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Role of interleukin-5 in allergic fungal sinusitis: deeper insight

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Abstract

Background Chronic rhinosinusitis with nasal polyps (CRSwNP) is an allergic response characterized by type 2 inflammatory reactions mediated by T helper 2 cells (Th2). Th2 is characterized by elevated type 2 cytokines related to the humoral response, including Interleukin-4 (IL-4), IL-5, IL-6, IL-9, IL-10, IL-13, IL-25 and IL-33. Allergic fungal sinusitis (AFS) is a distinguishable form of CRSwNP and is characterized by primary localized disease with non-invasive fungal hyphae, which causes immunoglobulin E (IgE)-mediated mucosal hypersensitivity resulting in the formation of eosinophilic mucin. Interleukin-5 (IL-5) is a pro-inflammatory factor that plays a very important role in eosinophil biology.

Objective To explore the relation between IL-5 tissue protein expression and AFS.

Methods A prospective study performed on 70 patients divided into 2 groups (50 cases of AFS and 20 control who underwent septoplasty and partial inferior turbinectomy) to assess the role of IL5 in AFS compared to control.

Results IL-5 was overexpressed in polyps of AFS patients compared to the control group denoting AFS as an eosinophilic mediated type 2 inflammation and highlighting a positive correlation with Lund MacKay radiological score and Sino-nasal Outcome Test (SNOT-22) score for severity of chronic rhinosinusitis (CRS) symptoms.

Conclusion IL-5 plays a pivotal role in the pathogenesis and severity of AFS. Thus, our results provide encouraging evidence supporting targeting IL5 as an eligible therapy of promising benefits in AFS.

Keywords Chronic rhinosinusitis, Allergic fungal sinusitis, Functional endoscopic sinus surgery, IL5

Background

CRS is clinically classified into two phenotypes based on the presence or absence of nasal polyps on endoscopic examination: CRS with (CRSwNP) and without (CRSsNP) nasal polyps [1], AFS is a non-invasive subtype of CRSwNP. It was first defined in 1994 using the following criteria: type I hypersensitivity to fungi, nasal polyposis, characteristic computed tomography findings, eosinophilic mucus without fungal invasion, and positive fungal stain or culture [2, 3]. AFS is the most common type of fungal sinusitis and tends to have greater quantitative serum immunoglobulin E levels and higher Lund-Mackay scale scores than chronic rhinosinusitis [4].

Immunologic characterization of sinonasal mucosal tissue from CRSwNP including AFS patients showed elevated Th2 cytokines such as IL-4, IL-5, and IL-13. In addition, eosinophils also have a notably elevated presence within the diseased tissues. It was hypothesized that a Th2 response should be triggered in the memory T cells of these patients when challenged with fungi [5].

IL-5 is a pro-inflammatory factor that plays a very important role in eosinophil biology. It is the factor responsible for the differentiation, growth, activation, survival, and recruitment of eosinophils into the airways. It also prevents apoptosis of these cells. Eosinophils secrete numerous mediators of type 2

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inflammation, including granule proteins, enzymes, cytokines, chemokines, growth factors, lipids, and oxidation products. Due to its properties, IL-5 may prolong the survival of eosinophils, which is important in the development of inflammation. The association of IL-5 with most eosinophil-induced diseases is indicated [6].

Aim of the work

This study is designed to explore the relation between IL-5 tissue protein expression and AFS.

Methods

A prospective case–control study performed at the Otorhinolaryngology Department, Faculty of Medicine, Ain Shams University. Between 2020 and 2022

Study population

The current study consists of: Study group (1): includes 50 patients diagnosed with AFS with nasal polyps who underwent functional endoscopic sinus surgery (FESS). Study group (2): includes 20 control patients with a deviated nasal septum and inferior turbinate hypertrophy who underwent septoplasty and partial inferior turbinectomy.

Inclusion criteria All adult patients with AFS diagnosed according to Bent and Kuhn's [2] criteria: Presence of nasal polyposis, characteristic computed tomography (CT) findings, eosinophilic mucus without fungal invasion, and positive fungal culture.

Exclusion criteria Acute sinusitis. Invasive acute or chronic fungal sinusitis. Chronic granulomatous inflammations. Patients who used oral or nasal steroids within the last 4 weeks were excluded to guarantee the specification of the targeted study sample and avoid additional variables that might bias our results.

Ethical considerations

Study procedures abided by a strict protocol which was fully explained to all patients before the acquisition of their written consent.

Study procedures

All patients were subjected Full history taking (Allergy history, Asthma, Aspirin sensitivity, and tobacco use) and otorhinolaryngological examination. SNOT score was performed for all patients. Endoscopic examination of the nasal cavity. CT scan of Paranasal sinus and grading according to Lund-Mackay CT Scoring.

Biopsy was obtained from the patients during FESS from polyps in AFS patients and from turbinate or septal mucosa in the control group.

Histopathological and immunohistochemical studies

Procedures For each case, a pair of slide sets was prepared for conventional Hematoxylin and Eosin (H& E) and IL5 stained slides. After serial cuts of 4 um thickness from paraffin-embedded tissue sections. Sections were prepared on conventional glass slides where hematoxylin was added for 45 s, washed, and then the slide was treated with eosin for 20 s to obtain H& E stained slides. Sections prepared for IL5 immunostaining were put on positively charged slides and incubated with purified anti-mouse/human IL-5 antibody (for 90 min at room temperature followed by incubation with goat anti-mouse immunoglobulin (Santa Cruz Biotechnology, Santa Cruz, CA, USA) for 1 h at room temperature. Visualization of the immunoreactions was done via 15 min incubation in streptavidin-conjugate peroxidase. Decolorization was followed using a 3,3-diaminobenzidine tetrahydrochloride solution, and then the sections were counterstained with hematoxylin. Proper positive and negative control tissue sections were incorporated to validate immunohistochemical expression results.

Evaluation method Each set of slides was coded and handled to the pathologist blinded by its clinical background to allow unbiased assessment of histopathological and immunohistochemical results. Histopathological assessment was done by the pathologist for each specimen slides through low-power scanning using a ($\times 10$) magnification lens to assess the overall quality of the section, determine the distribution pattern of the inflammation, and spot the nature of the stromal reaction (reactive edema versus fibrosis). Higher magnifications of ($\times 20$) and ($\times 40$) were then followed to observe inflammatory cell type, epitheliotropism, basement membrane (BM) thickening, and presence or absence of fungal mud. Immunohistochemical evaluation was done for each IL5 stained slide by low power scanning ($\times 10$) to detect the average IL5 expression percentage (Av) in comparison to the total inflammatory cell population burden [7]. Staining intensity was regarded as weak (1+), moderate (2+) and strong (3+). Additionally, the hot spots showing IL5 condensed expression were evaluated and the percentage of IL5 stained cells among these hot spots (Hs) was recorded to test any probably added value of such a pattern. Collaboration of histopathological findings with those of IL5 was done after separate evaluation of each set. Merging these results with the clinical background

for statistical studies and correlations were adopted after such blinded pathological evaluation to highlight significant findings of probable predictive or pathogenic insights. Data collected from study groups subjected to statistical analysis.

Statistical methods

Statistical analysis was done using Data were analyzed using IBM© SPSS© Statistics version 23 (IBM© Corp., Armonk, NY) and MedCalc® Statistical Software version 20 (MedCalc Software Ltd, Ostend, Belgium.

Results

Both groups matched statistically regarding age, sex, and smoking status.

There was a statistically significant difference between the two groups regarding the pattern of inflammation, edema and fibrosis being more in the AFS group with *p*-value (< 0.001). However, there was no statistically significant difference between the two groups regarding epithelial tropism, Neutrophils or BM thickening with *p*-value (> 0.05) (Table 1).

IL-5 HS (%) was higher in the AFS group (median = 30) compared to the control group (median = 6.5), *p*-value = 0.001, also IL-5 AV (%) was higher in the AFS group (median = 8.5) compared to the control group (median = 4), *p*-value < 0.001. For IL-5 intensity, 48% of the AFS group had strong IL-5 intensity while only 5% of the control group had strong IL-5 intensity, 4% of the AFS group had weak IL-5 intensity while 55% of the control group had weak IL-5 intensity, *p*-value < 0.001 (Table 2) (Figs. 1, 2 and 3).

Table 2 IL-5 assay in cases and controls

Variable	AFS (*N* = 50)	Control (*N* = 20)	*p*-value†
IL-5 HS (%), median (IQR)	30.0 (10.0 – 40.0)	6.5 (4.0 – 25.0)	**.001**
IL-5 AV (%), median (IQR)	8.5 (5.0 – 20.0)	4 (2.0 – 5.0)	**< .001**
IL-5 intensity			
Weak	4 (8.0%)	11 (55.0%)	**< .001**
Moderate	22 (44.0%)	8 (40.0%)	
Strong	24 (48.0%)	1 (5.0%)	

† Mann-Whitney test

For IL-5 HS, AUC = 0.759, Best cut-off point > 6.0%, *p*-value < 0.001. For IL-5 AV, AUC = 0.814, Best cut-off point > 5.0%, *p*-value < 0.001. Using ROC curve analysis our statistical analysis proposed two cut-off values as a diagnostic discriminator among the two study groups: one for Av. score (5%) and another for HS. Score (6%) in the assessment of IL5 expression. DeLong method was used to compare the two ROC curves for discrimination between cases and controls using IL-5 HS or IL-5 AV. No statistically significant difference was found between them. This means that IL-5 HS and IL-5 AV have the same discrimination ability (Table 3) (Figs. 4 and 5).

Our study showed a strong positive correlation between the SNOT-22 score and IL-5 HS, Spearman's rho = 0.711, *p*-value < 0.001. A moderate positive correlation was found between the SNOT-22 score and IL-5 AV, Spearman's rho = 0.526, *p*-value < 0.001. It also showed a high statistically significant correlation between IL-5 and Lund-Mackay score (*p*-value < 0.001) with a strong correlation with IL-5 Hs and a moderate correlation with IL-5 AV (Table 4).

Table 1 Results of histopathology in cases and controls

Variable		AFS (*N* = 50)	Control (*N* = *20*)	*p*-value
Pattern of inflammation, n (%)	Diffuse	27 (54.0%)	19 (95.0%)	**.001**†
	Patchy	23 (46.0%)	1 (5.0%)	
Epithelial tropism, n (%)	Absent	23 46.0% ()	8 (40.0%)	.648†
	Present	27 (54.0%)	12 (60.0%)	
Neutrophils, n (%)	Unremarkable	31 (62.0%)	15 (75.0%)	.146‡
	Minimal	13 (26.0%)	5 (25.0%)	
	Marked	6 (12.0%)	0 (0.0%)	
Edema, n (%)	Minimal	28 (56.0%)	20 (100.0%)	**< .001**†
	Marked	22 (44.0%)	0 (0.0%)	
Fibrosis, n (%)	Unremarkable	28 (56.0%)	0 (0.0%)	**< .001**‡
	Minimal	21 (42.0%)	5 (25.0%)	
	Marked	1 (2.0%)	15 (75.0%)	
BM, n/N (%)	Absent	19/46 (41.3%)	10/20 (50.0%)	.513†
	Present	27/46 (58.7%)	10/20 (50.0%)	

† Pearson chi-squared test

‡ Linear-by-linear association

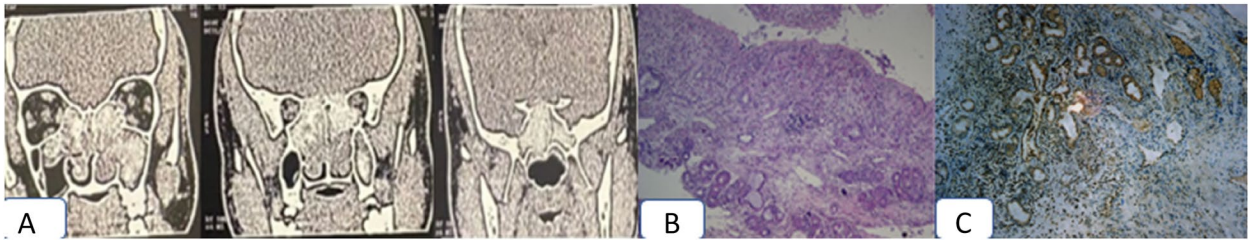

Fig. 1 A case of AFS **A** CT scan shows Lund MacKay score 23, **B** Histopathology section showing dense diffuse subepithelial inflammatory infiltrate, **C** Same case shows strong IL-5 expression

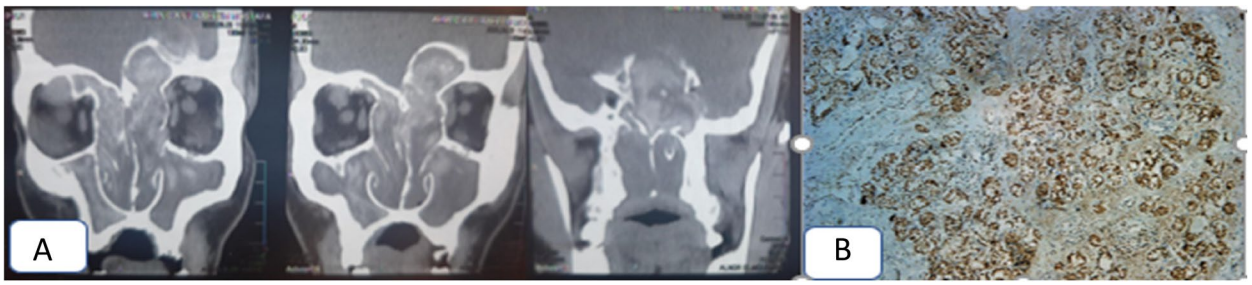

Fig. 2 A case of AFS **A** CT scan shows Lund MacKay score 24 with bone expansion and erosion, **B** Same case shows strong IL-5 expression

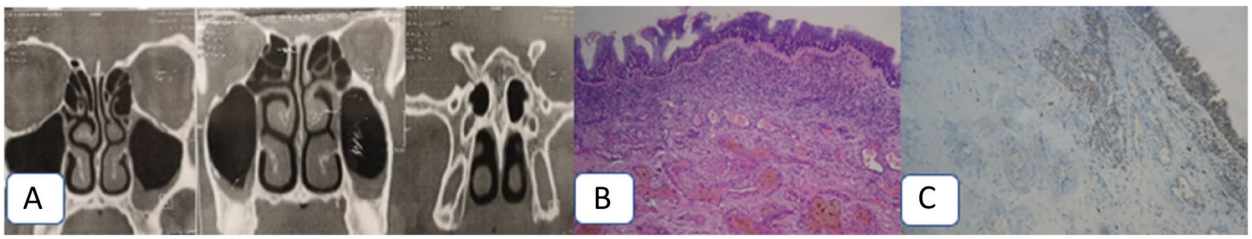

Fig. 3 A control patient with hypertrophied inferior turbinate. **A** CT scan shows Lund MacKay score 2, **B** Histopathology section, **C** Same case shows weak IL-5 expression

It also showed a statistically significant correlation between IL-5 intensity and SNOT-22 score with p-value (0.002) (Table 5).

There was no statistically significant correlation between IL-5 intensity and any of the histopathological features with p-value (> 0.05) (Table 6).

Discussion

The role of interleukins in CRSwNP is now established in several studies, AFS being the most common type of fungal sinusitis is an important focus of such studies, but few studies adopted AFS as a separate entity from CRSwNP.

This study was designed to correlate IL5 in polyps of patients diagnosed with AFS as regard the histopathological finding, Lund MacKay score, and SNOT 22 score in comparison to turbinate tissue of patients who underwent septoplasty and turbinectomy.

The current study showed a statistically significant difference between the AFS and control group regarding the pattern of inflammation, edema and fibrosis being more in the AFS group. The predominance of the diffuse inflammatory reaction pattern in the AFS group reflects a host tissue reaction of more manifest magnitude than those of the control group.

Neutrophils were unremarkable in 62% of AFS patients, minimal in 26% and marked in 12% denoting weak contribution of neutrophils in AFS pathogenesis.

This study showed a high statistically significant difference between the AFS and the control group regarding IL-5 assay being more in the AFS group. Thus, the expression of IL-5 was more prominent in the nasal polyps of patients with AFS than in the nasal mucosa of the control group. The significant differences among AFS and control groups regarding IL-5 expression whether in average or hot spot assessment

Table 3 Response-operating characteristic (ROC) curve analysis for discrimination between cases and controls using IL-5 and comparison of the (ROC) curves for discrimination between cases and controls using IL-5 HS or IL-5 AV

Variable	IL-5 HS	IL-5 AV
Area under the ROC curve (AUC)	0.759	0.814
ΔAUC	0.055	
SE for ΔAUC	0.0551	
95% CI for ΔAUC	-0.053 to 0.163	
Standard Error	0.064	0.050
95% Confidence interval (CI)	0.642 to 0.854	0.704 to 0.897
z statistic	4.032	6.265
p-Value (AUC = 0.5)[†]	**< .001**	**< .001**
Youden index J	0.42	0.54
Best cut-off criterion	> 6.0%	> 5.0%
Sensitivity	92%	64%
Specificity	50%	90%
z-value	0.999	
p-value[†]	.318	

[†] DeLong method

methods highlight the specific role of this cytokine in AFS inflammatory response and there was no statistically significant difference between IL-5 HS and IL-5 AV so both can be used as a method for IL-5 correlations.

Our result is supported by a study performed by Manning and Holman [8] showed that eosinophilic mediators predominated over neutrophil-derived mediators in the AFS specimens, whereas in the control group eosinophil and neutrophil mediators were equal, findings that lend further support for a noninfectious, immunologically mediated process.

Also, Millien et al. [9] intranasally stimulated mice with fungal protease from *Aspergillus oryzae* and observed categorical features of allergic airway disease marked by eosinophilia, increased mucin expression, and increased canonical type 2 cytokines IL-4, IL-5, and IL-13.

A study performed by Bachert et al. [5] found that IL-5 was found in 18 of 23 nasal polyps but it was detectable in only one sample of tissue from 18 control subjects.

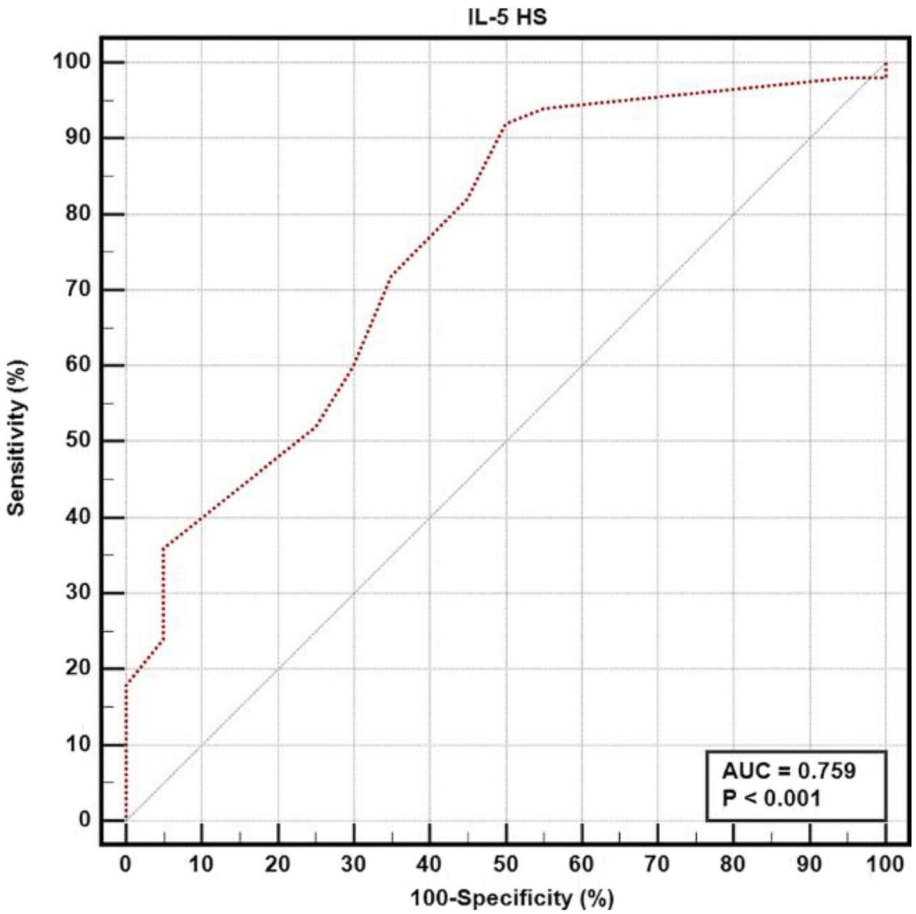

Fig. 4 Response-operating characteristic (ROC) curve analysis for discrimination between cases and controls using IL-5 HS. IL-5 HS has fair discriminative value. Area under the ROC curve (AUC) = .759 (95% CI = 0.642 to 0.854, *p*-value < .001). Best cut-off criterion > 6.0% (sensitivity = 92%, specificity = 50%, J-index = .42)

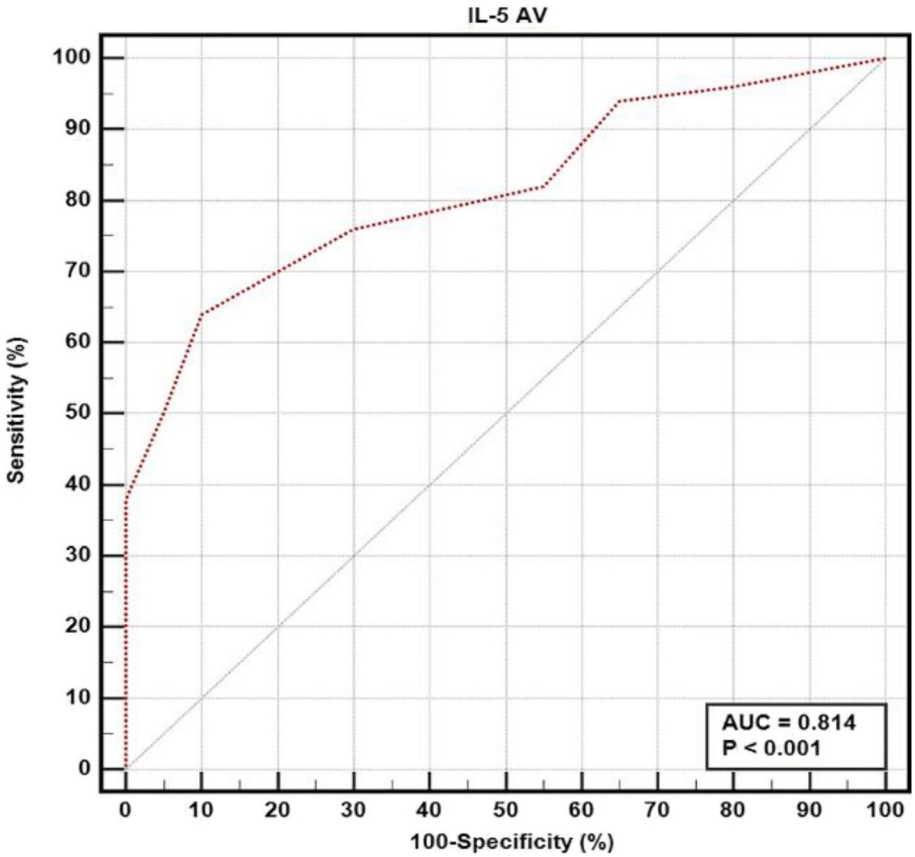

Fig. 5 Response-operating characteristic (ROC) curve analysis for discrimination between cases and controls using IL-5 AV. IL-5 AV has good discriminative value. Area under the ROC curve (AUC) = .814 (95% CI = 0.704 to 0.897, *p*-value < .001). Best cut-off criterion > 5.0% (sensitivity = 64%, specificity = 90%, J-index = .54)

Table 4 Correlation of IL-5 with SNOT-22 score and Lund-Mackay score

Variable		IL-5 HS	IL-5 AV
Lund-Mackay score	Spearman's rho	.729**	.453**
	p-value	**< .001**	**.001**
SNOT-22 score	Spearman's rho	.711**	.526**
	p-value	**< .001**	**< .001**

** Correlation is significant at the 0.01 level (2-tailed)

Table 5 Correlation between IL-5 intensity and SNOT-22 score

Variable		IL-5 intensity
SNOT-22 score	Kendall's tau-b	.437**
	p-value	**.002**

** Correlation is significant at the 0.01 level (2-tailed)

Table 6 Correlation between IL-5 intensity and histopathological features

		IL-5 intensity
Pattern of inflammation	Kendall's tau-b	-.030
	p-value	.828
Neutrophils	Kendall's tau-b	.194
	p-value	.145
Edema	Kendall's tau-b	.130
	p-value	.349
Fibrosis	Kendall's tau-b	-.135
	p-value	.325
Epithelial tropism	Rank-biserial correlation	.140
	p-value	.334
BM	Rank-biserial correlation	.195
	p-value	.194

Immunohistochemistry revealed an abundant number of IL-5 + cells, of which 69.5% could be identified as eosinophils by morphology.

A study performed by Grgić et al. [10] included 30 adults (age ≥ 18 years) patients with CRSwNP who had been surgically treated for their disease. The

immunoreactivity to IL-5 was distributed as follows: seven specimens showed a strong reaction (+++); seven had a moderate reaction; 11 had a weak reaction; and in five, no immunoreactivity to IL-5 was detected.

Another study performed by Xu et al. [11] found that IL-5 concentration in the polyp tissues was significantly higher than that in inferior turbinate mucosa ($P < 0.05$). There was no significant difference in inferior turbinate mucosa between the patients with nasal polyps and healthy volunteers ($P > 0.05$). IL-5 concentration in polyp tissues was markedly higher in patients with an extensive polypoid change of nasal mucosa, history of previous polypectomy and allergic rhinitis compared with those without these features ($P < 0.05$).

Tyler and Luong [12] investigated several type 2 inflammatory cytokines in different clinical subtypes of CRS: Similarly, AFS (45 patients) and CRSwNP (38 patients) exhibited increased expression of IL-5 when compared with healthy control (17 patients). Meanwhile, our study focused only on AFS correlation with IL5.

This study showed no statistically significant correlation between IL-5 intensity and any of the histopathological features (pattern of inflammation, epithelial tropism, neutrophils and basement membrane thickening, tissue edema and fibrosis) this might be due to the multiple cytokines involved in the pathophysiology and histopathological pattern of inflammation occurring in AFS. To our knowledge, no previous studies mentioned the correlation between IL-5 and histopathological features in AFS.

Interestingly, this study showed a high statistically significant correlation between IL-5 and SNOT-22 score with a strong correlation with IL-5 Hs and a moderate correlation with IL-5 AV and a moderate statistically significant correlation between IL-5 intensity and SNOT-22 score. this not only endorses our claims of the IL5's key role in inflammation but also highlights that such role echoes on the patient's clinical status, thus emphasizing the presence of direct and indirect pathogenic effects of IL5 that attributes to the severity of symptoms Moreover, the superior significance of HS scoring as compared to Av.score might suggest an augmented effect of IL5 paracrine cross-talks when eosinophils are clustered.

It also showed a high statistically significant correlation between IL-5 and Lund-Mackay score with a strong correlation with IL-5 Hs and a moderate correlation with IL-5 AV.

In patients with CRSwNP, the serum level of IL-5, POSTN and IL-33 positively correlated with the Lund-Mackay score, according to CT images. also, Significant relationships were also found between the serum level of IL-5, POSTN and IL-33 and disease severity, as determined by VAS score [13].

De Corso et al. [14] performed a study on 2 groups of patients: the first was characterized by high levels of IL-4, IL-5, IL-6, and a high-grade eosinophil count (type 2–high). In the second (type-2 low), lower levels of cytokines were detected in nasal secretions and eosinophilic inflammation was poor or absent. Interestingly, they observed that type 2-high patients showed poorer clinical performance with a substantially higher subjective and objective disease severity as documented by clinical scores such as SNOT-22 and Lund MacKay score.

A study performed by Bachert et al. [15] proved inhibitory effects on nasal polyposis can be also exerted by anti-IL-5 monoclonal antibodies such as mepolizumab and reslizumab. SNOT-22 score was reported to be improved by both these drugs. Mepolizumab also improved nasal polyposis visual analog scale (VAS) score and endoscopic nasal polyp score, as well as significantly decreased the need for surgical treatment of nasal polyp.

Also, a study performed by Shilpika et al. [16] identified 247 patients who received anti-asthma biologic therapy and had co-existent CRS. Of these, 181 patients (73.3%) had CRSwNP and 66 (26.7%) had CRSsNP. The biologics utilized were omalizumab (51.0%), mepolizumab (46.6%), benralizumab (10.5%), reslizumab (1.6%), and dupilumab (2.4%). Anti-interleukin-5 (anti-IL-5) intervention was associated with significant improvement in CT scores (CRS overall, CRSwNP subgroup, CRSsNP subgroup) and SNOT-22 scores (CRS overall, CRSwNP subgroup).

Thus, our study confirms that the endotyping of AFS is type 2 eosinophilic mediated inflammation skewing towards data coming from the American and European cohorts about CRSwNP [17] and not type 1 as data coming from the Asian population [18].

Limitation of this study

We are aware of some limitations in our study, for example the sample size; a larger size with a higher number of enrolled candidates would have validated our results on more solid grounds, however, we had set our priority on using strictly delineated inclusion and exclusion criteria to guarantee the reliability of our results and their genuine association to the chosen group. As such, we can assure that such findings are reliable even though we are acquainted that their verification requires larger scope research work.

Moreover, we would advise using image analyzing techniques in the assessment of the histopathological parameters to obtain more objectivity of the data regarding measurements and scores. Nonetheless, we tried to overcome such a point by blinding the pathologist from all underlying clinical backgrounds to guarantee an unbiased evaluation of all histopathological and IL5 immunohistochemical results.

Conclusion

IL-5 is overexpressed in polyps of AFS patients compared to the control group confirming AFS is an eosinophilic mediated type 2 inflammation and IL-5 has a positive correlation with Lund MacKay radiological score and SNOT-22 score for severity of CRS symptoms. Thus, IL-5 plays a pivotal role in the pathogenesis and severity of AFS. So, our results provide encouraging evidence supporting targeting IL5 as an eligible therapy of promising benefits in AFS.

Abbreviations

CRSwNP	Chronic rhinosinusitis with nasal polyps
Th2	T helper 2
IL-5	Interleukin-5
AFS	Allergic fungal sinusitis
IgE	Immunoglobulin E
SNOT	Sino-nasal Outcome Test
CRS	Chronic rhinosinusitis
CRSsNP	Chronic rhinosinusitis without nasal polyps
FESS	Functional Endoscopic Sinus Surgery
CT	Computed tomography
H&E	Hematoxylin and Eosin
Hs	Hot spots
AV	Average
BM	Basement membrane
IQR	Interquartile range
AUC	Area under the curve
ROC	Response-operating characteristic
CI	Confidence interval
VAS	Visual analog scale

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Authors' contributions

HAM have made design of the work and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work. AGS have made substantial contributions to the conception and approved the submitted version and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work. MMK have drafted the work or substantively revised it and approved the submitted version and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work. LSS have made interpretation of data and approved the submitted version and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work. AHM have drafted the work or substantively revised it and approved the submitted version and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work. MMM (corresponding author) ensured that all listed authors had approved the manuscript before submission, including the names and order of authors, and that all authors received the submission and all substantive correspondence with editors, as well as the full reviews, verified that all data, figures, materials (including reagents), and code, even those developed or provided by other authors, comply with the transparency and reproducibility standards of both the field and journal.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Declarations

Ethics approval and consent to participate

Informed consent from participants obtained to participate in the study at otorhinolaryngology department Faculty of Medicine Ain Shams University. Approved by an ethical committee of Faculty of Medicine Ain Shams University before the start of the recruitment (FMASU M D 264/2020).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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