

Table 1. Results of patch testing with antifungal allergens

Antimycotics	Conc. (%)	Tests	?	+	++	+++	ir	% positive	Exact 95% CI
Ciclopiroxolamine	1	1094	13	4	0	0	0	0.4	0.1–0.93
Nystatin	2	1177	4	2	0	1	1	0.3	0.05–0.74
Clotrimazole	5	1180	5	3	0	0	0	0.3	0.05–0.74
Croconazole HCl	1	1094	6	0	2	0	0	0.2	0.02–0.66
Ketoconazole	2	1104	0	0	0	0	0	0.0	0.0–0.27

All allergens in petrolatum; CI, confidence interval.

suspected allergic contact dermatitis caused by antifungal drugs, would have yielded higher percentages of positive reactions. Interestingly, the high sensitizing potential of croconazole observed in East Asia (4, 5) could not be confirmed, after sporadic reports on CA to this AF in Germany [e.g. (3)]. This is possibly because of a limited exposure, as only one brand specialty containing croconazole has been on the market, and this was not among the 'top prescriptions', e.g. in 2002 [$< 70\,000$ prescriptions (7)]. In accordance with previous evidence, simultaneous positive reactions, which could indicate cross-reactivity among the chemically related imidazoles (or previous co-exposure) has been found to be rare (4). The rather high proportion of doubtful patch test reactions we have observed points to difficulties in the patch test diagnosis of CA to these AF. Patch test reactions to products are generally difficult to interpret, i.e. because of possible irritancy under patch test conditions or the possibility of other ingredients causing CA. Hence, our data regarding the concordance between commercial allergens and product testing should be interpreted with caution – not to mention the small size of the clinical sub-sample ($n = 35$). Still, the results could indicate that AF products may be more sensitive to diagnose CA than petrolatum-based preparations, for instance because of reasons of bioavailability.

*Department of Dermatology
Municipal Medical Center of Bielefeld
Academic Teaching Hospital
An der Rosenhöhe 27
D-33647 Bielefeld
Germany

Tel.: +49 521 9438800
Fax: +49 521 9438899
E-mail: isaak.effendy@sk-bielefeld.de

Accepted for publication 25 February 2008
Allergy 2008; 63:946–947
© 2008 The Authors
Journal compilation © 2008 Blackwell
Munksgaard
DOI: 10.1111/j.1398-9995.2008.01728.x

References

1. Raulin C, Frosch PJ. Contact allergy to imidazole antimycotics. *Contact Dermatitis* 1988;**18**:76–80.
2. Barranco R, Tornero P, Barrio M, Frutos C, Rodriguez A, Rubio M. Type IV hypersensitivity to oral nystatin. *Contact Dermatitis* 2001;**45**:60.
3. Steinman A, Mayer G, Breit R, Agathos M. Allergic contact dermatitis from croconazole without cross-sensitivity to clotrimazole and bifonazole. *Contact Dermatitis* 1996;**35**:255–256.
4. Doooms-Goossens A, Matura M, Drieghe J, Degreef H. Contact allergy to imidazoles used as antimycotic agents. *Contact Dermatitis* 1995;**33**:73–77.
5. Yoneyama E. [Allergic contact dermatitis due to topical imidazole antimycotics. The sensitizing ability of active ingredients and cross-sensitivity]. *Nippon Ika Daigaku Zasshi* 1996;**63**:356–364.
6. Uter W, Schnuch A, Geier J, Frosch PJ. The epidemiology of contact dermatitis. The information network of departments of dermatology (IVDK) in Germany. *Eur J Dermatol* 1998;**8**:36–40.
7. Fricke U. Antimykotika [Antimycotics]. In: Schwabe U, Paffrath D, editors. *Arzneiverordnungsreport [Drug Prescription Report]* 2002. Berlin: Springer, 2003:233–251.

Elevated levels of tryptase in children with nummular eczema

L. Lange*, E. Rietschel, N. Hunzelmann, K. Hartmann

Key words: atopic dermatitis; atopic eczema; mast cells; nummular eczema; tryptase.

Tryptases are serine proteases primarily expressed in mast cells. Elevated levels of total tryptase in serum are known to be associated with systemic mastocytosis and anaphylaxis (1).

Increased tryptase has also been reported in acute myelocytic leukemia, myelodysplastic syndromes, hypereosinophilic syndrome, renal failure, and treatment of onchocerciasis. To our knowledge, increased tryptase in eczema has not been described so far. We report on three children with nummular eczema (NE) showing elevated tryptase. NE or discoid eczema is characterized by coin-shaped plaques of eczema with a chronic course (2). Bacterial infections have been discussed as eliciting factors.

A 3-year-old boy presented with about 20 erythematous plaques, some of them covered by yellow crusts. A skin biopsy showed subacute dermatitis with increased numbers of mast cells confirming the clinical diagnosis of NE. Total IgE was 253 kU/l, screening tests for specific IgE were negative. Surprisingly, total tryptase was elevated to 71.6 µg/l (ImmunoCAP Tryptase; Phadia AB, Freiburg, Germany). Reexamination excluded cutaneous mastocytosis and a careful history failed to reveal anaphylaxis in the past. Lesions of NE improved under topical steroids and pimecrolimus. Seven months later, the patient still showed mild eczema and tryptase was 20.6 µg/l. On follow-ups 4 and 5 months later, tryptase was 9.5 and 19.9 µg/l respectively.

This is the first observation of elevated tryptase levels in nummular eczema. Nummular eczema should be added to the differential diagnosis in subjects with elevated tryptase.

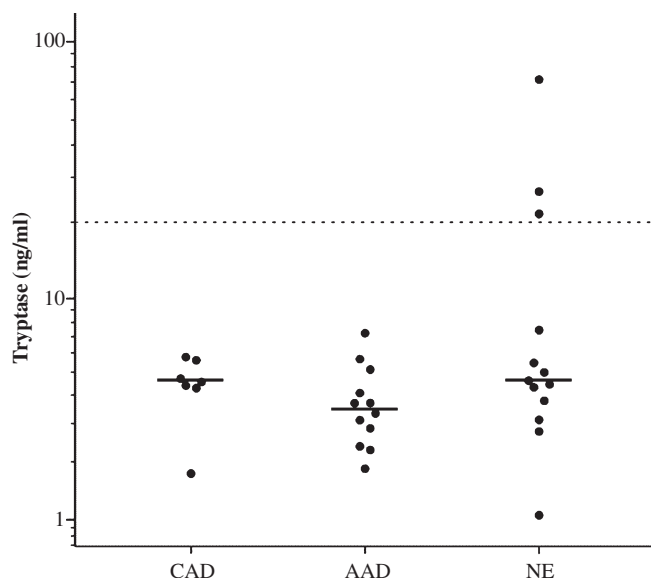


Figure 1. Elevated levels of total tryptase in a subgroup of patients with nummular eczema (NE, $n = 14$, median of total tryptase: 4.51 $\mu\text{g/l}$, SD: 18.72 $\mu\text{g/l}$), compared with acute exacerbation of atopic dermatitis (AAD, $n = 12$, median: 3.5 $\mu\text{g/l}$, SD: 1.54 $\mu\text{g/l}$) and chronic active atopic dermatitis (CAD, $n = 7$, median: 4.54 $\mu\text{g/l}$, SD: 1.32 $\mu\text{g/l}$). Dots represent single patients, bars represent the median of each group.

To investigate whether elevated tryptase is characteristic for NE, total tryptase was measured retrospectively in sera from 31 other children with eczema (Fig. 1). The 32 patients investigated in total (mean age: 34.8 months) were divided into three groups: 13 children with NE (including the index patient above), 12 children with acute exacerbation of atopic dermatitis (AD) defined by a SCORAD index of > 50 (AAD), and seven children with chronic active AD defined by continuous need for topical anti-inflammatory therapy during the last 6 months (CAD). Within the group of NE, two other patients were identified with tryptase $> 20 \mu\text{g/l}$. One patient was a 4-year-old girl with a tryptase level of 26.4 $\mu\text{g/l}$ and a decrease 6 months later to 5.15 $\mu\text{g/l}$. The other patient was a 7-month-old boy with a tryptase level of 21.6 $\mu\text{g/l}$. Unfortunately he was not available for follow-up measurement of tryptase. Both patients showed no signs of cutaneous mastocytosis, had not experienced anaphylaxis, and failed to reveal specific IgE to common allergens. In contrast to the group of NE, there were no patients with elevated tryptase ($> 20 \mu\text{g/l}$) within the groups of AAD and CAD. Overall,

however, tryptase levels between the three groups were not significantly different (Fig. 1). As expected, total IgE was significantly lower in NE (mean: 48 kU/l) compared with AAD (831 kU/l, $P < 0.0001$, chi-squared test) and CAD (1170 kU/l, $P < 0.0001$) and fewer sensitizations to allergens were observed in NE compared with AAD and CAD ($P < 0.0001$).

In agreement with our results, two previous studies failed to demonstrate elevated levels of tryptase in AD (3, 4). Unexpected, however, was the elevated tryptase in three out of 14 children with NE. This may in part be due to increased numbers of mast cells in cutaneous lesions. Confirming previous reports (5), a skin biopsy of the first patient demonstrated increased numbers of mast cells. In addition, it has been shown that mast cells in NE are mainly tryptase-positive and chymase-negative whereas normal cutaneous mast cells usually express both tryptase and chymase (5). Thus, the relative amount of tryptase per mast cell may be higher in NE compared with healthy skin. Furthermore, increased mast cell degranulation and release of tryptase could be related to the colonization of cutaneous lesions by bacteria. Bacterial

infections activate mast cells by different mechanisms, including stimulation of Toll-like and complement receptors and activation of the Fc epsilon receptor by bacterial toxin-specific IgE. In response to stimulation, mast cells release mediators aimed at combating the infection (6). Within these mediators, tryptase may also play a significant role (7). Supporting this hypothesis, our index patient presented initially with yellow crusts typical of impetiginization by *Staphylococcus aureus*. Signs of systemic infection such as leukocytosis or increased C-reactive protein were not observed in this patient as well as in the other patients with NE. Therefore, local inflammation rather than systemic infection may be related to tryptase release in NE.

On the other hand, increased mast cell numbers, a predominance of tryptase-positive mast cells and colonization by bacteria have all also been described in AD (5). Further studies are needed to elucidate pathogenetic factors that specifically cause elevated tryptase in NE compared with AD.

*Children's Hospital
University of Cologne
Kerpener Str. 62
50924 Cologne
Germany
Tel.: +49 221 478 4359
Fax: +49 221 478 3330
E-mail: lars.lange@uk-koeln.de

Accepted for publication 27 February 2008
Allergy 2008; 63:947–949
© 2008 The Authors
Journal compilation © 2008 Blackwell
Munksgaard
DOI: 10.1111/j.1398-9995.2008.01731.x

References

- Schwartz LB. Diagnostic value of tryptase in anaphylaxis and mastocytosis. *Immunol Allergy Clin North Am* 2006;26:451–463.
- Burton JL, Holden CA. Discoid eczema. In: Champion RH, Burton JL, Burns DA, Breathnach SM, editors. *Textbook of Dermatology*. 6th ed. Oxford: Blackwell Science, 1998:646–648.
- Kristjansson S, Shimizu T, Strannegard IL, Wennergren G. Eosinophil cationic protein, myeloperoxidase and tryptase in children with asthma and atopic dermatitis. *Pediatr Allergy Immunol* 1994;5:223–229.

4. Amon U, Memmel U, Stoll R, Amon S. Comparison of severity scoring of atopic dermatitis values and serum levels of eosinophil cationic protein and mast cell tryptase for routine evaluation of atopic dermatitis. *Acta Derm Venereol* 2000;**80**:284–286.
5. Jarvikallio A, Naukkarinen A, Harvima IT, Aalto ML, Horsmanheimo M. Quantitative analysis of tryptase- and chymase-containing mast cells in atopic dermatitis and nummular eczema. *Br J Dermatol* 1997;**136**:871–877.
6. Dawicki W, Marshall JS. New and emerging roles for mast cells in host defense. *Curr Opin Immunol* 2007;**19**:31–38.
7. McNeil HP, Adachi R, Stevens RL. Mast cell-restricted tryptases: structure and function in inflammation and pathogen defense. *J Biol Chem* 2007;**282**:20785–20789.

Aspirin tolerance and leukotriene biosynthesis in Churg-Strauss syndrome

W. Szczeklik*, L. Mastalerz, B. Sokolowska, M. Sanak, E. Nizankowska-Mogilnicka

Key words: aspirin; asthma; Churg–Strauss syndrome; leukotrienes.

Churg–Strauss syndrome (CSS) is a rare, diffuse, small-vessel vasculitis characterized by asthma, eosinophilia and tissue

infiltration by eosinophils (1, 2). Several clinical features of CSS are similar to those of aspirin-induced asthma (AIA), namely asthma, sinusitis with nasal polyposis and eosinophilia (3).

Eosinophil is believed to be a principal cell responsible for cysteinyl-leukotrienes (cys-LTs) overproduction in AIA (4). In patients with CSS urinary leukotriene E4 (LTE4) raises in exacerbation and decreases in remission (5). The similarities between these two clinical syndromes formed a rationale for our study.

We studied 12 patients with CSS in clinical remission (Table 1). None of the patients gave a history of asthmatic attack after ingestion of aspirin (ASA). They all underwent single-blind, placebo-controlled oral aspirin provocation test (6), coupled with urinary LTE4 measurement (ELISA; Cayman Chemicals, Ann Arbor, MI, USA) at base, and then every 2 h until 6 h after the last dose of placebo or aspirin. The test took 2 days; placebo was administered on the first day, and aspirin in incremental doses on the second. The study was approved by the Jagiellonian University Ethics Committee, and all patients gave informed consent to participate.

Aspirin is well tolerated and does not precipitate cysteinyl-leukotrienes overproduction in Churg-Strauss syndrome during remission.

Aspirin was very well tolerated; all subjects reached the cumulative dose of 500 mg without any adverse reaction or a fall in the forced expiratory volume in 1 s (FEV₁) exceeding 20% of the baseline value. Consecutive mean LTE4 values showed no significant changes either on the day of placebo or on the day of aspirin administration. Our results indicate that aspirin can be safely administered to patients with CSS in remission. Caution might still be warranted during exacerbations, which often are accompanied by tremendous cys-LTs overproduction. In two of our patients with cardiac involvement basal urinary LTE4 rose 25-fold and 11-fold during exacerbation. When remission was achieved the values returned almost to normal limits and both patients tolerated aspirin challenge very well. Despite clinical similarities, different mechanisms for induction of eosinophil might operate in CSS and AIA. Thus, serum IL-5 levels are markedly elevated in the former syndrome (5), but not in the later. Eosinophil function, however, is far more complex than that driven by IL-5 and determined by its genotype and interaction with target tissues.

*Department of Medicine
Jagiellonian University
Kraków
Poland
Tel.: +48 12 430 51 69
Fax: +48 12 430 52 03
E-mail: wszczeklik@gmail.com

Table 1. Clinical and laboratory profile of the studied group

Sex (F/M ratio)	9/3
Age (year)	42 ± 8.5
Duration of CSS (year)	7.5
CT-scan paranasal sinus abnormality	12 (100%)
Nasal polyps	5 (42%)
Atopy (yes/no)	11 (92%)
Asthma	12 (100%)
FEV ₁ %	97.43 ± 11.7
Blood eosinophil count (per mm ³)	197.5 (0.3–1217.2)*
Serum IgE (IU/ml)	51.85 (19.21–341.9)*
Urinary LTE4 at base (pg/mg creatinine)	346.3 (139.9–606.0)*
Patients on oral corticosteroids	9 (75%) average dose of 5.4 mg ± 3.8 methylprednisolone

Values are expressed as mean ± SD.

*Median (5th percentile – 95th percentile).

CSS, Churg–Strauss syndrome; LTE4, leukotriene E4.

Accepted for publication 29 February 2008

Allergy 2008; 63:949–950

© 2008 The Authors

Journal compilation © 2008 Blackwell

Munksgaard

DOI: 10.1111/j.1398-9995.2008.01734.x

References

1. Churg J, Strauss L. Allergic angitis and periarteritis nodosa. *Am J Pathol* 1951;**27**:277–301.
2. Pagnoux C, Guilpain P, Guillemin L. Churg–Strauss syndrome. *Curr Opin Rheumatol* 2007;**19**:25–32.
3. Stevenson DD, Szczeklik A. Clinical and pathologic perspectives on aspirin sensitivity and asthma. *J Allergy Clin Immunol* 2006;**118**:773–786.