Clinical & Experimental Allergy

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RESEARCH LETTER

Sputum TGF-β Level Is Increased in Allergic Rhinitis and Related to Small Airways Dysfunction

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To the Editor,

We have previously documented peripheral airway hyperresponsiveness (AHR) in patients with allergic rhinitis such as that seen in asthma, by measuring the slope (S) of phase III of the single-breath washout test (SBWT) of helium (S_{He}) before and after sputum induction, here considered as an indirect airway challenge [1]. S_{He} is expected to increase when airway calibre decreases at the onset of the acinus [2]. As in asthma, airway hyperresponsiveness (AHR) is partly associated with structural changes in the airways, such as airway remodelling [3], we hypothesized that certain remodelling activities could also occur in the airways of patients suffering from allergic rhinitis without clinically obvious features of asthma. Consequently, we sought to detect an increased expression of TGF-β, the emblematic mediator of airway remodelling in asthma, in the induced sputum supernatants of patients with allergic rhinitis, in the same manner as that observed in asthmatics [4, 5]. We also sought to establish, in a subgroup of patients with allergic rhinitis, whether the magnitude of the increase in S_{He} observed after an airway challenge [1] could be related to the level of TGF-β in the sputum.

For that purpose, TGF-β levels assessed by Enzyme Linked Immunosorbent Assay (ELISA), (R&D Systems Inc., Minneapolis, MN, USA), were compared in the induced sputum supernatants of patients suffering from seasonal allergic rhinitis without asthma and with a negative airway challenge test ($n = 33$), moderate-to-mild asthma ($n = 75$, of whom 65% were atopic), and non-atopic healthy controls ($n = 19$). Sputum cell counts were also recorded. S_{He} of the SBWT were measured in 19 patients with allergic rhinitis before and after sputum induction. This was not done in asthma patients because salbutamol was added to the hypertonic saline used to perform sputum induction in these patients. Allergic rhinitis and asthma were defined according to ARIA and GINA guidelines. Healthy controls had no rhinitis or asthma symptoms, and they had no positivity on skin prick testing to common aeroallergens.

The local ethics committee approved the study and participants signed informed consent (P2014/088).

The rhinitis and asthma groups differed from the control group in terms of FENO (mean of 30.8 and 29.6 ppb, respectively, compared to 10.2 ppb; $p < 0.001$) and sputum eosinophil count (median (interquartile range) of 1.2% (0%–2.5%) and 1.1% (0.2%–8.8%), respectively, compared to 0% (0%–0%); $p < 0.001$). The rhinitis group differed from the asthma group in terms of age (mean of 37 vs. 46 years; $p = 0.016$), sex ratio (37.5% vs. 63.5% females; $p = 0.013$), and forced expiratory volume in one second/forced vital capacity (FEV1/FVC) ratio (mean of 84.6% vs. 77.5%; $p = 0.003$). The median dose of inhaled corticosteroids (ICS) in the asthma group was 200 μg per day.

As shown in Figure 1A, median TGF-ß levels were significantly higher in sputum supernatants of patients with allergic rhinitis (11.3 $pg.ml^{-1}$, $p = 0.006$) and asthma patients (11.5 $pg.ml^{-1}$, $p = 0.006$) when compared to controls (5.4 $pg.ml^{-1}$). There were

Summary Box

- Sputum TGF-β level is increased in allergic rhinitis and appears linked to peripheral airway dysfunction.
- These results suggest that a clinically silent airway remodelling process is present in allergic rhinitis.

no significant differences between allergic asthma and rhinitis ($p = 0.987$). No significant correlation between TGF-ß and sputum eosinophils or FENO or FEV1/FVC ratio could be established in patients with allergic rhinitis ($p = 0.953$, 0.603, 0.084, and 0.306, respectively), nor in asthma patients ($p = 0.815$, 0.240, 0.657, and 0.809, respectively). Allergen exposed rhinitis presented increased inflammatory markers (2% vs 0.2% for sputum eosinophils, $p = 0.007$; 36.5 vs 21.5 ppb for FeNO, $p = 0.048$; inside ($n = 16$) and outside ($n = 17$) the pollen season, respectively) but not increased TGF-ß levels (12.0 vs 8.9 $pg.ml^{-1}$; $p = 0.564$). Figure 1B presents the significant positive Spearman correlation between S_{He} change after-before induction and TGF-ß level in the subgroup of 19 allergic rhinitis patients.

Thus an increased expression of TGF-β, similar to that observed in allergic asthmatics, is detectable in the lower airways of patients with allergic rhinitis, suggesting the presence of a remodelling process at this level. To our knowledge and somewhat strangely, such a process has only been reported once in the past and in a minimal number of patients ($n = 8$) [6]. Bronchial epithelial cells and eosinophils are considered the main sources of TGF-β present in asthmatic airways, whose expression is mainly regulated by interleukin 13 (IL-13) [7] and interleukin-33 (IL-33) [8]. In this regard, it may be relevant to note that we have previously documented higher levels of interleukin-33 (IL-33), an alarmin secreted by epithelial cells, in the induced sputum of patients with allergic rhinitis without asthma compared to healthy controls, with levels similar to those observed in the induced sputum of asthmatic patients [9]. In addition, a link was observed in 19 patients with allergic rhinitis between the TGF-β expression in their lower respiratory tract and the degree of peripheral airway dysfunction induced by inhalation of hypertonic saline.

Finally, this study has some limitations. First, it should be noted that TGF-β is not a mediator specific to airway remodelling alone but can also be elevated in cases of inflammation without fibrosis. However, in our study, TGF-beta levels were not more elevated in rhinitis during the pollen season than outside despite more elevated inflammatory markers. Secondly, the cross-sectional nature of the study, the small number of patients who performed the SBWT during the sputum induction, and the relatively low dose of ICS used by asthmatic patients suggest caution in generalising the results.

Together, these results suggest that a clinically silent airway remodelling process that impacts peripheral airway reactivity is also present in allergic rhinitis, adding a stone to the concept of "one airway, one disease" linking rhinitis and asthma.

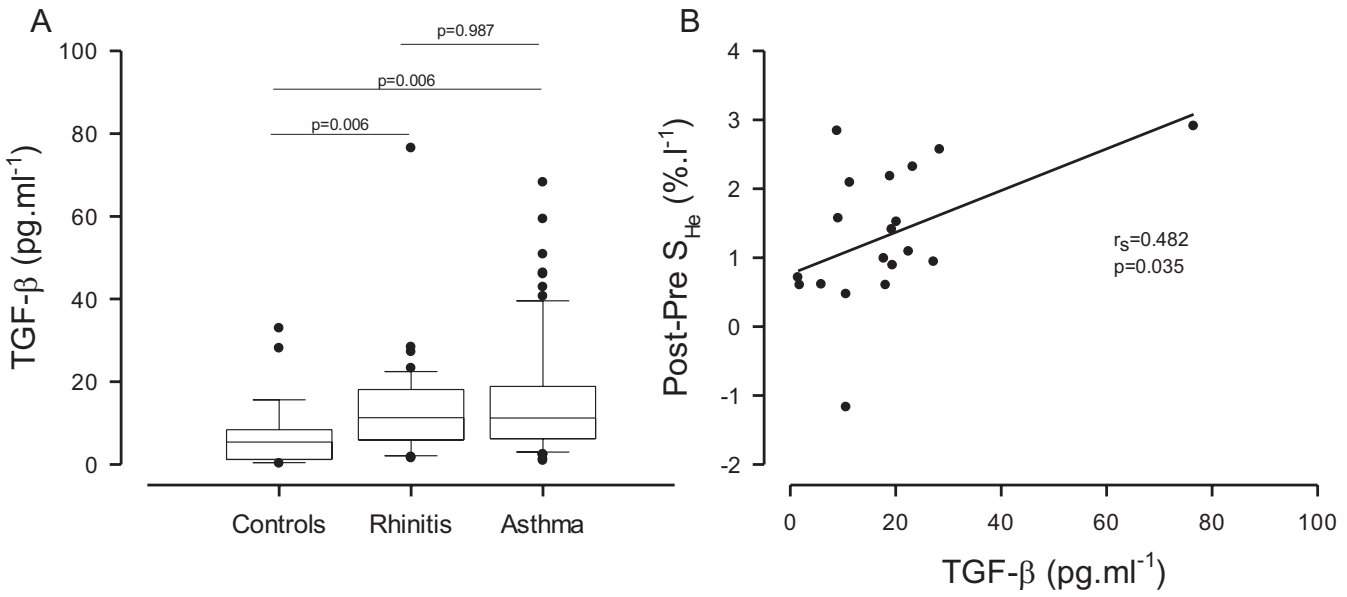

FIGURE 1 | (A) Box plots of TGF-β levels in sputum supernatants of study populations. The mean horizontal line is the median, the box is the interquartile range, and the whiskers are the 10% and 90% percentiles. The *p*-values come from a post hoc Dunn test of a Kruskal Wallis analysis. (B) Post-Pre S_{He} difference as a function of TGF-β level in the subgroup of 19 allergic rhinitis patients. The Spearman correlation coefficient r_s and the associated *p*-value are also indicated. The solid line is the regression line provided as a guide.

Author Contributions

M.V. and M.H. performed the sputum induction technique and TGF-β dosages. F.S. and R.L. participated in the study's design and helped draft the manuscript. A.V.M. conceived the study, participated in the design of the study, performed the statistical analysis, and helped draft the manuscript.A.M. and A.H. conceived the study, participated in the design of the study, and drafted the manuscript. All authors approved the manuscript content.

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Ethics Statement

The local ethics committee approved the study and participants signed informed consent (P2014/088).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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