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Differences in Expression of Inflammatory Mediator in Mucosal and Polyp Tissue between Chronic Rhinosinusitis and Recurrent Chronic Rhinosinusitis

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Abstract

BACKGROUND: Chronic rhinosinusitis with nasal polyps (CRSwNP) remains a challenging clinical entity with its propensity for recurrence. This disease decreases the patients' quality of life and creates a high economic burden. An effort to investigate the aetiology of recurrent polyps has to be more alert.

AIM: This study aims to prove the differences in expression of IL-5, IL-8, IL-17A and TGF-β1 in mucosal and polyp tissue between CRSwNP and recurrent CRSwNP and also to determine which expression of cytokines that have the main role in mucosal and polyp tissue in recurrent CRSwNP.

MATERIAL AND METHODS: An observational study was conducted with a comparative cross-sectional design of CRS patients with 15 recurrent CRSwNP and CRSwNP who had never undergone surgery for as many as 15 polyps. Mucosal specimens of nasal polyps are taken by brushing, and polyp tissue specimens are taken during surgical removal of nasal polyps. Specimens from the polyp mucosa were examined by ELISA while the polyp tissue specimens were carried out immunohistochemistry (IHC).

RESULTS: The result showed that there is a significant difference in IL-5 expression in the polyp mucosal between CRSwNP with recurrent CRSwNP, where expression is higher in recurrent CRSwNP. The expression of IL-8, IL-17 and TGF-β1 were lower in recurrent CRSwNP, but the difference was not significant. In nasal polyp tissue, there is a significant difference in TGF-β1 and IL-8 expression between CRSwNP and recurrent CRSwNP, where the expression of both cytokines is lower in recurrent CRSwNP. Interleukin-5 expression was higher in recurrent CRSwNP than CRSwNP, but the difference was not significant. In the polyps mucosal, IL-5 has the main role in recurrent CRSwNP polyp, whereas TGF-β has the main role in polyp tissue.

CONCLUSION: This study concluded that the expression of IL-5 in the mucosa could be examined with simple techniques like brushing before polypectomy or FESS was performed to determine the possibility of polyps recurrencies.

Introduction

Chronic rhinosinusitis (CRS) is one of the chronic diseases that is often encountered in the community. This disease decreases the quality of life of patients, besides causing economic burdens due to the high cost of treatment [1], [2], [3]. Rinia et al. (2007) stated that the prevalence of nasal polyps in the general population reached 0.5-4.3%. Therefore polyps become one of the most common cases in chronic upper respiratory tract infections [4]. The prevalence of chronic rhinosinusitis in Europe reaches 19.7% [2]. Rhinosinusitis with polyps often recurrence. Polyps often grow back after surgery, so patients have to experience repeated surgeries. According to Kosem et al., (2010), the rate of recurrence in nasal polyps reaches 10% [5]. Until now, there has been no benchmark for predicting cases that will experience recurrence after polypectomy [6].

Some factors that are thought to underlie the

occurrence of nasal polyps are genetic factors, allergic factors, irritants and pollutants, the role of bacterial and fungal infections, and anatomical variations in the lateral nasal wall and local immunological balance disorders that cause chronic inflammation [2]. The differences in inflammatory patterns in CRS with polyps (CRSwNP) are, the eosinophilic Th2 inflammation pattern is commonly found in Caucasian races while neutrophilic Th1/Th17 inflammation pattern is found in Asian races [1], [7].

Various factors involved in the pathogenesis of CRSwNP make it challenging in determining the immunological phenotype and management of CRS with polyps where the tendency for recurrence is high. The difficulties in identifying trends in recurrence of CRSwNP occurred due to complex problems and the number of factors involved in CRSwNP. It is necessary to look for markers to be used as predictors in monitoring the possibility of CRSwNP being recurrent and efforts to find methods that are easy and not invasive for taking nasal polyp specimens. This study aimed to prove the differences in expression of IL-5, IL-8, IL-17A and TGF-β1 in mucosal and polyp tissue between CRSwNP and recurrent CRSwNP and also to determine which expression of cytokines that have the main role in mucosal and polyp tissue in recurrent CRSwNP.

Material and Methods

Sample

Samples were obtained from CRSwNP patients who visited the Ear, Nose and Throat (ENT) clinic in the Public Central Hospital Dr M Djamil Padang and several hospitals in West Sumatera on August 2016 until September 2018. There was 15 patient CRSwNP dan 15 patient with recurrent CRSwNP. Before the study, approval of the study was asked of respondents before the operation. Samples were taken from CRSwNP patients aged 18 to 55 years who did not use anti-allergic drugs during the washout period before brushing (chlorpheniramine 3 days, cetirizine, fexofenadine, loratadine, respectively 5 days and 2 weeks for corticosteroids).

Sampling

Brushing was performed on nasal polyps mucosa with the nasoendoscopy in a circular motion by using a modified gynecologic cytology brush. Before brushing the polyp, a cotton tampon containing lidocaine and adrenaline installed with a ratio of 4:1 for 10 minutes on the nasal cavity. Brushing was done on the mucosa of the polyp in a circular motion ten times clockwise. Samples obtained from brushing were inserted into a sterile bottle containing PBS liquid and immediately taken to the Biomedical laboratory in the Faculty of Medicine, Andalas University and stored at a temperature of -80°C.

Retrieval of nasal polyp tissue is performed during surgical removal of the polyp by FESS (Functional Endoscopy Sinus Surgery). When FESS was performed, polyp tissue samples were put into neutral formalin liquid and immediately taken to the Anatomy Pathology Laboratory of the Andalas University Medical School to make paraffin blocks.

ELISA

In this research, human IL-5, IL-17 and TGF-β1 were used from R&D and human IL-8 from BT lab to examining nasal mucous polyps.

IHC

Immunohistochemical staining techniques using the Labeled Streptavidin-Biotin Complex (LSAB) method were carried out by manual procedure. The staining results of the preparations were measured and calculated using a microscope to assess the expression of IL-5, IL-8, IL-17, and TGF- β1. Positive values are the results of assessments of the brown intensity of epithelium and stroma seen in the light microscope.

Statistical Analysis

We use SPSS program version 17.0.0.0.

Results

Characteristic

In this study, the percentage of males in recurrent CRSwNP was higher than CRSwNP, which was 80%:66.7%, while the percentage of female in CRSwNP was higher than recurrent CRSwNP at 33.3%:20% and statistically the difference was not significant ($p > 0.05$). The percentage of the male is higher than female, which is 66.7%:33.3% in CRSwNP and 80%:20% in recurrent CRSwNP. The mean age was higher in the recurrent CRSwNP group (41.40 ± 10.23 years) than in the CRSwNP (36.20 ± 11.61 years) and was not significant ($p > 0.05$).

Table 1: Characteristics of respondents based on gender and age

Characteristics	CRSwNP (n = 15)	recurrent CRSwNP (n = 15)	p
Sex			
Male	10 (66.7 %)	12 (80%)	0.682
Female	5 (33.3 %)	3 (20%)	
Age	36.20 ± 11.61	41.40 ± 10.23	0.204

In this study, the mean mucosal IL-5 expression was higher in recurrent CRSwNP (2.75 ± 2.02) than CRSwNP (0.86 ± 0.13), and a statistically significant difference was found ($p < 0.05$). The mean interleukin-8 mucosal expression was higher in CRSwNP (327.51 ± 33.16) than recurrent CRSwNP (304.35 ± 34.86), but the difference was not statistically significant ($p > 0.05$). Similar to IL-8, the mean IL-17 expression in the CRSwNP mucosa (26.56 ± 22.07) is higher than the recurrent CRSwNP (20.13 ± 16.78), and statistically, the difference was not significant between CRSwNP and recurrent CRSwNP ($p > 0.05$). The mean TGF-β1 expression in the polyps mucosa was also higher in CRSwNP (32.40 ± 33.84) than recurrent CRSwNP (24.51 ± 17.03), and the difference was also not significant between the two groups ($p > 0.05$) (Table 2).

Table 2: Expression of IL-5, IL-8, IL-17, and TGF-β1 in mucosa between CRSwNP and recurrent CRSwNP

Cytokine	n	CRSwNP	recurrent CRSwNP	p
		Mean ± SD (pg/dl)	Mean ± SD (pg/dl)	
IL-5	15	0.86 ± 0.13	2.75 ± 2.02	0.003
IL-8	15	327.51 ± 33.16	304.35 ± 34.86	0.073
IL-17	15	26.56 ± 22.07	20.13 ± 16.78	0.418
TGF-β1	15	32.40 ± 33.84	24.51 ± 17.03	0.427

In Table 3, the mean of IL-5 expression in polyp tissue was higher in recurrent CRSwNP (78.80 ± 15.01) than CRSwNP (63.46 ± 27.28), and the difference was not statistically significant ($p > 0.05$). The mean of IL-8 expression in polyp tissue was found higher in CRSwNP 90.20 ± 14.78) than recurrent CRSwNP (78.33 ± 18.79) and there were significant differences between the two groups ($p > 0.05$).

Table 3: Differences in the expression of IL-5 IL-8, IL-17, and TGF- β1 tissue between CRSwNP with recurrent CRSwNP

Cytokine	n	CRSwNP	recurrent CRSwNP	p
		Mean ± SD (per 100 cells)	Mean ± SD (per 100 cells)	
IL-5	15	63.46 ± 27.28	78.80 ± 15.01	0.067
IL-8	15	90.20 ± 14.78	78.33 ± 18.79	0.014
IL-17	15	89.40 ± 16.48	77.13 ± 29.64	0.274
TGF-β1	15	93.66 ± 7.37	85.33 ± 12.38	0.035

The mean of IL-17 expression in CRSwNP tissue (89.40 ± 16.48) was also higher than recurrent CRSwNP (77.13 ± 29.64) but did not have a significant difference between the two groups ($p > 0,05$). On tissue, similar to IL-8, the mean TGF-β1 expression was higher in CRSwNP (93.66 ± 7.37) than recurrent CRSwNP (85.33 ± 12.38) and also there were significant differences between CRSwNP and recurrent CRSwNP ($p > 0.05$).

Table 4: Multivariate cytokine test on the mucosa of recurrent CRSwNP

Cytokine	P	Exp(B)
Step 1		
IL-5	0.051	0.000
IL-8	0.091	1.046
IL-17	0.423	1.042
TGF-β1	0.284	1.032
Step 2		
IL-5	0.040	0.000
IL-8	0.102	1.044
TGF-β1	0.226	1.044

Cytokines that have the most role in recurrent CRSwNP

The results of the mucosal analysis found that the cytokine that had the main role in the polyps mucosa in the recurrent CRSwNP was IL-5 (Table 4). Whereas in tissues, based on the analysis, TGF-β1 was the main role in polyp tissue in recurrent CRSwNP was (Table 5).

Table 5: The multivariate cytokine test on the tissue of recurrent CRSwNP

Cytokine	P	Exp (B)
Step 1		
IL-5	0.143	0.964
IL-8	0.072	1.060
IL-17	0.819	0.994
TGF-β1	0.104	1.097
Step 2		
IL-5	0.136	0.966
IL-8	0.061	1.057
TGF-β1	0.102	1.097
Step 3		
IL-8	0.073	1.048
TGF-β1	0.054	1.106

Discussion

In this study, specimens were taken from mucosal in recurrent CRSwNP and CRSwNP polyps using the brushing technique. In these specimens, cytokine IL-5, IL-8, IL-17 and TGF-β1 expression were examined by ELISA technique. It was found that only IL-5 expression had a significant difference between the mucosal CRSwNP recurrent and CRSwNP ($p < 0.05$). Polyp tissue specimens were taken during surgical removal of polyps with the FESS technique, and then the IHC examination was carried out.

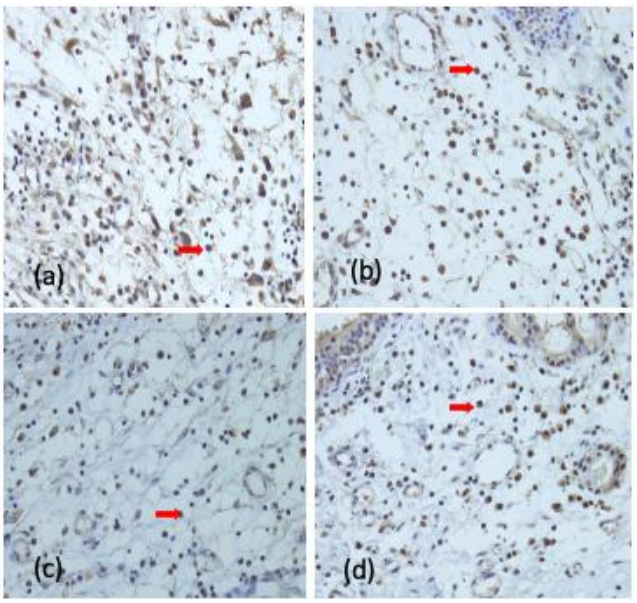

Figure 1: Description of cell expression that produces cytokines in CRSwNP tissue with 40 X 10 enlargement: a) description of IL-5 expression; b) description of IL-8 expression; c) description of IL-17 expression; d) description of TGF-β1 expression. Red arrows indicate cells that contained positive cytokines

The results showed that only TGF-β1 and IL-8 had significant differences ($p < 0.05$) between CRSwNP and CRSwNP recurrent; both expressions were lower in recurrent CRSwNP than CRSwNP.

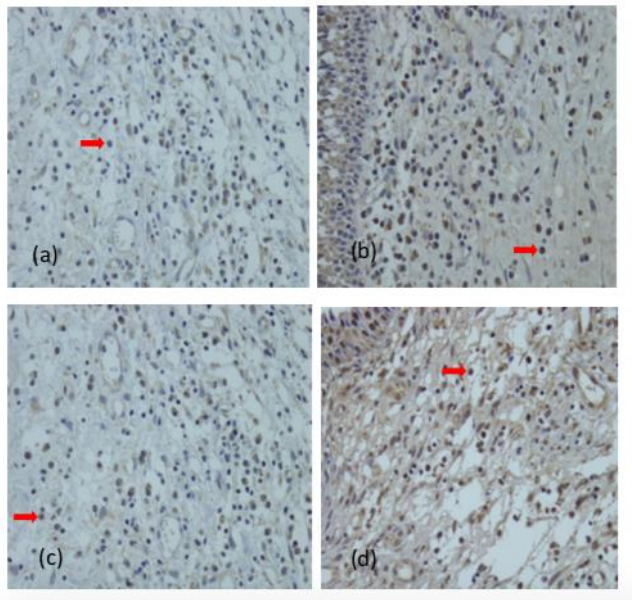

Figure 2: Description of cell expression that produces cytokines in recurrent CRSwNP tissue with 40X10 enlargement: a) description of IL-5 expression; b) description of IL-8 expression; c) description of IL-17 expression; d) description of TGF-β1 expression. Red arrows indicate cells that contained positive cytokines

Expression of IL-5 was found to be higher in mucosal CRSwNP recurrent (2.75 ± 2.02) than CRSwNP (0.86 ± 0.13) and statistically significant differences ($p < 0.05$). In polyp tissue, IL-5 expression in CRSwNP recurrent (78.8 ± 15.01) was also higher than CRSwNP (63.46 ± 27.28). Interleukin-5 is a cytokine that plays an important role in the differentiation, development, maturation and chemokine processes of eosinophils [8]. One study state that IL-5 and Eosinophil Cationic protein (ECP) is eosinophilic type inflammatory biomarkers that can be used as predictors and diagnostics in the future [9]. Research on the relationship of IL-5 and eosinophils with recurrence of nasal polyps has been carried out. Wei et al., (2018) conducted a multivariate analysis of recurrent CRSwNP in China obtaining IL-5 expression in polyp tissue as well as higher recurrence of CRSwNP than non-recurrent polyp CRS and was statistically significant ($p = 0.001$) [10]. Van Zele et al., (2014) obtained IL-5 expression which was also higher in recurrent CRSwNP (482.8pg/ml) than non-recurrent polyp CRS (144.7 pg/ml) and was statistically significant ($p < 0.05$). Based on their studies, it was found that the type of Th2 inflammation and eosinophilic inflammation were the main risk factors for recurrence [1]. In another study also reported that eosinophil counts by histopathological examination could be used as an easy method to do as a predictor of postoperative nasal polyps recurrence [11]. In this study, the expression of tissue IL-5 in recurrent CRSwNP was higher than CRSwNP because IL-5 is a cytokine that plays an important role in the differentiation, development, maturation and chemokines of eosinophils where eosinophils are closely related to the recurrence of nasal polyps.

This study found that the mean mucosal IL-8 expression was higher in CRSwNP (327.51 ± 33.16) than recurrent CRSwNP (304.35 ± 34.86), but the differences in IL-8 expression were not statistically significant ($p > 0.05$). In the polyp tissue, it was also found that the mean IL-8 expression was higher in CRSwNP (90.20 ± 14.78) than in the recurrent CRSwNP (78.33 ± 18.79) and had a significant relationship ($p < 0.05$).In another study conducted by Wei et al., (2018) it was found that the mean IL-8 was also higher in CRSwNP (5080.1 pg/ml) than recurrent CRSwNP (2481.9 pg/ml) and was statistically significant [10]. Interleukin-8 is produced by monocytes, lymphocytes, endothelial granulocytes. Interleukin-8 is an inflammatory cytokine that has strong neutrophil chemotaxis activity and can induce degranulation, respiratory burst, adherence, deformation, Ca2+ mobilisation and increased regulation of neutrophils CD11b/CD18 [12]. Interleukin-8 will stimulate deformation and degranulation of neutrophils, thus releasing elastase, lactoferrin, fibronectin. Also, IL-8 can stimulate transendothelial neutrophil migration by increasing regulation of α2 integrins [13]. In addition to neutrophils, IL-8 is also a very important chemokine for eosinophils in all types of CRS and nasal polyps. Interleukin-8 is secreted by the ductal cells of the glandular and epithelial cells, attracting neutrophils to the mucosa [14], [15]. In this study, IL-8 expression in CRSwNP was higher than recurrent CRSwNP, and the difference was significant because IL-8 is a neutrophilic chemoactrant while recurrent CRSwNP is more identical to eosinophilic polyps.

The results of the ELISA examination of the polyp mucosa in this study obtained an average Interleukin-17 expression in CRSwNP (26.56 ± 22.07) was higher than the recurrent CRSwNP (20,13 ± 16,78), and the difference was not significant ($p = 0.41$). In nasal polyp tissue, the mean IL-17 expression was also higher in CRSwNP (89.40 ± 16.48) than recurrent CRSwNP (77.13 ± 29.64). Van Zele et al. (2014) conducted a cohort study comparing the expression of IL-17 between non-recurrent CRSwNP and recurrent CRSwNP. The results showed that IL-17 expression in CRSwNP was also higher than recurrent CRSwNP, and there were no significant differences between the two groups ($p = 0.202$). Van Zele et al., (2014) explained that induction of IL-17 is associated with a decreasing in the expression of IL-5 and ECP which means that it decreases eosinophilic inflammation while IL-17 can modulate life and prolong neutrophil life by decreasing neutrophil apoptosis. Th17 cells through IL-17 induce secretion of IL-6 and IL-8 in fibroblast, endothelial and epithelial cells (1). Jiang et al., (2011) also reported that there were no significant differences in

expression of IL- 17 between CRSwNP type eosinophilic and non-eosinophilic ($p > 0.05$) and found that IL-17 affected the growth of nasal polyps with thickening of lamina basal cells and glandular hyperplasia [16]. Wei et al., (2018), in their study, also found there was no significant difference in IL-17 expression between CRSwNP and recurrent CRSwNP [10]. In this study, it can be concluded that IL-17 has no effect on the recurrence of CRSwNP but affects the growth of nasal polyps by extending the life of neutrophils, thickening of lamina basal cells and glandular hyperplasia.

On the polyps mucosa, the mean TGF-β1 expression was also higher in CRSwNP (32.40 ± 33.84) than in recurrent CRSwNP (24.51 ± 17.03), and there were no significant differences between these two group ($p > 0,05$). Transforming Growth Factor-β1 expression was higher in CRSwNP (93.66 ± 7.37) than recurrent CRSwNP (85.33 ± 12.38) in nasal polyp tissue, and there were statistically significant differences between the two groups ($p < 0.05$). Transforming Growth Factor Beta1 is a mediator associated with tissue remodelling. Physiologically TGF-β1 is a counter-regulatory cytokine against inflammation and initiates the process of repair and formation of fibrosis [17]. Transforming Growth Factor Beta1 is the main regulator of the immune system as a basic role in the production and secretion of the extra cellular matrix (ECM) and fibrosis molecules [18]. Other theories speculate that TGF-β1 reduce the effects of the proliferation of growth factors, such as platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF), which controls the proliferation of epithelial cells of nasal polyps, so that reduced the expression of TGF-β1 or inactivation of receptors of TGF-β1, therefore can explain the hyperproliferation abnormalities [19]. Van Zele reported there was no significant difference in TGF-β1 expression between recurrent and non-recurrent polyps. This explains that remodelling factors only have a role at the beginning of the development of nasal polyps but subsequently do not affect the occurrence of recurrence and prognosis of the disease [1]. In this study, it was found that TGF-β1 tissue expression in recurrent CRSwNP was lower than CRSwNP, and the difference was statistically significant. It is explained there is an imbalance between fibrinolysis and fibrinogenesis, reduced effect of proliferative inhibition by TGF-β1 so that the lower expression of TGF-β1 in tissues can predict recurrence in nasal polyps.

Based on the results of multivariate analysis, it was found that the cytokine had the main role in CRS polyp recurrence on the ELISA examination taken from the mucosal polyp was IL-5 ($p < 0.05$), whereas from the IHC examination was TGF-β1. In the mucosa, the cytokine that has the main role in recurrence is IL-5, where IL-5 is an interleukin that is important for the differentiation, maturation and survival of eosinophils. The increasing of IL-5 shows a predominant T helper 2 (Th2) response, which increases infiltration of inflammatory cells, especially eosinophil [20]. Lou (2018), reported that IL-5 is an eosinophilic type of inflammatory biomarker that can be used as a predictor and diagnostics in the future [9]. Eosinophilic inflammation in CRS polyp has been widely studied as a positive predictor of nasal polyps recurrence [15], [21], [22], [23].

Thus, it can be concluded that the examination of the expression of IL-5 in the mucosa with simple techniques such as brushing in this study before polypectomy or FESS in CRSwNP can be used to determine the possibility of polyps currencies.

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