Decrease of Airway Allergies After Lung Transplantation Is Associated With Reduced Basophils and Eosinophils

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ABSTRACT

Background. Allergies are hypersensitive reactions of the immune system on antigen exposure similar to immune reactions after transplantation (Tx). Their activity can change after Tx. The lung as a transplantable organ is challenged two-fold, by antigens from the blood and the air environment. Herein we analyzed if airway allergies change after lung Tx.

Methods. We systematically reviewed patients' airway allergies before and after lung Tx between 1992 and 2014. The course of lymphocytes, thrombocytes, and leukocytes, among them neutrophils, eosinophils, and basophils, was analyzed in patients in whom airway allergies have changed and in whom they did not change.

Results. From 362 lung transplanted patients, 44 patients had suffered from allergies before Tx (12.2%). In 20 of these patients (45.5%), airway allergies disappeared completely within 1 year after lung Tx and were persistently absent thereafter. In these patients, basophils and eosinophils decreased significantly ($P < .0012$); in contrast, cells did not decrease in patients whose allergies did not disappear. Leukocytes overall, and in particular, neutrophils, decreased significantly in patients whose allergy disappeared ($P < .014$, $P < .012$, respectively).

Conclusions. Airway allergies disappeared in almost half of cases after lung Tx. Along with this reduction, basophils and eosinophils decreased as potentially responsible cells for this phenomenon. These findings may stimulate intensified research on basophils and eosinophils as major drivers of airway allergies.

ALLERGIES are a result of dysfunctional immune responses. Although the term "allergy" has been used to describe various kinds of hypersensitivity reactions such as adverse drug reactions, only immune-mediated hypersensitivity reactions are referred to as allergies. Several markers such as allergen-specific immunoglobulin (Ig)E and eosinophils have been identified and proven to come along with an increased risk of developing allergic symptoms [1]. A variety of risk factors for the development of allergies were identified, such as environment [2] and genetics [3], but also protective factors such as long-term exposure to corresponding allergens [4] or commensal bacteria [5]. The immune systems of patients who have allergic diseases show a lack of tolerance toward exogenous agents. Similarly, a lack of immune tolerance toward graft antigens can be observed in patients undergoing organ transplantation (Tx) [6]. Biochemical mechanisms involved in allergic reactions show some similarities to graft rejection after solid-organ Tx. Eosinophilic inflammations and recruitment of IgE-producing B cells, which play a major role in allergic reactions, are, for instance, regulated by $CD4^+$ T cells that are key players in transplant rejection mechanisms also [7]. Some studies have shown that allergies can change their activity after Tx. New sensitizations following solid-organ Tx from a non-atopic donor to a non-atopic recipient can occur even in 57% [8]. An increase of de novo allergies after pediatric liver Tx was also proven in a recent study [9]. In addition to the development of new allergies, donors' allergies can also be transferred to the recipient, which has been shown to occur mostly after bone marrow Tx [10,11].

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Cases of allergy transfer after Tx of solid organs such as the lung also have been reported [12].

The lung plays a unique role among all solid transplantable organs as this organ is challenged not only by circulatory but also by airborne agents, which makes it a highly immunogenic organ. Numerous studies have proven that allergies cause symptoms predominantly in the upper and lower respiratory tract [13–15]. Pollen, dust mites, and animal hair are frequent airborne allergens to cause respiratory symptoms including cough and asthma, which are paralleled by eosinophilic inflammation [16].

In this study, we hypothesized that allergies change their activity after lung Tx. To evaluate this, we retrospectively assessed the prevalence of allergies before and after lung Tx. Furthermore, we analyzed which cells are affected as possible inducers of allergies.

METHODS

Study Design

This retrospective prevalence study was performed at the Division of Thoracic Surgery of the University Hospital of Zurich. The study was approved by the ethics committee of Zurich (KEK-ZH 2014-0475). We systematically reviewed the clinical records of all patients who underwent lung Tx at our institution between 1992 and 2014 (n = 414) with the use of our electronic health record software.

Patients

Patients were considered who were lung-transplanted between 1992 and 2014. From these, only those patients were included who were diagnosed for an allergy of the upper and lower airways, clinically diagnosed as bronchial asthma with or without rhinitis symptoms. This also included the criteria that the exposure to allergens could not be avoided such as to pollen, house dust mites, or animal hair. Patients with drug, food, or insect sting allergies were excluded because they can easily avoid exposure to the allergen, which made the evaluation of allergy status after Tx impossible. Likewise, patients with drug allergies were excluded because these reactions can be confused with adverse drug events or other non-allergic hypersensitivity reactions. All eligible patients were questioned for the presence of airway allergies before Tx and whether and when these allergies disappeared after Tx.

All patients received uniformly the same immunosuppressive medication, immediately after transplant in a weight-adapted dose, followed by dose reduction during the post-operative course. This was cyclosporine, prednisone, and mycophenolate. In both groups, there was no extra steroid pulse therapy given during the first year after Tx because no patient experienced acute rejection episodes (maximum stage A2 in 3 of 20 patients, 15%). All patients received antiviral prophylaxis. The allergy status of 3 patients after Tx could not be assessed because they either had died shortly after Tx or not enough time had passed since Tx to evaluate their status.

End Points

The primary end point was the change of allergy prevalence after lung Tx during the first year after Tx. Secondary end points included the blood cell counts before and after Tx between those patients whose allergic symptoms vanished after Tx and those who did not have any improvement of their allergic symptoms also during the first year after Tx. The courses of leukocytes, lymphocytes, thrombocytes, neutrophils, eosinophils, and basophils of patients whose allergies disappeared after Tx and a control group of patients whose allergy status did not change after Tx (n = 3, controls) were analyzed and compared. In detail, we compared the cell counts of a blood test performed before Tx to the average of all cell counts of blood tests performed during the first year after Tx. The diagnosis leading to Tx as well as the immunosuppressive drug regimen of both cohorts were recorded.

Statistical Analysis

The paired t test was used to assess the significance of eosinophil and basophil cell count change. The Mann-Whitney U test was performed to analyze the significance of differences between cell counts before transplant and in changing ratios (after/before) between both groups. A value of $P \leq .05$ was considered significant. Means were presented with standard deviations.

RESULTS

Prevalence of Allergies

There was no access to the medical records of 52 of 414 patients because of missing digitalization or data protection policies according to patients' wills. Of the remaining 362 patients, we selected those who had pre-existing allergies prior to Tx. From the total of 362 patients included in this study, 44 (12.2%) had airway allergies as categorized above before to Tx. In 20 of these patients (45.5%), allergies disappeared completely within 1 year after lung Tx and were persistently absent thereafter. Specifically for patients who had cystic fibrosis (CF), allergies disappeared non-significantly in 8 of 22 patients (36.4%; $P = .7396$). Allergy prevalence among lung Tx patients was reduced from 12.2% before Tx to 6.6% after Tx. Figure 1 provides an overview flow diagram of the patients included in our study. Table 1 shows the underlying diseases leading to lung Tx in patients in whom allergies disappeared and in those in whom they did not disappear.

Course of Cells Before and After Transplant

To give an overview, in patients whose allergies disappeared after Tx, the average cell numbers of all blood tests performed during the first year after Tx showed a reduction

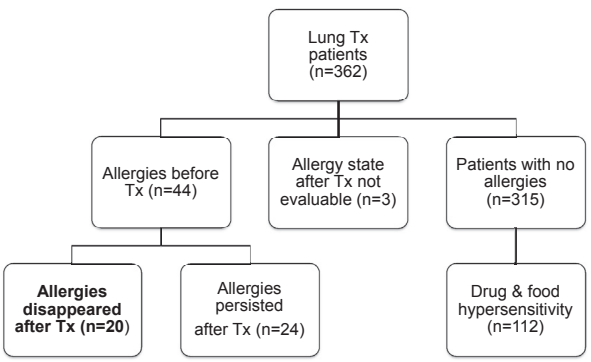

Fig 1. Overview flow diagram of all patients included in the study.