Tryptase and histamine in patients with angioedema due to C1-inhibitor deficiency (Hereditary Angioedema, HAE) and in patients with mastocytosis

Tryptaza i histamina u chorych z napadowym obrzękiem naczynioruchowym w przebiegu niedoboru C1 inhibitora i u chorych z mastocytozą

Aleksander Obtułowicz [1], Magdalena Pirowska [1], Wojciech Dyga [2], Ewa Czarnobilska [2], Anna Wojas-Pelc [1]

[1] The Jagiellonian University, Medical College, Department of Dermatology
[2] The Jagiellonian University, Medical College, Department of Clinical and Environmental Allergology

Summary

Introduction. Tryptase and histamine levels may serve as an indicator of mast cells stimulation related to various diseases, such as mastocytosis, IgE-related allergy, confirming their participation in the pathogenesis.

Aim. Analyse tryptase and histamine levels and assess the correlation between tryptase and histamine levels in serum of the different groups of study patients.

Material and methods. The determinations were performed in 14 mastocytotic patients, including 6 patients with the systemic mastocytosis and 8 with urticaria pigmentosa, in 14 with innate angio-motor oedema due to C1 inhibitor deficiency, and in 10 healthy controls. Tryptase levels were determined using PhadiaUniCAP TRYPTASE reagents. Histamine concentrations were measured using HISTAMINE ELISA kit (LaborDiagnostikaNord).

Results. In 6 patients with systemic mastocytosis, the level of tryptase was high (>60 μg/L). In the majority of the patients with urticaria pigmentosa, the level of tryptase was elevated, but it did not exceed 60 μg/L. In half of the patients with systemic urticaria, the level of histamine was elevated, but it was not correlated with the increased level of tryptase. In the people with hereditary angioedema due to C1 inhibitor deficiency, the serum levels of tryptase and histamine were normal. In that group, no correlation was shown to occur between the levels of the study parameters.

Conclusions. No correlation was found between tryptase and histamine levels. Thus, it seems reasonable to conclude that the mediators are released from the mast cells independently.

Keywords: *tryptase, histamine, mastocytosis, hereditary angioedema*

Streszczenie

Wprowadzenie. Poziom tryptazy i histaminy w surowicy może być wskaźnikiem pobudzenia komórek tucznych w przebiegu wielu chorób takich jak mastocytoza, alergia IgE zależna, obrzęki napadowe, potwierdzając ich udział w patomechanizmie tych schorzeń.

Cel pracy. Analiza poziomu tryptazy i histaminy w surowicy oraz ocena zależności pomiędzy ich poziomem w surowicy badanych grup chorych.

Materiał i metody. Badania wykonano u 14 chorych z mastocytozą, w tym u 6 chorych z mastocytozą układową i u 8 z pokrzywką barwną, u 14 chorych z wrodzonym obrzękiem naczynioruchowym w przebiegu niedoboru C1 inhibitora w okresie napadu obrzęku oraz u 10 osób zdrowych stanowiących grupę kontrolną. U badanych oznaczono poziom tryptazy w surowicy metodą FEIA z wykorzystaniem aparatu UniCAP 100 Phadia oraz poziom histaminy w surowicy oznaczano metodą ELISA (Labor Diagnostika Nord).

Wyniki. U 6 chorych z rozpoznaniem mastocytozy układowej wykazano wysoki poziom tryptazy (>60 μg/L). U większości chorych z pokrzywką barwną poziom tryptazy był podwyższony, jednak nie przekraczał 60 μg/L. Poziom histaminy w surowicy u połowy chorych z mastocytozą systemową był podwyższony, nie korelował jednak ze wzrostem poziomu tryptazy. U osób z wrodzonym obrzękiem naczynioruchowym oznaczany w czasie obrzęku poziom tryptazy i histaminy w surowicy pozostawał w normie. W grupie tej nie wykazano również korelacji pomiędzy poziomami badanych parametrów.

Wnioski. W obu badanych grupach chorych nie stwierdzono korelacji pomiędzy poziomem tryptazy i histaminy, co sugeruje niezależność wydzielania tych mediatorów z komórek tucznych.

Słowa kluczowe: *tryptaza, histamina, mastocytoza, dziedziczny obrzęk naczynioruchowy*

www.alergia-astma-immunologia.eu

Przyjęto do druku: 19.03.2015

Adres do korespondencji / Address for correspondence
dr n. med. Aleksander Obtułowicz
The Jagiellonian University, Medical College
Department of Dermatology
Skawińskastr 8, Str, 31-066 Krakow, Poland
e-mail: aleksander.obtulowicz@uj.edu.pl

The mast cells originate from a lineage of hematopoietic marrow cells; they colonise vascularised tissue, where they mature [1, 2]. In human, two subpopulations of mast cells are identified: tryptase-positive (MCT) and tryptase- and chymase-positive (MTCT). The contribution of mast cells to the immunologic and nonimmunologic response of the system is very active [3, 4].

Due to the fact that they differ by the profile of released cytokines, they have a special place in the system's reactivity [2, 5]. In the immunologic mechanism, they take part in allergic reactions, anaphylactic reactions, innate anti-infection and anti-parasitic immunity. In the nonimmunologic mechanism they participate in remodeling and angiogenesis [3, 4]. Lately, also their contribution to delayed type hypersensitivity and angioedema has been discussed [2, 3, 6]. Among the released mediators, the highest clinical significance is attributed to histamine and tryptase [7-9].

The contribution of mast cells in the origin of inflammation has been known for many years [4, 10]. Their important role has been shown e.g. in allergic diseases, such as asthma and atopic dermatitis, but also in ischemic heart disease, chronic inflammatory bowel diseases or in chronic prostatitis and psoriasis [4, 11-13]. It should be noted that the activation of mastocytes in different diseases is not always accompanied by the same symptoms and generalised reactions [4, 10, 14]. An explanation of this phenomenon is the capacity of active mastocytes of differentiated or selective release of mediatiors, which is documented by the presented results of studies [3, 4].

A mastocyte is a cell engaged in early stages of allergic reactions, taking part also in the innate immunologic response against various pathogens [8, 15]. It is considered that the most important mediators are biogenic amines: histamine, serotonine, proteoglycanes, enzymes: tryptase, chimase, hydrolases, prostaglandines and numerous cytokines and growth factors, as: Il1,4,5,6,8,10, 13, SCF, TNF alfa/beta, GM-CSF, SCF, bFGF, PDGF, MIP-1alfa, VPF/VEGF [16-18].

In the pathogenesis of mastocytosis, the contribution of mast cells is irrefutable. Mastocytosis is a rare disease characterised by an accumulation of mast cells in tissues and organs [16]. The concentration of tryptase in subjects with mastocytosis is considered as an important diagnostic parameter, helping to plan the treatment and to monitor the disease course [19]. The clinical symptoms of mastocytosis depend on the mediators released from mast cells (tryptase, histamine, heparin, leukotrienes, etc.) as well as on the organ involved [20].

The hereditary angioedema (HAE) is a rare disease. It occurs in subjects with a deficiency of C1-esterase inhibitor (type I) or with its disfunction (type II). Furthermore, a type III edema is distinguished, where disfunctions or mutations of factor XII gene are found with a normal activity and level of C1-esterase [8, 21, 22]. It can be life-threatening in case of edema of face, throat or larynx, causing a risk of airway occlusion.

As there is still more evidence [7, 23-25] that the activation of mast cells is accompanied by a selective release of mediators, without cell disintegration, an attempt was made to simultaneously determine serum levels of tryptase and histamine as indicators of the stimulation of mast cells, in patients with HAE (hereditary angioedema due to C1-inhibitor deficiency) and mastocytosis.

The aim of the study was:

analysis of tryptase and histamine serum levels in adult subjects with mastocytosis, with hereditary angioedema in subjects with C1-inhibitor deficiency and in healthy subjects,

evaluation of the correlation of tryptase and histamine serum level as an indicator of mast cells stimulation.

MATERIALS AND METHODS

Serum tryptase level of subjects was determined by the FEIA method using UniCAP 100 (Phadia) device. According to the method, normal serum tryptase level should be < 11.4 ug/L. Serum histamine level was determined by the ELISA method (Labor Diagnostika Nord), in which normal serum histamine level is < 1 ng/ml.

The tests included:

1. 14 subjects with mastocytosis (5 women and 9 men, aged 29-56). In this group, 6 subjects were diagnosed with systemic mastocytosis and 8 subjects with urticaria pigmentosa.
2. 14 subjects (6 women and 8 men aged 24-52) in a severe attack of hereditary angioedema in the course of deficiency of C1-inhibitor.
3. 10 healthy subjects (7 women and 3 men, aged 28-49).

RESULTS

In subjects with mastocytosis (Fig. 1), the mean serum tryptase level was 95.40 ng/ml (SD 75.94). In this group, in 6 subjects with systemic mastocytosis (#9-14) the tryptase level was significantly increased and it was within the limits of 107.6 – 200 ng/ml, 169.9 (ng/ml) on average (SD 46.8). In the remaining 8 subjects (#1-8) with urticaria pigmentosa, this level in 6 of them was slightly increased and it oscillated between the values of 5.55-59.1 ng/ml, with an average of 35.9 (ng/ml) (SD 20.4) and in 2 subjects only it was within the normal range. Mean concentration of tryptase in the reference group was 3.51 ng/ml (Fig. 1).

The mean serum histamine level in subjects with mastocytosis was 1.63 ng/ml (SD 1.28). In 6 subjects it was within the normal range, in 8 it was increased, within the limits of 1.6-5 ng/ml (Fig. 2). An increase of the serum histamine level (>1ng/ml) was observed in subjects with systemic mastocytosis as well as in those with urticaria pigmentosa. Mean concentration of histamine in the reference group was 0.24 ng/ml.

In subjects with HAE, the serum tryptase level was within the normal range in all studied cases and it was on average 2.31 ng/ml (SD 2.38) (Fig. 3). The histamine level in serum in these subjects was also within the normal range, with an exception of two subjects where a slight increase of this concentration was shown (Fig. 4). On average it was 0.26 ng/ml (SD 0.3).

No correlation was shown between tryptase and histamine serum levels in subjects with HAE, correlation coefficient = 0.17 (<0.2).

No correlation was shown between tryptase and histamine levels in subjects with mastocytosis. The correlation coefficient between the studied mediators of mast cells was 0.04 (<0.2).

The correlation between the studied mediators of mast cells was not shown also in subjects with HAE, correlation coefficient: 0.17 (<0.2).

In subjects with systemic mastocytosis the tryptase level was found to be significantly higher than in subjects with urticaria pigmentosa. In the first group, the average level was higher than 107 ng/ml, in the second one it was lower than 60 ng/ml. In 50% of subjects with mastocytosis, the histamine level was increased, in subjects with systemic mastocytosis as well as in those with urticaria pigmentosa. No correlation was shown between the histamine level and the type of mastocytosis.

Based on the obtained results, no correlation was shown between the levels of the studied mediators in the analysed group of subjects – the result was non statistically significant.

In subjects with HAE studied during at attack of angioedema, the tryptase level was within a normal range, similarly as the histamine level, which only in two cases was increased (non statistically significant). The levels of the studied parameters in the analysed studied group were not correlated – the result was non statistically significant.

Based on the obtained results, no correlation was found between the levels of tryptase and histamine in both studied group of subjects, which confirms the independence of the release of the studied mediators from the mast cells.

DISCUSSION

The activation of mastocytes occurs via different mechanisms. Apart from the IgE-dependent reaction, there are multiple stimuli activating mastocytes via a non-specific route. The most important internal factors include drugs and food. Environmental factors include venoms of insects and physical factors (mechanical irritation/trauma), exposition to heat or cold [26].

The stimulation of mast cells may occur also in subjects with HAE during an uncontrolled activation of the complement system, leading to an increase of anaphylactotoxins (C3a and C5a), released from mast cells in the receptor mechanism [27]. Furthermore, studies from recent years (Renné, Bossi) indicate that in subjects with HAE, the induction of angioedema may occur also due to an activation of mast cells with the release of high-molecular-weight heparin, activating directly (by-passing the C1-inhibitor) the factor XII and kallikrein [8, 28-30].

The results of the presented studies indicate that the measurement of serum tryptase and histamine levels in both studied diseases may be important in their diagnosis and in studies of their pathomechanism. The lack of correlation between tryptase and histamine levels in both studied groups of subjects suggest the independence of their release from mast cells during their activation.

The attention is drawn to an increased histamine level in half of the subjects with mastocytosis, which indicates the possibility of an active contribution of this mediator in the development of some symptoms of the disease, e.g. itching – this can explain the effectiveness of antihistamine drugs reported by subjects.

This indicates that apart from the tryptase level, in some subjects with mastocytosis, histamine, released independently from the release of tryptase, can be important in the development of symptoms. There is a question whether the increase of histamine in these subjects is a result of action of another cause factor than the one increasing the release of tryptase.

In subjects with HAE, examined in the period of edema, an increase of the tryptase level was not shown. On the other hand, an increase of the histamine level in 2 cases requires studies on more subjects, especially in subjects with HAE with history suggesting that edemas are induced by food, drugs or chemicals. An increase of this mediator's level in these cases might be a result of an activation of mast cells or of the appearance of complement-derived histamine during the activation of the complement system [8, 27]. This might explain the efficiency of anti-histamine drugs

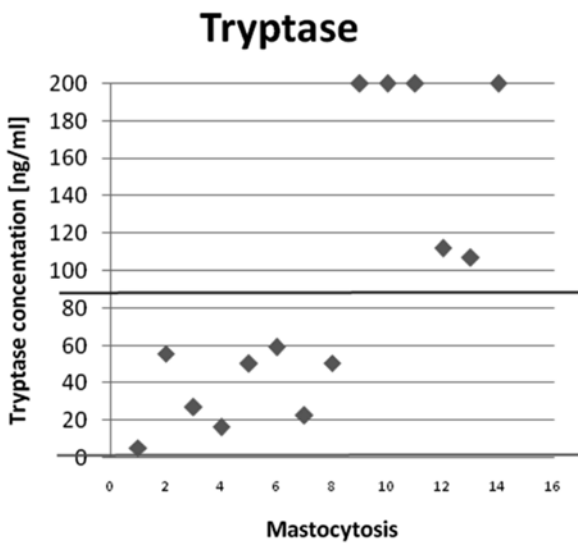

Fig. 1. Tryptase level in subjects with mastocytosis

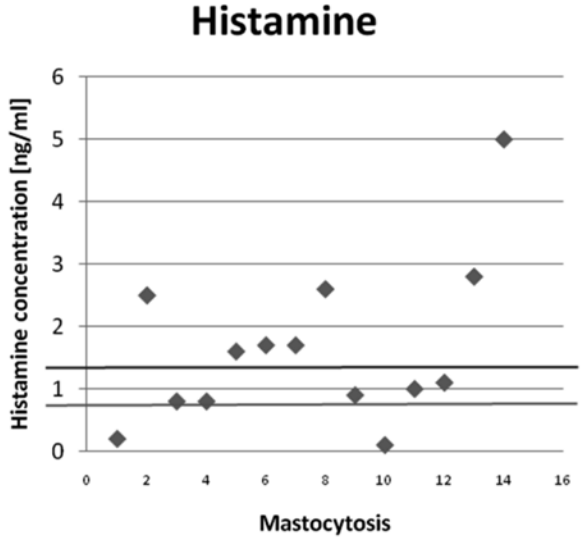

Fig. 2. Histamine level in subjects with mastocytosis

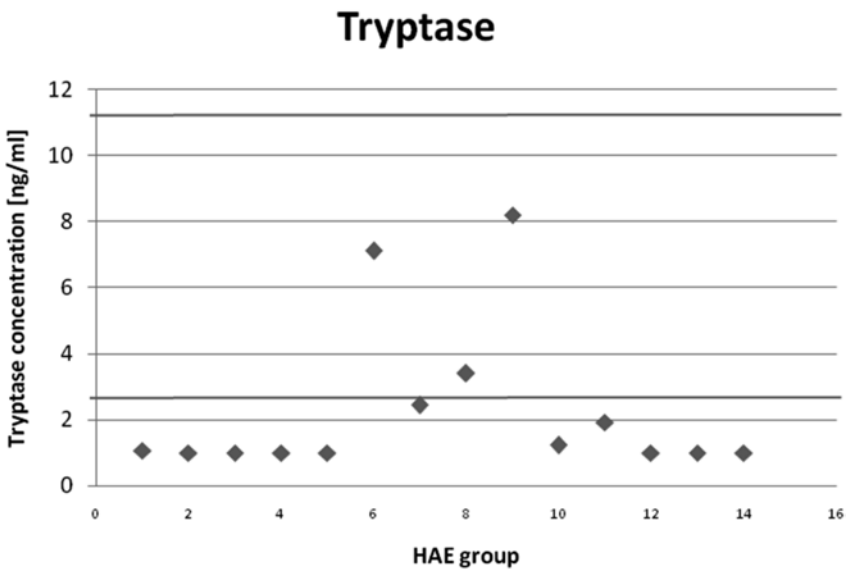

Fig. 3. Tryptase level in subjects with HAE

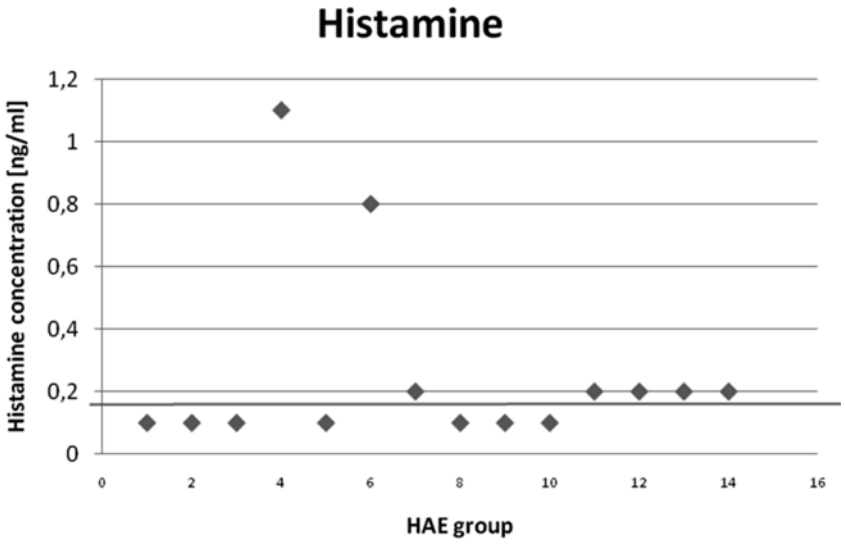

Fig. 4. Histamine level in subjects with HAE

administered in early stages of edema formation, reported by some subjects with HAE.

The introduction of the term "mast cells activation syndrome" by Valent [7, 31] made us aware of the existence of a dependence between individual mediators released by mastocytes and the variety of clinical symptoms [7, 32, 33]. The mast cells, depending on the conditions of micro-environment where they undergo an activation, seem to release various inflammatory mediators, inducing a local reaction [3]. The knowledge and understanding of the mechanisms of diversified release of mediators from mast cells will allow in the future to introduce selective inhibitors in order to manage the symptoms that are mediator-dependent. The knowledge of this phenomenon explains the non-effectiveness of mono-treatment, observed in subjects, and the need of simultaneous use of blockers of different mediators released by mast cells.

CONCLUSIONS

1. No correlation is present between tryptase and histamine serum levels in subjects with mastocytosis and HAE.
2. In subjects with mastocytosis, in 50% an increase of histamine level is observed.
3. The knowledge and understanding of the mechanisms of differentiated release of tryptase and histamine might allow in the future for an individual choice of effective drugs.

References

1. Rodewald HR, Dessing M, Dvorak AM, et al. Identification of a committed precursos for the mast cell lineage. Science 1996; 271: 818-22.
2. Obtułowicz K, Obtułowicz A, Stobiecki M, et al. Mastocyty i mastocytoza. Alergologia Immunologia 2009; 6: 21-6.
3. Nazimek K, Marcinkiewicz J, Bryniarski K. Funkcje mastocytów w nadwrażliwości typu późnego. Alergologia Immunologia 2013; 10: 10-14.
4. Theoharides TC, Kempuraj D, Tagen M, et al. Differential release of mast cell mediators and the pathogenesis of inflammation. Immunol Rev 2007; 217: 65-78.
5. Marshall JS. Mast-cell responses to pathogens. Nat Rev Immunol 2004; 4: 787-99.
6. Bjorkqvist J, Renné T, Muller F. Emerging functions of the plasma contact system In hereditary angioedema. Journal of Angioedema 2011; 1: 7-13.
7. Valent P. Mast cell activation syndromes: definition and classification. Allergy 2013; 68: 417-24.
8. Renné T. The procoagulat and proinflammatory plasma contact system. Semin Immunopatol 2012; 34: 31-41.
9. Galli SJ, Grimbaldeston M, Tsai M. Immunomodulatory mast cells: negative, as well as positive, regulators of immunity. Nat Rev Immunol 2008; 8: 478-86.
10. Theoharides TC, Cochrane DE. Critical role of Mast cells In inflammatory diseases and the effect of acute stress. J Neuroimmunol 2004; 146: 1-12.
11. Paus R., Theoharides TC, Arck PC. Neuroimmunoendocrine circuitry of the brainskin connection. Trends Immunol 2006; 27: 32-9.
12. Theoharides TC, Kalogeromitros D. The critical role of mast cell in allergy and inflammation. Ann NY Acad Sci 2006; 1088: 78-99.
13. Navi D, Saegusa J, Liu FT. Mast cells and immunological skin diseases. Clinic Rev Allerg Immunol 2007; 33: 144-55.
14. Taub D, Dastych J, Inamura N, et al. Bone marrow-derived Marine nast. Cells migrate, but do not degranulate, in response to chemokines. J Immunol 1995; 154: 2393-402.
15. Marshall JS. Mast-cell responses to pathogens. Nat Rev Immunol 2004; 4: 787-99.
16. Obtułowicz A, Antoszczyk G, Dyga W, et al. Stężenie tryptazy i objawy anafilaksji na jad owadów w programowaniu leczenia chorych z mastocytozą. Alergologia Immunologia 2012; 9: 216-19.
17. Lange M, Renke J, Gleń J, et al. Tryptazamastocytowa, interleukina 6 oraz index SCORMA jako wykładnik ciężkości przebiegu mastocytozy u dzieci. Post Dermatol i Alergol 2010; 4: 238-45.
18. Dereń-Wagemann I, Kuliszkiewicz-Janus M, Kuliczkowski K. Mastocytoza- rozpoznawanie i leczenie postępy. Hig Med. Dosw 2009; 63: 564-76.
19. Niedoszytko M, Jassem E, Kruszewski J. Mastocytoza. Benkowski, Bydgoszcz 2007.
20. Obtułowicz K, Obtułowicz A, Stobiecki M, et al. Mastocyty i mastocytoza. Alergologia Immunologia 2009; 6: 21-6.
21. Cichon S, Martin L, Hennies HC, et al. Increased activity of coagulation Factor XII (Hageman Factor) causes hereditary angioedema type III. Am J Hum Genet 2006; 79: 1098-104.
22. Dewald G, Bork K. Missense mutations in the coagulation factor XII (Hageman factor) gene in hereditary angioedema with normal C1 inhibitor. Biochem Biophys Res Commun 2006; 343: 1286-9.
23. Theoharides TC, Bondy PK, Tsakalos ND, et al. Differential release of serotonin and histamine from mast cell. Nature 1982; 297: 229-31.
24. Kops SK, Theoharides TC, Cronin CT, et al. Ultrastructural characteristics of rat peritoneal mast cell undergoing differential release of serotonin without histamine and without degranulation. Cell Tissue Res 1990; 262: 415-24.
25. Kops SK, Van Loveren H, Rosenstein RW, et al. Mast cell activation and vascular alterations in immediate hypersensitivity – like reactions induced by a t cell derived antigen-binding factor. Lab Invest 1984; 50: 421-34.
26. Marciniak J, Jutel M. Znaczenie mastocytozy w reakcjach anafilaktycznych. Post Dermatol Alergol 2006; 1: 17-20.
27. Sullivan KE. The complement system. Middleton's Allergy,7th Ed, 2009, Mosby Comp. 89-114.
28. Noga O, Brunnee T, Schaper C, Kunkel G. Heparin, derived from the mast cells of human lungs is responsible for the generation of kinins in allergic reactions due to the activation of the contact system. Int Arch Allergy Immunol 1999; 120: 310-16.
29. Brunnee T, Reddigari SR, Shibayama Y, et al. Mast cell derived heparin activates the contact system: a link to kinin generation in allergic reactions. Clin Exp Allergy 1997; 27: 653-63.
30. Hojima Y, Cochrane CG, Wiggins RC, et al. In vitro activation of the contact (Hageman factor) system of plasma by heparin and chondroitin sulfate E. Blood 1984; 63: 1453-9.
31. Valant P, Akin C, Arock M, et al. Definitions, criteria and global classification of mast cell disorder with special reference to mast cell activation syndromes: a consensus proposal. Int Arch Immunol 2012; 157: 215-25.
32. Bossi F, Frossi B, Radillo O, et al. Mast cell are critically involved in serum – mediated vascular leakage in chronic urticaria beyond high affinity IgE receptor stimulation. Allergy 2011; 66: 1538-45.
33. Holgate ST, Robinson C, Church MK, et al. The contribution of mast cell mediators to acute allergic reactions in human skin and airways. Allergy 1988; 43: 22-31.