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Simultaneous occurrence of chronic autoimmune urticaria and non-allergic asthma: a common mechanism?

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Key words

Anti-FcεRI autoantibodies, autologous serum skin test, histamine-releasing factors, chronic urticaria, non-allergic asthma.

Summary

Chronic urticaria is now considered as an autoimmune disorder due to histamine-releasing autoantibodies in 40-50% of cases. These histamine releasing-autoantibodies directed against the high affinity IgE receptor or against IgE can be detected in vivo by autologous serum skin test (ASST) or in vitro by a functional assay employing basophils. ASST positivity has been found also in patients with non-allergic asthma, but its relevance to the disease mechanism remains to be defined. Here, we report two women aged 43 and 75 years who complained simultaneous occurrence of chronic urticaria and asthma. Circulating histamine-releasing factors were detected in both patients by ASST and basophil histamine release assay whereas other possible causes of urticaria and asthma were excluded by clinical and laboratory investigations. The elder woman had associated autoimmune thyroiditis. We suggest that circulating histamine-releasing factors, probably represented by histamine-releasing autoantibodies, might be involved in the pathophysiology of both chronic urticaria and asthma.

Introduction

It is now recognized that chronic urticaria (CU), once considered as a mysterious disorder, has an autoimmune/autoreactive origin in about 40-50% of cases (1). In 1986 Grattan observed that the intradermal injection of autologous serum causes a wheal-and-flare reaction in about half CU patients suggesting the presence of circulating histamine-releasing factors as a possible pathogenic factor (2). Subsequently, skin reactivity to autologous serum in CU patients was found to be associated with functional autoantibodies directed against the α subunit of the high affinity IgE receptor (FcεRI) or against IgE (3, 4). However, histamine-releasing autoantibodies have been detected in about 30% of CU patients, whereas about 50% of the patients show skin reactivity to intradermal injection of autologous serum (5). Furthermore, if Na-citrate autologous plasma is used instead of autologous serum, the proportion of positive patients increases up to 80% (6). It appears indeed that vasoactive and permeability factors other than histamine-releasing autoantibodies are involved in the disease. This view is also supported by the observation that sera from CU patients containing anti-FcεRI autoantibodies retained their ability to induce a wheal-and-flare reaction upon intradermal injection after depletion of IgG (7). Although not all aspects of the CU pathomechanism have been revealed, the recent advances have changed the clinical approach to the

patient, with avoidance of extenuating restriction diets and judicious use of immunosuppressive drugs, namely ciclosporin, in those cases which are not adequately controlled by anti-histamines and steroids. In contrast to CU, "non-allergic" asthma remains nowadays a mysterious disorder. It has been ascertained that allergic and non-allergic asthma share a common background characterized by inflammatory changes of respiratory airways, and the immunopathological differences that can be detected are quite subtle. However, in allergic asthma bronchial inflammation and respiratory symptoms are triggered by allergen exposure and consequent IgE-mediated mast-cell degranulation, followed by recruitment and activation of other inflammatory cells including eosinophils, basophils and T lymphocytes (8). In contrast, the event which provokes bronchial inflammation in "non-allergic asthma" is still elusive. Local expression of epsilon germline gene transcripts and RNA for the epsilon heavy chain of IgE has been found in the bronchial mucosa of allergic and non-allergic asthmatics, but the possible contribution of IgE antibodies to the mechanism of non-allergic asthma has not been elucidated (9). We have recently shown that intradermal injection of autologous serum causes a wheal and flare reaction in about half the patients with non-allergic asthma (10). *In vitro* evidence for histamine-releasing autoantibodies was found only in a minority of patients and so we hypothesized that a hitherto uncharacterized vasoactive factor could account for skin reactivity to autologous serum (10, 11). Here, we report the presence of serum histamine-releasing factors in two patients who complained simultaneous occurrence of urticaria and asthma symptoms.

Case report

Two women aged 43 and 75 years were evaluated at the outpatient Allergy Clinic of the Ospedale Maggiore Policlinico of Milan, Italy, because of CU with angioedema lasting from five years and six months, respectively. Both patients reported that urticaria onset was associated with the simultaneous appearance of asthmatic symptoms. The younger patient had positive skin prick tests for grass pollens and ragweed, but asthmatic symptoms were perennial and apparently unrelated to pollen exposure. After antihistamine treatment (ebastine and levo-cetirizine, respectively) had been stopped for five days, both patients underwent intradermal testing wih 0.05 mL of both sterile autologous serum (ASST) and saline as negative control, as described by Sabroe et al. (12). After coagulation for 30 min at room temperature, blood samples were centrifuged at 500 g for 10 minutes and serum was immediately used for intradermal tests. A skin prick test with histamine 10 mg/mL was used as positive control. Readings were taken at 30 minutes. The diameter of serum-induced wheal was 4 mm in the younger patient and 8 mm in the older patient, in the absence of any wheal induced by injection of saline solution. The diameters of control wheals induced by histamine were 6 mm and 5 mm, respectively. The response to intradermal injection of autologous serum was therefore considered positive in both cases. Sera from both patients were tested for histamine-releasing activity using basophils of a normal donor showing a 30% net histamine release following challenge with an optimal dose of rabbit polyclonal antihuman IgE antiserum (final dilution 1/5000, Sigma Chemical, St. Louis, MO, USA), as described (13). Histamine concentration in the cell supernatant was measured by an automated fluorometric technique and results were expressed as % net histamine release. Histamine release induced by control sera from 20 normal subjects was below 5%, and this value was used as cut-off, also taking into consideration our previous experience (13). Sera from both patients contained significant histamine-releasing activity (21.4% net release in the younger patient and 9.8% in the older patient). Other possible causes of urticaria and angioedema (chronic infections, parasitoses, food allergy, and C1 inhibitor deficiency) were excluded. The older patient had associated hypothyroidism due to autoimmune thyroiditis with a high titre of anti-thyroid peroxidase antibodies, and was being treated with levo-thyroxine since the age of 60. In both patients the diagnosis of asthma was confirmed by respiratory function tests showing mild to moderate obstruction which was reversible after albuterol inhalation. In the younger patient baseline forced expiratory volume in 1 second (FEV1) was 1.32 L (47% of predicted) and increased up to 1.79 L (36% increase) after inhalation of 200 mcg albuterol. In the older patient baseline FEV1 was 1.25 L (58% of predicted) and increased up to 1.5 L (20% increase) after inhalation of 200 mcg albuterol. Clinical features and results of the investigations are summarized in the table 1. Both patients received local treatment with a combination of steroid and bronchodilator (budesonide and formoterol) and oral montelukast (10 mg once a day). Treatment of urticaria was with H1 antihistamines (ebastine and levocetirizine, respectively) and occasionally with short courses of oral prednisone.

Table 1 - Characteristics of the two patients who complained simultaneous onset of urticaria and asthma symptoms

Patient	Age	Sex	Atopy	ASST	BHRA	Anti-TPO antibodies	FEV1 L (% predicted)	Post BD FEV1 increase
1	43	F	Yes	Positive	Positive	Negative	1.32 (47)	36%
2	75	F	No	Positive	Positive	Positive	1.25 (58)	20%

ASST: autologous serum skin test; BD: bronchodilator (200 mcg albuterol); BHRA: basophil histamine release assay; FEV1: forced expiratory volume in 1 second; TPO: thyroid peroxidase

Discussion

The patients reported are peculiar in that they complained simultaneous onset of urticaria and asthma symptoms, an association suggesting that a common mechanism underlies both disorders. ASST and basophil histamine release assay were positive in both patients indicating that CU had an autoimmune/autoreactive origin linked to circulating histamine-releasing factors, probably histamine-releasing autoantibodies. In fact, skin reactivity to autologous serum in CU patients was found to be associated with functional autoantibodies directed against the α subunit of the high affinity IgE receptor (FcεRI) or against IgE (3, 4). Unfortunately, a routine *in vitro* assay able to detect circulating and functionally active anti-FcεRIα and/or anti-IgE autoantibodies is still lacking. ASST has been indeed considered as an *in vivo* screening test for histamine-releasing autoantibodies directed against the high affinity IgE receptor or against IgE (12), and basophil histamine release assay has been used as a confirmatory test showing the presence of functionally active histamine-releasing autoantibodies (14). The results of *in vivo* and *in vitro* tests for circulating histamine-releasing factors suggested that CU and, possibly, asthma had an autoimmune/autoreactive origin in both patients. In addition, the association with autoimmune thyroiditis in the elder patient was another element supporting the theory of an autoimmune aetiology of CU. A high prevalence of autoimmune thyroiditis has been found in patients with CU (15), particularly in those with a positive ASST who presumably have circulating histamine-releasing autoantibodies (16). Conversely, no clear association between autoimmune thyroiditis and asthma has been demonstrated. Data regarding the association of asthma with other autoimmune disorders, such as type 1 diabetes, rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease and multiple sclerosis are rather controversial (17). The association of CU and asthma is not surprising, since it has been observed that bronchial hyperreactivity is common in patients with CU, probably as a result of the chronic activation of mast cells, basophils and eosinophils (18). In fact, it has been demonstrated that sera from CU patients can induce the release of histamine and leukotriene C4 from basophils (19), and both mediators are involved in the mechanism of asthma. In addition, Puccetti et al. have shown that sera from about 80% of CU patients contain autoantibodies directed against CD23, the low-affinity IgE receptor which is located on eosinophils (20). The anti FcεRII/CD23 autoantibodies can activate eosinophils inducing the release of major basic protein which in turn provokes histamine release from mast cells. The eosinophil-mediated activation of mast cells may be relevant to the pathophysiology of CU and asthma. Previously, we investigated the presence of circulating histamine-releasing factors in patients with non-allergic asthma and, in spite of a frequent ASST positivity (about 50% of patients, we found *in vitro* evidence for circulating histamine-releasing factors only in a minority of patients (16%) (11). This may be due to relatively low sensitivity of the basophil histamine release assay, but could also be explained by a low prevalence of histamine-releasing autoantibodies in patients with non-allergic asthma. We suppose indeed that non-allergic asthma is a heterogeneous disorder which may be sustained by different mechanisms. In some patients, like those described in the present report, circulating histamine-releasing factors, probably represented by histamine-releasing autoantibodies, may contribute to the disease pathophysiology. This view is also supported by the recent findings by Sun et al. who detected histamine-releasing autoantibodies directed against the high affinity IgE receptor in about 30% of asthmatic patients (21).

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