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Updates on Biomarkers in Chronic Rhinosinusitis

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만성 비부비동염 바이오마커에 대한 최신 지견

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Chronic rhinosinusitis (CRS) is a highly prevalent disease that imposes a significant socioeconomic burden. Since the emergence of inflammatory endotyping in the mid-2010S, the development of therapeutics targeting specific inflammatory endotypes of CRS has highlighted the need for biomarkers that are non-invasive, accurate, and both biologically and clinically meaningful. Here, we summarized recent updates on biomarkers derived from peripheral blood, nasal tissue, and nasal fluid samples to predict inflammatory endotypes. Furthermore, given that the tendency of recurrence and refractoriness remains a major challenge in the treatment of CRS, predicting clinical outcomes and prognosis before the initiation of treatment is crucial. Therefore, this review also discusses recently identified biomarkers for predicting recurrent and refractory CRS. Through this overview of research findings, we aim to provide insights into the current state of CRS biomarkers and future directions for developing novel biomarkers.
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Introduction to Chronic Rhinosinusitis and Clinical Needs for Biomarkers

Chronic rhinosinusitis (CRS) is an inflammatory disease of the mucosa of the nasal cavity and paranasal sinuses. Its cardinal symptoms include nasal obstruction, nasal secretion, facial pain/pressure, and smell loss.[1)] CRS is traditionally classified based on the presence of nasal polyps (NPs): CRS with NPs (CRSwNP), CRS without NPs (CRSsNP). Approximately 10% of the general population is affected by CRS.[2)] Patients with CRS experience impaired quality of life, increased healthcare cost/utilization, and time lost from work. The chronicity of the disease necessitates long-term medication or surgery, leading to a significant socioeconomic burden.[3-5)]

Recent studies have shown that inflammation in CRS is heterogeneous and manifests as type 1/2/3 (T1/T2/T3) inflammatory endotypes (Fig. 1).[2)] Inflammatory endotypes are characterized by the increased expression of T cell-derived cytokines. T2 CRS exhibits predominant eosinophilic infiltration into the tissue and elevated expression of T2 cytokines, including interleukin (IL)-4, IL-5, and IL-13, whereas non-T2 CRS comprises sub-endotypes with type 1 and/or type 3 inflammation.[1,2)] Accumulating evidence has shown that clinical presentations and treatment responses differ based on inflammatory endotypes.[6)] Therefore, identifying the inflammatory endotype is crucial for selecting treatment options for patients with CRS. As biologics targeting T2 inflammation have demonstrated great efficacy in real-world settings, identifying suitable candidates for biologics is critical. Considering that only 25%–63% of patients with CRSwNP exhibit T2 inflammatory profiles in East Asia,[7,8)] accurate methods for

distinguishing T2 CRS are particularly needed in these countries. In this context, global efforts are underway to develop biomarkers that can accurately predict the inflammatory endotypes of CRS.

Although a combination of medical management, endoscopic sinus surgery (ESS), and biologics has significantly improved outcomes for patients with CRS, recurrence and refractoriness remain major challenges, particularly as these patients often require repeated operations and medication. Given that CRS is a heterogeneous disease including a variety of conditions with different clinical manifestations and immuno-pathophysiology, predicting clinical outcomes and prognosis before the initiation of treatment would help clinicians to achieve personalized treatment of each patient. Therefore, there is a growing need for non-invasive and accurate biomarkers to predict prognosis.

A biomarker is defined as a characteristic that is measured as an indicator of normal physiological processes, pathogenic processes, or responses to an exposure or intervention. Biomarkers can be derived from physiologic, radiographic, histologic, or molecular features.[9] Biomarkers can be classified into several types. Diagnostic biomarkers identify the presence of a disease or a specific disease subtype. Monitoring biomarkers are repeatedly measured to evaluate treatment effectiveness or assess alterations in disease conditions. Predictive biomarkers are used to forecast individuals or groups who are predisposed to favorable or unfavorable outcomes. Prognostic biomarkers determine the progression of diseases, recurrence, or the probability of clinical events. Safety biomarkers indicate toxicity as an adverse event before or after a treatment or intervention, such as hepatic or renal toxicity during medical therapies.

Good biomarkers are those that can be measured feasibly, accurately, and reliably at a low cost. They not only support diagnosis but also influence clinical decision-making.[9] Ideally, they should be biologically and clinically meaningful, with changes in the biomarker reflecting the changes in clinical course. Biomarkers need to be validated through the following steps: analytical validation (to demonstrate that the assay estimates the intended analyte and assess the accuracy and robustness of the assay), clinical validation (to determine the sensitivity, specificity, failure rates, and indeterminate rates of the assay), and clinical utility (to assess whether the assay provides biologically meaningful information for clinical decisions or reduces associated costs).[10]

In this review, we summarize the latest knowledge on biomarkers for predicting the inflammatory endotypes of CRS and those for nonsteroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (N-ERD). Additionally, we describe and discuss prognostic biomarkers for recurrent and refractory CRS.

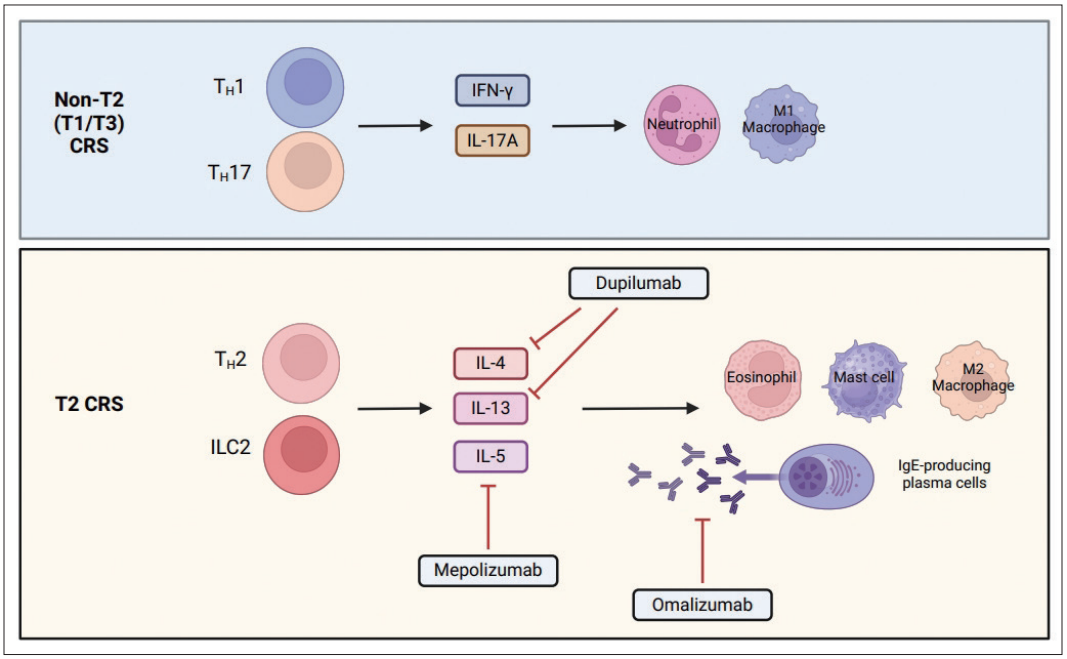

Fig. 1. Inflammatory endotypes of CRS and currently used biologics. A schematic illustration summarizing the inflammatory endotypes of CRS and the biologics currently in use. CRS, chronic rhinosinusitis. This figure was created in BioRender.com.

Search Strategy and Study Selection

The authors performed a literature search for articles published up to November 23, 2024 without any restriction on the year of publication. The search terms included "Chronic Rhinosinusitis," "Nasal polyps," "Biomarkers," "Endotypes," "Diagnosis, "Prognosis," "Recurrent," and "Refractory," using the Boolean operators "OR" and "AND." Studies were reviewed and selected based on the following criteria: 1) full-text articles written in English, 2) analyses involving patients with CRS, and 3) analysis of biomarkers for differential diagnosis and prognosis. The authors conducted a full-text review of eligible articles. Any disagreements were discussed until a consensus was reached.

Biomarkers for Predicting Inflammatory Endotypes of CRS

Biomarkers for T2 CRS

Blood biomarkers for T2 CRS

The cardinal features of T2 CRS, often referred to as eosinophilic CRS (ECRS), include substantial eosinophil infiltration and increased expression of T2 cytokines, including IL-4, IL-5, and IL-13, in the nasal tissue. Traditionally, blood eosinophil count and serum immunoglobulin E (IgE) levels have been widely used to predict T2 CRS. Recently, the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS)/European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA) guidelines suggested peripheral eosinophilia (blood eosinophil count ≥150/μL) and elevated serum total IgE levels (IgE ≥100 IU/mL) as evidence of T2 inflammation.[11,12] Cardell, et al. also reported that blood eosinophils >150/μL, high serum IgE levels, and *Staphylococcus aureus* enterotoxin-specific IgE indicate a likelihood of T2 CRSwNP >90%, >90%, 100%, respectively.[13,14] It was also reported that blood eosinophil >300/μL and comorbid asthma can predict T2 CRSwNP.[15] However, the cut-off values for blood eosinophil counts and total IgE levels lack robust scientific background and remain inconclusive.

Additionally, several proteins associated with T2 inflammation have been suggested as blood biomarkers for predicting T2 CRS. A previous study reported that serum soluble suppressor of tumorigenicity 2 (sST2), which is part of the interleukin-1 receptor family and a decoy receptor for IL-33, is useful for differentiating T2 CRSwNP.[16] Because the IL-33/ST2 axis is critically involved in T2 inflammation, the combination of IL-33 and sST2 demonstrated greater predictive potential for T2 CRSwNP. Periostin, a protein encoded by the *POSTN* gene, is induced by T2 cytokines, and highly expressed in IL-5^{high} CRSwNP.[17] Increased periostin levels in both serum and nasal tissue are associated with T2 inflammation.[18,19] The expression of serum soluble semaphorin 4D (SEMA4D), derived from activated eosinophils, was elevated in ECRS than in non-ECRS (NECRS), and its levels significantly correlated with JESREC scores, blood eosinophil counts, and NP scores.[20] S100A4 is a pro-inflammatory factor involved in T2 inflammation by promoting the recruitment of eosinophils. Therefore, serum S100A4 was also suggested as a useful marker for evaluating disease severity and differentiating endotypes in CRS.[21] Furthermore, serum B cell-activating factor (BAFF) concentrations were significantly elevated in ECRS compared to NECRS and controls. Given that BAFF was found to be involved in the recruitment of eosinophils and its serum levels positively correlated with blood eosinophil counts and percentages, tissue eosinophil counts, and serum total IgE, serum BAFF was suggested as a promising biomarker for distinguishing T2 CRSwNP from non-T2 endotypes.[22]

Although blood biomarkers are relatively noninvasive and easy to obtain, they have some limitations. The expression levels of blood biomarkers may be influenced by systemic diseases or conditions. For example, blood eosinophil count and serum IgE can be affected by the presence of other allergic diseases.[15] Furthermore, despite showing a significant correlation with tissue eosinophilic inflammation, the accuracy of blood biomarkers may be lower than that of local nasal biomarkers.

Nasal biomarkers for T2 CRS

As described above, the infiltration of eosinophils in tissues is a hallmark of T2 inflammation and can be assessed through hematoxylin & eosin (H&E) staining. This method is currently considered the gold standard for diagnosing T2 CRS or ECRS. However, there is no consensus on precise cut-off values or counting methods.[23,24] Additionally, obtaining information on tissue eosinophil counts requires invasive procedures, such as biopsy and surgery, and time-consuming histopathological evaluation.

Several proteins associated with eosinophilic inflammation have been investigated as nasal biomarkers for T2 CRS. Because Charcot-Leyden crystal (CLC) formation is the consequence of eosinophil extracellular trap cell death, it may re-

flect tissue T2 inflammation.[25] C-C motif chemokine ligand 26 (CCL26; eotaxin-3) is a ligand for CC chemokine receptor 3 (CCR3) that recruits eosinophils and is induced by T2 cytokines, suggesting its role in T2 inflammation. Previous studies have found that CCL26 is expressed in the nasal tissue of T2 CRS.[8,26] Additionally, L26 levels in nasal lavage fluid (NLF) predicted T2 CRS with an area under curve (AUC) of 0.778 (sensitivity: 64%, specificity: 80%).[26] Because eosinophil cationic protein (ECP) is a protein in the granules of eosinophils, it is frequently used as a marker of eosinophils. In receiver operating characteristic (ROC) curve analysis, ECP in NLF predicts T2 CRSsNP with an AUC of 0.767 (sensitivity: 64%, specificity: 80%).[26] Epithelial-derived cystatin SN, encoded by the gene CST1, is induced by IL-4/13 and is closely associated with eosinophilic inflammation.[27] The expression of cystatin SN in nasal tissues was significantly higher in eosinophilic CRSwNP than in the controls and non-eosinophilic CRSwNP.[27,28] The robust association was supported by the positive correlation of cystatin SN expression and tissue eosinophil percentage.[29] In vitro experiments revealed that cystatin SN upregulated the expression of CCL11/eotaxin-1 and periostin in nasal fibroblasts.[28] Additionally, cystatin SN induced the recruitment and activation of eosinophils through IL-5[27] as well as the infiltration of T helper (T_H) 2 cells in the nasal mucosa.[29] Moreover, a recent study performing transcriptomic analysis revealed that a combination of CCL13, CCL18, and cystatin SN can predict T2 CRS efficiently with an AUC of 0.956.[8]

Nasal biomarkers derived from nasal secretion and tissue biopsy samples are more suitable for reflecting local nasal inflammation and the tissue microenvironment but are more challenging to obtain compared to blood biomarkers. Furthermore, several studies have reported inconsistencies in the correlation between protein expression in nasal secretions and those in tissue biopsy.[30,31] It is expected that nasal secretions primarily contain proteins secreted by epithelial cells on the apical side, whereas tissue samples encompass the entire range of proteins expressed within the tissue environment. Additionally, the standardization of sampling procedures is a critical prerequisite for the application of these nasal biomarkers in real-world clinical practice. Moreover, the sampling location should be standardized to minimize variability between samples.

Other biomarkers for T2 CRS

Urinary leukotriene E4 (uLTE4) has been studied as a biomarker to predict T2 CRS. At the calculated optimum cut-off value 106 pg/mg creatinine, the ROC analysis of uLTE4 level was statistically significant with an AUC of 0.728 (sensitivity: 56.9%, specificity: 86.2%).[32] Multivariate logistic regression and artificial neural network machine learning models using uLTE4, blood eosinophil count, and polyp status were also evaluated to predict T2 CRS, showing that both the sensitivity and specificity were over 80%.[32] Additionally, fractional exhaled NO (FeNO) has been proposed as a marker of T2 disease, with NPs being a stable determinant of increased FeNO.[33,34]

With advancements in genomic technologies, recent studies have investigated CRS at the genomic level. The *ALOX15* gene encodes arachidonate-15-lipoxygenase (15-LO), which is involved in the metabolism of polyunsaturated fatty acids, such as arachidonic acid and linoleic acid. 15-LO is highly expressed in epithelial cells, eosinophils, macrophages, and mast cells in CRS. It induces CCL26 through extracellular signal-regulated kinase activity upon IL-13 stimulation, thereby being associated with T2 inflammation.[24,35] A landmark genome-wide association study in Iceland and the UK found that single nucleotide variant in *ALOX15*, a loss-of function missense variant p.Thr560Met, was associated with a 36% and 68% decline in the risk of CRS and CRSwNP, respectively.[36] Additionally, rs1888909 in the IL-33 region and rs1837253 in the TSLP region were found to be relevant in CRSwNP. In particular, rs1837253 in the TSLP region correlated with tissue eosinophil counts in CRSwNP.[24,37] These variants may play a critical role in T2 inflammation in CRSwNP.[24] In contrast, *INPP4A* mRNA in tissue negatively correlated with T2 CRSwNP. At the cut-off value 0.4, *INPP4A* predicted T2 CRSwNP among CRSwNP patients with an AUC of 0.8906 (sensitivity: 68.75%, specificity: 93.755%).[38] Moreover, *AIF1*, *C1QA*, *C1QB*, *C3AR1*, *CCR1*, *CD163*, *CD4*, *CD53*, *CD86*, *CSF1R*, *CYBB*, *FCER1G*, *FCGR3A*, *IL10RA*, *ITGB2*, *LAPTM5*, *PLEK*, and *TYROBP* in tissue were identified as potential M2 macrophage-related biomarkers in CRSwNP.[39]

Biomarkers for non-T2 CRS

Inflammation in non-T2 CRS is typically associated with elevated expression of T1 and/or T3 cytokines, such as interferon (IFN)-γ and IL-17A. Non-T2 CRS frequently involves neutrophil infiltration and increased frequencies of T_H1 and/or T_H17 cells.[40] Macrophages shift toward M1 phenotypes, producing reactive oxygen species and IL-1β. In addition, there is an upregulation of IFN-γ-induced chemokines (*CXCL9*,

CXCL10, *CXCL11*), IL-17A-induced molecules (*SAA*, *CHI3L1*, *CXCL5*, *CCL20*), neutrophil activators, and chemokines (*CSF3*, *CXCL1*, *CXCL2*, *CXCL5*, *CXCL6*).

The representative T1 and T3 cytokines, IFN-γ and IL-17A, are considered potential biomarkers in non-T2 CRS, but their cut-off values and suitability remain unclear. Because IFN-γ is expressed at low levels in tissues, tissue IFN-γ may not be appropriate as a biomarker.[7] However, it can be used to identify T1 inflammation at the mRNA level. Several studies have shown that the mRNA expression of *IFNG* is a suitable biomarker for the T1 CRSsNP.[24,26] In contrast, IFN-γ was rarely detected in NLF samples from patients with CRSsNP, making it unsuitable as a biomarker based on NLF samples.[26] Instead, the IFN-γ-induced chemokines CXCL9 and CXCL10 in NLF can predict T1 CRS in tissue, with AUC values of 0.869 and 0.815, respectively. These findings suggest that NLF CXCL9 and CXCL10 can be considered promising biomarkers to predict T1 CRSsNP.[26] Similar to IFN-γ, IL-17A is expressed at low levels in tissues.[7] However, *IL17A* mRNA expression positively correlated with mRNA expression levels of *IL17F*, *CSF3*, *SAA1*, and *IL1B*, suggesting its potential utility at the mRNA level.[26] However, in NLF samples, IL-17A is not a useful biomarker, as its detectability using Luminex assays was only 11.6%.[26]

Several neutrophil-associated factors have been investigated as biomarkers for non-T2 CRS. Colony stimulating factor 3 (CSF3), also known as granulocyte CSF (G-CSF), regulates the production, differentiation, and function of granulocytes, particularly neutrophils. Tissue G-CSF expression was significantly higher in the non-T2 endotype than in the T2 endotype regardless of the presence of NPs.[41] *CSF3* mRNA expression in tissue was also significantly higher in non-T2 CRSwNP in T2 CRSwNP.[8] Additionally, CSF3 in NLF showed good efficacy for predicting the T3 endotype among CRSsNP with an AUC of 0.662.[26] Neutrophil extracellular traps (NETs), formed by the extrusion of nuclear chromatin into the extracellular space by neutrophils, are suggested to play an important role in the pathophysiology of CRS. Immunofluorescence staining showed that NETs were significantly increased in non-T2 NP compared to T2 NP.[42] Lipocalin-2 (LCN2), also known as neutrophilic gelatinase-associated lipocalin, is found in neutrophil secondary granules and is associated with T3 inflammation markers, including IL-17A, G-CSF, and IL-8. LCN2 levels were increased in nasal secretions of non-eosinophilic CRSwNP compared to eosinophilic CRSwNP.[43] LCN2 expression in nasal secretions significantly correlated with pus discharge observed in endoscopic examination, symptoms of thick nasal discharge, and radiographic opacification of the maxillary sinus. Additionally, LCN2 expression levels in nasal secretions exhibited high accuracy in distinguishing non-eosinophilic CRSwNP from controls and eosinophilic CRSwNP, with an AUC of 0.816. Therefore, LCN2 in nasal secretions could be used as a non-invasive biomarker for predicting non-T2 CRSwNP.[43]

Biomarkers for N-ERD

N-ERD, also known as aspirin-exacerbated respiratory disease, is characterized by the clinical triad of CRSwNP, asthma, and hypersensitivity to NSAIDs.[44] Patients with N-ERD typically exhibit severe T2 inflammation in the airway mucosa. Dysregulation of arachidonic acid metabolism leads to increased production of cysteinyl leukotrienes (CysLTs), which are mainly produced by the 5-LO pathway, along with reduced production of the anti-inflammatory prostaglandin E2 (PGE2). Aspirin and cyclooxygenase-1 (COX-1) inhibitors cause hypersensitivity reactions by depleting PGE2, which is produced by the COX pathway.[45]

uLTE4 is well-known to be elevated in N-ERD and is considered a potential biomarker for diagnosis and monitoring of N-ERD.[46-48] In N-ERD, increased activation of the 5-LO pathway leads to the conversion of AA to LTA4. LTC4 is then generated from LTA4 by LTC4 synthase. LTC4 is subsequently converted to LTD4 and its metabolite LTE4. LTE4, produced by mast cells, eosinophils, neutrophils, and basophils, is closely associated with T2 inflammation.[45] A significant increase in uLTE4 levels was observed before and after aspiring challenge testing in patients with N-ERD, but not in those with aspirin-tolerant asthma.[49]

The aspirin hypersensitivity diagnostic index (AHDI) was developed using a machine learning algorithm (linear discriminant analysis) to diagnose aspirin hypersensitivity and differentiate N-ERD with aspirin-tolerant asthma.[50] The formula for AHDI is composed of three components: 1) measurements of urinary biomarkers (uLTE4 and u15-oxo-ETE), 2) correction for CRSwNP using the Lund-Mackay CT score, and 3) adjustment for sex-related differences in eicosanoid metabolism. With a cut-off value of 160.38 for uLTE4, the AHDI showed an AUC of 0.889 (sensitivity: 81.97%, specificity of 87.23%), and an accuracy of 86.87% in predicting N-ERD. AHDI was reported to have a diagnostic value comparable to that of the oral aspirin challenge, which is currently the gold standard, in the studied asthma patients.[50] Addi-

tionally, plasma or urine 15-oxo-ETE was suggested to be another biomarker for N-ERD.[50]

Prognostic Biomarkers for CRS

Biomarkers for recurrence

Appropriate medical management in combination with ESS is the current standard treatment for CRS. Additionally, the advent of biologics has significantly improved treatment outcomes for patients with CRS.[51] However, approximately 40% of patients of CRS experience polyp recurrence within 12 months even after ESS and glucocorticoid therapy.[52] The long-term recurrence rate is about 60%−70%.[53] Therefore, it is important to identify prognostic biomarkers to determine the probability of recurrence.

Several measures of disease severity are associated with polyp recurrence, including higher post-ESS modified Lund-Mackay (MLM), modified Lund-Kennedy, and 22-item Sinonasal Outcomes Test (SNOT-22) scores. High levels of ECP, anti-dsDNA IgG, IL-5, pre-ESS MLM scores, and asthma comorbidity are risk factors for polyp recurrence after ESS. A model combining these factors (ECP, anti-dsDNA IgG, IL-5, MLM, and asthma comorbidity) predicts polyp recurrence with improved accuracy (AUC: 0.89).[54]

Factors derived from nasal tissue and mucus could serve as biomarkers for recurrence. Eosinophilic infiltration (>20%) and IL-5 expression in CRSwNP were associated with a higher rate of polyp recurrence following ESS.[55] In contrast, neutrophilic and lymphocytic infiltration, as well as IL-8 expression, were not associated with polyp recurrence in that study.[55] CLC from nasal brush samples could predict recurrent NPs in CRSwNP with an AUC of 0.932 (sensitivity: 92.00%, specificity: 88.46%).[56] At a cut-off value of 34.24 ng/mL for CLC concentration in nasal secretion, postoperative polyp recurrence could be predicted with a sensitivity of 92.6% and a specificity of 87.5%. Higher concentrations were associated with a higher risk of recurrence (hazard ratio [HR]: 11.31).[57] The nasal microbiota taxa consist of several phyla and genera in the nasal cavity, and their composition varies based on factors such as age, environmental exposures, and disease states. Nasal microbiota collected through nasal swabs were analyzed to construct a model that predicts polyp recurrence with an accuracy of 91.4%.[58] The chemoattractant receptor-homologous molecule expressed on T_H2 cells (CRTH2) is a receptor for prostaglandin D2 (PGD2), and is expressed on T_H2 cells, eosinophils, basophils, and ILC2s. CRTH2 contributes to the chemotaxis and activation of these immune cells and is significantly upregulated in T2 inflammatory diseases. A previous study reported that polyp recurrence was predicted with an AUC of 0.9107 (sensitivity: 87.50%, specificity: 85.71%) based on CRTH2 expression, exhibiting better accuracy than using eosinophil number or comorbid asthma as predictors.[59] A recent study revealed that both serum and tissue expression levels of CSF1R, which is selectively expressed on tissue $CD206^+$ M2 macrophages and promotes M2 polarization, were significantly higher in patients with recurrence than in those without.[60] Serine protease inhibitor (serpinF2) is a serine protease inhibitor, and its signaling pathways are significantly altered in CRSwNP. Lower levels of serpinF2 in nasal mucus correlated with higher NP scores, suggesting that serpinF2 is inversely associated with early recurrences.[61] Heme oxygenase-1 (HO-1) was found to be expressed in macrophages in CRS and was significantly increased in the tissues of CRSwNP. The number of HO-1 positive cells was negatively correlated with preoperative SNOT-22 scores, and the number of HO-1 positive cells was suggested as a biomarker of postoperative recurrence of CRSwNP.[62]

Multiple circulating factors in the peripheral blood have been investigated as prognostic biomarkers for CRS recurrence. Serum uric acid can predict postoperative recurrence of CRSwNP, with a cut-off value of 6.9 mg/dL and an AUC of 0.682.[63] Serum periostin predicted recurrences of CRSwNP with an AUC of 0.595 (sensitivity: 60.7%, specificity: 61.9% at a cut-off value of 115.5ng/mL).[64] Eotaxin and RANTES play roles in eosinophil migration and activation through CCR3 on eosinophils. ROC curve analysis showed that serum eotaxin had an AUC of 0.729 and RANTES had an AUC of 0.776 for predicting CRSwNP recurrence.[65] Another study suggested that serum sST2 and IL-33 could be potential biomarkers for predicting postoperative recurrence of CRSwNP. The combination of serum sST2 and IL-33 demonstrated improved accuracy and practicability with an AUC of 0.883.[16] Soluble BAFF increases eosinophil recruitment and T2 inflammation in NP tissue, contributing to a higher risk of recurrence and poor prognosis. Therefore, serum BAFF may serve as a predictive biomarker for postoperative recurrence of CRSwNP with an AUC of 0.842.[22] Given that B7-H4, which is widely expressed on most antigen-presenting cells and M2 macrophages, is important in the function of macrophages, it may be involved in the pathogenesis of CRSwNP. Tissue (AUC: 0.788) and serum (AUC: 0.852) levels of B7-H4 were identified as useful biomarkers for predicting postoperative

recurrence in CRSwNP.[66] Additionally, serum IgG4 levels were reported to be associated with post-operative recurrence. Post-operative recurrence was predicted with an AUC of 0.610 (sensitivity: 39.7%, specificity: 80.5% at a cut-off value of 95 mg/dL).[67] The combination of serum IgG4 and serum periostin could be a better biomarker for predicting postoperative prognosis.[67] The elevation of molecules related to eicosanoid metabolism, including LTE4, PGD2, and 15(S)-hydroxyeicosatetraenoic acid (15(s)-HETE), leads to a greater eosinophilic burden, increasing the risk of polyp recurrence. Accordingly, these molecules could serve as predictors of polyp recurrence.[68]

Biomarkers for refractory CRS

Recently, given the frequent recurrence of CRS, the definition of disease states in CRS has been updated, with an emphasis on the concepts of refractoriness and difficult-to-treat CRS.[11,69] Biomarkers from nasal tissue and nasal secretions have been investigated to predict refractory CRS. Cystatin SN from nasal secretions was used to predict postoperative uncontrolled status with an AUC of 0.974.[70] At an optimal cut-off value 2.63 μg/mL (Youden index: 0.911), postoperative uncontrolled status was predicted with a sensitivity of 97.8% and a specificity of 93.3%.[70] Cystatin SN concentrations higher than the cut-off value correlated with worse disease control status.[70] Neutrophilia (defined as more than 20 human neutrophil elastase (HNE)-positive cells per high-power field) is also closely associated with refractory CRS. Tissue neutrophilia had the highest HR of 4.38 for refractory CRSwNP in East Asians compared to other analyzed risk factors. The frequency of HNE-positive cells and IL-36α expression were significantly increased in the refractory group compared to the controlled group.[71] A higher number of subepithelial HNE-positive neutrophils could serve as a biomarker for refractory CRSwNP.[72] Another study conducted in China similarly reported that high tissue neutrophil numbers were associated with difficult-to-treat disease in patients with CRSwNP.[73] Additionally, single nucleotide polymorphism (SNP) can influence the refractoriness of CRS. A modified *CD8A* gene (SNP rs3810831) may affect MHC class I function, potentially leading to a decline in circulating $CD8^+$ lymphocytes and contributing to the development of refractory CRS. Major allele homozygosity of *CD8A* (rs3810831) has been associated with a higher frequency of affected relatives and increased disease severity.[74]

Moreover, responsiveness to steroid or macrolide therapy has been investigated. Patients with neutrophilia exhibited a reduced response to oral corticosteroid therapy.[75] CLC concentrations in nasal fluid were negatively associated with steroid responsiveness. Steroid responsiveness was predicted with an AUC of 0.897 (sensitivity: 89.6%, specificity: 78% at a cut-off value of 30.065 ng/mL).[76] The expression of mucin 1 (MUC1) and MUC4, transmembrane mucins expressed in the nasal mucosa, is altered in CRS and regulated by corticosteroids.[77,78] The MUC4/MUC1 ratio was suggested to be negatively associated with corticosteroid responsiveness in CRSwNP.[78,79] Headache Visual Analogue Scale (VAS) scores, elevated levels of IL-8, elevated levels of IgG3 in nasal tissue in patients with CRS were associated with refractoriness to postoperative glucocorticoid treatment (odds ratio [OR] up to 29.9).[80] Refractoriness to fluticasone propionate-based postoperative treatment was predicted with an accuracy of 89.3% using a classification tree. Additionally, overall VAS scores and elevated levels of IgG4 in nasal tissue are associated with refractoriness to clarithromycin (OR: 82.3). The predictive accuracy was 87.8% based on the classification tree.[80]

Future Perspectives and Concluding Remarks

In recent years, precision medicine has been in the spotlight as a treatment approach, highlighting the need for appropriate biomarkers to predict endotypes, recurrence, and refractory disease. The currently proposed biomarkers in CRS are summarized in Tables 1 and 2. Good biomarkers should be easily and rapidly obtained using non-invasive methods and be biologically meaningful enough to influence clinical decision-making. This is particularly important for monitoring biomarkers, as repeated follow-up of biomarkers after medical interventions is essential for predicting treatment efficacy and prognosis. Non-invasive sampling methods, such as nasal brushing, nasal swab, and epithelial lining fluid, have been proven effective and easy to utilize. However, the procedures for collecting and measuring biomarkers should be standardized.

While many studies have focused on identifying single variables as biomarkers for CRS, the disease is highly heterogenous with diverse factors contributing to its pathogenesis. Currently, researchers are conducting analyses with multiple biomarkers simultaneously using machine learning techniques, such as polygenic risk score. Additionally, studies have implemented with multivariable analysis to improve the accuracy, sensitivity, and specificity of biomarkers for CRS.[24] Al-

though numerous biomarker candidates for CRS have been proposed, several limitations remain to be addressed. First, most studies lack independent validation cohorts, underscoring the need for further research to validate the predictive efficacy of these biomarkers. Second, the expression and utility of biomarkers may vary across inflammatory endotypes of CRS and among racial groups. For instance, biomarker candidates associated with T2 inflammation may not effectively predict disease recurrence in non-T2 CRS. Additionally, as the frequency of each endotype differs based on race or geographic region, appropriate biomarkers may vary accordingly. Third, while extensive research has been conducted to iden-

Table 1. Biomarkers for classifying endotypes of CRS

Endotype	Sample type	Biomarker	AUC	Characteristics and implications	Ref
T2	Serum	sST2/IL-33	0.823	Part of the IL-1 receptor family; critically involved in T2 inflammation	16)
		Periostin	0.656	Protein encoded by the *POSTN* gene; induced by T2 cytokines	19)
		BAFF	0.809	Involved in the recruitment of eosinophils; correlated with blood eosinophil counts and percentages, tissue eosinophil counts, and serum total IgE	22)
		S100A4	0.726	Promote the recruitment of eosinophils	21)
		SEMA4D	-	Derived from activated eosinophils; its levels correlated with JESREC scores, blood eosinophil counts, and NP scores	20)
	Nasal fluid	CCL26	0.778	Recruit eosinophils; induced by T2 cytokines	26)
		ECP	0.767	Protein in the granules of eosinophils; used as a marker of eosinophils	26)
	Nasal tissue	Eosinophilic infiltration	-	The gold standard for diagnosing T2 CRS	23,24)
		Cystatin SN	-	Induced by IL-4/13; correlated with eosinophilic inflammation	27-29)
		Combination of *CCL13*, *CCL18*, and *CST1*	0.956	Can predict T2 CRS with high accuracy based on transcriptomic analysis	8)
		INPP4A (negatively correlated)	0.8906	mRNA levels in tissue negatively correlated with T2 CRSwNP	38)
		Periostin	-	Protein encoded by the *POSTN* gene; induced by T2 cytokines	18)
		CLC	-	Consequence of eosinophil extracellular trap cell death; reflect tissue T2 inflammation	25)
		15-lipoxygenase (*ALOX15*)		Involved in the metabolism of polyunsaturated fatty acids; expressed in epithelial cells, eosinophils, macrophages, mast cells; associated with T2 inflammation	35)
	Urine	LTE4	0.728	Produced by mast cells, eosinophils, neutrophils, and basophils; closely associated with T2 inflammation; multivariate logistic regression and artificial neural network machine learning models using uLTE4, blood eosinophil count, polyp status demonstrated high predictive accuracy	32)
		FeNO	0.848	A marker of T2 disease; NP is a stable determinant of increased FeNO	33)
Non-T2	Nasal fluid	LCN2	0.816	Found in neutrophil secondary granules; associated with T3 inflammation markers	43)
	Nasal tissue	NETs	-	Formed by the extrusion of nuclear chromatin into the extracellular space by neutrophils	42)
T1	Nasal fluid	CXCL9	0.869	IFN-γ-induced chemokines	26)
		CXCL10	0.815	IFN-γ-induced chemokines	26)
	Nasal tissue	*IFNG* (mRNA)	-	Tissue mRNA expression of *IFNG* is a suitable biomarker	24,26)
T3	Nasal fluid	CSF3	0.662	Regulates the production, differentiation, and function of granulocytes	26)
	Nasal tissue	*IL17A* (mRNA)	-	Its mRNA expression correlated with *IL17F*, *CSF3*, *SAA1*, and *IL1B* mRNA levels	24,26)

AHDI, aspirin hypersensitivity diagnostic index; AUC, area under curve; BAFF, B cell-activating factor; CCL26, C-C motif chemokine ligand 26; CLC, Charcot-Leyden crystal; CSF3, colony stimulating factor 3; ECP, eosinophil cationic protein; IL-33, interleukin-33; LTE4, leukotriene E4; LCN2, lipocalin-2; NETs, neutrophil extracellular traps; SEMA4D, semaphorin 4D; sST2, serum soluble suppressor of tumorigenicity 2

Table 2. Biomarkers for predicting recurrence and refractoriness of CRS

Variable	Sample type	Biomarker	AUC	Characteristics and implications	Ref
Recurrence	Serum	Uric acid	0.682	Prognostic biomarkers for recurrence with a cut-off value of 6.9 mg/dL	63)
		Periostin	0.595	Predicts recurrence with a cut-off value of 115.5 ng/mL	64)
		Eotaxin	0.729	Eosinophil migration and activation through CCR3 on eosinophils	65)
		RANTES	0.776	Eosinophil migration and activation through CCR3 on eosinophils	65)
		sST2 and IL-33	0.883	Combination of sST2 and IL-33 demonstrated high practicability	16)
		BAFF	0.842	Increases eosinophil recruitment and T2 inflammation in NP tissue	22)
		IgG4	0.610	Associated with post-operative recurrence; combination of IgG4 and periostin could be better	67)
		CSF1R	0.776	Selectively expressed on tissue $CD206^+$ M2 macrophages; promotes M2 polarization	60)
		B7-H4	0.852	Expressed on most antigen-presenting cells and M2 macrophages	66)
	Nasal fluid	SerpinF2 (negatively correlated)	-	Serpin; its signaling pathways is altered in CRSwNP	61)
		CLC	0.933	Predicts recurrence with a cut-off value of 34.24 ng/mL	57)
	Nasal brush	CLC	0.932	Predicts recurrent NPs in CRSwNP	56)
	Nasal swab	Nasal microbiota taxa	-	Analyzed to construct a model that predicts polyp recurrence with an accuracy of 91.4%	58)
	Nasal tissue	CRTH2	0.9107	Receptor for prostaglandin D2; expressed on T_H2 cells, eosinophils, basophils, and ILC2s	59)
		CSF1R	0.819	Selectively expressed on tissue $CD206^+$ M2 macrophages; promotes M2 polarization	60)
		HO-1	0.80	Expressed in macrophages in CRS; increased in tissues of CRSwNP	62)
		B7-H4	0.788	Expressed on most antigen-presenting cells and M2 macrophages	66)
		Eosinophilic infiltration (>20%), IL-5 expression	-	Associated with a higher rate of polyp recurrence following ESS	55)
		LTE4, PGD2, 15(s)-HETE	-	Molecules related to eicosanoid metabolism; leads to a greater eosinophilic burden	68)
	Combined	ECP, anti-dsDNA, IgG, IL-5, MLM, asthma comorbidity	0.89	Risk factors for polyp recurrence after ESS	54)
Refractoriness	Nasal fluid	Cystatin SN	0.974	Predicts postoperative uncontrolled status	70)
	Nasal tissue	Neturophilia	-	Neutrophilia (>20 HNE-positive cells/HPF) is associated with refractory CRS	71,72)
		SNP (*CD8A*, rs3810831)	-	May affect MHC class I function, potentially contributing to refractory CRS	74)
Steroid refractoriness	Nasal fluid	CLC	0.897	Negatively associated with steroid responsiveness	76)
	Nasal tissue	Neutrophilia	-	Reduced response to oral corticosteroid therapy	75)
		MUC4/MUC1	-	Transmembrane mucins expressed in the nasal mucosa; altered in CRS and regulated by corticosteroids	78,79)
		IL-8, IgG3	-	Associated with refractoriness to postoperative glucocorticoid treatment	80)
		Headache VAS scores	-	Associated with refractoriness to postoperative glucocorticoid treatment	80)
Macrolide refractoriness	Nasal tissue	IgG4	-	Associated with refractoriness to clarithromycin	80)
		Overall VAS scores	-	Associated with refractoriness to clarithromycin	80)

AUC, area under curve; BAFF, B cell-activating factor; CLC, Charcot-Leyden crystal; CRTH2, chemoattractant receptor-homologous molecule expressed on T_H2 cells; CSF1R, colony stimulating factor 1 receptor; ECP, eosinophil cationic protein; HNE, human neutrophil elastase; HO-1, heme oxygenase-1; HPF, high-power field; IgG4, immunoglobulin G4; IL-33, interleukin-33; Serpin, serine protease inhibitor; LTE4, leukotriene E4; MLM, modified Lund-Mackay; MUC, mucin; PGD2, prostaglandin D2; SNP, single nucleotide polymorphism; sST2, serum soluble suppressor of tumorigenicity 2; VAS, Visual Analogue Scale; 15(s)-HETE, 15(S)-hydroxyeicosatetraenoic acid

tify reliable biomarkers for T2 CRS, there is a greater need for studies focusing on biomarkers for non-T2 CRS. Furthermore, although many studies have focused on detecting biomarkers for diagnostic purposes, greater emphasis should be placed on their applications to clinical decision-making for treatment. A deeper understanding of the molecular and inflammatory mechanisms underlying the pathogenesis of CRS could aid in identifying and validating novel biomarkers specific to each inflammatory endotype and effective biomarkers for predicting therapeutic efficacy. Additionally, recent advances in experimental technologies, including single-cell and spatial multiomics analyses, as well as machine learning techniques, could facilitate the identification of promising biomarkers, ultimately improving treatment outcomes of patients with CRS.

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Conceptualization: Yeong-Jun Jeon, Min-Seok Rha. Data curation: Yeong-Jun Jeon. Formal analysis: Yeong-Jun Jeon. Funding acquisition: Min-Seok Rha. Investigation: Yeong-Jun Jeon, Min-Seok Rha. Methodology: Yeong-Jun Jeon. Supervision: Min-Seok Rha. Visualization: Yeong-Jun Jeon, Min-Seok Rha. Writing—original draft: Yeong-Jun Jeon. Writing—review & editing: Min-Seok Rha.

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정답 및 해설

답 ③

해 설 고막 이완부(pars flaccida)의 함입(retraction)으로 인해 발생한 진주종 중이염으로, 측두골 전산화단층촬영상에서는 상고실 측벽의 미란 및 상고실 내 연부조직 소견이 확인된다. 본 증례에서는 이소골의 파과가 의심되지만, 측반고리관 미란은 관찰되지 않았다.
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