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CORRELATION BETWEEN HISTOPATHOLOGICAL FINDINGS AND CLINICAL OUTCOMES IN CHRONIC RHINOSINUSITIS

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Abstract

Introduction: Chronic rhinosinusitis, a particular kind of chronic inflammation of the sinuses, causes facial pain and nasal congestion. The disease's onset is influenced by immunopathological processes and inflammation involving eosinophils, as well as genetic and environmental factors.

Objective: The purpose of this study is to delineate the relationship of current histological characteristics of CRS with patient outcomes and investigate the role of eosinophils, goblet cells in the mucus layer, and inflammatory cytokines such as periostin and interleukin 33 (IL 33).

Materials and Method: A cross-sectional study was conducted on 100 CRS patients at Niazi Medical College Sargodha, Pakistan. A histological evaluation of tissue samples was later collected following the clinical assessment. The levels of biomarkers were analyzed using immunohistochemical techniques.

Results: Positive correlations between the density of goblet cells, the thickness of the mucus layer, the count of eosinophils, and signs of nasal obstruction (positive Sneezing Perception Test), facial pain (positive Brief Facial Pain Inventory), and anosmia (positive Sniffin'Sticks) were found. In addition, a higher level of periostin and IL 33 was related to more severe CRS.

Keywords: Interleukin-33, periostin, chronic rhinosinusitis, nasal polyps, eosinophilic infiltration, and biomarkers.

INTRODUCTION

Chronic rhinosinusitis (CRS) is a common pathology of the respiratory system caused by inflammation of the paranasal sinuses and the nasal mucosa due to nasal obstruction, facial pain, and anosmia. There are many symptoms of CRS, and the overall histological features, characterized by eosinophilia, thickness of the mucosa, and fibrosis, are changed from the general histological features (1), while environmental and genetic variations are involved. Knowing prognostic factors in CRS will help us know more about the disease, develop therapeutic targets, and understand the disease's natural history. By demonstrating the observations present in these works, CRS has been shown to have typical and pathological alterations that relate to the severity of disease and life expectancy. For example, eosinophil occupancy is markedly elevated in CRSwNP and worsens the severity of the disease (2). Infiltration of the rise of sinonasal mucosa inflammation activity, tissue remodeling, chronicity of the symptoms, and resistance to conventional treatment are compounded by the eosinophil infiltration of sinonasal mucosa.

Similarly, other CRS changes with detrimental respiratory nasal mucosa, including epithelial thickness and new vessel formation, predict poor outcomes (19). Histopathological indexes also suggest the degree and outcomes of doubtful diseases and these findings. Compared to CRS, other types of inflammation can differ in their type and severity, as seen by different types of infiltrating cells and their response to treatment. The pathogenesis of CRS has been described in so much detail, and it has already proved that some important cytokines and immune cells are involved in the pathophysiology of the disease. Furthermore, the levels of IL-33 were increased in CRS patients with nasal polyps, which could be related to their eosinophilia and tissue remodeling (5). In addition, Th1 and Th2 cytokine balance were important for patients' CRS outcomes. More specifically, Th2 dominant inflammation, which could be found in CRSwNP patients, is associated with increased nasal polyposis and higher symptom burden (6).

Other research on CRS has also found changing ideas on how the disease works regarding pathophysiology, including the inflammatory processes associated with the disease. For example, in South China, the inflammatory CRS has changed from a neutrophilic pattern to a mixed one during the last eighteen years (7). Such a change can be associated with the manifestation of CRS symptoms, and pollution has been related to the worsening of CRS symptoms (8). Chronic exposure to environmental allergens like particulate matter and ozone could also predispose a person to develop CRS through changes in immunity within the nasal mucosa, which has been more recently investigated. These also suggest the need for more research about all the factors that lead to the development of CRS, including histopathogenic and environmental.

However, the relationship between the histopathological changes and outcomes is essential in understanding the disease process and helpful in handling such cases. In CRS, targeted therapies have come out through endotyping the disease processes and applying appropriate anti-inflammatory biologicals (10). For instance, therapies using monoclonal antibodies targeting IL-4 and IL-13 because these cytokines are central to Th2-driven inflammation have been found to reduce the severity and size of nasal polyps in patients with CRS. In addition, using biological agents tends to effectively manage CRSwNP for patients who poorly respond to conventional therapies (11). These progressions of therapy manifest the importance of the employment of Histopathologic examinations together with clinical data in formulating strategies for the patients.

Apart from the specific inflammation markers in CRS, research elaborating on other biomarkers, like the periostin factor, has also been conducted about the intensity of the disease. Periostin has been nominated as one of the aggravating factors in eosinophilic CRS and is also known to have a significant relation to the severity of nasal polyps (12). Periostin may become a biomarker for the prognosis of the CRS outcomes as the identified levels indicate disease progression to worse forms of the condition. In addition, other studies have also pointed to the involvement of proliferating cell nuclear antigen (PCNA) in the proliferation of epithelial cells in CRS with nasal polyps (13). These observations indicate that the measurement of these biomarkers, together with histopathological analyses, may improve the knowledge of the pathophysiology of CRS and help establish an effective prognosis for the disease. CRS management is complex and should involve medical procedures. In some patients with chronic conditions, sinus medications may not deliver sufficient relief, making endoscopic sinus surgery (ESS) useful to remove polyps and allow better sinus passages.

Nevertheless, the patients who undergo surgery are also likely to experience the recurrence of CRS symptoms, which requires further treatment and management (14). As mentioned earlier, biological therapies can be considered viable in patients with refractory CRS, especially those with NP (15). These therapies act directly on the agents that cause the inflammation process and thus are more physically and clinically effective than a conventional approach. Finally, documenting histopathological changes and clinical data in managing chronic rhinosinusitis is significant in advancing pathogenic understanding of the disease. Several histopathological characteristics, including eosinophil infiltration, mucosal remodeling, and the density of various biomarkers, are positively correlated with the severity of the disease as well as the efficacy of the treatment. By integrating such histological examinations into clinical practice, practitioners can monitor the disease progression and prognosis of clinical conditions, as well as adjust therapies according to patient needs.

The identification of biomarkers related to CRS and the study of the molecular pathophysiology of this disease will also advance decision-making processes for the therapeutic management of this pathology.

Objective

The objective of this study is to investigate the correlation between histopathological findings and clinical outcomes in chronic rhinosinusitis, aiming to identify key biomarkers that predict disease severity and treatment response.

MATERIALS AND METHODS

Study Design: Cross-sectional, Observational design.

Setting: The study was conducted at Niazi Medical College Sargodha, Pakistan.

Duration: The research was conducted from January 2024 to June 2024.

Inclusion Criteria:

Patients of 18 years and above with a documented diagnosis of CRS, with or without nasal polyps, were enrolled. Participants who previously agreed to participate in the study that involves a clinical examination and biopsy only were included.

Exclusion Criteria

Individuals with a history of acute rhinosinusitis, recent sinus surgery, or other inflammatory disorders affecting the nasal and sinus mucosa were not included. Furthermore, those who were refusing to participate in the study or having contraindications to biopsy were not included.

Methods

This work included patients diagnosed with chronic rhinosinusitis (CRS) in the tertiary care hospital. Further assessment incorporated the results of standardized history and physical examination, endoscopic exam – specifically nasal endoscopy and imaging studies to confirm the diagnosis of CRS. Histological examination was done on biopsies taken from the nasal mucosa of patients and processed using routine histopathological techniques, including Hematoxylin and Eosin Staining, to determine inflammatory cell infiltration, tissue remodeling, and other pathological changes. The four conventional histopathological assessments, including eosinophil infiltration, goblet cell hyperplasia, and mucosal thickening, were correlated with clinical scores and symptoms and their resolution. Immunohistochemistry for IL-33 and periostin was performed to gain a deeper insight into the disease's biomarkers. Lastly, statistical analyses were conducted to determine the correlation between histopathological features and clinical results, which established the foundation for managing CRS.

RESULTS

This study included 100 patients who met the diagnostic criteria for CRS. These patients include 40 patient who had CRS without nasal polyps, and 60 patients of CRS with nasal polyps. The ratio of male patients to female patients was 1: 1.3; the mean patient age was 42.3 years old.The demographics of the patients are presented in Table 1.

Table 1: Demographic Characteristics of CRS Patients

Parameter	Value
Total Participants	100
Male	42 (42%)
Female	58 (58%)
Average Age (years)	42.3
CRSwNP (with polyps)	60 (60%)
CRSsNP (without polyps)	40 (40%)

According to histopathological assessment, the extent of EOS was significantly higher in CRSwNP compared to CRSsNP patients, wherein EOS was noted in 75% of CRSwNP patients and 30% of CRSsNP patients. This difference significantly differed at $p < 0.01$, showing strong evidence of the link between eosinophilic inflammation and nasal polyps. Goblet cell hyperplasia as a feature of mucosal remodeling was evident and was recorded in 65% of CRSwNP patients with moderate to severe hyperplasia. However, the comparable data in CRSsNP patients were observed in only 40% of cases.

Table 2: Histopathological Findings in CRS Patients

Histopathological Feature	CRSwNP (n=60)	CRSsNP (n=40)	p-value
Eosinophilic Infiltration (%)	75%	30%	< 0.01
Goblet Cell Hyperplasia (%)	65%	40%	< 0.05
Mucosal Thickness (mm)	2.4 ± 0.5	1.8 ± 0.3	< 0.01

Patient symptoms confirmed that those with eosinophilic infiltration had worse nasal obstruction, facial pain, and loss of smell than those without it. The overall severity score of these symptoms was higher among patients with eosinophilic inflammation than those without eosinophil inflammation ($p < 0.05$). Additionally, patients with higher goblet cell hyperplasia scores had increased symptomatology and lower efficacy in corticosteroids for treating symptoms. This is well illustrated in the fact that soils belonging to this group undergo more surgery than the rest.

Table 3: Clinical Outcomes Based on Histopathological Findings

Clinical Outcome	Eosinophilic Infiltration (+)	Eosinophilic Infiltration (-)	p-value
Nasal Obstruction Severity	7.2 ± 1.1	5.6 ± 1.3	< 0.05
Facial Pain Severity	6.9 ± 1.0	5.1 ± 1.2	< 0.05
Loss of Smell (Severity)	6.8 ± 1.3	5.3 ± 1.4	< 0.05
Surgical Interventions (%)	55%	30%	< 0.05

Consistent with higher inflammation, the serum IL-33 level was significantly elevated in patients with CRSwNP compared with those with CRSsNP (130 ± 20 pg/ml; $p < 0.01$). Elevated periostin levels were also found in CRSsNP patients and were correlated to more severe clinical symptoms as well as to increased eosinophilic infiltration, similar to CRSwNP patients. Moreover, there was a strong correlation between the total severity of CRS and findings of higher goblet cell counts of eosinophil presence in CRS patients. When nasal polyps are present, histopathological analysis is a valuable tool for predicting disease progression and evaluating the effect of treatment. Research to understand the roles of periostin and other biomarkers, such as IL-33, in CRS is needed to diagnose and treat CRS better.

DISCUSSION

Chronic rhinosinusitis (CRS) is a chronic inflammatory disorder, the mucosa of which is inflamed due to persistent inflammation of the nasal and sinus mucosa, but numerous interconnected combined factors are a determining factor for CRS. Symptoms include chronic nasal discharge, anosmia, facial pain, and nasal obstruction, all of which cause substantial deterioration in the quality of health and are a primary reason why anyone affected with the function is significantly impacted by symptoms. Immunoinflammatory mechanisms are closely linked to the onset and progression of CRS; histopathological changes with immunoinflammatory mechanisms are crucial. This study addresses whether the pathological markers of CRS (eosinophilic infiltration, goblet cell metaplasia, mucosal thickening, and periostin and IL-33 expression) correlate with the clinical outcomes of the disease.

This research also revealed a powerful link between eosinophilia and the development of nasal polyps, one of the key defining characteristics of CRSwNP. More severe sinonasal diseases are linked to eosinophils driven primarily by Th2-mediated inflammation. This study's findings echo previous research, replicating that eosinophils in CRSwNP are higher than in CRSsNP (1,4) and are known to be important to the development and persistence of nasal polyps (1,4). The fact that eosinophil infiltration is dispersed in CRS underlines its pathophysiological role since it matches clinical signs of nasal obstruction, facial pain, and olfactory dysfunction. This lends credibility to the idea that biologicals that limit their effects on eosinophils could use eosinophil inflammation as a marker of the severity of the illness and become a target for therapy (5).

Another of these histopathologic findings was goblet cell hyperplasia, which was consistent with mucosal remodeling and was higher in CRSwNP patients than in CRSsNP patients. It points out that goblet cells are concerned with mucus production, and since these cells multiply due to inflammation, they produce more mucus, causing nasal blockage (6). This direct relationship between goblet cell hyperplasia and the complaint score, especially the nasal obstruction, proves that mucosal remodeling plays a central role in the progression of the disease. This is well supported by strengthened literature showing that in different forms of CRS, particularly in those with nasal polyps, the major histopathological changes include mucosal remodeling, goblet cell hyperplasia, and subepithelial fibrosis. However, in this study, patients with goblet cell hyperplasia had more severe inflammation, necessitating surgery and pointing to the chronicity of the disease condition. This means that such histological features such as goblet cell proliferation are not only indicators of disease progression but also of the surgery requirement.

The other histopathological factor, the mucosal thickness, was significantly higher in the CRSwNP patient group than in the CRSsNP patient group. The mucosa becomes thicker due to processes associated with inflammation changes, remodeling of the sinus walls, and poor draining and persistent symptoms. This agrees with previous studies that pointed out that patients suffering from nasal polyps have increased density in the sinus mucosa because of inflammation and constant swelling (7). Such histopathological evaluation of the disease burden focuses on the relation between mucosal thickness and disease severity. It may also be helpful to get a thicker layer of mucosa for determining disease activity and progression and as a potential site to treat with corticosteroids or other anti-inflammatory biological agents that reduce the size of the mucosa (9).

It also focused on the role of inflammatory cytokines such as IL-33 and periostin in predicting pulmonary fibrosis. IL-33 is an alarm and promotor of Th2-type inflammation. In this study, Th2-type inflammation characterized CRSwNP. It was found that the level of the protein IL-33 was significantly elevated in CRSwNP patients dependent on eosinophilia and symptoms. This agrees with other published papers that have established a relationship between IL-33 and CRS, particularly in patients with nasal polyps (8, 10). It may also be helpful as a therapeutic agent in severe or refractory CRS given the multiple roles of IL-33 in innate as well as adaptive immune systems.

For example, periostin, a matricellular protein described to play a role in tissue remodeling and fibrosis, was increased in the CRSwNP group and related to a numerically higher eosinophil infiltration. Among them, periostin has been considered essential in CRS, specifically in eosinophilic inflammatory diseases, and the symptoms' extent of the nasal polyps and chronicity (11). Hence, the higher levels of periostin established in this work can imply the likelihood of its being used as an index to predict disease growth and treatment effectiveness. This quantification of periostin might help the clinician to identify the patient who likely develop the severe form of CRS and then adjust the approach to the problem.

This again further points to the fact that the clinical findings observed in this study were highly comparable with the histopathological findings. The patients with eosinophilic infiltration and goblet cell hyperplasia reported a higher Numerical Rating Scale score of nasal obstruction, facial pain, and loss of smell. These patients also required endoscopic sinus surgery or ESS surgery to ease this condition. As it has been observed from the studies of other authors, eosinophilic inflammation and mucosal remodeling indicate poor medication response and a higher risk of surgery (12, 13). Biologic therapies that affect cytokines IL-4, IL-5, and IL-13 have been successfully applied for CRSwNP

treatment and are shown to improve patient outcomes (9). These may be safer alternatives to systemic corticosteroids, with less toxicity and systemic side effects, better results for patients with eosinophil-driven inflammation and nasal polyps, and possibly reducing the need for surgery.
Finally, this study's results could generate further interest in histopathologic entities such as eosinophil infiltration, goblet cell proliferation, and mucosal thickening, as well as diagnosis and management of CRS. This indicates that the use of tissue pathology can provide a means to determine the microenvironment causing the disease's severity, aiding in prognosis and treatment strategies. Moreover, the study suggests that inflammatory proteins such as IL 33 and periostin can be univocally studied as valuable biomarkers in assessing disease severity and response to treatment. These findings are further validated by further research and the study of the efficacy of treatments aimed at these biomarkers for managing CRS.

CONCLUSION

In conclusion, it indicates a significant correlation between pathological changes and clinical outcomes, especially in patients with nasal polyps (CRSwNP). A close correlation of symptoms, such as facial pain, hyposmia, and nasal obstruction, with goblet cell metaplasia, marked eosinophilia and submucosal edema was observed. Furthermore, IL-33 and periostin levels were increased in CRSwNP patients and correlated with the degree of eosinophilic inflammation and disease severity. Advancing the understanding of CRS and the effects of treatment remains an invaluable tool via histopathological analysis. The most inclusive approach to managing CRS is integrating histopathological findings, biomarker profiles, and clinical observations. The ability to target therapies that address unique disease characteristics, such as elevated eosinophils, as seen in this study, may offer some potential to improve treatment outcomes in chronic or treatment-resistant cases. Therefore, more studies are needed to establish the biomarkers as declared and credible in the framework of CRS.

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