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Mini Review

Type 2 inflammation in pediatrics: an overview

Ilaria Maria Vella[1,2], Elena Monti[1,2], Mariano Di Rosa[1,2], Amelia Licari[1,2]

[1] Pediatric Unit, Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Italy; [2] Pediatric Clinic, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

SUMMARY

Atopic dermatitis, bronchial asthma, and food allergy are chronic diseases that can be associated with each other in childhood according to different trajectories. The two main mechanisms that these diseases share are barrier damage and activation of immune cells that release type 2 inflammatory cytokines. Biological therapies can be beneficial in severe forms of these diseases, even in children. In atopic dermatitis, therapy with dupilumab is indicated from the age of 6 months. For asthma, the choice of the most appropriate biological drug must consider various aspects, including the patient's age, features of the inflammation, and the presence of comorbidities and associated diseases.

KEYWORDS: type 2 inflammation, atopic dermatitis, asthma, eosinophilic esophagitis

INTRODUCTION

Recent advances in immuno-allergology have opened new horizons in the understanding of multiple pathologies characterized by type 2 inflammation: atopic dermatitis (AD), food allergy, allergic rhinitis, asthma, chronic rhinosinusitis with nasal polyps, and eosinophilic esophagitis (EoE).

The term "atopic march" has been used to describe the temporal progression of these pathologies in children, which is driven by genetic and environmental factors and supported by type 2 immune responses. Starting from AD and food allergies in early childhood to the development of asthma and allergic rhinitis in older children, these pathologies can follow each other and, sometimes, overlap in the same patient [1]. More recently, EoE has also been included in the allergic march as a later manifestation of food allergy [2].

Recent studies have highlighted the considerable heterogeneity underlying these pathologies and that they tend to associate with each other according to different spatial and temporal trajectories rather than a simplistic linear progression.

Overall, the main pathophysiological mechanisms these pathologies share are barrier damage and the activation of immune cells that release type 2 inflammatory cytokines.

ATOPIC DERMATITIS

The first event in the atopic march is often represented by a dysfunction of the skin barrier that initially determines the transdermal entry of allergens (including inhaled and food allergens) and, subsequently, activates epithelial cells to release inflammatory cytokines such as thymic stromal lymphopoietin (TSLP), interleukin (IL)-25, and IL-33 [3]. These cytokines, also known as "alarmins," initiate type 2 inflammation in the dermis, activating various immune cells [e.g., basophils, mast cells, dendritic cells, eosinophils, innate lymphoid cells (ILC)-2, type 2 helper T lymphocytes (Th2)] to secrete cytokines such as IL-4 and IL-13.

In the acute phase of type 2 inflammation, the uncontrolled production of IL-4 and IL-13

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CORRESPONDENCE

Amelia Licari
amelia.licari@unipv.it

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contributes to the pathogenesis of the clinical manifestations of AD at different levels. IL-4 and IL-13 can: i) alter the differentiation of keratinocytes, suppressing the expression of terminal differentiation proteins (such as filaggrin, loricrin, and involucrin); ii) worsen barrier damage, altering the structure of tight junctions and reducing the production of ceramides and filaggrin by epidermal keratinocytes; iii) reduce the endogenous production of antimicrobial peptides (such as AMPs and beta-defensins), increasing the susceptibility to infections, particularly from *S. aureus*; and iv) stimulate B lymphocytes to produce IgE specific for allergens [3]. In the chronic inflammatory phase, IL-13 is also responsible for the increased collagen deposition in the skin, which is the first step of the chronic remodeling processes stimulated by type 2 inflammation. Finally, IL-4, IL-13, and IL-31 are directly responsible for activating non-histaminergic skin fibers that are responsible for pruritus [3].

Genetic factors also play a key role in the initiation and progression of the atopic march: it has been shown that subjects with loss-of-function mutations of the *FLG* gene encoding filaggrin, a protein of the stratum corneum that plays an important role in maintaining skin pH and hydration, have an increased risk of developing severe AD and subsequently other allergic disorders, such as food allergy and asthma [3].

According to the above, AD can, therefore, be considered the first clinical manifestation of type 2 inflammation in the context of the atopic march. Childhood-onset is associated with an increased risk of developing allergic rhinitis and/or asthma later in life.

The diagnosis of AD is clinical: erythematous lesions, papules, vesicles, crusted lesions from scratching for severe pruritus, lichenification, and xerosis are the main clinical features. In the first years of life, the lesions are mainly localized to the face, the extensor surface of the limbs, and the trunk. Subsequently, lichenified and excoriated lesions of even larger size can be observed in the folds, hands, wrists, feet, and eyelids, in the upper part of the trunk, in the shoulders, and in the scalp [4,5]. In moderate-to-severe forms, an objective assessment of the severity over time is necessary, using validated scores for the pediatric age, such as the SCORAD index (Severity Scoring of Atopic Dermatitis) or the EASI (Eczema Area and Severity Index). It is also useful to objectively assess pruritus using a numerical scale (e.g., NRS, Numerical Rating Scale), the presence of skin lesions on visible and/or sensitive areas, and the patient's quality of life (e.g., using the Children's Dermatology Life Quality Index questionnaire); these assessments are essential for the complete evaluation of the multidimensional impact of the disease in pediatrics. The therapy, which currently offers a broad, integrated approach, is modulated on these severity stratification criteria, aiming to control inflammation, improve symptoms, and allow long-term control of relapses [4,5]. In particular, in severe forms of severe AD, a monoclonal antibody directed against the alpha chain of the IL-4 receptor, dupilumab, is indicated, starting from the age of 6 months [6,7].

ASTHMA

As with AD, pediatric asthma has also seen an innovative re-evaluation of the mechanisms involved in the immune response, previously called Th2-type but now defined as type 2. This definition integrates the innate and adaptive components into the concept of immune response.

In airway diseases, both Th2 lymphocytes and ILC-2 play a central pathogenetic role linked to producing IL-4, IL-5, and IL-13, which have pleiotropic effects in promoting type 2 inflammation. Among the most important, IL-5 promotes the activation and recruitment of eosinophils in the airways, while IL-4 and IL-13: i) increase the expression of adhesion molecules and favor the formation of perivascular infiltrates, thus amplifying the recruitment of inflammatory cells into the airways; ii) promote the recruitment of basophils and mast cells and favor the isotype switch of B lymphocytes towards the production of IgE; iii) directly intervene in the processes of tissue damage and subsequent repair, increasing the production of growth factors (such as TGF-beta and VEGF) by smooth muscle cells and fibroblasts and stimulating the uncontrolled deposition of collagen at the level of the reticular basement membrane [3]; and iv) a vicious circle is therefore triggered that worsens bronchial hyperreactivity and airway obstruction and can lead to so-called bronchial remodeling in the long term. IL-13 promotes the metaplasia of mucinous goblet cells, increases mucus production, and directly induces bronchial hyperreactivity by acting on airway smooth muscle cells [3].

Type 2 inflammation in asthma is present in more than 80% of pediatric patients and can be characterized non-invasively through a series of biomarkers. In particular, patients with asthma with type 2 inflammation have been defined based on an eosinophil count $\geq$ 150/µL and/or exhaled nitric oxide (FeNO) $\geq$ 20 ppb and/or sputum eosinophils $\geq$ 2% [8].

Characterizing these biomarkers is very important in the management of patients with a severe disease phenotype that is characterized by chronic and difficult-to-control respiratory symptoms and severe acute attacks, which often require oral steroid therapy or additional therapy with biological drugs [9].

The biological drugs currently used for the management of severe asthma primarily target circulating IgE (omalizumab), IL-5 (mepolizumab and reslizumab), the IL-5 receptor (benralizumab), and the alpha chain of the IL-4 receptor (dupilumab).

In choosing the most appropriate biological drug, the pediatric allergist must consider the patient's age, features of the underlying type of inflammation through the evaluation of biomarkers, and the presence of comorbidities and associated pathologies [6].

EOSINOPHILIC ESOPHAGITIS

EoE is a chronic, immune-mediated inflammatory disease of the esophagus characterized by a predominance of eosinophilic infiltration in esophageal mucosa, which infiltrates and thickens, similarly to what occurs in AD. In recent decades, the incidence of

EoE in children has increased significantly, with wide geographic variability. The average age of diagnosis is between 6 and 10 years, with 25% of cases being under 5 years of age.

The pathogenesis of EoE involves both genetic and environmental factors. The genetic component involves the overexpression of eotaxin-3, which amplifies eosinophil chemotaxis and activation, and the amplified expression of IL-13 and other type 2 inflammatory cytokines, such as IL-4, IL-5, IL-25, IL-33, and TSLP after exposure to environmental and food allergens, with a consequent increase in the recruitment and activation of eosinophils in esophageal mucosa [10]. EoE can be considered a manifestation of food allergy with mixed pathogenesis, IgE, and/or cell-mediated.

The clinical manifestations, which vary depending on age, may include feeding disorders and reflux symptoms, including cough, vomiting, dysphagia, and food impaction. Another characteristic that this disease shares with other atopic diseases, such as asthma, is the progression to a fibrotic phenotype if left untreated [11].

The standard therapy for EoE is based on proton pump inhibitors, corticosteroids to suppress inflammation, and/or elimination diets of trigger food allergens. Whatever treatment is chosen, its duration must be continued for years, if not for life, as the disease has a chronic relapsing course in most patients. Any discontinuation of treatment must be monitored to avoid prolonged relapses, with the consequent risk of developing fibrosis.

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