

minutes as well as 24 hours after exposure. In epicutaneous patch testing with standard allergens and Bextra, the tests with benzalkonium chloride and cetalkonium chloride were + (according to the International Contact Dermatitis Research Group criteria),¹⁰ and in the test with Bextra, a +++ delayed-type skin reaction with a peak response on day 3 developed. In addition, patch testing with single components of Bextra revealed +++ skin reactions to the pure active substance valdecoxib (1% and 10% in aqua) with peak responses on days 2 and 3 (Fig 1, C). To exclude valdecoxib-induced irritant responses, healthy individuals (n = 4) were patch-tested with valdecoxib (1%, 10%) and demonstrated no skin reactions.

Nonimmunological hypersensitivity reaction to non-specific NSAIDs is a well-known and frequent cause of skin reactions. An increasing number of studies suggest that the COX-2-selective antagonists can be safely taken by patients who develop cutaneous reactions caused by nonselective NSAIDs.^{3,4,6} However, here we report that the COX-2-selective inhibitor valdecoxib may induce severe allergic skin reactions.

Because valdecoxib and celecoxib have an analogous chemical structure,^{7,8} one could expect a cross-reaction between these 2 drugs. However, in previous reports showing allergic skin reactions to celecoxib, tests with other specific COX-2 inhibitors were either negative⁸ or not mentioned.⁵ A scratch test with celecoxib demonstrated no reaction in our patient. Although these findings suggest that a cross-reaction is unlikely, further studies are necessary to confirm this.

To the best of our knowledge, this is the first report of valdecoxib-induced skin allergy confirmed by a positive patch test. The presented case shows that the COX-2-selective inhibitors valdecoxib may cause severe allergic cutaneous reactions, adding a new aspect to the side effect profile of this drug.

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REFERENCES

- Dieppe PA, Ebrahim S, Martin RM, Juni P. Lessons from the withdrawal of rofecoxib. *BMJ* 2004;329:867-8.
- Szczeklik A, Stevenson DD. Aspirin-induced asthma: advances in pathogenesis, diagnosis, and management. *J Allergy Clin Immunol* 2003;111:913-21.
- Kruse R, Ruzicka T, Grewe M. Intolerance reactions due to the selective cyclooxygenase type II inhibitors rofecoxib and celecoxib: results of oral provocation tests in patients with NSAID hypersensitivity. *Acta Derm Venereol* 2003;83:183-5.
- Sanchez Borges M, Capriles-Hulett A, Caballero-Fonseca F, Perez CR. Tolerability to new COX-2 inhibitors in NSAID-sensitive patients with cutaneous reactions. *Ann Allergy Asthma Immunol* 2001;87:201-4.
- Grob M, Sheidegger P, Wuthrich B. Allergic skin reaction to celecoxib. *Dermatology* 2000;201:383.
- Munoz-Bellido FJ, Terron M, Leon A. Safety of rofecoxib in nonsteroidal anti-inflammatory drugs intolerance. *Allergy* 2003;58:1072-5.
- Chavez ML, DeKorte CJ. Valdecoxib: a review. *Clin Ther* 2003;25:817-51.
- Alonso JC, Ortega JD, Gonzalo MJ. Cutaneous reaction to oral celecoxib with positive patch test. *Contact Dermatitis* 2004;50:48-9.
- Goeschke B, Braathen LR. Acute generalized exanthematic pustulosis: a case and an overview of side effects affecting the skin caused by celecoxib and other COX-2 inhibitors reported so far. *Dermatology* 2004;209:53-6.
- Wilkinson DS, Fregert S, Magnusson H, Bandmann HJ, Calnan CD, Cronin E, et al. Terminology of contact dermatitis. *Acta Derm Venereol* 1970;50:287-92.

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Eosinophilic esophagitis is frequently associated with IgE-mediated allergic airway diseases

To the Editor:

Eosinophilic esophagitis (EE) is a chronic, IL-5-driven inflammatory disorder of the esophagus.¹ It is characterized clinically by acute and recurrent dysphagia to solid food, occasionally leading to food impaction, vomiting, and abdominal pain, as well as typical endoscopic features and histopathologic findings.¹

Previous observations revealing (1) that more than 70% of adult and 80% of pediatric patients with EE have allergic disorders,^{2,3} (2) that the pattern of inflammatory cells and cytokine expression in EE¹ is similar to the findings in allergic diseases of the airways⁴ or the skin,⁵ (3) that the medication effective in asthma also works in EE,⁶ and (4) that allergen challenge of the upper airways leads to eosinophilia in the esophagus in a mouse model of EE⁷ raise the question of whether EE can be considered an additional manifestation of atopy. This study was designed to investigate whether EE in adults is connected to airway or food allergies. Therefore we investigated the frequency and onset of concomitant atopic diseases and systematically analyzed the allergen sensitization pattern.

We prospectively examined 31 patients (6 female and 25 male patients; age range, 18-66 years; mean age, 37 ± 2.3 years) with previously diagnosed EE.¹ The mean duration of EE was 12 ± 1.7 years (range, 1-40 years). Specific serum IgG levels were determined to exclude *Anisakis simplex* infections as a cause of EE, but all patients had completely negative results. A detailed history of all patients, including current or previous physician-diagnosed atopic diseases, was obtained by means of a questionnaire. Written informed consent was obtained from all patients. The study was approved by the Medical Ethics Committee of Kantonsspital Olten. Total IgE and specific IgE levels to the aeroallergens grass pollen, birch pollen, mugwort pollen, cat dander, and house dust mites and the food allergens cow's milk, egg white, wheat flour, rye flour, and gluten were determined by using the UniCAP system (Pharmacia Diagnostics, Dübendorf, Switzerland). For skin prick tests (SPTs), a standard protocol of 14 aeroallergens and 14 food allergens was applied with allergen extracts (ALK, Horsholm, Denmark), as well as with 3 native probes of

food (wheat grain, rye grain, and soy milk). A wheal of 3 mm in diameter or more without reaction of the negative control after 15 minutes was considered positive. Data are given as mean values with SEs or median values with ranges. The paired *t* test was used to compare patient groups.

Our data showed that EE is frequently associated with atopic diseases. Twenty-one (68%) patients with EE experienced or had experienced allergic diseases, such as rhinitis, bronchial asthma, and/or atopic dermatitis, of which allergic rhinitis was the most common disease reported. Nineteen (61%) patients had increased total IgE levels (>100 kU/L). In 7 of the 12 patients with total IgE levels of less than 100 kU/L, allergen-specific IgE to more than one aeroallergen, food allergen, or both was detected (23%). We therefore considered only 5 (16%) patients to be nonatopic. The total IgE levels in these nonatopic patients (18.8 ± 7.8 kU/L; range, 2-45 kU/L) were significantly lower than in the patients with total IgE levels of less than 100 kU/L but with detectable allergen-specific IgE (48.4 ± 8.3 kU/L; range, 23-81 kU/L; $P = .03$).

Specific IgE to aeroallergens, food allergens, or both was observed in 24 (80%) of 30 investigated patients. The SPT revealed a sensitization to aeroallergens, food allergens, or both in 26 (84%) patients. In 12 of 19 patients with positive SPT reactions to food allergens, cross-reacting aeroallergens were identified. The disease severity did not differ between patients with or without sensitization to aeroallergens, food allergens, or both (frequency score, 2.5 ± 0.3 vs 2.6 ± 0.7). Sixteen (52%) patients with EE were sensitized to wheat and rye. In 14 (45%) patients allergen-specific IgE to wheat (median, 2.46 kU/L; range, 0.36-21.80 kU/L) and rye (median, 1.60 kU/L; range, 0.39-12.00 kU/L) was observed, whereas SPT responses were positive in 8 (26%) patients only. Of the 16 patients with positive SPT responses, serum IgE to wheat and rye, or both, 15 patients also reacted to grass pollen. Clearly, the clinical relevance of the food sensitization needs to be demonstrated in subsequent studies.

In the interview 29 (94%) patients reported food-related intolerance reactions, such as oral allergy symptoms, urticaria, diarrhea, or dysphagia. None of the patients with EE tolerated dry and solid foods, such as rice or bread, without liquid intake. Of the 26 (84%) patients who experienced EE symptoms on the intake of certain foods, 18 had a positive SPT response, allergen-specific IgE, or both to food. Eight patients reported dysphagia after intake of bread, but all connected these symptoms with the difficulty to swallow solid foods. In 5 of these 8 patients with reported bread intolerance, sensitizations to wheat and rye (median IgE levels of 1.69 kU/L [range, 0.36-21.8 kU/L] and 1.49 kU/L [range, 0.39-12.00 kU/L], respectively) were found.

In patients with EE with concomitant allergic rhinitis, the age of onset of allergic rhinitis (median, 6 years; range, 2-27 years) was significantly earlier than that of dysphagia (median, 22 years; range, 7-39 years; $P < .001$; Fig 1).

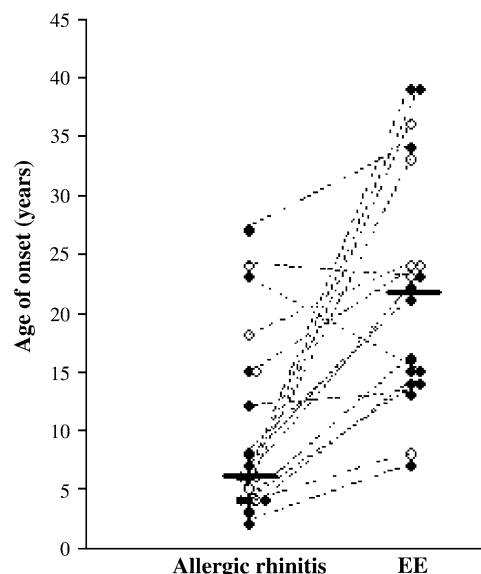


FIG 1. In patients with EE and concomitant allergic airway diseases ($n = 19$), allergic rhinitis mostly preceded the onset of EE symptoms ($n = 17$). The *black dots* represent patients with specific IgE, positive SPT responses, or both to grass pollen, wheat, and rye, and the *white dots* represent patients sensitized to pollens but without cosensitization to cereal. The *black bars* indicate the median age of disease onset.

Therefore the mean durations of allergic rhinitis (23 ± 3.7 years) and that of bronchial asthma (23 ± 4.5 years) were significantly longer than the mean duration of EE (12 ± 1.7 years, $P = .022$). Because sensitizations to grass pollen, wheat, and rye were observed in 15 patients, we checked whether these patients had concomitant allergic airway diseases. Indeed, 13 of these 15 patients had allergic rhinitis, and 8 had also bronchial asthma. In 11 patients EE occurred after the onset of allergic rhinitis, 1 patient reported simultaneous onset, and in only 1 patient was EE present before allergic rhinitis.

The results of our study confirm previous observations inasmuch as concomitant atopic diseases were observed in 68% and a sensitization to aeroallergens in 77%. These frequencies are markedly greater than those expected in the general population of industrialized countries, which were estimated to be 13.5% and 32.3%, respectively.⁸

In addition to the high frequency of aeroallergen sensitization, we observed food allergen sensitization in more than 50% of the patients. In adult patients with EE, a high frequency of sensitization to plant-derived food allergens cross-reacting with pollens, especially to cereals, such as wheat and rye, and grass pollens, was observed. In contrast, in children with EE, among whom more than 80% are sensitized to aeroallergens, milk and egg have been identified as relevant allergens for EE.³ In a prospective birth cohort study, the incidence of food allergen sensitization, mainly to egg and milk, decreased from 10% at year 1 to 3% at year 6, whereas the sensitization to inhalant allergens showed an inverse trend, with an increase of the incidence from 1.5% to 8%.⁹ Therefore the shift in the allergen spectrum of patients with EE from

childhood to adulthood is similar to that observed in atopic patients. Although aeroallergen sensitization is common, exacerbation of EE during the pollen season is rare.¹⁰

Our findings that allergic airway diseases precede EE suggest that the initial sensitization might take place in the airways. Therefore it appears that EE is just an additional involvement of another organ, the esophagus, in a preexisting IgE-mediated allergic syndrome. Because the relevant allergens do not change in this process, it is possible that factors unrelated to atopy determine the susceptibility for the development of EE in patients with allergic rhinitis with or without bronchial asthma. Our study provides further information that EE should be considered an additional manifestation of atopy. Therefore the concept of the united airways⁴ can be extended to the upper gastrointestinal tract because the allergic inflammation can obviously also reach the esophagus.

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REFERENCES

1. Straumann A, Simon HU. The physiological and pathophysiological roles of eosinophils in the gastrointestinal tract. *Allergy* 2004;59:15-25.
2. Vitellas KM, Bennett WF, Bova JG, Johnston JC, Cladwell JH, Mayle JE. Idiopathic eosinophilic esophagitis. *Radiology* 1993;186:789-93.
3. Spergel JM, Beausoleil JL, Mascarenhas M, Liacouras CA. The use of skin prick tests and patch tests to identify the causative foods in eosinophilic esophagitis. *J Allergy Clin Immunol* 2002;109:363-8.
4. Bousquet J, Vignola AM, Demoly P. Links between rhinitis and asthma. *Allergy* 2003;58:691-706.
5. Simon D, Vassina E, Yousefi S, Kozlowski E, Braathen L, Simon HU. Reduced dermal infiltration of cytokine-expressing cells in atopic dermatitis following short-term topical tacrolimus treatment. *J Allergy Clin Immunol* 2004;114:887-95.
6. Noel RJ, Putnam PE, Collins MH, Assaad AH, Guajardo JR, Jameson SC, et al. Clinical and immunopathologic effects of swallowed fluticasone for eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2004;2:568-75.
7. Mishra A, Hogan SP, Brandt EB, Rothenberg ME. An etiological role for aeroallergens and eosinophils in experimental esophagitis. *J Clin Invest* 2001;107:83-90.
8. Wuethrich B, Schindler C, Leuenberger P, Ackermann-Liebrich U. Prevalence of atopy and pollinosis in the adult population of Switzerland (SAPALDIA study). Swiss study on air pollution and lung diseases in adults. *Int Arch Allergy Immunol* 1995;106:149-56.
9. Kulig M, Bergmann R, Klettke U, Wahn V, Tacke U, Wahn U. Natural course of sensitization to food and inhalant allergens during the first 6 years of life. *J Allergy Clin Immunol* 1999;103:1173-9.
10. Fogg MI, Ruchelli E, Spergel JM. Pollen and eosinophilic esophagitis. *J Allergy Clin Immunol* 2003;112:796-7.

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Use of GM-CSF in the treatment of colitis associated with chronic granulomatous disease

To the Editor:

Chronic granulomatous disease (CGD) is a primary immunodeficiency characterized by the inability of phagocytes to kill ingested catalase-positive organisms.¹ In addition to increased susceptibility to bacterial and fungal infections, patients have a higher incidence of mucosal inflammatory disorders¹ such as colitis, enteritis, and gastric outlet obstruction. Antibiotics and steroids have been the main treatment options for the management of colitis associated with CGD. Immunomodulatory agents, found to be effective in inflammatory bowel disease, have also been used; however, recent reports of infectious complications associated with these medications preclude their broader use. Some success has been reported with the use of granulocyte colony-stimulating factor (G-CSF) and GM-CSF in the treatment of mucosal inflammation in glycogen storage disease Ib and Crohn's disease.^{2,3} Here we report a case of severe colitis and anal fissure associated with CGD that improved with GM-CSF treatment.

MG is a 19-year-old male with CGD diagnosed by nitroblue tetrazolium assay at 5 months of age after evaluation for cellulitis and frequent upper respiratory tract infections. He did well until 15 years of age, when he developed left cervical adenitis, which failed to improve on oral antibiotics, forming an abscess that required incision and drainage and intravenous antibiotics. He was subsequently started on IFN- γ 100 μ g subcutaneously 3 times a week.

He did well until 18 years of age, when he developed a rectal abscess that required incision and drainage. Subsequently, an enterocutaneous fistula developed, associated with abdominal and rectal pain with bloody stools. He was diagnosed with Crohn's-like colitis. Mesalamine, cortisone enemas, and 5-aminosalicylic acid suppository therapy were initiated. After debridement of the fistula, he experienced worsening of bloody stools, abdominal pain, and severe rectal pain. Surgical closure of the fistula was attempted twice without success.

Because of worsening colitis, he was treated with 1 dose of infliximab (5 mg/kg/dose). Initially, his gastrointestinal symptoms improved; however, he concurrently developed tooth pain, swelling, and fever. His right upper wisdom tooth abscessed and was removed. Post-operatively, he continued to have fevers (40°C) and worsening severe rectal pain, and he was admitted to his