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ORIGINAL STUDY

Aberrant Expression of Soluble Programmed Death-ligand 1 and Inducible Costimulator Ligand in Patients With Nasal Polyps

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Abstract

Aim: **We aimed to measure the levels of soluble programmed death-ligand 1 (sPD-L1) and soluble inducible costimulator ligand (sICOS-L) in patients with nasal polyps and to compare their levels between a group with allergic rhinitis (AR) with nasal polyps and another with allergic fungal rhinosinusitis (AFRS). The study also aimed to assess the relationship between their levels and disease severity.**

Patients and methods: **The study included 35 patients admitted for endoscopic sinus surgery for nasal polyps, who were divided into 17 with AR and 18 with AFRS and 20 controls. Radiologic computed tomography (CT) score of Lund−Mackay was used to assess the severity of chronic rhinosinusitis. Complete blood cell count was done for all patients. Serum PD-L1 and ICOS-L levels were quantified using enzyme-linked immunosorbent assay.**

Results: **A significant decrease was observed in sPD-L1 levels in both groups of patients compared with controls. Only patients with AFRS had a significantly lower level of sICOS-L than controls and was lower than in AR patients. Only patients with AFRS showed positive correlations between sPD-L1 and the total CT score, and also between sICOS-L and both total CT score and eosinophil percentage. A positive correlation was detected between ICOS-L and PD-L1 levels.**

Conclusions: **The present results suggest a potential protective role of sPD-L1 in AR and AFRS, and only of sICOS-L in AFRS. Thus, their manipulation represents a promising therapeutic approach to AR and AFRS. They also have the potential for future use as biomarkers for the assessment of AFRS severity. However, further studies are warranted to clarify their complex role in these types of allergies.**

Keywords: Allergic fungal rhinosinusitis, Allergic rhinitis, Nasal polyps, Soluble inducible costimulator ligand, Soluble programmed death-ligand 1

1. Introduction

Allergic rhinitis (AR) and chronic rhinosinusitis (CRS) with nasal polyps (CRSwNP) are chronic inflammatory disorders of the upper airway. Both are characterized by persistent and aberrant type 2 inflammation [1]. Allergic fungal rhinosinusitis (AFRS) is a noninvasive, recurrent subtype of CRSwNP [2]. History of AR has been reported in 66% of AFRS patients [3]. In atopic patients, fungi provoke allergic responses leading to the inflammation of sinus mucosa and consequently obstruction of the sinus ostia impeding mucus drainage [4]. Both AR and AFRS are IgE-mediated hypersensitivity disorders promoting eosinophil recruitment to the inflammatory site [4,5].

T cell activation requires two signals. The initial signal is delivered by T-cell receptors recognizing

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the peptide-bound major histocompatibility complex and a second signal provided through costimulatory molecules. The costimulatory molecules can be divided into those delivering positive costimulatory signals and others delivering negative signals [6–8].

Inducible costimulator (ICOS)/inducible costimulatory ligand (ICOS-L) are inducible positive costimulatory molecules. Alternatively, programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) represents major negative costimulatory molecules. They have central roles in retaining immune homeostasis and in disease development and progression [9]. Despite the fact that PD-1 is a potent coinhibitory receptor, PD-L1 has shown both stimulatory and inhibitory functions [10–12]. These observations advocate the presence of another receptor for PD-L1 distinct from PD-1 to deliver stimulatory signals [13].

Human plasma harbors soluble forms of these molecules, which are generated mainly through shedding of the membrane form or by alternative splicing of their mRNA transcripts with exclusion of the transmembrane domain [14]. However, their precise chemical nature and functions are inadequately documented. Lately, soluble forms of these molecules have been broadly explored. Elevated plasma levels were reported in disease progression, autoimmune disorders, infections, and tumors [15–18].

Although the majority of the reports assessed sPD-L1 and sICOS-L proteins in many types of cancer, and in various inflammatory pathologies, few data are available about their effects in allergic disorders. Also, the contribution of these molecules to disease progression is not always clear, sPD-L1 and sICOS-L might have a role in the pathogenesis of AR and AFRS probably through the induction of inflammatory response by promoting Th2-type immune response [19,20]. More work is needed to characterize better the contribution of sPD-L1 and sICOS-L in AR and AFRS. Thereby, we aimed to measure the levels of sPD-L1 and sICOS-L in patients with nasal polyps and compare their levels between a group with AR and another with AFRS and also to assess the relationship between their levels and disease severity.

2. Patients and methods

Thirty-five adult patients admitted to the Department of Otorhinolaryngology, Assiut University Hospital for endoscopic sinus surgery of nasal polyps were enrolled in this study during the period from October 2019 to March 2021. They were divided into two groups: the first group included 17 patients with AR and the second group included 18 patients with AFRS. The diagnosis of AFRS was in accordance with the criteria of Bent and Kuhn [21]. Patients having autoimmune disorders, malignancy, infectious disorders, or receiving immunotherapy were excluded from the study. In addition, 20 age-matched and sex-matched healthy volunteers were enrolled as a control group.

Table 1. Demographic, radiologic, and laboratory characteristics of patients.

Variables	Patients ($N = 35$) [n (%)]	Group A ($N = 17$) [n (%)]	Group B ($N = 18$) [n (%)]	P value
Age (years)	37.2 ± 3	41 ± 4	33.6 ± 5	0.07
Sex				
Male	15 (71.4)	13 (76.5)	20 (55.6)	0.2
Female	6 (28.6)	4 (23.5)	8 (44.4)	
Lund–Mackay total score				
8	1 (2.9)	–	1 (5.6)	0.5
11	1 (2.9)	1 (5.9)	–	
15	2 (5.7)	1 (5.9)	1 (5.6)	
16	4 (11.4)	3 (17.6)	1 (5.6)	
18	2 (5.7)	1 (5.9)	1 (5.6)	
19	3 (8.6)	1 (5.9)	2 (11.1)	
20	1 (2.9)	1 (5.9)	–	
21	4 (11.4)	2 (11.8)	2 (11.1)	
22	6 (17.1)	3 (17.6)	3 (16.7)	
23	3 (8.6)	2 (11.8)	1 (5.6)	
24	8 (22.9)	2 (11.8)	6 (33.3)	
White blood cell count				
TLC	7 ± 0.4	7 ± 0.6	7 ± 0.5	0.9
Neutrophil percent/count	52.6 ± 2/3.8 ± 0.3	56.5 ± 3/4.2 ± 0.5	49 ± 3/3.4 ± 0.4	0.06/0.3
Eosinophil percent/count	3.3 ± 0.4/0.3 ± 0.03	3.2 ± 0.6/0.2 ± 0.04	3.4 ± 0.5/0.3 ± 0.05	0.7/0.5

Group A, allergic rhinitis; group B, allergic fungal rhinosinusitis; TLC, total leukocyte count.
The P value is between groups A and B.

All patients were subjected to non-contrast computed tomography (CT) scans, with 3 mm coronal, axial, and sagittal cross-sections, using soft-tissue and bone window settings. Radiologic CT score of Lund–Mackay was used to assess the severity of CRS. The opacification of each sinus was scored from 0 to 2 and the ostiomeatal complex was scored only 0 if not occluded or 2 if occluded, which gives a maximum score of 12 for each side and 24 for the total score [22]. Complete blood cell count was done for all patients.

2.1. Quantification of soluble programmed death-ligand 1 and inducible costimulator ligand levels in serum

Two milliliters of whole blood sample was collected on a plain vacutainer tube during the endoscopic sinus surgery. Blood was left to clot by leaving it undisturbed at room temperature. The clot was removed by centrifuging at 2000–3000 rpm for 20 min, and serum was collected and stored at −20 °C till use. Serum sPD-L1 and sICOS-L levels were quantified using the commercially available sandwich enzyme-linked immunosorbent assay kit (SinoGeneClon Biotech Co. Ltd, HangZhou, China), following the manufacturer's instructions (Catalog no. SG-15257 and SG-15324, respectively).

2.2. Statistical analysis

Data were analyzed using IBM Statistical Package for the Social Sciences, version 25 (IBM SPSS Statistics, Chicago, Illinois, USA). Quantitative data were presented as mean ± SE, whereas qualitative data were displayed as numbers (percentages). The normality of data distribution was evaluated by the Shapiro–Wilk test. Independent sample *t* test was used to compare normally distributed variables, whereas Mann–Whitney *U* was used to compare nonnormally distributed variables. Correlations were tested using Kendall's tau and Spearman's correlation coefficient. A *P* value of less than 0.05 was considered significant.

3. Results

3.1. Demographic, radiologic, and laboratory features of patients

As presented in Table 1, no differences were found between the two groups of patients in age, sex, white blood cell count, and Lund–Mackay total score. The average age of all patients was 37.2 ± 3, and most of them were males. The mean total leukocyte count was 7 ± 0.4. The neutrophil mean percentage and count were 52.6 ± 2 and 3.8 ± 0.3, respectively. On the other hand, the eosinophil

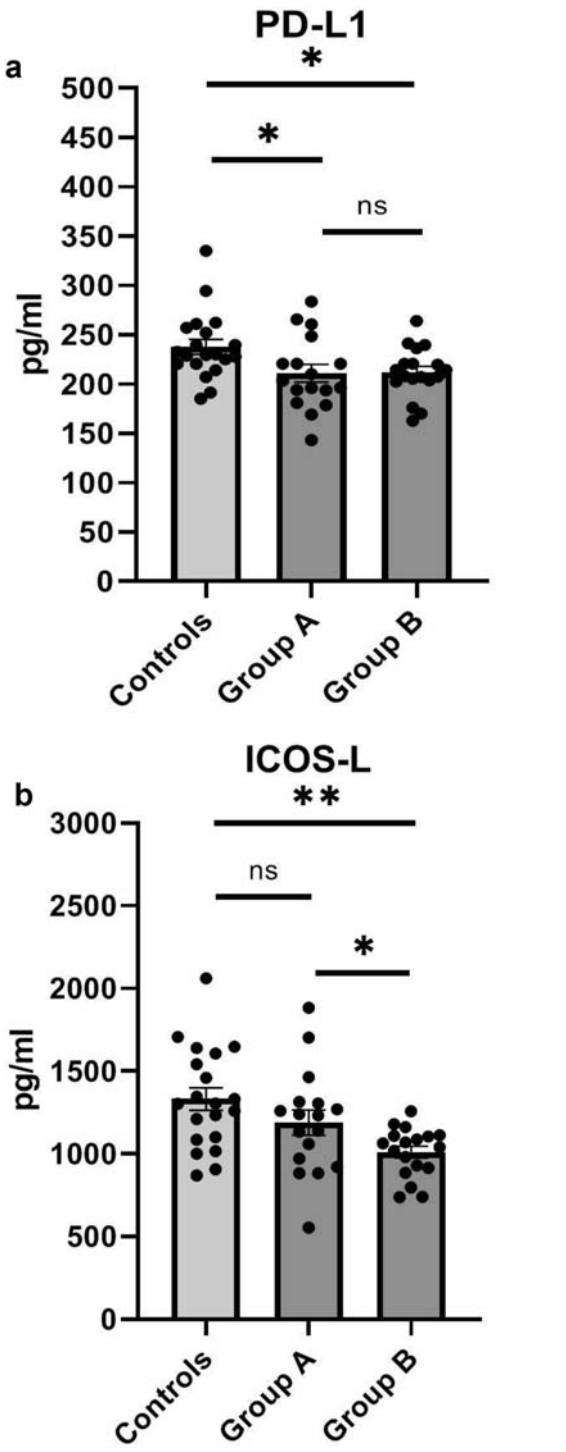

*Fig. 1. Serum levels of (a) PD-L1 and (b) ICOS-L in allergic rhinitis (group A = 17) and allergic fungal rhinosinusitis (group B = 18) in comparison with healthy controls. P value *indicates less than 0.05, **less than 0.01, and NS indicates nonsignificant. ICOS-L, inducible costimulator ligand; PD-L1, programmed death-ligand 1.*

mean percentage and count were 3.3 ± 0.4 and 0.3 ± 0.03, respectively. About 53% of patients with AR were assigned a total score greater than 20, while about 67% of patients with AFRS showed a total score greater than 20.

3.2. Serum levels of programmed death-ligand 1 and inducible costimulator ligand in patients with allergic rhinitis and allergic fungal rhinosinusitis in comparison with healthy controls

A significant decrease was observed in serum level of PD-L1 in all patients compared with healthy controls (211.5 ± 5 vs. 237.7 ± 8, P=0.006). As illustrated in Fig. 1, both groups with AR and AFRS had lower levels of serum PD-L1 than controls (210.9 ± 9 vs. 237.7 ± 8, P=0.02 and 212 ± 6 vs. 237.7 ± 8, P=0.01, respectively). No noticeable differences were detected between the two groups of patients (P=0.7).

Likewise, the serum level of ICOS-L showed a marked decrease in all patients compared with healthy controls (1097.5 ± 44 vs. 1331.7 ± 68, P=0.01). Only patients with AFRS had lower levels of serum ICOS-L than controls (1010.7 ± 35 vs. 1331.7 ± 68, P=0.001, respectively), which was also lower than that in patients with AR (1010.7 ± 35 vs. 1189.5 ± 77, P=0.04).

3.3. Correlations of serum levels of programmed death-ligand 1 and inducible costimulator ligand with white blood cell count and the radiologic staging score

Only in patients with AFRS, sPD-L1 had a positive correlation with the total CT score (r = 0.5, P=0.003). Also, sICOS-L related directly with total CT score (r = 0.3, P=0.04) and eosinophil percentage (r = 0.5, P=0.02). In addition, a positive correlation was detected between ICOS-L and PD-L1 serum levels (r = 0.5, P=0.04).

4. Discussion

In recent years, the roles of soluble costimulatory molecules in disease progression and their therapeutic potential have received growing attention [23]. However, their contribution in allergic disorders, particularly AR and AFRS, is still not clear. Thereby, we aimed to measure sPD-L1 and sICOS-L in patients with nasal polyps and compare their levels between a group with AR and another with AFRS and also to assess the relationship between their levels and disease severity.

A significant decrease was observed in serum levels of PD-L1 in both groups of patients compared with healthy controls, with no significant difference between the two patient groups. Only patients with AFRS had a significantly lower level of serum ICOS-L than controls and was even lower than its level in patients with AR. It is worth mentioning that only patients with AFRS showed positive correlations between sPD-L1 and the total CT score and also between sICOS-L and both total CT score and eosinophil percentage. In addition, a positive correlation was detected between ICOS-L and PD-L1 levels merely in this group of patients.

AR is the most common of all atopic diseases. Data about changes in sPD-L1 levels in peripheral blood of AR patients are lacking and yet controversial. In line with our findings, Kalmarzi and colleagues previously found a significant decrease in sPD-L1 level in AR patients compared with normal individuals. Still, they detected a significant negative association between sPD-L1 and disease severity, symptom intensity, as well as eosinophil count in AR patients. Furthermore, sPD-L1 was significantly lower in severe AR patients than patients with mild or moderate disease [24]. They assumed that sPD-L1 behave differently in the various stages of allergic inflammation. PD-1 ligation enhances T helper-2 (Th2)-mediated responses and Th2 cytokine secretion in early-phase reactions. In contrast, it suppresses allergic responses in later phases by inhibiting Th2 cytokines, inducing anti-inflammatory cytokines and promoting regulatory T cells [24]. Our findings support their hypothesis that sPD-L1 has protective features in AR development and thus its modulation may be considered a proper therapeutic method for hindering disease progression.

More recently, other authors [19] have suggested that PD-L1 is highly expressed on the surface of immune cells in peripheral blood and nasal mucosa of AR (AR) patients. Against our findings, they also noticed that sPD-1 and sPD-L1 increased in peripheral blood of AR patients, and sPD-L1 was positively correlating with IgE concentration. They proposed that the PD-1/PD-L1-signaling pathway promotes AR inflammatory response by inducing Th2-type immune response. Contradictory to the previous two studies, patients with AR in the current study did not show any significant correlations with total CT score and either eosinophil count or percentage.

A previous study reported a higher PD-1 expression by T cells and epithelial cells in nasal polyp tissue homogenates of patients with CRS than controls. PD-1 expression was also directly proportional with the total CT score and tissue IL-5 expression signifying a central contribution in the

pathophysiology of CRSwNP. However, PD-L1/PD-L2 expression in tissues was considerably lower than that in healthy controls [25].

Evidence suggested that blockade of PD-1/PD-L1 pathway improves patients' survival in both fungal and bacterial sepsis [26,27] and reduces viral load in murine models infected with HIV-1 and hepatitis B [28,29]. Wurster and colleagues found that in comparison with isotype-treated infected control mice, blocking PD-1 in a murine invasive pulmonary aspergillosis model increases proinflammatory cytokines and neutrophil-attracting chemokines in the infected lung causing leukocyte accumulation, enhanced fungal clearance from the lungs, and improved survival, even without antifungals [30]. They deduced that PD-1 inhibition boosts the control of *Aspergillus* lung infection by activating innate immune cell responses [31]. Thus, through the inhibition of PD-1/PD-L1 pathway, sPD-L1 may offer a crucial role in the control of fungal CRS, which probably explains the low level of sPD-L1 observed in patients with AFRS in the present study. It can be postulated that in the late stages of AFRS, production of sPD-L1 increases to control the fungal infection through the activation of innate immune cells. The positive correlation noticed between sPD-L1 and the total CT score may support this proposition.

On the other hand, ICOS is expressed primarily on the activated or memory T cells [32]. Its ligand, ICOS-L, is expressed on B cells, dendritic cells, macrophages, and T cells [33,34]. Ligation of ICOS has shown to be of particular importance in humoral immune responses [35]. The ICOS/ICOS-L interaction augments IL-4 production, leading to Th2 polarization [36,37]. The authors previously concluded that Th2 cells show a more robust expression of ICOS on its surface than Th1 cells [36,38]. Loss of this vital costimulatory axis essentially blocks follicular helper T (Tfh) and Th2 functions [35]. Thus, ICOS/ICOS-L may contribute to Th2 polarization in AR.

In addition, Lownik et al. [20] confirmed the implication of ICOS-L shedding in both ICOS/ICOS-L expression and function. They demonstrated earlier that if ICOS-L shedding is blocked, ICOS will be significantly internalized and degraded. High ICOS-L on B cell surface owing to the loss of its shedding resulted in the loss of Tfh differentiation in numerous immunization models [20] and defective Th2-mediated responses in a house dust mite-induced allergic asthma model [6]. Thus, the lower levels of sICOS-L observed in patients with AFRS of the present study may reflect decreased shedding of membrane ICOS-L, which may be a defensive mechanism aiming the down-regulation of proinflammatory signaling cascade provoked by this interaction. This hypothesis is also supported by the positive correlations detected between sICOS-L and both total CT score and eosinophil percentage.

Collectively, these findings indicate the complex role jointly played by sPD-L1 and sICOS-L in the pathogenesis, progression, and control of AFRS. This was underlined by the positive correlation between ICOS-L and PD-L1 levels only in this group of patients.

5. Conclusions

Altogether, the present results suggest a potential protective role of sPD-L1 in AR and AFRS, and only of sICOS-L in AFRS. Thus, their manipulation represents a promising therapeutic approach to AR and AFRS. They also have the potential for future use as biomarkers for the assessment of AFRS severity. However, further studies are warranted to clarify their complex role in these types of allergies.

Conflicts of Interest

There are no conflicts of interest.

Ethical approval

The Faculty of Medicine Ethics Committee, Assiut University, reviewed and accepted the study protocol (IRB. No.17300596), according to the latest revision of the Declaration of Helsinki.

Consent statement

All patients gave written informed consent to participate in the study.

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