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LETTER TO THE EDITOR
EDİTÖRE MEKTUP

Asthma phenotype and endotype definitions

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To the Editor,

Studies on asthma phenotypes and endotypes have been increasing in recent years. Asthma has no longer simple divisions like intrinsic and extrinsic asthma; it has evolved into many groups of asthma phenotypes according to clinical, laboratory, functional, inflammatory characteristics, and response to treatment. Understanding asthma phenotypes and endotypes has become even more critical as many biological therapies have begun to offer a targeted approach to treat the underlying inflammation in asthma (1).

Phenotype definition means the classification of asthma based on observable and clinical features. They are visible features based on the relationship between genes and the environment. These properties depend on clinical, biochemical, functional, and pharmacological conditions. Phenotypes may change over time, but they represent a useful initial criterion for discriminating between patients and a potential predictor of response to treatment (2). Some of these phenotypes are;

- According to clinical features: early-onset asthma, late-onset asthma, allergic asthma, non-allergic asthma, aspirin-induced asthma, premenstrual asthma, exercise-induced asthma
- According to physiological features: asthma with wide reversibility interval, asthma with low FEV₁, asthma with fixed airflow obstruction

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- According to treatment response: steroid-resistant asthma, steroid-sensitive asthma
- According to prognostic factors: brittle asthma, near-fatal asthma, benign asthma
- According to their inflammatory phenotypes: eosinophilic, neutrophilic, mixed, paucigranulocytic asthma (2,3).

In addition, asthma phenotypes were categorized by algorithmic cluster analysis. Multi-center, large-scale studies have been conducted using different cluster analysis techniques to detect asthma phenotypes (4-7). The results of all these studies show that there are consistently similar asthma phenotypes (8):

- Early-onset allergic asthma,
- Early-onset allergic moderate-severe asthma,
- Late-onset non-allergic eosinophilic asthma
- Late-onset non-allergic non-eosinophilic asthma.

The association of phenotypes of asthma, which is quite heterogeneous, with cellular, molecular, immunological, and pathophysiological mechanisms is called endotype. Endotypes, based on the pathophysiology of the disease, can provide more information for "precision medicine" and "personalized medicine" (9,10). Endotypes are classified into two main groups; type 2 high [T helper 2 (Th2) and innate lymphoid cells type 2 (ILC2) play a role in the underlying immunopathobiology] and type 2 low [T helper 2 (Th2) and innate lymphoid cells type 2 (ILC2) not playing a role in the underlying immunopathobiology]. These endotypes are taken into consideration when planning the use of biological treatments in severe asthma. Endotypes were defined by the expression level of cytokines released from classical CD4 + Th2 cells and non-classical ILC2 cells. When it was shown that these cytokines were not only secreted from Th2 cells but could also be secreted by ILC2s, the term "Th2 type endotype" was changed to "type 2 endotype" (11).

If we make these definitions concrete;

We can compare phenotypes to siblings: The phenotypic characteristics of siblings are more than an "X" person who has no blood relation.

We can compare endotypes to fraternal twins: The similarity in phenotypic and genotypic traits of fraternal twins will be even greater.

We can compare subendotypes to identical twins: Almost all phenotypic and genotypic features of identical twins are very similar to each other.

What does this phenotypic and endotypic classification facilitate in asthma?

- It enables the development of more effective therapies
- Determination of biological markers, and
- A clearer understanding of the immunopathophysiology and genetics of the disease in studies conducted in groups with similar characteristics.

In asthma, attention has started to focus on molecular pathways and mechanisms related to endotypes. Sorting asthma patients by endotype plays a role in determining treatment options (12). Type 2 asthma endotype consists of Th2 cells of adaptive immunity, ILC2 of innate immunity, eosinophils, mast cells, specific IgE, IL 4, IL 5, IL 9, IL 13, TSLP, and alarmins (IL 25, IL 33, TSLP). In daily practice, the T2-rich asthma endotype is defined through simple, inexpensive, and easily accessible biomarkers that can be used routinely and clinically. In this sense, T2 asthma in GINA is defined by the presence of one or more of the skin prick test (DPT) against aeroallergens and/or specific IgE positivity, blood eosinophilia, sputum eosinophilia, elevated FeNO, oral corticosteroid (OCS) dependence. In cases where these criteria are not met, it is recommended to show that there is no elevated FeNO and blood eosinophilia at least three times at different times before it is called non-T2 asthma (13). However, using these parameters may be insufficient to say subendotype. Because they are also eosinophilic and atopic phenotypes, both can coexist and may occur via Th2 dominant or ILC2 dominant. What is important here is which pathway is responsible for this Type 2 rich asthma phenotype. In this case, the subendotype can be mentioned. For example, if the main pathway leading to this inflammation is identified in the eosinophilic asthma phenotype (also classified as type 2 asthma endotype) and is clinically relevant, we can talk about asthma endotypes.

Example 1. The dominant mechanism underlying in a type 2 asthma phenotype/endotype with early-onset allergic rhinitis and marked respiratory symptoms associated with allergen exposure and blood peripheral eosinophilia is Th2 cells, allergen-specific IgE, mast cell degranulation, and the early and late phase allergic inflammation secondary to these. Allergens

can also contribute to ILC2 activation by stimulating alarmins. But, the dominant mechanism is the Th2 pathway (11). This is an asthma subendotype; that is, an identical twin.

Example 2. In asthma phenotype accompanied by chronic rhinosinusitis/nasal polyps, high eosinophilia, triggered by viral infections or toxic pollutants and where there is no clinic compatible with atopy, it is the pathway dominated by ILC2 and accompanied by leukotriene synthesis metabolism disorder, which forms the type 2 rich asthma phenotype/endotype. Here too, native Th2 cells and specific IgE formation may contribute. However, ILC2 and leukotriene synthesis metabolism disorder plays a role in the primary mechanism (11). This is also an asthma subendotype; that is, it is an identical twin.

Many cell types, mediators, and immune pathways determine the inflammatory pathways in asthma. These pathways show possible individual differences in patients. They may change over time with environmental interactions and create a much more complex inflammatory process than distinguishing between type 2 inflammation and non-type 2 inflammation (14). Besides, it will be discussed that endotypes have much more specific subendotypes and that certain cytokines and mediators are predominant. Different T2 rich or T2 poor asthma endotypes will be developed, and appropriate treatment modalities for much more specific personalized medicine will be developed in the future.

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