PROF. GEERT VERLEDEN (Orcid ID : 0000-0003-3048-2429)

Article type : Invited Commentary

The role of tissue eosinophils after lung transplantation: back into business?

Geert M. Verleden, MD, PhD, FERS
Dept Repir Dis and Lung Transplantation Unit
University Hospital Gasthuisberg,
Leuven, Belgium

Address for correspondence: prof Geert M. Verleden, MD, PhD, FERS
Dept Respir Dis and Lung Transplantation Unit
University Hospital Gasthuisberg
49, Herestraat,
B-3000 Leuven, Belgium
Phone: + 32 16 34 6802
Fax: + 32 16 34 6803
Mail: geert.verleden@uzleuven.be

Eosinophils are granulocytes, developing in the bone marrow. Differentiation and survival of these cells is dependent on interleukin (IL)-5 through the IL5Rα (1). Their half-life in the blood is around 1.8 days and after migration to different organs, they contribute in remodeling, metabolic and microbiome homeostasis, and may act as sentinels for infection (especially parasitic), fibrosis and cancer (2).

The role of the eosinophil is very well known in allergic asthma, which is driven by T helper 2 cells, secreting IL 4, 5 and 13 which leads to eosinophilic airways inflammation (3). In nonallergic eosinophilic asthma, on the other hand, type 2 innate lymphoid cells (ILC2), are responsible for eosinophilic inflammation, again through the production of the same type 2 chemokines, however, with some steroid resistance of the eosinophil (3).

Several authors have investigated the potential role of eosinophils in lung transplantation. Early data all pointed to a possible role in acute rejection. Dosanjh et al. described an increased eosinophilic cationic protein (a marker of activated eosinophils) in broncho-alveolar lavage (BAL) fluid of patients with acute rejection (4). Other investigators also demonstrated increased BAL eosinophilia, which seemed to be linked with acute rejection, although causality remained unclear (5, 6, 7). Furthermore, Greenland et al. demonstrated that BAL cell immunophenotyping, including eosinophilia, facilitated the diagnosis of lung allograft rejection (7). More recently, Frye et al. showed that an increasing percentage of BAL eosinophils in surveillance bronchoscopies after lung transplantation, increased the probability of biopsy-proven acute rejection (8). The presence of eosinophils in transbronchial biopsies after lung transplantation has long been recognized and is also associated with acute rejection (≥A2) (9, 10).

In the current issue of the journal, Darley et al. (11) publish a retrospective study where they revised the presence of eosinophils in transbronchial biopsies (taken in the first two years after lung transplantation) and found it to be a predictor of the development of chronic lung allograft dysfunction (CLAD) and reduced survival (11). They reviewed 8887 biopsies from 1440 patients, transplanted between Jan 2001 and July, 2018 with a median survival of 8.28 years. All biopsy reports were screened for the presence of "eosinophils". Whenever one biopsy report mentioned the presence of eosinophils, patients were categorized in the eosinophil group. When no report mentioned the presence of eosinophils, patients were classified as "without eosinophils". The first biopsy showing tissue eosinophilia was taken at a median of 48.5 days post-transplant. Concurrent BAL eosinophilia (>2% eosinophils) was recorded, as well as the maximum peripheral blood eosinophil count in the 2 weeks prior to the biopsy together with the medication intake at the time

of the biopsy. Multivariable cox proportional hazards analysis showed an increased risk of all-cause mortality with 51%, once eosinophils were detected in the biopsy. Furthermore they found an independent association with the development of CLAD (HR 1.35). When CLAD was further phenotyped according to the recently published guidelines (12), the presence of eosinophils only showed a trend towards the development of RAS or the mixed phenotype. Concurrent peak peripheral blood and BAL eosinophilia were also significantly higher in the eosinophil group. The authors concluded that eosinophils in biopsies after lung transplantation should be specifically looked for as it may have an important prognostic role after lung transplantation.

The study is very interesting as it again demonstrates that results of transbronchial biopsies not only impact on survival but may also predict the development of CLAD, even when already detected as soon as 1.5 months (median) after transplantation.. In fact, there are not many biomarkers that really predict the development of CLAD, although several pathological causes for its development have been acknowledged, amongst them acute rejection and lymphocytic bronchiolitis (12). In the present study, the patients with eosinophils in the biopsy also had more concurrent acute rejection (A grade), but this was significant in multivariate analysis. Now, we go a little bit deeper into the biopsies and specifically revealing the presence of tissue eosinophils seems to greatly impact the prognosis of the patients. On the other hand, we have no idea whether the presence of eosinophils on transbronchial biopsies, even in the absence of acute rejection, may prompt specific treatment. This will certainly need further investigation as to whether this would alter the prognosis.

This study further supports previous publications from our own group. We indeed demonstrated an increased presence of tissue eosinophilia (as well in airways, parenchyma and blood vessels) in end-stage CLAD lungs, which was more pronounced in RAS compared to bronchiolitis obliterans syndrome (BOS) (13). We also showed that BAL and blood eosinophilia are both a predictor of survival in patients already diagnosed with RAS (14). In the present study, the authors could not demonstrate that tissue eosinophilia specifically predicts the development of RAS, although there was a clear trend, neither was there an association with the presence of de novo donor-specific antibodies. This may be due to the low number of patients with RAS and mixed phenotype (only 29), which is a clear limitation of the study. Another limitation is the fact that the presence of eosinophils was only looked at in the reports of the biopsies, whereas the biopsies were not revised. A revision of all biopsies might have further strengthened the present results. The question remains, however, about the causality of this tissue eosinophilia (besides the already

mentioned increased A rejection grade). Most patients probably were on corticosteroid treatment, which is highly effective to treat eosinophilic lung diseases. Whether the present eosinophilia is T helper 2 or rather ILC2 induced is unknown, and will be important to further elucidate in order to be able to effectively treat this condition. Even drugs may induce eosinophilic lung disease, and this was also carefully evaluated in this study and did not seem to have a major influence. Irrespective of the cause of the tissue eosinophilia, this study adds important new insights in the lung transplant field.

Although the proof of the pudding would be a prospective trial, this retrospective study clearly indicates that pathologists should be advised to extensively look for the presence of eosinophils in any lung transplant biopsy, as it has major impact on the prognosis of our patients. To that respect, the authors should be congratulated for the tremendous effort they have put in this study to share these very important findings with us.

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