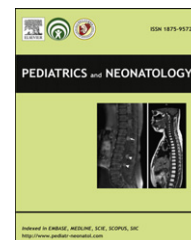


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ORIGINAL ARTICLE

Allergic Colitis in Infants Related to Cow's Milk: Clinical Characteristics, Pathologic Changes, and Immunologic Findings

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Key Words

allergic colitis;
IgE;
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milk protein allergy;
skin prick test

Background: Allergic colitis (AC) is an inflammatory condition characterized by eosinophils infiltrating the colonic wall. It can be a benign and/or severe illness among gastrointestinal diseases in infants.

Methods: We report five infants who, since January 2009, in whom AC under fibrotic endoscopic examinations has been diagnosed. The criterion for histopathologic diagnosis of AC in this study was five or more eosinophils per high-power field. Patients' clinical symptoms, pathologic findings, and immunologic studies, such as specific antibodies against component of cow's milk protein, were compared with those of allergic children without AC and those of non-atopic control children.

Results: Histopathologic examinations of biopsy specimens revealed acute inflammation with characteristic eosinophilic infiltration of lamina propria (5–15 eosinophils per high-power field) in all five patients. They all had strongly positive skin prick tests against milk protein, which were not correlated with *in vitro* allergen-specific immunoglobulin (Ig) E levels. In contrast, there were significantly higher levels of IgE antibodies, and lower specific IgG4 and IgA levels to components and whole milk proteins in AC, as compared to control children without AC.

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Conclusion: Endoscopic biopsy specimens of intestine confirm the diagnosis of AC. However, allergen skin prick test and IgE antibody to milk protein components also provide helpful diagnostic tools for this rare disease in children.

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1. Introduction

Cow's milk allergy was considered an infrequent disease until the 1980s, when an increasing frequency of this disease was noted, possibly due to a decrease in breastfeeding and a more frequent use of cow's milk-based infant formula feeding.^{1,2} During the past few decades, cow's milk allergy has become the most common food allergy in early childhood in Taiwan as well as in other parts of the world.^{3,4} However, much controversy still exists, possibly due to a lack of agreement on standard terminology and reliable diagnostic tests.⁵

In addition to the well-recognized, immediate-onset immunoglobulin (Ig) E-mediated allergies, there is increasing evidence to support the role of cow's milk protein-induced allergy in a spectrum of delayed-onset disorders ranging from gastrointestinal symptoms to chronic eczema and respiratory disorders.⁶ Among the food-allergic disorders affecting the gastrointestinal tract, there are myriad clinical manifestations (vomiting, diarrhea, growth failure, abdominal pain) and a broad range of severity and chronicity. Many of these disorders [e.g., cow's milk-induced proctocolitis, enterocolitis syndrome, gastroesophageal reflux, eosinophilic esophagitis (EE), and eosinophilic colitis (EC)] remain less well defined and frequently overlap.^{7–9}

Allergic colitis (AC) or proctocolitis induced in infants by cow's milk and/or soy protein, although rare, has been recognized for decades.⁹ This broad spectrum of symptoms typically begins in the first few months of life, usually presenting with colic-like symptoms and visible fresh blood mixed with mucus in the stool, but otherwise thriving, to the status in association with failure to thrive and possibly progressing to acidemia and shock.¹⁰ EC poses numerous diagnostic and therapeutic challenges. In this study we collected five infants with AC under fibrotic endoscopic examinations, in whom the condition was diagnosed since January 2009. Their clinical symptoms and pathologic findings were reported, and immunologic studies, such as specific antibodies (IgE, IgA, IgG1, and IgG4) against components of cow's milk protein were compared with those of allergic children without AC and those of nonatopic control children.

2. Materials and Methods

2.1. Study participants

We collected five infants who were admitted to our pediatric ward due to anemia, blood-tinged stools, and/or hypoalbuminemia. The diagnosis of AC was confirmed by

obtaining intestinal biopsy specimens during fibroblastic endoscopic examination. The criterion for histopathologic diagnosis of AC in this study was five or more eosinophils per high-power field.¹¹ Follow-up laboratory examinations and immunologic studies for cow's milk allergy in these patients were performed with the consent of their legal guardians. We also enrolled three groups of study populations, children with specific IgE antibody against cow's milk allergen and clinical symptoms related to cow's milk allergy (Group I), children with detectable IgE antibody levels against cow's milk but no clinical symptoms of cow's milk allergy (Group II), children without cow's milk allergy symptoms nor with IgE antibodies against cow's milk (Group III), five patients in each group, for the comparisons of their specific antibodies against components of cow's milk protein. The ethics committee of National Cheng Kung University Hospital approved this study project.

2.2. Skin prick tests

Skin prick tests with cow's milk extract and egg white allergens (Allermed, Mountain View, CA, USA) were performed in all study populations. Histamine (10 mg/mL) and physiologic saline served as positive and negative control agents, respectively. A wheal of 3 mm or larger was regarded as positive, according to European Academy of Allergy Asthma and Clinical Immunology (EAACI) guidelines.¹¹ Skin prick tests were always performed by the same experienced allergist (Y.M.C.). The reader of the prick test result was blind to the results of the challenge test.

2.3. Specific IgE and IgG subclass antibody against components of cow's milk

The determination of IgE, IgA, IgG1, and IgG4 antibodies to whey protein (W-1500 Sigma-Aldrich, San Louise, MO, USA), α -casein (C6780, Sigma-Aldrich), β -lactoglobulin (L3908, Sigma-Aldrich), regular infant formula (whole cow's milk), and hydrolyzed milk was performed with a sensitive enzyme-linked immunosorbent assay (ELISA) method, as described in detail by Oldeaus et al.¹² Briefly, 96-well microtiter plates (Life Technologies AB, Taby, Sweden) were coated with components of cow's milk proteins. Free-binding sites were blocked with bovine serum albumin. Human serum samples or buffer without added serum (blanks) were added to duplicate wells, and then monoclonal antibodies to human IgE (A80-108P, Bethyl Laboratories, Montgomery, TX, USA), antihuman IgA (A0295, clone GA-112, Sigma-Aldrich), antihuman IgG1 (B6775, clone 8c/6-39, Sigma-Aldrich), and antihuman IgG4 (B3648, clone HP-6025, Sigma-Aldrich) were added. After incubation and extensive washing with washing buffer, alkaline-

Table 1 Basic information of infants with eosinophilic enterocolitis.

Cases	A	B	C	D	E
Age (month of age)	11	9	22	1	22
Sex	F	M	F	F	M
White cell count (K/cmm)	11.0	6	10.5	11.9	7.2
Hb (g/dL)	6.5	7.7	4.1	15.4	12.9
Eosinophils (%)	4	3	2	0	3
Serum albumin/total protein (g/dL)	1.2/2.6	ND	1.8/2.7	ND	ND
BUN (mg/dL)	12	6	13	13	11
Creatinine (mg/dL)	0.32	0.29	0.2	0.88	0.31
AST/ALT (U/L)	31/19	61/29	40/15	72/17	—
Breastfeeding history (mo)	N	Y (9)	N	Y (1)	Y (19)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; Hb = hemoglobin; ND = not determined.

phosphatase-conjugated rabbit antimouse IgG was added, and *p*-nitrophenyl phosphate was used as a substrate to develop datable color. The optical density (OD) was read at 405 nm. Values were expressed as arbitrary units (AU) deduced from the OD of the reference serum curve, after subtracting the blanks. A coefficient of variation (CV) less than 15% was accepted for duplicate samples. Intra-assay CVs were less than 5%. Interassay CVs were less than 15%.

Circulating IgE antibodies to whole cow's milk, bovine β -lactoglobulin, bovine α -casein, and whey protein were also analyzed and confirmed with high-sensitivity protocol for the CAP-RAST system (Pharmacia, Uppsala, Sweden).

2.4. Statistics

Because the results were not normally distributed, nonparametric tests were used. Comparisons between groups with continuous variables were analyzed with the Kruskal-Wallis test. If there was an overall significant difference, pairwise comparisons between groups were

made with the Mann-Whitney *U*-test. A *p* value <0.05 was considered significant in all tests.

3. Results

3.1. Summary of clinical presentation of studied patients

Table 1 summarizes basic information of the five young infants with ACs. There were three female and two male infants, all younger than 24 months (age 1–22 months), who were admitted to our pediatric ward during January 2009 to December 2010 due to the major complaint of blood-tinged stools. Complete blood count of these patients showed that total white blood cell counts were normal, with mild elevation of eosinophil differential counts (0–4%). In contrast, marked anemia, iron deficiency, and hypoalbuminemia were noted in three of the five patients. Laboratory examinations of hepatic enzymes, blood urea nitrogen, and creatinine all were within normal ranges. Regarding their feeding histories, only two patients (Cases A and C) were fed with regular infant formula; the other three were solely breastfed from 1 to 19 months. The maternal daily diets of these three breastfed infants consumed regular amounts of milk and eggs (i.e., 1 cup of cow's milk and 1 egg per day).

3.2. Endoscopic and histopathologic examinations

To identify the cause of lower gastrointestinal bleeding, all patients underwent rectosigmoidoscopy performed with a flexible endoscope under general anesthesia. The evaluation was made and confirmed by microscopic examination of biopsy samples. Focal mucosal erythema, ecchymoses, and aphthous ulcerations were the most common endoscopic findings (**Figure 1**). Histopathologic examinations of biopsy specimens revealed acute inflammation with characteristic eosinophilic infiltration of lamina propria (5–15 eosinophils per high-power field, normal value below 5 eosinophils per high-power field), occasionally in association with lymphoid nodules (**Table 2**). Diseases that also have colonic tissue eosinophils, such as those caused by

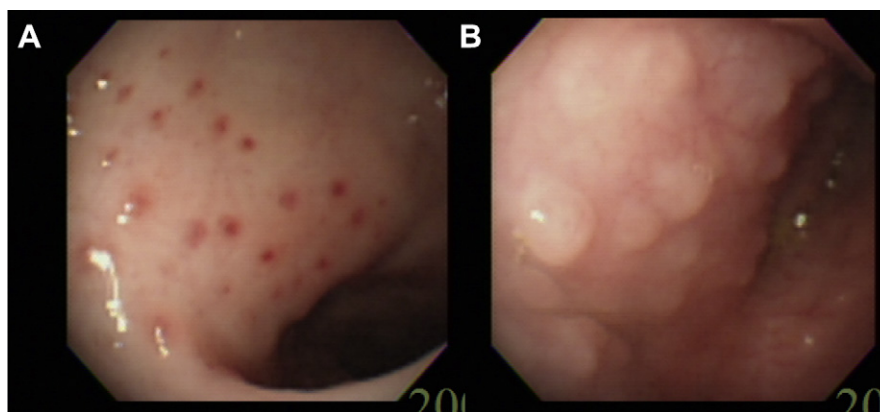


Figure 1 Endoscopic examination of infants with eosinophilic colitis. Focal mucosal erythema, ecchymoses, and aphthous ulcerations (A), as well as nodule-like lymph node hyperplasia (B) were common features.

Table 2 Histologic examinations of biopsy specimens.

Case	Pathologic findings	H&E stain (100×)	Eosinophils infiltration/ high-power field
A	Section of the small intestine shows mildly increased mature eosinophils infiltrating in the lamina propria.		9.5
B	Chronic inflammatory cell infiltration in duodenal mucosal tissue.		12
C	Nonspecific lymphocytic infiltration in the colonic mucosa.		5
D	Colonic mucosa with marked edema and lymphoplasmic infiltration. There are many but not heavy eosinophils in the lamina propria.		9.7
E	Nonspecific lymphocytic infiltration in the intestinal mucosa.		15

H&E = hematoxylin and eosin stain.

parasite or drug-induced, inflammatory bowel disease, and vascular connective tissue disorder, were ruled out because of the patients' young age and clinical histories.

3.3. Skin prick tests and specific IgE antibodies against milk proteins

All the patients underwent skin prick tests for total and specific (CAP[®]) IgE levels to cow's milk and egg white. Table 3 summarizes the results, which show that Cases A and C had higher total IgE than the range in those of the same age in the general population (<25 IU), as well as higher specific IgE antibody levels against cow's milk. Nonetheless, all patients showed strong reactions to cow's milk by the skin prick test (Figure 2); these results were not correlated to their respective levels of specific IgE of cow's milk.

3.4. Specific antibodies to components of milk protein

To further characterize the allergic reaction due to milk proteins in our study patients, we coated milk protein, α -casein, β -lactoglobulin, whey, and extensively hydrolyzed cow's milk on ELISA plates and incubated them with patient sera, detected with labeled antihuman IgE, IgA, IgG1, and IgG4 antibody. Table 4 shows the results of the specific antibodies against milk protein components in these five patients. There were high levels of specific IgE against components of milk protein, even to extensively hydrolyzed milk. In contrast, IgG4 subclass antibodies against components of milk protein were very low in these patients with AC.

To investigate the immunologic characteristics of these five infants with AC, we collected sera from children with antimilk IgE antibody and milk allergic symptoms (Group I), children with antimilk IgE antibody but no milk allergy history (Group II), and children without antimilk IgE antibody nor with milk allergic symptoms (Group III). Figure 3 reveals specific IgE, IgA, IgG1, and IgG4 antibodies against components or whole milk proteins among these four groups. There were significantly higher levels of IgE antibodies to components and whole milk proteins compared with Groups II and III ($p < 0.05$), respectively. In contrast, there were significantly lower specific IgG4 and IgA levels to whole milk protein compared with the other three groups ($p < 0.05$). It is interesting to note that there were also specific IgE, IgG1, and IgA antibodies detectable against hydrolyzed milk, but not in the other three groups.

4. Discussion

According to a recently published article,¹³ eosinophilic gastrointestinal disorders (EGID) may be categorized as EE, eosinophilic gastroenteritis, and EC. The clinical presentation of EGID depends on the segment of the gastrointestinal tract affected, the depth to which the eosinophils infiltrate the intestinal wall, and the local tissue response. The diagnosis of EE is made when esophageal biopsies show an increased number of eosinophils (15 per high-power field). EC can present primarily as a separate entity or a secondary manifestation of other diseases affecting the gut. The diagnosis of AC is more challenging because it lacks a clear definition. No guidelines exist. It remains, therefore, a diagnosis of exclusion. EC or enterocolitis is an uncommon disease in children¹⁴ and is especially rare in newborn

Table 3 Total IgE, allergen-specific IgE, and skin prick tests (wheal/flare after 30 minutes).

Cases	Total IgE (IU/mL)	Milk SPT(mm)	Antimilk IgE (AU)	Egg white SPT (mm)	Anti-egg white IgE (AU)
A	67.1	(10×15)/(20×25)	0.42	(10×10)/(30×30)	1.19
B	3.05	(6×5)/(20×15)	0.021	(3×3)/(3×3)	0.21
C	25.4	(10×10)/(20×15)	0.651	(3×3)/(3×3)	0.28
D	3.27	(8×10)/(23×25)	0.02	(9×10)/(20×25)	0.02
E	160	(10×13)/(20×23)	0.021	(10×12)/(15×20)	0.21

AU = arbitrary units; SPT = skin prick test.

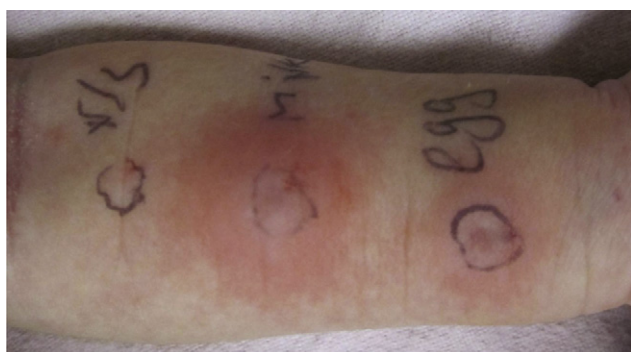


Figure 2 Skin prick tests with normal saline, cow's milk, and egg allergen.

infants.¹⁵ Its uncertain immunopathogenesis may be characterized by infiltration of the intestinal walls with eosinophils, absence of vasculitis, and peripheral blood eosinophilia.^{16–18} Although EC in infants is usually a short-lived disorder that responds to the exclusion of cow's milk protein from the diet,¹⁶ EC can be associated with a variety of chronic and debilitating gastrointestinal symptoms¹⁹ and severe illness that leads to ileal perforation and intestinal intussusceptions.^{20,21}

In this report, AC was diagnosed in five infants with similar findings: the colon was inflamed on visual inspection, and on histopathologic examinations, the lamina propria of rectal mucosa were infiltrated with

eosinophils.²² Although their symptoms and signs were compatible to those in other reports of EC in children, including nausea, vomiting, abdominal pain, gastrointestinal bleeding, diarrhea, weight loss, and ascites, in contrast to the previously common notion that EC in infants is usually a non-IgE-mediated disease,²³ we found there were strong reactions to cow's milk protein of skin prick tests in all five patients. Moreover, only two patients (Cases A and C) had sera antimilk IgE levels above 0.05 AU that could be considered IgE-mediated milk allergic syndrome, whereas with the skin prick test to milk allergen, these five patients with AC all revealed strongly positive results (Table 3). These inconsistent results between allergen skin prick tests and *in vitro* allergen-specific IgE antibodies were not infrequent in food protein-induced EC.²⁴

Although conditions such as milk protein-induced proctocolitis, enteropathy, and eosinophilic gastroenteropathies may all present with overlapping clinical features,²⁵ in our patients with milk protein-induced EC, it is interesting to note that there were three patients (Cases B, D, and E) for whom breastfeeding was exclusive without any ingestion of infant formula starting from birth (Table 1). Berezin et al,²⁶ in an attempt to define more precisely the clinical characteristics and course of milk protein intolerance, studied 22 infants (age 2–16 weeks), all of whom presented with the presence of gross blood in the stool hematochezia. Of these patients, 11 were receiving cow's milk, four were on soy protein, two were on cow's milk and soy milk, and five were breastfed. All mothers of breastfed infants ingested whole cow's milk during

Table 4 Specific antibodies against components of milk protein.

Case/antibodies	Cow's milk	Hydrolyzed milk protein	α -casein	β -lactoglobulin	Whey protein
IgE (OD)					
1	1.49	0.55	1.71	0.62	1.27
2	0.08	0.03	ND	0.06	0.01
3	0.62	ND	0.33	0.38	0.37
4	1.14	0.46	1.08	0.49	0.50
5	0.92	0.47	0.63	0.99	0.83
IgA (OD)					
1	ND	1.71	0.53	0.28	1.27
2	0.28	0.06	0.93	0.08	0.32
3	3.08	0.10	2.05	0.25	2.00
4	ND	1.08	0.14	0.06	0.50
5	ND	0.63	0.22	0.33	0.83
IgG1 (OD)					
1	ND	0.62	0.72	0.19	0.55
2	0.37	0.27	0.13	0.15	0.22
3	0.97	0.11	2.33	0.66	0.70
4	ND	0.49	0.69	0.15	0.46
5	ND	0.99	0.28	0.24	0.47
IgG4 (OD)					
1	0.02	ND	2.72	0.14	1.53
2	ND	ND	ND	ND	ND
3	2.67	ND	1.06	2.88	2.48
4	ND	ND	0.37	0.02	1.14
5	ND	ND	2.67	2.07	0.92

Ig = immunoglobulin; ND = not determined; OD = optical density.

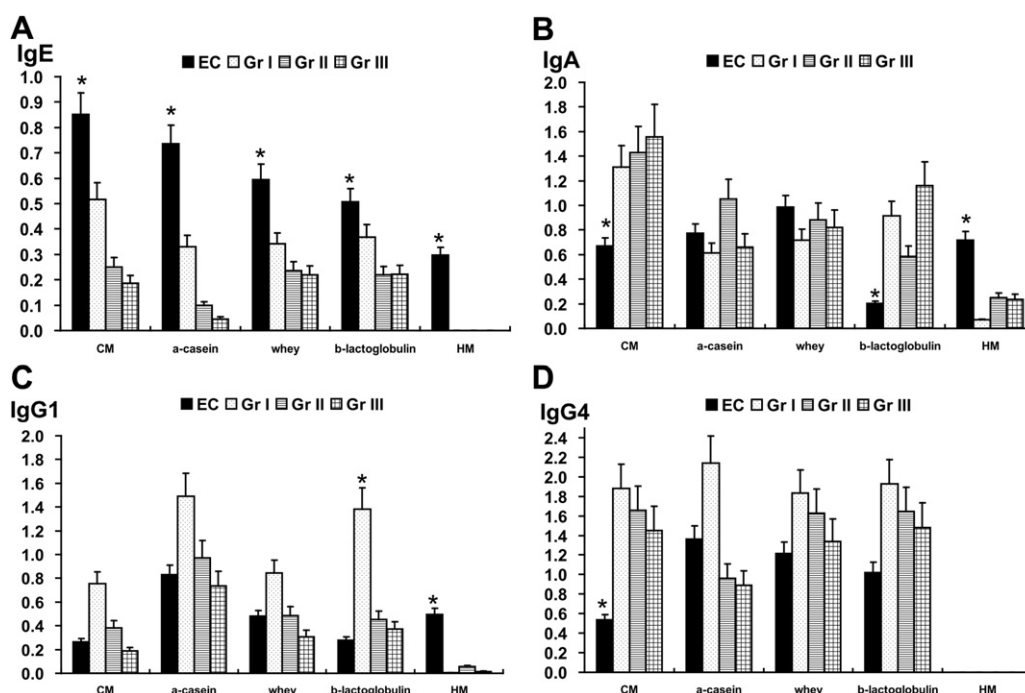


Figure 3 (A) Specific immunoglobulin (Ig)E, (B) IgA, (C) IgG1, and (D) IgG4 antibodies to components of milk protein in eosinophilic colitis (EC) and Groups 1–3 of the study population. CM = cow's milk; HM = human milk. * $p < 0.05$.

lactation. Rectal bleeding stopped in 19 of 22 infants within 1 week of transfer to a protein hydrolysate formula. Therefore, the cow's milk protein might have been present in the breast milk, which could sensitize and trigger milk protein-induced AC in these infants.

To our knowledge, there have not been any previous reports regarding the role of serum total IgE, IgA, IgG subclass antibody, and allergen-specific antibodies in milk protein-induced AC. In Table 4 and Figure 3, we show that there were significantly higher levels of IgE antibodies, and lower specific IgG4 and IgA levels to components and whole milk proteins in AC as compared to those in control patients without AC. Previously, Host et al²⁷ measured prospectively the development of serum IgE, IgG, IgG subclass, and IgE antibodies to dietary cow's milk proteins from birth (cord blood) to 12 months of age in 39 infants with cow's milk protein allergy. They found determination of IgG antibody and IgG subclass antibodies (IgG1 and IgG4) to bovine lactoglobulin and bovine whey in cord blood appeared unable to discern infants at high risk of development of cow's milk protein allergy. However, infants with persistent cow's milk protein allergy have an increased antibody response of specific IgE and IgG subclasses (IgG1 and IgG4) to cow's milk protein exposure. Further study also confirmed that clinical course and prognosis of cow's milk allergy were dependent on milk-specific IgE status in infants.²⁸

In summary, for an uncommon disease of milk protein-induced AC in infants, signs and symptoms of blood-tinged stools and anemia that rule out infection should alert clinicians of the possibility of milk protein allergy.²⁹ Although endoscopic biopsy specimens of the intestine may confirm the diagnosis of AC, allergen skin prick test and IgE antibody to milk protein components

also provide helpful diagnostic tools for this rare disease in children.

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