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[Case Report]

A male preterm infant with cow's milk allergy to human milk fortifier showing only severe respiratory symptoms

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Abstract

We report a male infant with a birthweight of 1,400 g at 29 weeks 2 days gestation diagnosed as having cow's milk allergy (CMA) due to human milk fortifier, who developed severe respiratory symptoms. The infant had no gastrointestinal symptoms ; rather, the initial symptoms were apnea attacks and wheezing with a prolonged expiratory phase that progressed to severe ventilatory insufficiency requiring mechanical ventilation. Aggravation of his general condition, which appeared to be due to sepsis, was improved by temporary starvation and respiratory care, but he relapsed on the resumption of enteral feeding of his mother's milk with a human milk fortifier. As a result, this event was interpreted as a positive oral food challenge test. The infant resumed complete breastfeeding without the fortifier and has not relapsed since. Examination of his serial cytokine profiles from residual serum revealed that although interleukin-5 was not increased, interferon (IFN)-γ was increased, suggesting some relation between the time course of IFN-γ and the infant's eosinophil count. These findings may indicate that the involvement of IFN-γ is one cause of the onset of this disease.

Key words : Cow's milk allergy, Human milk fortifier, Interferon gamma, Preterm, Respiratory symptoms

Introduction

Gastrointestinal food allergy in neonates in Japan has increased dramatically since the end of the 1990s and has become a relative common disease in recent years[1,2)]. In the neonatal period, food allergy revealed mainly through gastrointestinal symptoms such as bloody stool, vomiting and abdominal distension has recently been attracting attention as being indicative of gastrointestinal food allergy in neonates[3)]. It is often caused by protein contained mainly in cow's milk, and presently, the mechanism for the occurrence of this disease remains unclear. Although the present case does not conform to this concept in that the patient had no gastrointestinal symptoms, it was judged to be a conventional "neonatal cow's milk allergy" (CMA) due to human milk fortifier. The initial symptoms in this case were apnea attacks and wheezing with a prolonged expiratory phase. In this report, the relationship between symptoms and biomarkers was studied based on measurement of cytokine profiles and the eosinophil count.

Case Report

A boy with a birth weight of 1,400 g was born at 29 weeks 2 days of gestation by emergency cesarean section due to an indication of fetal distress. Both of his parents had pollen-related allergic rhinitis that occurred in adulthood but no history of atopic disease. However, since childhood, the father had di-

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arrhea every time he had ever eaten ice cream. After birth, the boy's respiratory management was continued with nasal CPAP after administration of artificial pulmonary surfactant to treat respiratory distress syndrome. Enteral feeding with his mother's milk was started from day 2, and he was receiving full enteral feeding (>100 mL/kg/24 h) by day 9. Fortification of human milk with HMS-1™ (Morinaga Milk Industry Co. Ltd., Tokyo, Japan) produced from nonhydrolyzed proteins of cow's milk was started from 12 days of age, at which time the frequency of apnea accompanied by bradycardia also increased, and ventilatory insufficiency strong enough to cause wheezing was recognized on day 17. He was tracheally intubated on the same day and placed on mechanical ventilation. At this same time, enteral feeding was stopped, and management with fluid replacement was started. Thereafter, his respiratory symptoms were promptly relieved. He was extubated, and enteral feeding was resumed with human milk only on day 19. Because blood, tracheal aspirate and nasal swab cultures were confirmed as negative, he was diagnosed as having no significant infection. Following resumption of HMS-1™ on day 21, his apnea attacks increased again. Because the number of peripheral eosinophils also increased and decreased in parallel with his respiratory symptoms, we diagnosed newborn CMA to HMS-1™. After changing enteral feeding to human milk only from day 35, the episodes of apnea gradually began to decrease. Examination of the temporal transition of peripheral blood leukocyte (WBC) counts and C-reactive protein (CRP) levels showed an increase in CRP and decrease in WBC count occurring on day 17, when respiratory symptoms worsened, and normalization of these values at 21 days of age. Simultaneous measurement of his cytokine profile using residual serum showed no increase in IL-5 but a significant increase in interferon (IFN)-γ[4]. His eosinophil count changed almost in parallel with the time course change of IFN-γ. Measurement of urinary β_2 microglobulin[5] (β_2-MG) at the same time also showed a change that paralleled the transition of IFN-γ (Fig. 1). His serum level of immunoglobulin (Ig)E was <5 IU/mL, and he was negative for cow's milk-specific IgE. Additional diagnostic tests such as allergen-specific lymphocyte stimulation test and fecal eosinophils were not performed at this time because the false-positive rate is high in this condition[1,2]. Changes in the profiles of 17 different cytokines including IFN-γ are shown in the table[2]. The Bio-Plex Human Cytokine 17-Plex Panel (Bio-Rad Laboratories, San Diego, CA, USA) and Luminex 100 system (Mirai Bio, Alameda, CA, USA) were used to measure serum concentration of the 17 cytokines[6]. This study was approved by the ethics committees of the Japanese Red Cross Musashino Hospital and University of Tokyo Hospital. The parents of the infant were informed of the study design, and their written informed consent was obtained for submission of this case report. The boy was discharged on day 76. He has been breast-fed along with a gradual increase in dairy products, and now at 2 years of age, his growth and development are within normal limits. At 18 months of age, an oral food challenge test was performed, and the result was negative. His milk-specific IgE remains negative after birth.

Discussion

According to our review of the literature, apneic attacks appear as a rare symptom of neonatal gastrointestinal allergy at a frequency of 4.5%[1,2]. This neonatal gastrointestinal allergy especially to cow's milk is one of the non-IgE-mediated food allergies. Particularly, when the site of the allergic reaction is the gastrointestinal tract, it is called gastrointestinal allergy[3]. Thus, the presence of gastrointestinal symptoms is essential for the diagnosis of this disease. Therefore, our patient, who had no gastrointestinal symptoms, did not meet these diagnostic criteria but, rather, the conventional diagnosis of CMA. Antigenicity of HMS-1™ is lower than that of bovine milk protein, but in regard to cellular immunity, T cells can recognize foreign matter with 6 peptides or more[7,8]. HMS-1™ was also stopped at the age of 17 days, at the same time that starvation was begun, and was resumed at 21 days after respiratory symptoms were relieved. This can be interpreted as positive for a clinical diagnosis of CMA by retrospectively applying an oral food tolerance challenge test.

Morita *et al.* classified 24 patients diagnosed as having CMA into preterm and term infants and examined their characteristics[9]. They found no significant differences in the onset of clinical symptoms and enteral feeding, but the onset time was significantly different between the preterm (23 days) and the full-term infants (3.5 days). Since there was no difference in the start time of enteral feeding, it is thought that the delay in onset in premature infants reflects the time required until corrected gestation at 30 to 32 weeks, by which time the immune mechanism of T-helper 2 (Th2) cytokines has matured. The initial onset in the present patient was 17 days

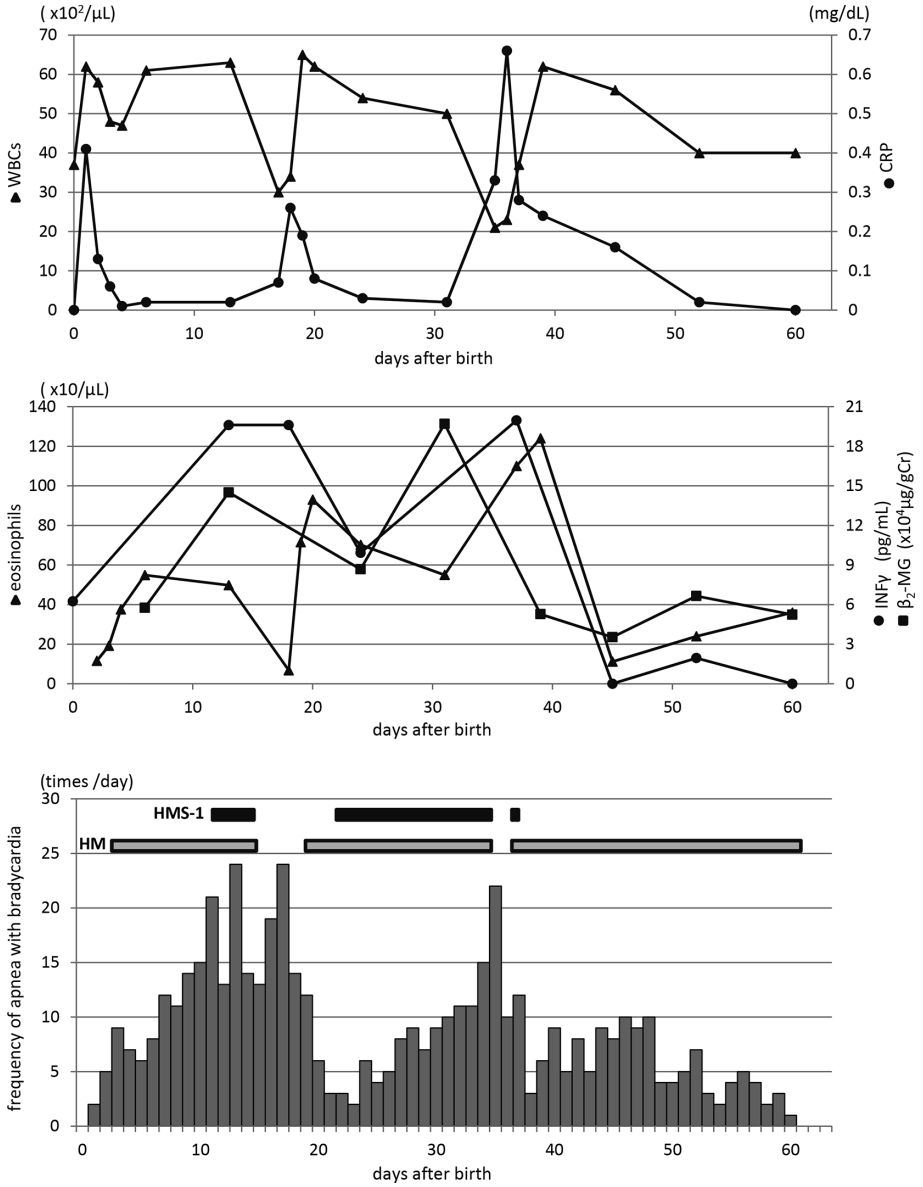

Fig. 1. Clinical course of the patient and the accompanying changes in IFNγ, urinary β2 MG, WBCs, eosinophils and CRP. The upper row shows the changes in WBCs (▲) and CRP (●). WBCs decreased once at 17 days after onset of HMS-1^{TM} therapy and decreased once again. CRP levels rose with HMS-1^{TM} therapy but then dropped after HMS-1^{TM} was interrupted. A similar pattern was observed around day 35 with re-administration of HMS-1^{TM} and exacerbation had worsened again. The middle row shows the transition of eosinophils (▲), IFNγ (●) and urinary β_2-MG (■). The three parameters increased up to 17, decreased after interruption of HMS-1^{TM} therapy, increased again after the restart of HMS-1^{TM} until day 32 when HMS-1^{TM} was terminated, and then remained within normal limits. The bottom row shows treatment periods with HMS-1^{TM}, feedings with human milk (HM) and the frequency of apnea episodes.

after birth, 31 weeks with corrected gestation, and it developed at the maturation stage of the Th2 strain described by Morita *et al.*

Although there are reports of CMA with both eosinophilia and elevated IL-5 associated with Th2 cytokines[4], there has been no clinical report of IFN-γ being associated with an increase in T-helper 1 (Th1) cytokines alone[10]. In their study of neonatal gastrointestinal food allergy, Kimura *et al.* showed that IL-5 and IFN-γ at onset were significantly higher compared with those in controls[11]. A previous study has shown that no interleukins have a significant correlation with gestational age, except for IL-6, IL-8, MCP-1 and MIP-1$_\beta$, which were inversely related to gestational age[4]. To the best of our knowledge, there is only one report in which 25 cytokines were examined during the first week of life[12], and there are no reports of serial changes of

Table. Serial changes of serum cytokine concentrations

	Patient						Control[4)]
Age (days)	UA	13d	18d	24d	37d	45d	UA
Proinflammatory cytokines, pg/mL							
TNF-α	4.01	8.54	4.01	1.66	OOR<	5.16	2.05±5.18
IL-1β	0.33	0.54	0.54	0.23	OOR<	0.01	0.60±6.01
IL-6	0.97	7.08	2.49	OOR<	OOR<	4.28	4.88±6.94
Th1 cytokines, pg/mL							
INFγ	6.25	**19.61**	**19.61**	9.92	OOR<	**19.61**	8.34±8.23
IL-2	OOR<	OOR<	OOR<	OOR<	OOR<	OOR<	9.49±12.6
IL-12	1.95	9.16	3.37	2.42	0.56	6.49	3.03±5.56
Th2 cytokines, pg/mL							
IL-4	0.49	0.72	**0.72**	0.37	OOR<	**0.8**	0.59±3.42
IL-5	0.5	0.86	1.93	0.5	0.1	**3.79**	0.65±2.24
IL-10	OOR<	**14.39**	1.05	OOR<	OOR<	**10.42**	0.99±3.27
IL-13	3.65	**3.97**	2.99	2.32	1.24	**7.62**	1.43±7.11
Th17 cytokine, pg/mL							
IL-17	OOR<	0.66	OOR<	OOR<	OOR<	OOR<	1.97±3.82
Growth factors, pg/mL							
IL-7	2.5	**2.34**	**2.89**	**2.81**	**2.42**	**4.44**	2.10±2.23
GM-CSF	OOR<	OOR<	OOR<	OOR<	OOR<	OOR<	15.1±5.24
G-CSF	**85.48**	**28.86**	8.21	5.10	2.32	**22.03**	10.1±6.93
Chemikines, pg/mL							
IL-8	15.17	28.04	10.7	13.55	12.06	9.89	13.0±3.65
MCP-1	5.90	56.6	56.6	16.37	65.88	41.72	68.0±2.69
MIP-1β	27.66	155.42	69.78	42.57	39.69	56.98	222.0±1.75

Bold value means higher than mean +2 SD of the control. OOR< means lower than out of measurement limit. *The control group included 224 newborn patients who were admitted to the NICU with various risks. Among them, gestational age was 33.5±4.1 weeks (mean±SD), birth weight 1,933±771 grams (mean±SD). The control data are shown as mean ± 1 SD. Means and standard devviations were calculated using only logarithmic transformed data that was above the measurable lower limit. Data are shown in reversed linear mode (pg/ml).

cytokines over several months after birth. That report measured 25 kinds of cytokines including the 17 cytokines examined in the present case, and in the group with 32 weeks gestation or less, no cytokines showed a significant increase over the first several weeks after birth. Therefore, the authors determined that it is appropriate to evaluate cytokine levels over a transition of several months after birth based on the cytokine levels measured from the umbilical artery. These results suggested that an increase in IFN-γ is involved in the cause of this disease. Furthermore, these authors classified the neonates into two groups, the early-onset group, whose onset was up to and including 10 days after birth, and the late-onset group, whose onset was 11 days or more after birth. Eosinophilia was the main symptom in the early-onset group, and significant positive correlations were recognized between the eosinophil count and IL-5 and between IL-5 and IFN-γ in the early-onset group, whereas there were no correlations in the late-onset group. Additionally, IL-5 levels were significantly higher in the early-onset group than in the late-onset group. In adults, Th1 and Th2 cells oppose each other, so IL-5 and IFN-γ cannot be positively correlated[13,14)]. In neonates, however, T cells are immature at birth, and the shift to Th1 dominance is revealed as early as 1 week after birth[15)]. Thereafter, Th1 cytokines increase and Th2 cytokines decrease[16)]. According to this report of Kimura *et al.*, our case would be classified into their late-onset group from the viewpoint of onset time. Our findings that IL-5 was not increased but IFN-γ was increased may indicate that there was some relation between the time course of IFN-γ and the eosinophil count. Because IFN-γ induces β_2-MG, the transition of β_2-MG in parallel with the transition of IFN-γ was convincing[5)], which is clearly different from the transition with respect to the onset of chronic lung disease reported by Nishimaki *et al.*[5)] Furthermore, INF-γ tended to

change in parallel with the eosinophil count and the CRP level. A previous study showed a good correlation between IFN-γ and CRP[4], and the same was recognized in the present case. It is possible that INF-γ is involved in the pathological condition of respiratory symptoms in neonatal CMA that does not particularly cause gastrointestinal symptoms. Furthermore, as WBC transition and wheezing were recognized in this patient, the target of the allergy was bronchial tissue, as evidenced by the accumulation of WBCs, which indicated it to be a type of inflammation. The immaturity of intestinal immune cells seems to have something to do with gastrointestinal manifestations. However, in the present case, the mechanism of the allergic reaction to milk for which only respiratory symptoms developed without the development of digestive symptoms cannot be explained at present. This is a valuable case elucidating the pathology of CMA showing only respiratory symptoms.

Author contributions

T.N. and T.K. designed the study, N.T. and K.K. measured the cytokine profiles. T.N. drafted the initial manuscript and prepared the figure. T.K., D.H., M.K. and H.T. reviewed or revised the manuscript. All authors read and approved the final manuscript.

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