

Case report

Adult onset of cow's milk protein allergy with small-intestinal mucosal IgE mast cells

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We report a female patient with adult onset of cow's milk protein allergy. For 1 year, she experienced repeated gastrointestinal symptoms and had a single exercise-induced anaphylactic reaction. In addition to positive skin tests and specific IgE to milk proteins and a positive challenge test, immunohistochemistry of the small intestine showed a marked increase of IgE-positive mast cells. This finding is highly specific and could provide an additional tool for diagnosing cow's milk protein allergy and possibly also other food allergies.

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Intolerance of cow's milk due to immunologic and nonimmunologic mechanisms is a common disease in infancy and childhood (1, 2). Cow's milk allergy has an estimated prevalence in the first 3 years of life of 2.3–2.8% (3) and was first recognized at the beginning of this century (1, 2). Adult onset of IgE-mediated allergy to cow's milk protein (CMP) has been described in several case reports and in a synopsis of 34 patients (4–10).

Diagnosis of food allergies should be based on a thorough patient history, clinical symptoms, skin tests, RAST, and elimination/rechallenge with the suspected food allergen and be confirmed by double-blind, placebo-controlled food challenge (DBPCFC) (11, 12). However, it is not always possible to perform all these tests, and results may not be unequivocally clear. Therefore, additional *in vivo* and *in vitro* tests would be helpful.

We report a female patient with adult onset of IgE-mediated CMP allergy. Diagnosis was confirmed by standard tests and by the presence of small-intestinal mucosal IgE mast cells and a positive cellular antigen stimulation test (CAST).

Case report

A 25-year-old female patient experienced an anaphylactic reaction which occurred after 20 min of strenuous exercise. The symptoms were swollen

eyes; sneezing; edema of the tongue, lips, and cheeks; and urticaria of the arms. She received emergency treatment with intravenous injection of glucocorticoids and antihistaminics but no epinephrine. Before exercising, she had eaten a salad with a dairy-food dressing.

She complained of a 1-year history of nausea and diarrhea, sometimes accompanied by abdominal cramps which occurred after intake of dairy foods. She disliked milk and cheese and generally excluded these foods from her diet, but had been eating other dairy foods regularly.

She had had hay fever earlier in life but had not experienced any symptoms for several years. Sporadic contact with cats caused cough and rhinorrhea. There were no other allergies known, and the patient had otherwise always been healthy.

Laboratory investigations

Routine skin prick tests were performed with aeroallergens and food allergens (Allergopharma, Hamburg, Germany). They were positive for grass and rye pollen and negative for all other allergens tested, including whole cow's milk, casein, α -lactalbumin, egg white and egg yolk, and Gruyère cheese. An intracutaneous skin test with whole cow's milk (0.1% w/v = 455 PNU/ml; Allergopharma, Hamburg, Germany) was positive, produ-

cing a wheal/flare reaction of 5/30 mm in diameter. This intracutaneous skin test has a specificity of 0.96 and a sensitivity of 0.94 and does not cause systemic side-effects (9).

Determination of specific IgE (CAP RAST FEIA, Pharmacia, Uppsala, Sweden) was positive for α -lactalbumin (1.04 kU/l, class 2), β -lactoglobulin (1.90 kU/l, class 2), and heat-stable casein (2.05 kU/l, class 2). A test result above class 1 is considered positive.

A cellular antigen stimulation test (CAST®, Bühlmann Laboratories, Schönenbuch, Switzerland) for measurement of sulfidoleukotrienes synthesized by basophil leukocytes after incubation with antigen (13) was positive for α -lactalbumin, β -lactoglobulin, and casein and negative for whole cow's milk. An intolerance of lactose was excluded by a negative H₂-test.

Biopsy of the intestinal mucosa (with an Olympus Q 10 endoscope) revealed a normal histology with intact villi, crypts, and inconspicuous density of leukocytes in the lamina propria. Immunohistochemically, the IgA-, IgG-, and IgM-plasma cell populations were of normal density and distribution. There was a markedly increased number of mast cells with IgE bound at the cell membrane (Fig. 1).

DBPCFC (performed with a commercially available dried and soluble milk powder [Sano Lait, Coop, Switzerland] in opaque gelatin capsules) did not cause any objective signs, but the patient experienced gastrointestinal symptoms (nausea, abdominal cramps, diarrhea) which occurred between 30 min and 6 h after intake of the first capsules.

After complete elimination of dairy food from her diet, the patient's gastrointestinal symptoms, which she had experienced for about 1 year, subsided. She also noted that headaches were occurring much less often than before. After repeated open reintroduction of dairy foods, the typical symptoms recurred.

Discussion

IgE-mediated allergies to CMP in adult patients have been reported with increasing frequency in the last years. Most adult patients are women 20–50 years of age, the oldest patient reported being 79 years old (4–10).

Diagnosis of food allergy cannot be established on clinical symptoms only, but has to be confirmed by *in vivo* and *in vitro* tests. Yet, no simple specific test is available (4, 14). Furthermore, food allergy should be differentiated from nonimmunologic food intolerance, pharmacologic reactions, and other gastrointestinal diseases causing similar symptoms (12, 15). In particular, there is evidently a discrepancy

between the claim of food intolerance and the results of DBPCFC (4, 11, 16).

Our patient's personal history – including a single event of an exercise-induced anaphylactic reaction – and results of *in vivo* and *in vitro* tests were compatible with a food allergy due to cow's milk. RAST, CAST, and an intracutaneous skin test were positive. However, these tests can be either false-positive or false-negative (11, 14).

The diagnosis of food allergy should be confirmed by DBPCFC as the state-of-the art technique (4). Furthermore, diagnosis is important to prevent fatal anaphylaxis and improve the patient's compliance with the diet, which should exclude only the offending food (17). However, DBPCFC needs the patient's informed consent, and requires resuscitation facilities and experienced personnel (11, 14). In addition it is time-consuming, cannot be performed in the case of severe anaphylactic reactions, and rarely may be false-negative (4, 12).

The symptoms of our patient were mainly confined to the gastrointestinal tract. DBPCFC did not reveal any objective signs, but there was a significantly increased number of IgE-positive mast cells in the biopsy specimens of the small-intestinal mucosa. Antigens react with specific surface IgE on mast cells, leading to release of mediators and causing inflammatory reactions (18). Therefore, the presence of IgE-positive mast cells in the small-intestinal mucosa provides strong evidence of food allergy.

Intestinal biopsy as a diagnostic tool in food allergy was already suggested by Shiner et al. in 1975 (19); however, histology of the jejunal mucosa after challenge showed changes ranging from normal to villous atrophy (19–22). Because lesions show a patchy distribution, jejunal biopsies should be taken from several sites. Intestinal mast cells were seen in reduced numbers after food-allergic reactions of the gut, probably due to degranulation (23), but in increased numbers after local antigen challenge of the gastric mucosa (24). Shiner et al. found two patients with an increased number of degranulated mast cells after oral challenge (19). Increased numbers of IgG- and IgE-containing plasma cells were detected in the mucosa of food-allergic children by immunofluorescence (19, 25–27). However, in some studies, an increase of IgM- and IgA-containing cells but low numbers of IgE-plasma cells were observed (28, 29). These conflicting views may be due to the application of different methods, antibodies, and interpretation of immunofluorescence results. Moreover, other authors described intestinal mucosal IgE-containing cells, but did not distinguish between plasma and mast cells (30). Rognum & Brandtzaeg demonstrated that IgE-positive cells in the intestinal

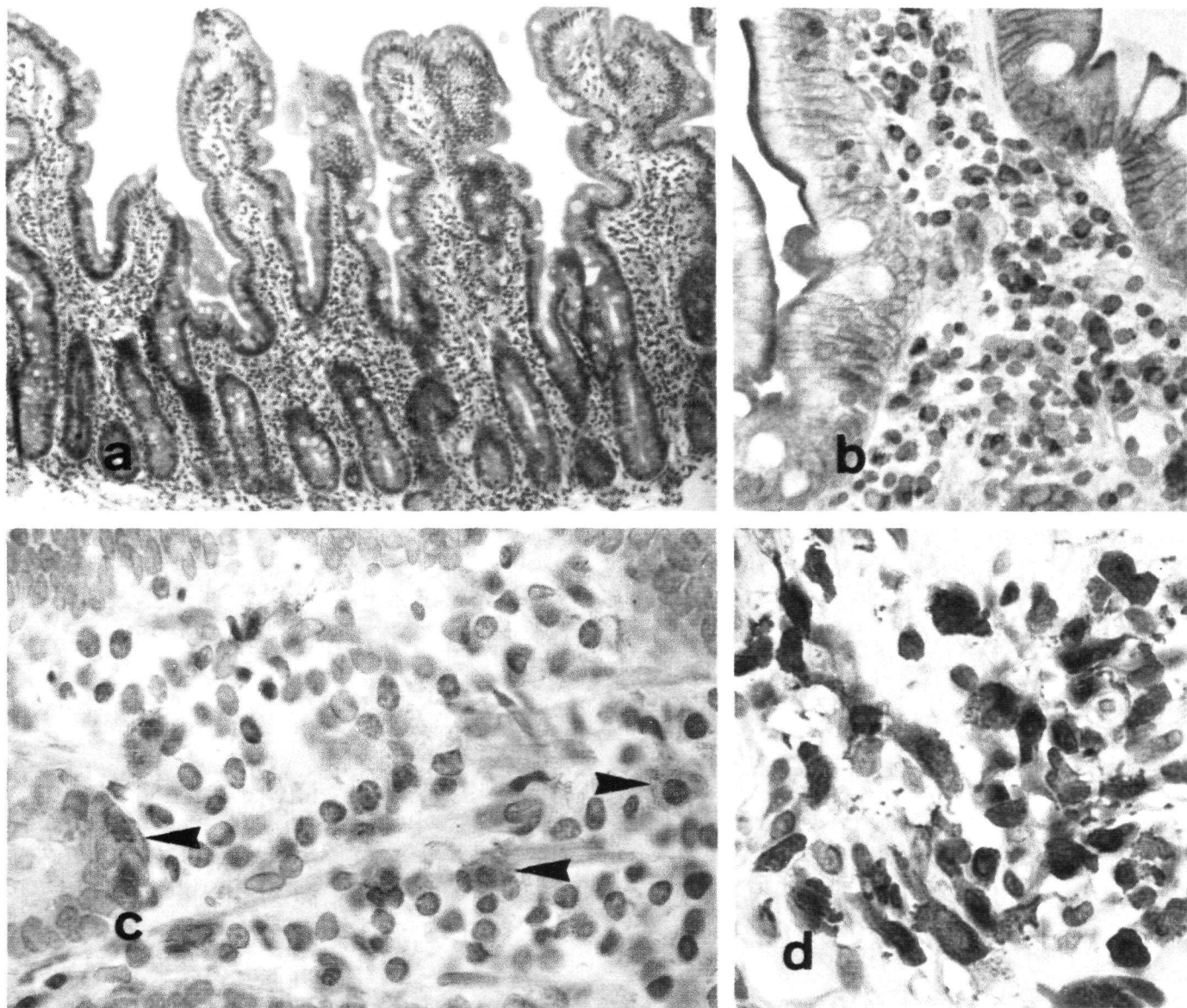


Fig. 1. Histologic and immunohistochemical findings in biopsies of small intestine in adult cow's milk protein allergy. a) Normal structure of small-intestinal mucosa (HE, $\times 105$). b) Normal distribution of IgA (purple-red stain) in plasma cells of lamina propria inside intact enterocytes and at their brush border (APAAP technique, $\times 520$). c) Demonstration of IgE (purple-red stain, arrows) at cell membrane of mast cells in lamina propria and in crypt epithelium (APAAP technique, $\times 810$). d) Mast cell cluster in lamina propria, demonstrated immunohistochemically with antibody against mast-cell tryptase (purple-red stain of cytoplasm, APAAP technique, $\times 810$).

mucosa are mainly mast cells (31). This is in agreement with our immunohistochemical findings, which showed a large number of IgE-positive mast cells in the small-intestinal lamina propria mucosae by using an antibody against mast-cell tryptase and thereby avoiding failure of detection because of previous degranulation (Fig. 1).

In conclusion, the presence of small-intestinal mucosal IgE-positive mast cells is evidence of, and provides a useful additional tool for diagnosing, CMP and possibly also other food allergies.

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References

1. Bahna SL, Gandhi MD. Milk hypersensitivity. I. Pathogenesis and symptomatology. *Ann Allergy* 1983; 50:218-23.
2. David TJ. Cow's milk intolerance. In: David TJ, editor. Food and food additive intolerance in childhood. Oxford: Blackwell Scientific, 1993:25-84.
3. Bock AS, Sampson HA. Food allergy in infancy. *Pediatr Clin North Am* 1994;41:1047-67.
4. Jessberger B, Rakoski J. Kuhmilchallergie beim Erwachsenen. *Allergologie* 1991;14:133-6.
5. Koers W, van der Elst MC, van Dijk AG, Berrens L. Cow's milk allergy in an adult patient. *Ann Allergy* 1986;56:267-9.
6. Olalde S, Bensabat Z, Vires R, Fernandez L, Cabeza NC, Rodriguez J. Allergy to cow's milk with onset in adult life. *Ann Allergy* 1989;62:185a-b.
7. Paganelli R, Sgambato F, Carbonari M, Buono G, Bonomo R, Pontesilli O. Cow's milk hypersensitivity in an elderly woman: clinical and immunologic findings. *Ann Allergy* 1986;56:480-3.
8. Pock-Steen OCh, Niordson AM. Milk sensitivity in dermatitis herpetiformis. *Br J Dermatol* 1970;83:614-19.
9. Stöger P, Wüthrich B. Type I allergy to cow milk proteins in adults. *Int Arch Allergy Appl Immunol* 1993;102:399-407.
10. Traenckner I, Abeck D, Vieluf D, Ring J. Ungewöhnlicher Verlauf einer Kuhmilchallergie. *Allergo J* 1993;2:A24.
11. Bock SA, Sampson HA, Atkins FM, et al. Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: a manual. *J Allergy Clin Immunol* 1988;82: 986-97.

12. Sampson HA, Metcalfe DD. Food allergies. *JAMA* 1992;268:2840-4.
13. de Weck AL, Stadler BM, Urwyler A, Wehner HU, Bühlmann RP. Cellular allergen stimulation test (CAST) – a new dimension in allergy diagnostics. *ACI News* 1993;5:9-14.
14. Bahna SL. Blind food challenge testing with wide-open eyes. *Ann Allergy* 1994;72:235-8.
15. Ferguson A. Food sensitivity or self-deception? *N Engl J Med* 1990;323:476-8.
16. Young E, Stoneham D, Petrukevitch A, Barton J, Rona R. A population study of food intolerance. *Lancet* 1994;343:1127-30.
17. Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 1992;327:380-4.
18. Galli SJ. New concepts about the mast cell. *N Engl J Med* 1993;328:257-65.
19. Shiner M, Ballard J, Brook CGD, Hermann S. Intestinal biopsy of cow's milk protein intolerance without acute symptoms. *Lancet* 1975;2:1060-3.
20. Iyngkaran N, Yadav M. Food allergy. In: March MN, editor. *Immunopathology of the small intestine*. New York: Wiley, 1987:415-49.
21. Kuitenen P, Visakorpi JK, Savilathi E, Pelkonen P. Malabsorption syndrome with cow's milk intolerance. Clinical findings and course in 54 cases. *Arch Dis Child* 1975;50:351-6.
22. Walker-Smith JA. Food sensitive enteropathies. *Clin Gastroenterol* 1986;15:55-69.
23. Kosnai I, Kuitunen P, Savilathi E, Sipponen P. Mast cells and eosinophils in the jejunal mucosa of patients with intestinal cow's milk allergy and celiac disease of childhood. *J Pediatr Gastroenterol Nutr* 1984;3:368-72.
24. Reimann HJ, Ring J, Ultsch B, Wendt P. Intra-gastric provocation under endoscopic control (IPEC) in food allergy: mast cell and histamine changes in gastric mucosa. *Clin Allergy* 1985;15:195-202.
25. Kilby A, Walker-Smith JA, Wood CB. Small-intestinal mucosa in cow's milk allergy. *Lancet* 1975;1:531.
26. Schrandt JJ, Dellevoet JJ, Arends JW, Forget PP, Kuijten R. Small intestinal mucosa IgE plasma cells and specific anti-cow milk IgE in children with cow milk protein intolerance. *Ann Allergy* 1993;70:406-9.
27. Shiner M, Ballard J, Smith ME. The small-intestinal mucosa in cow's milk allergy. *Lancet* 1975;1:136-40.
28. Perkkio M. Immunohistochemical study of intestinal biopsies from children with atopic eczema due to food allergy. *Allergy* 1980;35:573-80.
29. Savilathi E. Immunohistochemical study of the malabsorption syndrome with cow's milk intolerance. *Gut* 1973;14:491-501.
30. Rosekrans PC, Meijer CJ, Cornelisse CJ, Wal AM, Lindeman J. Use of morphometry and immunohistochemistry of small intestinal biopsy specimens in the diagnosis of food allergy. *J Clin Pathol* 1980;33:125-30.
31. Rognum TO, Brandtzaeg P. IgE-positive cells in human intestinal mucosa are mainly mast cells. *Int Arch Allergy Appl Immunol* 1989;89:256-60.

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