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Invited review

Allergy and risk of hematologic malignancies: Associations and mechanisms

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ABSTRACT

Increasing evidence indicates that a dysregulated immune system, as the one found in allergic disorders, can affect survival of tumor cells. A possible association between allergies and risk of hematologic malignancies has been examined in several epidemiological studies; however, results were not always consistent.

The aim of this review is to report the preclinical and clinical data, which support a correlation between allergy and hematologic neoplasms.

Immune system modulation could represent a powerful tool in the prevention and treatment of hematologic malignancies.

Contents

1. Introduction

Allergic diseases require sensitization of a predisposed individual to a specific antigen. Exposure of a susceptible individual to an allergen results in its processing by antigen presenting cells (APC), including macrophages and dendritic cells (DC) located throughout the body surfaces in contact the outside environment, such as nose, lungs, eyes, skin, and intestine. These APCs process the allergen protein and present the epitope bearing peptides via their MHC to particular T cell subsets. T cell responses depend on both cognate recognition through various ligand/receptor interactions and on the cytokine micro-environment, with IL-4 directing a T helper (Th)2 response and interferon (IFN)γ a Th1 profile.

Peripheral T cell tolerance to environmental antigens is crucial for a healthy immune response and no allergy. The balance between Th2 cells and T regulatory (Treg) cells has a critical role in the generation of immune responses to environmental antigens. Allergic individuals display an aberrant activation and expansion of Th2 cells. It appears that aberrant activation of Th2 cells in allergy is secondary to impaired mechanisms of peripheral T cell tolerance that is normally mediated by antigen-specific T cell anergy, Treg cells, and suppressive cytokines, IL-10 and TGF-β [1].

However, increasing evidence indicates that dysregulation of the immune system, as the one found in allergic dysregulation, can affect survival of tumor cells. [2].

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The aim of this review is to report the preclinical and clinical data, which support a correlation between allergy and hematologic neoplasms.

2. Allergy and hematologic malignancies

The majority of studies reported in literature have explored the relationship between allergy and lymphoma or acute lymphoblastic leukemia. In fact, it is only for these diseases that the strongest correlations with the allergic state have been detected, while for the other hematological diseases reports are sporadic and sometimes anecdotal.

A possible association between allergies and risk of hematologic malignancies (HM) has been examined in several epidemiological studies; however, results were not always consistent [3].

In contrast, inverse associations were reported mainly in case-control design studies. There have been several investigations regarding definition and measurement of allergies and the subtypes of HM assessed, however, an inverse association with history of allergies has been reported for HM as a group [4], lymphoma overall [5,6], Hodgkin's lymphoma (HL), Non Hodgkin lymphoma (NHL)[7–10], Acute Lymphoblastic Leukemia (ALL) [11,12], and multiple myeloma (MM)[13] (Table 1).

Shadman et al. used the Vitamins and Lifestyle (VITAL) cohort to examine the association between allergies and risk of hematologic malignancies. From 2000 to 2002, 66,212 participants, aged 50–76, completed a baseline questionnaire on cancer risk factors, medical conditions, allergies, and asthma. Through 2009, incident HMs (n5681) were identified via linkage to the Surveillance, Epidemiology, and End Results Cancer Registry.

After adjustment for factors possibly associated with HMs, a history of airborne allergy was associated with increased risk of HMs (hazard ratio [HR] = 1.19 [95% confidence interval: 1.01–1.41], $P = 0.039$) in Cox proportional hazards models. This association was limited to allergies to plants/grass/trees (HR = 1.26 [1.05–1.50], $P = 0.011$) and was strongest for some mature B-celllymphomas (HR = 1.50 [1.14–2.00], $P = 0.005$). Gender-stratified analyses revealed that the associations between airborne allergies overall and those to plants, grass, and trees were only seen in women (HR = 1.47 [1.14–1.91], $P = 0.004$; and HR = 1.73 [1.32–2.25], $P < 0.001$) but not men (HR = 1.03 [0.82–1.29], $P = 0.782$; and HR = 0.99 [0.77–1.27], $P = 0.960$) [14]. The study indicates a moderately increased risk of HMs in women but not in men with a history of allergies to airborne allergens, especially to plants, grass, or trees. However, this association was not uniform across all the subtypes of HM, rather it was primarily found in some mature B-cell neoplasms.

Several other studies have attempted to ascertain the risk of acute and chronic lymphoid malignancies in patients suffering from allergic diseases. In a US veterans study, a history of "total allergic conditions" as documented in the hospital records was associated with a diagnosis of NHL (risk ratio [RR] = 1.4 [1.3–1.5]). Significant associations were also observed with specific allergic conditions such as alveolitis, dermatitis, and erythema, but not asthma [15].

Other studies indicate a positive association, especially for Hodgkin Lymphoma (HL) [16,17] or no effect [18].

Moreover, in a population-based study from the Swedish cancer registries, an increased risk of lymphoplasmacytic lymphoma was reported in patients who had a history of "any type of allergy or chronic inflammatory conditions" based on previous hospital discharge information (RR = 1.2 [1.0–1.4]) [19].

Different works have shown a correlation between specific allergic diseases and hematological malignancies. In a Swedish cohort of more than 16,000 twins, the risk of leukemia was higher in patients with self-reported history of hives (RR = 2.1 [1.0–4.5]) while no association was found between different subtypes of allergies and incidence of leukemia, CLL, NHL or MM [20]

However, when evaluating risk of acute childhood leukemia in allergic patients, Chang et al. [21] utilized a population-based case-control design using medical claims data from the National Health Insurance Research Database of Taiwan. Eight hundred forty-six childhood ALL patients who were newly diagnosed during 2000 to 2008 and were older than 1 but less than 10 years of age were individually matched with 3374 controls based on sex, age, and time at diagnosis (reference date for the controls). Conditional logistic regression was performed to assess the association between childhood ALL and allergies. An increased risk of ALL was observed in those with allergy less than 1 year before ALL diagnosis (odds ratio (OR) = 1.7, 95% CI: 1.5, 2.0), more than 1 year allergy before ALL diagnosis (OR = 1.3, 95% CI: 1.1, 1.5), and before 1 year of age (OR = 1.4, 95% CI: 1.1, 1.7).

In this study, childhood ALL was positively associated with subject having allergies before 1 year of age less than 1 year before diagnosis, and more than 1 year before diagnosis.

Association between childhood ALL and allergies is contrary to the results of most previous studies. The inconsistency can partly be explained by the sources of exposure data (medical records *vs.* parental report), participation rate, and exposure latency.

Moreover, Nunez-Enriquez et al. conducted a multi institutional population-based case-control study on children with Down syndrome and found that asthma was a risk factor for development of acute leukemia (OR = 4.18 and 95% CI: 1.47–11.87) while, other allergies had no effect or were protective [22].

The intrinsic immune dysregulation that was well described in children with Down syndrome, likely had a significant role in the association between allergic phenomena and ALL [23].

However, Down syndrome might be a confounder in the relation between asthma and acute leukemia. Altogether, Down syndrome may be considered as the cause for both asthma and acute leukemia thus drawing a causative link between asthma and acute leukemia in this setting could be a raw conclusion [24].

Nonetheless, similar results were also reported by other authors. In fact, several papers suggest that asthma is a risk factor for AL in children with DS, whereas skin allergies seemed to protect the population from AL. Children with DS are more vulnerable to the effects of environmental factors that have been associated with the development of AL [25,26].

Finally, children born to mothers with allergies are more likely to have impairment of Tregs cells [27] and a decreased ability to respond to microbial challenges [28]. Similarly, higher maternal serum immunoglobulin E, an indicator of maternal allergy status, was associated with a higher risk of childhood ALL [29].

However, while prospective cohort studies suggested an increased risk of HM, case-control studies failed to confirm these findings, rather they have shown an inverse relationship [30].

In fact, it has been proposed that allergies influence the development of childhood leukemia. Different studies have been conducted in this field; however, their results are not conclusive, as several works have concluded that allergies are risk factors or protective factors [31–34].

Moreover, beyond this inverse association of allergic history with childhood ALL, a similar association is highlighted when serologic markers of allergic predisposition are used as an alternative measure of allergy.

In a study conducted on 252 cases of childhood (0–14 years) ALL, newly diagnosed allergen-specific IgEs, as markers of allergic predisposition, against 24 of the most prevalent respiratory and food allergens, were determined, using an enzyme immunoassay procedure for 199 children with ALL and 113 controls. Cases were compared with controls through frequency distributions and unconditional multiple logistic regression models to estimate ORs