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The Association between Allergies and Hematologic Tumors—A Review

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1. ABSTRACT

Introduction: Dysfunctions of the immune system in allergic diseases and hematological malignancies are the subject of many studies due to the mechanisms that link them. Chronic inflammation created in the immune response in an allergic reaction has been associated with developing neoplastic diseases. Many studies have been conducted to examine the correlation between them.

Aim of the study: This review examines the potential correlation between Allergies and Hematologic Tumors: acute lymphoblastic leukemia, childhood leukemias, non-Hodgkin and Hodgkin lymphomas.

Material and methods: An English-language literature review was conducted, analyzing studies from the PubMed database up to October 2024 regarding the correlation between Allergies and Hematologic Tumors. The review was performed using the PubMed database, with 50 works used.

Conclusion: The relationship between allergies and hematological tumors is unclear. According to some studies, this relationship does not exist; some state, however, that allergic diseases show correlations with hematological malignancies. The results of these studies do not provide a clear answer to whether this is a positive or negative relationship. Some studies suggest that allergies reduce the risk of hematological malignancies, while others contradict this, suggesting that allergies may increase the risk of hematological tumors. The results of studies showing an increased risk of hematological malignancies in people suffering from allergies can be due to the hypothesis of antigenic stimulation, which may explain the mechanism of correlation between those diseases. This hypothesis suggests that chronic immune stimulation predisposes to hematologic malignancies such as multiple myeloma, non-Hodgkin's lymphoma (NHL) and leukemia by promoting the development of randomly occurring pro-oncogenic mutations in actively dividing immune cells. Different results on this potential correlation showed that further studies are necessary.

Keywords: hematologic tumors, allergy, atopy, Hodgkin lymphoma, non-Hodgkin's lymphoma, leukemia.

2. INTRODUCTION

The relationship between allergic diseases and hematologic malignancies has garnered considerable interest due to the shared mechanisms involved in immune system dysregulation. Allergic reactions are characterized by immune responses that involve IgE antibodies, mast cells and the release of cytokines, which together create an environment of chronic inflammation. This chronic inflammatory state has been linked to both protective and harmful effects in cancer development. Some studies suggest that heightened immune surveillance in allergic individuals might lower cancer risk. There are reports, however, that chronic inflammation and immune dysregulation could promote oncogenesis, particularly in hematologic malignancies such as lymphomas and leukemias [1].

One of the key mechanisms involved in this relationship is the activity of Th2 cells, which are prominent in allergic responses. Th2-dominated immune profiles, characterized by elevated IL-4, IL-5 and IL-13 levels, can support an inflammatory environment promoting

cancer progression by stimulating cell proliferation and limiting apoptosis. This has been observed in certain lymphoid malignancies where increased Th2 cytokines correlate with disease progression [2].

Mast cells, important factors in allergic reactions, also play a dual role in cancer development. They release histamine and other mediators that can suppress tumor growth and, paradoxically, promote angiogenesis, which is critical for tumor survival and expansion. The exact impact of these factors varies depending on the type of malignancy and the tissue environment, but their involvement is evident in the pathophysiology of both allergic diseases and cancers, making them a point of interest in understanding these interactions [3].

Furthermore, genetic factors that predispose individuals to allergic diseases may also influence the risk of cancer development. Polymorphisms in immune-related genes have been linked to increased predisposition to allergy and certain hematologic cancers, suggesting a genetic overlap that might help explain observed epidemiological correlations [4]. The interplay between these genetic and environmental factors remains a focal area of research as we seek to understand how allergic pathways could influence cancer development or progression [5].

While the evidence is incomprehensive, there is growing support for both protective and promoting roles of allergic mechanisms in hematologic malignancies. A better understanding of this relationship could help develop new ways to prevent and treat these conditions by focusing on immune pathways [6].

3. STATE OF KNOWLEDGE

3.1. Acute lymphoblastic leukemia

Leukemias are a diverse group of tumors that result from malfunction of development or proliferation of leukocytes. Based on the acuteness of their evolution, they can be divided into acute and chronic, and based on the type of the affected cell, myelocytic and lymphocytic leukemia can be distinguished [7]. The most common leukemia in the pediatric population is acute lymphoblastic leukemia (ALL), accounting for almost 80% of all leukemias and around 25-30% of all cancers among children under 15 years old [8]. The incidence continues to increase [9].

ALL arises due to uncontrolled growth of clonal lymphoid cells, mostly of type pre-B and less frequently T or mature B cells [9]. The pathogenesis of ALL involves various

complicated pathways, with immune dysregulation impacting it significantly. Allergic reactions can cause dysfunctional immune responses, which is the reason for the suspected correlation between them and ALL development. Not only do those two diseases share risk factors, but also protective factors such as vaginal birth or daycare attendance. Even though, meta-analysis performed by Wallace et al. did not prove an unambiguous correlation between ALL and allergies, it was observed that patients with whichever allergy had increased risk of ALL developement compared to patients without allergic history [10]. Furthermore, a study by Lariou et al. demonstrated a strong association between acute lymphoblastic leukemia (ALL) incidence and IgE-induced hypersensitivity, especially to food allergens, and positive allergic history [11].

There have been reports of few cases of B-cell acute lymphoblastic leukemia (B-ALL) associated with eosinophilia. It is a rare condition which is characterized by absence of blasts in the peripheral blood smear and presence of eosinophilia both in blood and bone marrow. Allergic symptoms such as urticarial rash, fever, arthralgia, myalgia, sweating and dyspnea are present [12].

A study by da Conceição Nunes et al. suggests, however, that atopy and increased serum IgE levels are protective factors against the development of ALL [13]. Similar conclusion was drawn by Atmaj et al. when they proved an inverse association between asthma and ALL prevalence [14]. One of the protective mechanisms of atopy against ALL could be increased high-temperature requirement A (HTRA) protease levels, which can suppress cancer cells by leading them toward apoptosis. These proteases can suppress cancer cells by promoting apoptosis, which may not only prevent tumor development but also induce its remission [15].

The association between acute lymphoblastic leukemia and allergy remains unknown. Numerous studies have been conducted, but their results vary from confirmation of correlation to indication of inverse association. Various studies, however, state no obvious association overall [16]. Further research is necessary to fully understand the mechanisms linking ALL with allergies.

3.2. Other leukemias

Acute leukemias are most common in adults and young adults. Environmental factors associated with leukemia include ionizing radiation, chemotherapy, and carcinogenic chemicals such as benzene. Host factors include rare hereditary disorders, iatrogenic or

disease-related immunosuppression, and genetic abnormalities (often chromosomal translocations) [17,18].

Research by Melissa H. Bloodworth et al. established a connection between the ST2 gene and leukemia. Numerous in vivo and in vitro studies suggest that IL-33 and ST2 may play significant roles in the proliferation of leukemia cells. IL-33 mediates innate and acquired allergic inflammation in the lungs, which is influenced by immune responses [19].

Cytokinesis Dedicator 8 (DOCK8) is crucial for processes such as cytoskeletal rearrangement, immune cell trafficking and survival, and the maintenance of cell shape integrity. DOCK8 mutations are linked to higher susceptibility to infections and an increased risk of malignancy [20]. DOCK8-related immunodeficiency syndrome (DIDS) not only predisposes individuals to cancer but also manifests with symptoms such as skin eczema, elevated serum IgE levels, and recurrent sinus and lung infections [21].

Eosinophilic dermatitis associated with hematologic malignancies (EDHM) appears as various skin manifestations, including macular, vesicular-papular or vesicular pruritic rashes [22]. Chronic lymphocytic leukemia (CLL) is the most frequently associated malignancy with EDHM. Initially believed to be a hypersensitivity reaction to insect bites, it was found that many affected individuals had no exposure to insects. Studies revealed that up to 20% of lymphocytes in the infiltrate were B cells, suggesting a potential etiological role of leukemic B cells in EDHM [23].

Patients with conditions such as congenital agammaglobulinemia or those infected with HIV may experience eosinophilic responses triggered by factors like drugs, viruses, and insect bites. These triggers can lead to altered immunological processes dominated by Th2 responses. In CLL, there is an initial predominance of Th1 responses. As the disease progresses, however, Th2 responses become more pronounced. An increased Th2 response may inhibit cell apoptosis, exacerbating chronic lymphocytic leukemia. This response also leads to the excessive production of interleukin (IL) 4 and 5, which attract eosinophils, contributing to the eosinophilic infiltration observed in the skin [24].

Excessive amounts of IL-4 and IL-5 can cause a cytokine imbalance, promoting malignant B cell proliferation in patients with EDHM. High levels of IL-4 may alter the immune response, resulting in the eosinophilic infiltrate characteristic of EDHM [25].

The relationship between leukemias and allergies needs further investigation. Research is necessary to gain a more comprehensive understanding of this association.

3.3. Non-Hodgkin lymphomas

Non-Hodgkin lymphoma (NHL) refers to a group of blood cancers that includes all types of lymphoma except Hodgkin lymphomas. The course of lymphomas is varied and they can be either indolent or aggressive. Indolent lymphomas progress slowly and have few signs and symptoms. They account for about 40% of all NHL cases and include follicular lymphoma, lymphoplasmatic lymphoma, marginal zone lymphoma, and primary cutaneous anaplastic large cell lymphoma. Aggressive lymphoma, which makes up for 60% of all cases, grows and spreads quickly, often presenting specific B symptoms such as weight loss, night sweats, and fever. Without treatment, they can be fatal within a few weeks [26]. The main types include diffuse large B-cell lymphoma, Burkitt lymphoma, mantle Cell Lymphoma (MCL), peripheral T-cell lymphoma (PTCL), primary Mediastinal Large B-cell lymphoma (PMBCL), high-grade B-cell lymphomas (HGBCL) and Primary Central Nervous System (CNS) lymphoma [27].

A link between allergy and NHL is unclear. There is a lot of evidence suggesting that allergy is a potential risk factor for NHL, while other studies are contradictory to this. The survey conducted by Hofmann et al., published in 2015, found that agricultural allergens may influence NHL development. It was observed that farmers and their spouses with allergic rhinitis had a reduced risk of developing NHL. Decreased risk was linked with specific exposures, such as growing soybeans or handling stored grains and hay. Conversely, individuals who grew up on a farm had an increased risk of NHL. These results suggest that the immune response to agricultural allergens in adulthood may play a protective role against NHL, while farm exposures in early years might increase it [28]. Research by Wang et al. confirms a negative association between NHL and allergies. This study investigated this relationship using 162 twin pairs where one twin had NHL and the other did not. Results showed a strong negative association between NHL and seasonal hay fever and specific allergies. Additionally, a greater number of atopic conditions and a history of infectious mononucleosis were linked to a reduced NHL risk [29]. Another study found that specific allergic conditions like asthma, hay fever, food allergy, and allergic rhinitis may be associated with a reduced risk of NHL [30].

Evidence has emerged suggesting that certain allergic diseases may elevate the risk of developing non-Hodgkin lymphoma, a finding first reported in the late 20th century. A French case-control study found a potential association between allergies and an increased risk of

non-Hodgkin lymphoma (NHL). Additionally, factors associated with altered immune functions—such as a history of hematopoietic malignancy, hives, occupational exposure to benzene, and working in agriculture—could also increase susceptibility to NHL [31]. Furthermore, a study conducted in England found an increased risk of noncutaneous lymphoma among patients with atopic eczema, with greater disease severity correlating to a higher risk [32].

There were studies, however, that have not confirmed any link between these conditions. For example, a large prospective study by Nieters et al. found that high levels of total IgE typical for allergic diseases were not linked to the risk of multiple myeloma and B-cell NHL [33]. Briggs et al. also found no significant association between a general history of allergy and overall NHL risk, nor for major NHL subtypes (follicular, diffuse, small cell lymphocytic, and immunoblastic). There was also noted no influence from the most common specific allergies, such as those to plants, dust, food, animals, and medications [34].

However, a significant association was found for allergies to insects, which were linked to immunoblastic NHL, and for chemical allergies, associated with diffuse and small cell lymphocytic NHL. It implies that susceptibility to NHL may depend on the type of allergy, but these specific allergies were reported by relatively few participants. Therefore, it could be accidental and requires further research [34]. Additionally, allergic reactions to insect bites have also been observed in some patients with mantle cell lymphoma and diffuse large B-cell lymphoma, manifesting as eosinophilic eruptions associated with myeloproliferative disease [35].

The association between non-Hodgkin lymphoma and allergy remains unknown. Some reports have shown that a history of allergy decreases the risk of developing NHL; others indicate a notable increase, and many found no connection at all. Therefore, further research is needed to determine the relationship between allergies and NHL incidence.

3.4. Hodgkin lymphoma

Hodgkin lymphoma (HL) is the most common cancer of the lymphatic system among teenagers and young adults worldwide. It is among one of the most prevalent types of lymphomas and is successfully managed with standard first-line chemotherapy and, in some cases, radiotherapy [36,37]. Additionally, certain HLA genes that regulate the immune system have been associated with an increased risk of HL in genetic studies. These findings suggest that immune system dysfunction influences the development of HL [38].

Immunodeficiency syndromes, whether acquired, congenital, or iatrogenic, are recognized to elevate the risk of Hodgkin lymphoma. However, the impact of allergic immune dysregulation in this context remains inadequately understood. The antigenic stimulation hypothesis suggests chronic immune stimulation from various conditions, including allergic diseases, to predispose to hematologic malignancies. Altered immune responses could promote the development of randomly occurring pro-oncogenic mutations in actively dividing immune cells. The number of evidence supporting this hypothesis is increasing [38].

There is evidence of a significantly higher risk of lymphoma in individuals with atopic eczema compared to those without. However, only one cohort study and two case-control studies have explored how the severity of eczema is related to lymphoma. The cohort study on psoriasis found a two-fold increase in lymphoma risk for those with severe eczema [37].

Many studies focus on a specific subtype of Hodgkin lymphoma, which may limit the value of the research. The analysis should focus on classical Hodgkin lymphoma cases. For example, the nodular lymphocyte-predominant subtype represents a distinct clinical entity. It presents differently and requires different management approaches than classical HL subtypes [39].

In conclusion, HL is not significantly linked to any allergic condition [36]. Hodgkin lymphoma and allergic diseases were not the subject of many studies, and the findings have been inconsistent and inconclusive. Most previous studies could have limited ability to detect meaningful associations because they were small-scale or involved limited numbers of subjects exposed to allergic conditions [38]. Further prospective cohort studies are needed to better understand the potential link between allergic diseases and lymphoma risk [36].

3.5. Therapy in Hemato-Oncology

The relationship between oncology treatment and allergies and hypersensitivity reactions (HSRs) can be viewed from multiple angles. One perspective focuses on the interaction between pre-existing atopy and the administered treatments. Chemotherapy often results in pancytopenia, which diminishes the immune response and can consequently alleviate the severity of symptoms associated with atopic diseases. However, Whiteside et al. noted a significant difference between a decrease in the number of B lymphocytes and a disproportionately low decrease in plasma levels of antigen-specific IgE. A likely explanation is the chemoresistance of IgE-producing plasma cells [40]. Another perspective on the relationship between chemotherapy and allergies is IgE and its potential interactions as a

novel supplement to therapy with an immunological component. Recent research suggests that IgE plays a role in circulatory immunosurveillance by inducing pro-tumor macrophages to adopt a pro-inflammatory state with anti-tumor functions, promoting long tissue residency, and facilitating direct tumor cell killing [41].

The most common and by far most important issue for the course of therapy perspective are reactions induced by the administration of specific therapy components with varying toxicity and immunogenicity, often hindering the continuation of treatment and reducing its quality and safety. The most common drugs used in haematooncology chemotherapy are:

- Alkylating agents, e.g. Cyclophosphamide, Busulfan,
- Antimetabolites: Fludarabine, Cytarabine, Methotrexate
- Bacterial Enzyme: Asparaginase
- Epipodophyllotoxins: Etoposide
- Vinca Alkaloids: Vincristine, Vinblastine.

Most of these compounds rarely cause HSRs and are usually mild. The greatest risks of developing hypersensitivity, including anaphylactic reactions, are asparaginase, with incidences in 6–40% of cases and severe reactions in <10%, and etoposide responsible for reactions in up to 40% of patients treated, usually mild course [42]. The onset of HSR in a patient undergoing treatment necessitates the implementation of premedication, subjecting the patient to desensitization or discontinuation of treatment and the use of substitute medication, which may be associated with a decrease in treatment efficacy or increase of its toxicity.

Asparaginase is essential to acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) treatment, including in the pediatric population. It is commercially available in several forms. A natural enzyme isolated from *E.coli* strains, *Erwinia chrysanthemi*, l-asparaginase, due to its minimal antigenic cross-reactivity with asparaginase derived from *E.coli,* is a safe alternative in patients with HSR after classic asparaginase [43]. Pegylated *E.coli* asparaginase (pegaspargase) and PEGylated recombinant *E. chrysanthemi* L-asparaginase (pegcrisantaspase) are characterized by optimized pharmacokinetics and reduced immunogenicity [43,44]. HSRs vary from mild erythema to systemic anaphylaxis and may occur immediately after the first dose of asparaginase or with subsequent doses of the drug, as the risk of HSRs increases with repeated administrations, especially during the consolidation and reinduction phases [45]. The reaction involves specific IgE and IgM antibodies, most commonly against native *E. coli* asparaginase (39%–61% of patients) as it is a natural

bacterial protein, yet potentially it may also induce the production of antibodies as it was shown in the case of patients receiving pegaspargase (21%–29%) and native *Erwinia* asparaginase (8%–38%) [44].

Moreover, the study by Rau et al. introduced three pediatric ALL patients with documented pegaspargase-hypersensitivity. Continuation of therapy with pegcrisantaspase has induced hypersensitivity reactions with the presence of anti-PEG IgG and IgM antibodies. Despite numerous limitations of the study, it may raise questions about the effectiveness and immunogenicity of the PEGylation process and the need for further research for new, safer forms of the treatment [43].

Etoposide semisynthetic derivative of podophyllotoxine used in chemotherapy protocols of leukemia, lymphomas, and solid tumors. HSRs occur in approximately 1-3% of patients, although two retrospective reviews from over 30 years ago of pediatric patients found a much higher incidence of hypersensitivity of up to 51%; however, newer sources report around 27.1% incidence of hypersensitivity [46,47,48]. It may take the form of anaphylaxis or type IV hypersensitivity with flushing, dyspnea, swelling of the skin, or rash. Presumably, most hypersensitivity reactions to this drug are due not to etoposide itself but to its polysorbate 80 solvent, which is a mixture of fatty acid esters [48,49]. Another form of etoposide, etoposide phosphate, which is water-soluble and devoid of polysorbate 80, is usually effective as a substitute in patients with HSR induced by the primary formulation, but complications may also arise. An example from Polistena et al. shows a case of a 25-year patient with stage III relapsed Hodgkin lymphoma with mild HSRs after administration of carboplatin, ifosfamide, and etoposide phosphate in regimen Moskowitz ICE. An episode of flushing, dizziness, and erythematous rash was preceded by etoposide phosphate infusion, and drug administration was stopped immediately. The patient then decided to have another etoposide administration, this time in the BEAM protocol, preceded by desensitization. It proceeded without any complications [50]. Another example is a case of hypersensitivity to dextran, a component of etoposide phosphate, as described in a case report by Coterret et al. in which a severe anaphylactic reaction occurred in a 66-year-old patient with stage 3 enteropathy-associated T-cell lymphoma, immediately after administration of a methotrexate+etoposide phosphate cycle which required admission to intensive care unit [49].

The issue of HSRs to anti-neoplastic agents necessitates careful analysis on a case-by-case basis. Expanding studies to identify potential triggers for these reactions may assist in developing optimized drug formulations that minimize the risk of inducing hypersensitivity.

4. CONCLUSIONS

The relationship between allergic mechanisms and hematological tumors remains not fully understood. The hypothesis of antigenic stimulation suggests that chronic immunological stimulation during allergies promotes oncogenic mutations in actively dividing immune cells, which can lead to hematological diseases such as multiple myeloma, non-Hodgkin lymphomas, and leukemias.

Leukemias are multifactorial neoplastic diseases whose pathogenesis may be linked to immunological alterations, genetic mechanisms, and responses to various environmental factors. The association between leukemias and allergies is unclear. Many studies have been conducted, but their results range from confirming a correlation to indicating an inverse relationship. The connection between lymphoma and allergy is also unknown. Some reports suggest that a history of allergies decreases the risk of developing NHL, while others indicate a significant increase and many studies have found no association at all. Few studies have examined the relationship between allergies and Hodgkin lymphoma. Their findings have been inconsistent and ambiguous.

Given the inconclusiveness of the evidence, further research is needed. A better understanding of this relationship may provide insights into new preventive and therapeutic strategies for hematological tumors that target immune pathways.

5. DISCLOSURE

Conceptualization, Aleksandra Hrapkowicz, Joanna Szydziak, Kinga Janowska, Dominika Rehan, Julia Wołoszczak, Olga Szeidl, Agnieszka Mioskowska, Daria Dąbkowska; methodology, Aleksandra Hrapkowicz, Joanna Szydziak, Kinga Janowska, Dominika Rehan, Julia Wołoszczak, Olga Szeidl, Agnieszka Mioskowska, Daria Dąbkowska; check, Aleksandra Hrapkowicz, Joanna Szydziak, Kinga Janowska, Dominika Rehan, Julia Wołoszczak, Olga Szeidl, Agnieszka Mioskowska, Daria Dąbkowska; formal analysis, Aleksandra Hrapkowicz, Joanna Szydziak, Kinga Janowska, Dominika Rehan, Julia Wołoszczak, Olga Szeidl, Agnieszka Mioskowska, Daria Dąbkowska; investigation, Aleksandra Hrapkowicz, Joanna Szydziak, Kinga Janowska, Dominika Rehan, Julia Wołoszczak, Olga Szeidl, Agnieszka Mioskowska, Daria Dąbkowska; resources, Aleksandra Hrapkowicz, Joanna Szydziak, Kinga Janowska, Dominika Rehan, Julia Wołoszczak, Olga Szeidl, Agnieszka Mioskowska, Daria Dąbkowska; data curation, Aleksandra Hrapkowicz, Joanna Szydziak, Kinga Janowska, Dominika Rehan, Julia Wołoszczak, Olga Szeidl,

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