentectomies had acute obstruction of right hepatic vein. There were 3 liver transplantations (one primary transplantation and two rescue transplantations). One of the 2 rescue transplantations had acute graft failure. Therefore, 11 cases were alive with evidence of disease, while 1 case died due to transplantation related complications (graft failure after 4 days of transplantation).

3. Discussion

The current Children's Oncology Group (COG) hepatoblastoma protocol (AHEP0731), determines tumor extent from computed tomography (CT) imaging using the PRETEXT system [10], which is now referred to as POST-TEXT for studies obtained after treatment with neoadjuvant chemotherapy. Children with POST-TEXT III or IV tumors are referred to the pediatric liver transplant center and extreme liver resection at diagnosis if possible and no later than just after the second cycle of chemotherapy. This strategy is designed to prevent protracted courses of chemotherapy and ensure expeditious access to transplant for truly unresectable tumors. Meanwhile, Lautz et al. advocated that an excellent oncologic cure, comparable with that reported for primary transplantation, is possible with nontransplant resection in appropriately selected children with POST-TEXT III or IV hepatoblastomas [8].

The present study retrospectively analyzed the PRETEXT and POST-TEXT staging, surgical treatments, and clinical outcomes for 12 hepatoblastomas with PRETEXT III or IV and M (−). Two of 12 cases with PRETEXT III or IV, showed down staging in POST-TEXT after 2 cycles of CITA, and 1 case showed downstaging at the initial operation. Three cases (25%) showed downstaging in POST-TEXT at the time of the operation. Four of 7 cases with P2 or V3 in PRETEXT staging showed P2 or V3 in POST-TEXT staging after 2 cycles of CITA, and one case showed P2 or V3 in POST-TEXT staging at the initial operation, and then underwent primary liver transplantation. Six cases (86%) showed down staging in P or V factors at the initial operation. These 6 patients underwent liver resection at the initial operation. However, both cases that underwent rescue liver transplantation showed P2 or V3

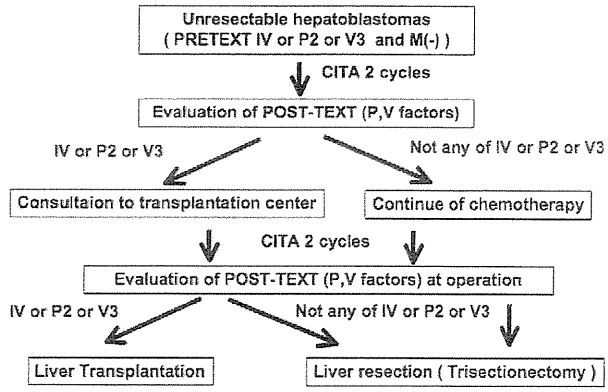

Fig. 1 Plan of surgical strategies for unresectable hepatoblastomas.

positive in POSTTEXT staging after 2 cycles of CITA. In the retrospective view of one patient (Case No. 3) who underwent rescue liver transplantation, if medical insurance was appropriate for transplantation for hepatoblastoma at right lobectomy (second operation), liver transplantation should have been performed. Another patient (Case No. 8) underwent rescue liver transplantation because the drainage area of RHV was extremely small, though the involvement of the RHV (right hepatic vein) was not found at POST-TEXT staging at the initial operation. Primary transplantation should therefore have been performed in this case as well. Regarding surgical complications, both mesohepatectomies had bile leak complications.

Preliminary plan of a surgical strategy for unresectable hepatoblastomas can be recommended from these results (Fig. 1). POST-TEXT staging and P, V factors should be evaluated after 2 cycles of CITA. The patients should be referred to the transplantation center if the POST-TEXT IV, or P2 or V3 is positive at that time. The final decision to perform either resection or transplantation should be determined based on POST-TEXT staging and P, V factors after an additional 2 cycles of CITA. Trisegmentectomy is recommended, because mesohepatectomies have a high rate of surgical complications, such as bile leaks. Careful treatment, such as backup transplantation should therefore be considered for cases presenting with POST-TEXT IV or P2 or V3 after the initial 2 cycles of CITA.

Acknowledgments

The English used in this manuscript was reviewed by Brian Quinn (Editor-in-Chief, Japan Medical Communication).

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Case report

Phrenic nerve palsy associated with birth trauma – Case reports and a literature review

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Abstract

Phrenic nerve palsy is a peripheral nerve disorder caused by excessive cervical extension due to birth trauma or cardiac surgery. We describe two new patients with phrenic nerve palsy associated with birth trauma. Both patients exhibited profound dyspnea and general hypotonia immediately after birth. A chest roentgenogram and fluoroscopy revealed elevation of the diaphragm, leading to a diagnosis of phrenic nerve palsy associated with birth trauma. Since they had intermittently exhibited dyspnea and recurrent infection, we performed video-assisted thoracoscopic surgery (VATS) plication in both cases, at an early and a late stage, respectively. Both patients subsequently exhibited a dramatic improvement in dyspnea and recurrent respiratory infection. Interestingly, the late stage operated infant exhibited spontaneous recovery at 7 months with cessation of mechanical ventilation once. However, this recovery was transient and subsequently led to an increased ventilation volume demand, finally resulting in surgical treatment at 15 months. Histological examination of the diaphragm at this time showed grouped muscle atrophy caused by phrenic nerve degeneration. To our knowledge, this is the first pathologically proven report of grouped muscle atrophy of the diaphragm due to phrenic nerve degeneration, suggesting that partial impairment of phrenic nerves resulted in respiratory dysfunction with incomplete recovery. We conclude that recently developed VATS plication is a safe and effective treatment for infants with phrenic nerve palsy, and should be considered as a surgical treatment at an early period.

Keywords: Phrenic nerve palsy; Birth trauma; Plication; Video assisted thoracoscopic surgery

1. Introduction

Phrenic nerve palsy associated with birth trauma is a rare but notable disease to be distinguished from neuromuscular diseases in neonates presenting with weakness of the respiratory muscles [1,2]. Although diaphragmatic plication can be attempted if no spontaneous improvement is obtained, it still remains controversial as to when proceeding to diaphragmatic plication antecedes conservative therapy [1,2]. Recently, the thoracoscopic plication approach, rather than traditional open thoracotomy surgery, was applied to infants with lung diseases due to its safe and effective technique [1–3]. We herein describe two new cases and review the literature

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to discuss suitable management of phrenic nerve palsy associated with birth trauma.

2. Case reports

2.1. Patient 1

A Japanese boy was born in the breech position at 37 weeks' gestation, weighing 2402 g. After birth, he immediately exhibited tachypnea, cyanosis, and Erb's palsy on his right side. He was admitted to the neonatal intensive care unit in another hospital. On admission, he exhibited prominent respiratory failure with paradoxical movement. He also showed tachycardia of 156 per minute, increased systolic blood pressure of 64 mmHg, and tachypnea of 78 per minute. Data on blood gas analysis of the vein showed pH 7.337, PCO_2 50.8 mmHg, and HCO_3^- 26.6 mEq/L. A chest roentgenogram revealed elevation of the right diaphragm (Fig. 1A), and ultrasonography revealed no movement of the diaphragm. Thus, he was diagnosed as having right phrenic nerve palsy associated with birth trauma. He was mechanically ventilated for 2 months, but exhibited no spontaneous improvement. He was finally transferred to our hospital to perform video-assisted thoracoscopic surgery (VATS) plication. After surgery, respiratory dysfunction had dramatically improved with a downward shift of the diaphragm on the chest roentgenogram (Fig. 1B), and he was subsequently discharged without any respiratory disturbance. Erb's palsy of patient 1 did not recover at all. Thus, we performed an additional operation of nerve transfer at 9 months. Erb's palsy was reconfirmed at that time by electrophysiological examinations of C5 to C6 nerve stimulation.

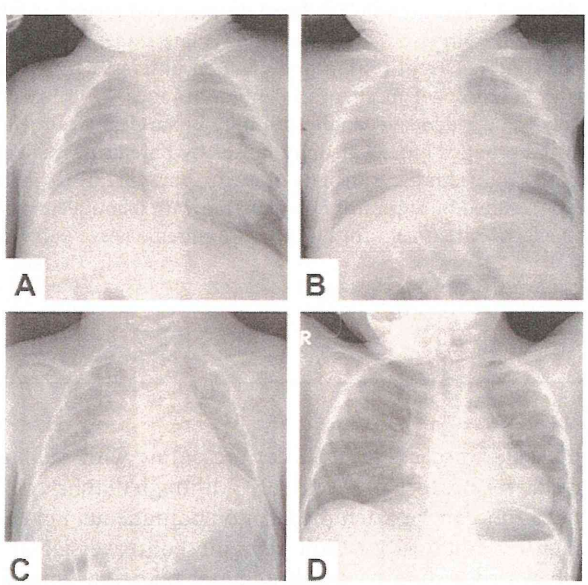

Fig. 1. A chest roentgenogram of patient 1 prior to surgical plication revealed an elevation of the right diaphragm up to the 7th intercostals, and no malformation of costal arches (A). After diaphragmatic plication, the right diaphragm shifted downward at 2 months (B). A chest roentgenogram of patient 2 prior to surgical plication revealed bilateral elevation of the diaphragm up to the 7th intercostals, and no malformation of costal arches (C). After diaphragmaticplication, bilateral diaphragms were shifted downward at 15 months (D).

2.2. Patient 2

A Japanese girl was born at 38 weeks' gestation in a normal position, weighing 2535 g after an uneventful pregnancy, except for mild hydramnios. Her parents were non-consanguineous with no family history of neuromuscular disease. Apgar scores were 6 and 8 at 1 and 5 min, respectively. After birth, she immediately presented with tachypnea, paradoxical breathing, and generalized hypotonia, and she was admitted to our hospital. On admission, her vital signs were as follows: heart rate 127 bpm, systolic blood pressure 72 mmHg, respiratory rate 40 bpm, and oxygen saturation 97% on room air. Data on blood gas analysis showed pH 7.354, PCO_2 45 mmHg, and HCO_3^- 25.5 mEq/L. She was treated with oxygen therapy for the next several days. Bilateral diaphragms were elevated up to the seventh intercostals on the chest roentgenogram (Fig. 1C). Diaphragmatic movements were not observed on a fluoroscopic examination. Laboratory investigations were all within normal limits. Brain magnetic resonance imaging showed a large subdural hematoma in the posterior fossa, suggesting that excessive mechanical compression had been placed on the skull with cervical cord extension on her birth. Thus, we diagnosed her as having phrenic nerve palsy associated with birth trauma. We started mechanical ventilation at 4 months due to hypercapnea. Since spontaneous recovery was thereafter observed at 7 months, she was successfully extubated and was equipped with nocturnal non-invasive positive pressure ventilation. However, respiratory recovery remained incomplete and she repeatedly exhibited respiratory distress and respiratory tract infections. Therefore, we performed bilateral VATS plication at 15 months. Histological examination of her diaphragm, obtained during VATS plication, revealed coarse fibrosis with grouped muscle atrophy (Fig. 2A) and comparative preservation of other muscle fibers, suggesting phrenic nerve degeneration (Fig. 2B). There was no myopathic change in the remaining muscle of the diaphragm. After bilateral VATS plication, there was a downward bilateral shift of the diaphragm on the chest roentgenogram (Fig. 1D). She dramatically improved and it became possible for her to breathe alone without respiratory distress. Thereafter, she has not been admitted to hospital for any respiratory distress, and has had normal developmental milestones.

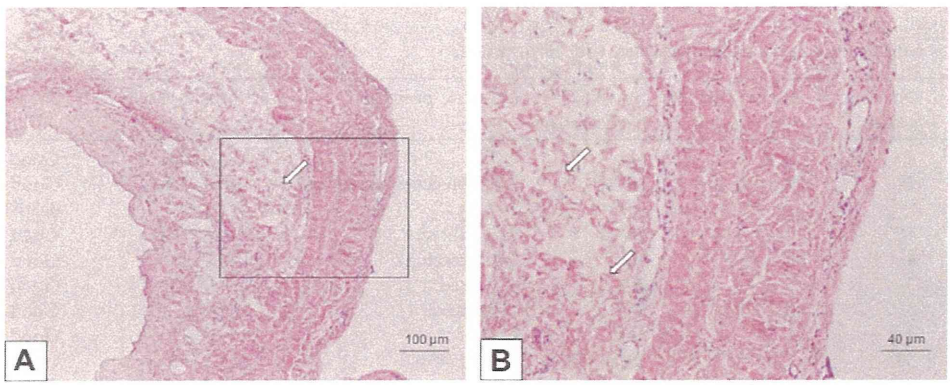

Fig. 2. Histological examination of the diaphragm obtained at plication showed coarse fibrosis (arrows, A), suggesting comparative preservation of other muscle fibers in the diaphragm (B). There was no myopathic change in the remaining muscle of the diaphragm. (hematoxylin eosin staining). Bars: 100 μm (A), and 40 μm (B), respectively. Diaphragm sections were fixed with formalin and embedded in paraffin.

3. Discussion

We described two new patients of phrenic nerve palsy associated with birth trauma. Both patients successfully underwent VATS plication at 2 and 15 months old, respectively, resulting in immediate improvements in respiratory dysfunction. A histological specimen of the diaphragm in one late operated patient revealed grouped muscle atrophy, probably due to phrenic nerve degeneration (Fig. 2B), suggesting that histological examination helps us to understand the functional grade of phrenic nerve palsy, i.e., grouped muscle atrophy indicating partial respiratory dysfunction with limited recovery as shown in this patient. To our knowledge, this is the first pathologically proven report of grouped muscle atrophy of the diaphragm due to phrenic nerve degeneration.

Phrenic nerve palsy associated with birth trauma is a rare condition with an incidence of 1 per 15,000–30,000 live births [2,3]. The first report was described in 1933 [4], and approximately one hundred patients with phrenic nerve palsy associated with birth trauma have been reported. The main reason for phrenic nerve palsy is overextension of the cervical cord during the birthing procedure with subsequent phrenic nerve injury, occasionally in combination with brachial plexus palsy. We briefly summarized previous studies of phrenic nerve palsy associated with birth trauma, demonstrating these clinical features as 4% of mortality, right side dominancy (80%), an association with brachial plexus palsy (78%), or an abnormal obstetric position such as breech (64%) (Table 1) [1,2,5–9]. The frequency of phrenic nerve palsy associated birth trauma seems to have decreased due to improved obstetric management, but clinicians still need to be aware of this disorder because proper treatment, i.e., surgical diaphragm plication, is necessary for maintaining adequate respiratory function in infants.

In our study, patient 1 clinically exhibited the typical course of phrenic nerve palsy associated with birth trauma. He was in a breech position at birth, and had right brachial plexus palsy. On the chest roentgenogram, the right diaphragm was elevated, which necessitated mechanical ventilation. Since spontaneous phrenic nerve recovery had not occurred during the first 2 months, VATS plication was performed, resulting in a dramatic improvement in pulmonary dysfunction.

Patient 2 exhibited an incomplete spontaneous recovery as mechanical ventilation was no longer necessary at 7 months. Since complete remission had not been accomplished, VATS plication was performed at 15 months. Biopsied specimens of the diaphragm showed grouped muscle atrophy caused by phrenic nerve degeneration, suggesting that partial impairment of phrenic nerves resulted in respiratory dysfunction with incomplete recovery. Patient 2 did not show any improvements in the diaphragm at the time of spontaneous remission. The reason why the patient showed spontaneous remission remains to be elucidated, but it may be due to growth of internal and external intercostal muscles, which work to supplement diaphragmatic movement. Long term cessation in diaphragmatic movement may be related to the histological changes seen in this patient.

The most suitable timing of surgical plication for phrenic nerve palsy remains to be determined. Initially, a conservative approach using prolonged mechanical ventilation was proposed because spontaneous recovery of phrenic nerve palsy could be expected within the first 6–12 months of life [6,10]. However, a recent finding showed that spontaneous recovery was limited after 1–2 months of age, suggesting that early surgical plication is necessary to obtain a complete resolution of respiratory failure and to gain enough space for subsequent lung development [1,2,5]. The outcome of the presented two cases suggests that serious loss of diaphragmatic

Table 1
A review of studies with phrenic nerve palsy associated with birth trauma.

Author (year)	Number of patients	Phrenic nerve palsy (side)	Brachial plexus palsy	Obstetric position	Phrenic plication (approach)	Respiratory outcome
Bowerson (2010)[1]	4	R 4	4/4	N.D.	3/4 (TS 3)	Good 4
Stramrood (2009)[2]	14	R 10;L 3; B 1	10/14	9/14 (breech 8, transverse 1)	10/14 (TS 3; TA 7)	Good 12; handicapped 1; dead 1
De Vries (1998)[5]	18	R 14; L 4	14/18	11/18 (breech 11)	13/18 (N.D.)	Good 18
Zifko (1995)[6]	4	R 3; B 1	4/4	3/4 (breech 3)	1/4 (N.D.)	Good 4
Commare (1994)[7]	3	B 3	2/3	3/3 (breech 3)	1/3 (N.D.)	Good 2; handicapped 1
Jawad (1991)[8]	3	R 2; B 1	3/3	1/3 (breech 1)	2/3 (TA 2)	Good 3
Smith (1986)[9]	4	N.D.	2/4	N.D.	3/4 (N.D.)	Good 3; dead 1
	50	R 33; L 7; B 6	39/50 (78%)	27/42 (64%)	33/50 (66%)	Good 46; handicapped 2; dead 2 (mortality 4%)

Abbreviations: TA, thoractomy; TS, thoracoscopy; N.D., not described; R, right; L, left; B, bilateral.

movement on the initial evaluation indicates necessary of early plication, no matter how moderate the respiratory dysfunction looks. Thus, in any cases showing incomplete recovery of phrenic nerve palsy after birth, proceeding to a surgical intervention such as VATS plication, as shown in the patient 2, may be necessary.

Surgical diaphragmatic plication is the most effective treatment for phrenic nerve palsy in infants [10]. Of note, the VATS approach, also called video assisted thoracoscopy, has recently become available for children [3]. This VATS seems to be less invasive, safe, and effective than the classical thoracotomy approach for infants with pulmonary and thoracic diseases. Although some reports have already proposed its therapeutic efficacy [1–3], clinical application to phrenic nerve palsy still remains limited. In our series, both cases were successfully operated on using the VATS approach at 2 months and 15 months, respectively. Therefore, this less invasive therapy should be applied to patients with phrenic nerve palsy associated with birth trauma.

Phrenic nerve palsy causes respiratory distress via two mechanisms. First, impairment of caudal diaphragmatic contraction, which causes the major change in thoracic volume, overloads intercostal muscles and the contralateral diaphragm. Compensated contractions result in paradoxical respiration and fatigue of the respiratory muscles. This also develops into a nutrition problem due to the increased energy expenditure from breathing [5]. Second, an elevated diaphragm also causes atelectasis or ventilation–perfusion mismatch, which could increase susceptibility to respiratory infection and relative hypoxia at motion [5]. In particular, phrenic nerve palsy in infants often causes severe respiratory failure because of the relatively low reserve in respiratory function and high dependency on abdominal respiratory.

In conclusion, early diagnosis and consideration for surgical plication is highly preferable for patients with phrenic nerve palsy associated with birth trauma. Thoracoscopic plication should be considered at an early period because it is less invasive and safer than other procedures.

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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.[1] However, there have so far been few cases of FA described after other types of solid organ transplantation such as the kidney[2] or heart.[3] 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.[1,4] 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 familial 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 rule 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

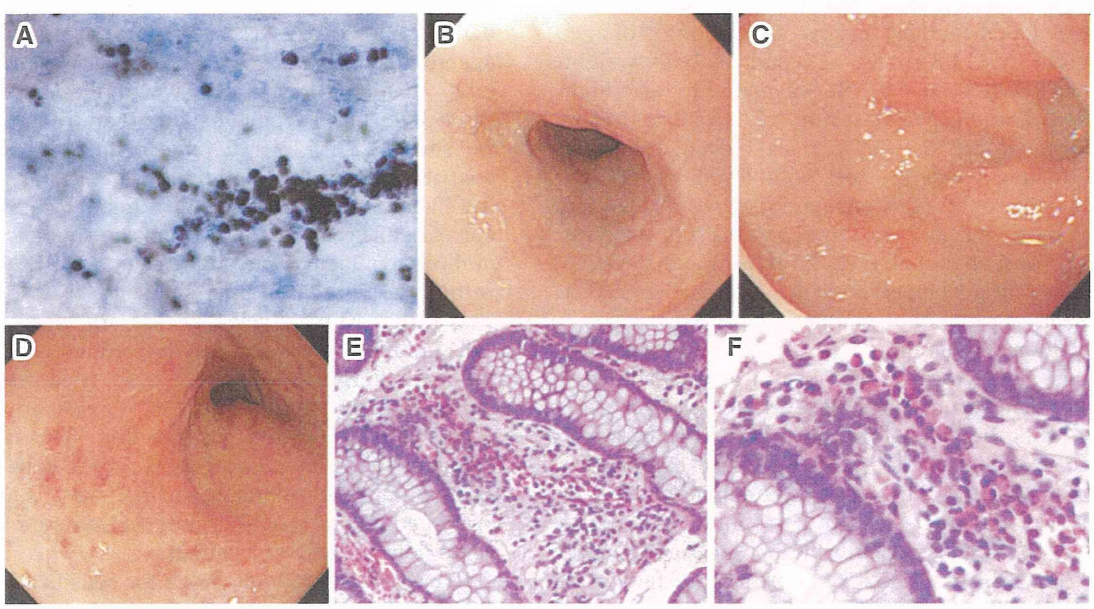

Fig. 1 Gastrointestinal eosinophilic inflammation. (**A**) Cluster of eosinophils in stool mucous. (×400, Hansel's stain). (**B**) Pan-edema of esophageal wall in case 2. (**C**) Erythema on duodenal wall in case 2. (**D**) Erythema and erosion on colon wall in case 2. (**E-F**) Dense eosinophilic infiltration of colon wall in case 2 (×100 & ×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.[1,4] 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,[1,5] while food allergy rarely occurred after kidney transplantation using tacrolimus.[2] In addition, a recent report showed that changing the immunosuppressive drug from tacrolimus to CsA improved the symptoms associated with FA.[4] 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,[6] which may cause an increased absorption of food proteins, and (ii) it suppresses Th1 cells more strongly than CsA,[7] thus leading to Th2-skewing.[8] 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.[9] 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.[10] It has been shown that Kupffer cells, LESCs and liver dendritic cells uptake and present gut-derived antigens, including food allergens, to naïve T cells, thus resulting in immune tolerance both in $CD8^+$ T cells and $CD4^+$ T cells.[10] 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 CBSC 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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