Autoimmune Diseases and Asthma

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Cellular immune mechanisms comprise 2 types of response, namely the T1 response and the T2 response [1]. Asthma is a heterogeneous disease characterized by chronic inflammation of the airways. Various cells and cytokines, mainly those of the T2 profile [2], intervene in the pathogenesis of asthma, whereas the T1/T17 profile predominates in autoimmune diseases. The immunologic paradigm TI/T2 predicts a negative association between autoimmune (T1) and allergic diseases (T2) [1]. However, some authors propose autoimmunity as the key pathological mechanism of so-called intrinsic asthma, while others consider it an additional phenomenon to allergy in the development of asthma. Co-occurrence of allergy and autoimmunity in the same patient and the presence of autoantibodies in both entities support the hypothesis of autoimmunity in asthma [3-5]. Other factors that corroborate this hypothesis are the role that T-cell dysregulation and mast cells have in both diseases [2-5].

With the aim of analyzing the inflammatory profile of patients with asthma and autoimmune diseases, we describe a series of consecutive asthmatic patients (diagnosed according to GINA criteria [2] at least 1 year before inclusion in the study) with a known concomitant autoimmune disease attended during the year 2016 in a certified multidisciplinary severe asthma unit.

After signing the informed consent document, patients were included in the study and phenotyped as T2-high or T2-low according to the following criteria proposed by Woodruff et al [6] and Kraft [7]: the T2-high phenotype was defined as total IgE >100 IU/mL and peripheral blood eosinophilia >140/mm^3; the phenotype was considered T2-low if only 1 or neither of these 2 criteria was met. Pulmonary function parameters and other inflammatory biomarkers (fractional exhaled nitric oxide [FeNO] and serum periostin) were registered. Asthma control was assessed based on the presence of at least 1 exacerbation during the previous year and on the results of the Asthma Control Test (ACT).

Table. Concomitant Autoimmune Diseases

Autoimmune Disease	No.[a]
Autoimmune thyroiditis	5
Psoriasis	4
Rheumatoid arthritis	3
Systemic lupus erythematosus	2
Sjögren syndrome	2
Autoimmune hepatitis	2
Autoimmune gastritis	1
Raynaud syndrome	1
Antiphospholipid syndrome	1
Chronic immune thrombocytopenia	1
Myasthenia gravis	1
Amyopathic dermatomyositis	1
Guillain-Barré syndrome	1
	25

[a]A patient could have more than one autoimmune disease.

We included 18 asthmatic patients with at least 1 concomitant autoimmune disease (Table). The median (IQR) age was 52.5 (27-78) years, and 83% were female. Nine patients had been smokers (current smokers, 3; ex-smokers, 6; median pack-years, 15) and 5 patients fulfilled the criteria for asthma-COPD overlap syndrome. Eight patients (44%) were atopic and 6 (33%) had aspirin-exacerbated respiratory disease. The associated comorbidities were chronic rhinosinusitis (33%), sleep apnea-hypopnea syndrome (11%), gastroesophageal reflux (33%), bronchiectasis (28%), and psychiatric disorders (28%). The inflammatory biomarker values (expressed as median [minimum-maximum value]) were as follows: blood eosinophils, 200/mm^3 (100-800); blood neutrophils, 3200/mm^3 (2400-6600); total IgE, 94 IU/mL (2-2717); FeNO, 20 ppb (12-50); and serum periostin, 29.91 ng/mL (15-85.99). Spirometric values (expressed as median [minimum-maximum value]) were as follows: forced vital capacity (FVC), 3120 mL (1780-4580); %FVC, 101% (71-126); forced expiratory volume in the first second (FEV_1), 2315 mL (1320-3890); %FEV_1, 92% (64-129); and %FEV_1/FVC, 70% (63-91). Seven patients (39%) had chronic airflow limitation (all 7 had been smokers).

The molecular asthma phenotype was T2-low in 61% of patients (n=11). As for severity, no patients had mild asthma, 33% (n=6) had moderate asthma, and 67% (n=12) had severe asthma. According to the ACT scores, disease was controlled in 55% of patients, partially controlled in 27%, and uncontrolled in 18%. In the previous year, 67% of patients had had at least 1 exacerbation, none of which required admission to the intensive care unit.

When considering patients according to asthma severity, we found that 50% of patients with moderate asthma had a T2-low phenotype and median serum periostin of 16.28 ng/mL. According to the ACT scores, disease was controlled in 75% and partially controlled in 25%. At least 1 exacerbation during the previous year was recorded in 67%. All patients were treated with low or medium doses of inhaled corticosteroids and a long-acting $ß_2$-agonist; 33% were also treated with tiotropium.

Sixty-seven percent of patients with severe asthma had a T2-low phenotype and median serum periostin of 34.06 ng/mL. According to the ACT scores, disease was controlled in 43%, partially controlled in 28%, and uncontrolled in 29%. Severe asthma guidelines (ERS/ATS [8] and SEPAR [9]) consider an ACT score <20 as uncontrolled asthma; therefore, 57% of patients with severe asthma had uncontrolled disease. At least 1 exacerbation during the previous year was recorded in 67%. All patients were treated with high doses of inhaled corticosteroids and long-acting $ß_2$-agonists. Additionally, 58% were treated with tiotropium, 67% with a leukotriene receptor antagonist, 8% with macrolides, 8% with omalizumab, and 25% with mepolizumab.

The results of the series we present show that the T2-low profile predominated and was associated with low levels of serum periostin [10]. However, 44% of patients were atopic, thus contradicting the theory that the T1 profile suppressed the development of atopy. Evidence of T2 inflammation was detected in 39% of patients, and in 33% of those with severe disease, leading us to believe that these patients could benefit from anti-T2 monoclonal antibodies. Nonetheless, asthma was uncontrolled in >50% of patients with severe asthma, and 67% had had at least 1 exacerbation during the previous year. These results support our hypothesis that the association between asthma and autoimmune disease leads to more severe and difficult-to-treat asthma. Given that the pathophysiology has yet to be established, we think it is important to determine the inflammatory profile of these patients when we consider a biological treatment, because they could be good candidates for new therapies, even though they have a concomitant autoimmune disease.

Our study is limited by the fact that the case series is small and heterogeneous. Nonetheless, it tries to highlight the importance of the association between asthma and concomitant autoimmune disease, which, to our knowledge, has not been suitably addressed elsewhere. It would be interesting to perform prospective studies with larger samples to clarify the complex underlying mechanisms of asthma in these patients and, consequently, to identify the best therapeutic targets.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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