Original Article

Associations Between Inflammatory Endotypes and Clinical Presentations in Chronic Rhinosinusitis

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What is already known about this topic? Clinically, patients with chronic rhinosinusitis (CRS) present with various symptoms including rhinorrhea, nasal congestion, smell loss, and/or facial pressure/pain. In addition, the sinonasal tissue of patients with CRS is characterized by a heterogeneous pattern of inflammation.

What does this article add to our knowledge? This study investigates the associations between various inflammatory endotypes and clinical phenotypes in CRS and demonstrates that certain inflammatory markers can be linked with particular clinical signs and symptoms.

How does this study impact current management guidelines? The identified association of certain inflammatory endotypes with specific clinical presentations can be useful in the diagnosis of CRS. Identifying and understanding these associations could lead to improved targeted therapies and more personalized treatment options for patients with CRS.

BACKGROUND: Chronic rhinosinusitis (CRS) is a heterogeneous disease characterized by mucosal inflammation in the nose and paranasal sinuses. Inflammation in CRS is also heterogeneous and is mainly characterized by type 2 (T2) inflammation, but subsets of patients show type 1 (T1) and type 3 (T3) inflammation. Whether inflammatory endotypes are associated with clinical phenotypes has yet to be explored in detail.

OBJECTIVE: To identify associations between inflammatory endotypes and clinical presentations in CRS.

METHODS: We compared 121 patients with nonpolypoid CRS (CRSsNP) and 134 patients with polypoid CRS (CRSwNP) and identified inflammatory endotypes using markers including IFN-γ (T1), eosinophil cationic protein (T2), Charcot-Leyden crystal galectin (T2), and IL-17A (T3). We collected clinical parameters from medical and surgical records and examined whether there were any associations between endotype and clinical features.

RESULTS: The presence of nasal polyps, asthma comorbidity, smell loss, and allergic mucin was significantly associated with the presence of T2 endotype in all patients with CRS. The T1 endotype was significantly more common in females, and the presence of pus was significantly associated with T3 endotype in all patients with CRS. We further analyzed these associations in CRSsNP and CRSwNP separately and found that smell loss was still associated with T2 endotype and pus with the T3 endotype

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Abbreviations used
CLC- Charcot-Leyden crystal galectin
CRS- chronic rhinosinusitis
CRSsNP- CRS without nasal polyps
CRSwNP- CRS with nasal polyps
NP- nasal polyp
OR- odds ratio
T1- type 1
T2- type 2
T3- type 3

in both CRSsNP and CRSwNP. Importantly, patients with CRS with T2 and T3 mixed endotype tended to have clinical presentations shared by both T2 and T3 endotypes. CONCLUSIONS: Clinical presentations are directly associated with inflammatory endotypes in CRS. Identification of inflammatory endotypes may allow for more precise and personalized medical treatments in CRS. **© 2019 American Academy of Allergy, Asthma & Immunology** **(J Allergy Clin Immunol Pract 2019;7:2812-20)**

Key words: *Chronic rhinosinusitis; Clinical presentation; Endotype-phenotype association; Inflammatory endotype*

INTRODUCTION

Chronic rhinosinusitis (CRS) is a heterogeneous disease that affects approximately 12.5% of Americans, is responsible for more than 400,000 surgeries annually, produces significant morbidity, and costs our health system an estimated $22 billion to 32 billion annually.[1-4] Most investigators accept a paradigm in which CRS is divided into the 2 main phenotypes: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP). In Western countries, CRSwNP is well known to be characterized by type 2 (T2) inflammation with pronounced eosinophilia and the presence of high levels of T2 cytokines, such as IL-5 and IL-13.[5-9] In contrast, CRSsNP is less well characterized despite 80% of all patients with CRS having this phenotype.[1,2,10] Recently, we comprehensively characterized inflammatory patterns by using IFN-γ as a type 1 (T1) marker, Charcot-Leyden crystal galectin (CLC) mRNA or eosinophil cationic protein as T2 markers, and IL-17A as a type 3 (T3) marker in patients with CRS who had undergone surgery at our institution. We found that inflammation in CRSsNP is highly heterogeneous, much more so than what was observed in CRSwNP.[7] Similar to other studies in the United States and Europe, we reported that the most frequent inflammatory endotype in CRSsNP was T2, as opposed to T1 or T3.[7-9,11,12] In addition, on further analysis, we identified subsets of patients who had more than 1 type of inflammatory endotype, as characterized by concurrent elevations in T1, T2, and/or T3 markers.[7] Although these studies shed light onto the different molecular mechanisms underlying CRS, it remains unknown whether (or how) this inflammation impacts the clinical presentation. Specifically, patients with CRS experience diverse sinonasal and systemic symptoms,[13-15] but the relationship between a particular clinical phenotype and an inflammatory endotype is not well defined.

TABLE I. Clinical characteristics of patients with CRSsNP and patients with CRSwNP

Characteristic	CRSsNP % (n = 121)	CRSwNP % (n = 134)	*P* value
Age (y), median (range)	38 (19-74)	45 (20-76)	.071
Sex (female)	**57.0**	35.1	**<.001**
Atopy*	43.7	**64.3**	**.002**
Asthma	29.8	**44.0**	**.019**
Current smoker	4.1	5.2	.681
Nasal congestion/obstruction/blockage	89.3	94.0	.172
Rhinorrhea/post−nasal drip/nasal drainage	**84.3**	69.2	**.005**
Purulent nasal drainage	19.8	19.5	.954
Sinus pressure/pain	**73.6**	54.9	**.002**
Headache/migraine	**25.6**	14.3	**.023**
Fatigue/fever/feel poor	**14.9**	5.3	**.010**
Smell loss/reduced taste	33.9	**72.2**	**<.001**
Ear fullness/pain/popping	17.4	13.5	.399
Eye watering/itching	8.3	6.8	.651
Cough	**24.8**	8.3	**<.001**
History of FESS (>2)	12.4	**30.6**	**.001**
Intraoperative pus†	15.0	10.3	.271
Allergic mucin†	2.7	**11.9**	**.007**

FESS, Functional endoscopic sinus surgery.
The *P* value was determined by the χ^2 test or Mann−Whitney test.
The values in bold are statistically significantly different from the comparator. The *P* values are listed and are in bold if $P < .05$.
*CRSsNP (n = 119) and CRSwNP (n = 112).
†CRSsNP (n = 113) and CRSwNP (n = 126).

In the past decade, several groups have examined the association between endotypes and phenotypes in asthma. The Severe Asthma Research Program and the Unbiased BIOmarkers in PREDiction of respiratory disease outcomes studies both identified asthma phenotypes and related them to inflammatory endotypes, including gene expression profiles, eosinophilia, and neutrophilia.[16-21] In contrast to asthma, however, investigations into the association between endotype and phenotype of CRS remain scarce, except for the known association of T2 inflammation with nasal polyps (NPs) and asthma.[8,22] In this study, we hypothesized that certain CRS inflammatory endotypes are associated with specific clinical presentations. We therefore set out to define the endotype-phenotype associations in CRS by examining clinical characteristics of patients with CRS evaluated in our previously published endotyping study.[7]

METHODS

Patients and tissue collection

We used mRNA and protein data from our published study, which included 255 patients with CRS.[7] All patients with CRS were recruited from the Otolaryngology clinic and the Northwestern Sinus Center of Northwestern Medicine. All patients with CRS met the criteria for CRS as defined by the International Consensus Statement on Allergy and Rhinology: Rhinosinusitis.[2] Patients with an established immunodeficiency, pregnancy, coagulation disorder, or diagnosis of aspirin hypersensitivity, classic allergic fungal sinusitis, eosinophilic granulomatous polyangiitis (Churg-Strauss syndrome), or cystic fibrosis were excluded from the study.

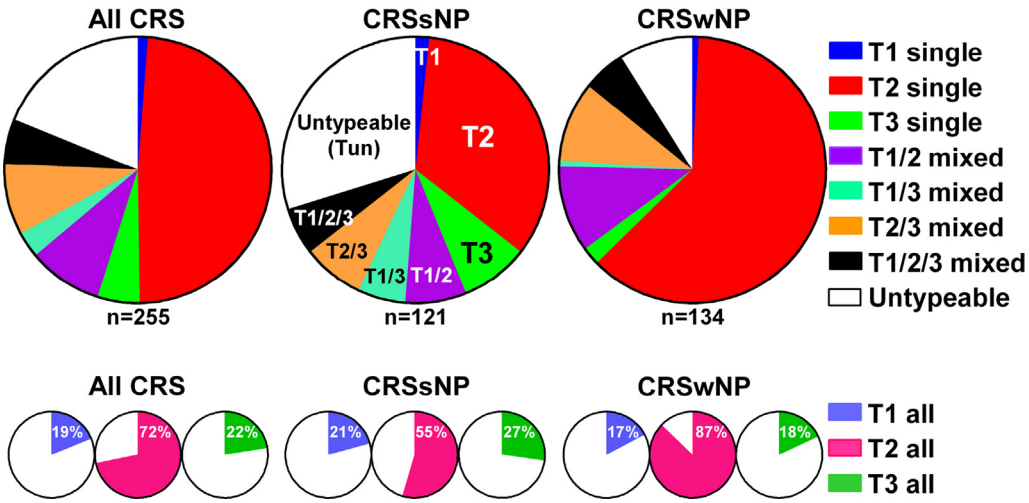

FIGURE 1. Patterns of inflammatory endotypes in patients with CRS.

Characteristics of subjects in this study are presented in Table I. All subjects signed informed consent, and the study was approved by the Institutional Review Board of Northwestern University Feinberg School of Medicine (Institutional Review Board project no. STU00016917).

CRS Endotyping

We determined mRNA and protein for endotypic markers in ethmoid and NP tissues.[7] Only a minor subset of patients had matched data for mRNA and protein. Endotyping was blinded to the clinical parameters. For T1 inflammation, we evaluated gene expression and protein levels of IFN-γ. For T2 inflammation, we evaluated CLC mRNA and eosinophil cationic protein levels. For T3 inflammation, we measured IL-17A gene expression and protein levels.[7] If a donor had both mRNA and protein data available, the mRNA results were used. If a CRSwNP donor had both ethmoid and NP tissue available, the NP data were used. We used a cutoff of greater than 90th percentile of the expression in control ethmoid tissue to define endotypes. Control patients were undergoing surgery for non-CRS–indicated procedures such as cranial tumor resection or septoplasty, and their clinical characteristics are presented in Table E1 in this article's Online Repository at www.jaci-inpractice.org.

For the analysis of endotype-phenotype associations, we primarily compared clinical presentations with the presence and/or absence of specific endotypes. We secondarily compared untypeable patients, that is, those who did not have any elevation in T1, T2, or T3 inflammation, with patients who had a single endotype (eg, they had only T2 inflammatory profile) as well as with patients who had a mixed endotype (eg, they had both T1 and T2 inflammatory profiles).

CRS Phenotyping

The medical records for each study subject were manually reviewed to obtain information about various clinical and demographic parameters. Reviewers of the medical record were blinded to the endotyping results. Information was gathered from outpatient clinic visits within the 6 months before the subject's sinus surgery and the operative notes from the day of the procedure. Patients were determined to have asthma and/or atopy if there was a physician diagnosis listed in the clinical record. The clinical symptoms reviewed included nasal congestion, obstruction, blockage, rhinorrhea, post–nasal drip, nasal drainage, purulent nasal drainage, sinus pressure/pain, headache, fatigue, fever, smell loss, reduced taste, ear fullness, ear pain, ear popping, eye watering, eye itching, and cough. For the data analysis, similar symptoms (eg, nasal congestion, obstruction, and blockage) were grouped together in one category. A history of physician-diagnosed migraine was included with the symptom of headache. In the surgical report, 2 additional parameters, namely, the presence of intraoperative pus and allergic mucin, were identified. In some instances, information regarding atopy status or the presence of pus or allergic mucin during surgery was not identified in the medical records. If this information was not available, those patients were excluded from these specific analyses.

Statistical analysis

All statistical calculations were performed using Graphpad Prism version 6.07 (GraphPad Software, La Jolla, Calif), SAS version 9.4 (SAS Institute Inc, Cary, NC), and R 3.3.3 (R Foundation, Vienna, Austria). The chi-square test was used for comparisons among different patient groups. The Kruskal-Wallis test with Dunn's correction was used to compare means among different groups regarding age. Separate logistic regression analyses were performed for the dependent variables' intraoperative pus, each specific symptom, history of more than 2 functional endoscopic sinus surgeries, and allergic mucin. The main predictor was endotype, with additional covariates including age, sex, asthma, atopy, and NP. The corresponding odds ratio (OR), 95% CI, and P value were calculated by logistic regression. A P value of less than .05 was considered significant.

RESULTS

Inflammatory endotypes in CRS

We analyzed our published data,[7] which included 121 patients with CRSsNP and 134 patients with CRSwNP, and defined inflammatory endotypes by using the 90th percentile of expression of markers in control ethmoid tissue as the threshold. Among patients with CRSsNP, the overall frequency of having any T1, T2, or T3 inflammation was 21%, 55%, and 27%, respectively, of which 1.7%, 34%, or 8.3% had evidence of only

TABLE II. Comparisons of clinical presentations and inflammatory endotypes in all patients with CRS, patients with CRSsNP, and patients with CRSwNP

	T1 endotype			T2 endotype			T3 endotype		
All CRS	**Absence % (n = 207)**	**Presence % (n = 48)**	***P* value**	**Absence % (n = 72)**	**Presence % (n = 187)**	***P* value**	**Absence % (n = 198)**	**Presence % (n = 57)**	***P* value**
NP	53.6	47.9	.476	23.6	**63.9**	**<.001**	55.6	42.1	.073
Sex (female)	42.0	**64.6**	**.005**	51.4	44.3	.304	44.9	50.9	.429
Asthma	36.2	41.7	.483	26.4	**41.5**	**.024**	38.4	33.3	.487
Rhinorrhea/post–nasal drip/nasal drainage	75.7	79.2	.614	**84.7**	73.1	**.049**	75.6	78.9	.604
Headache/migraine	21.4	12.5	.165	20.8	19.2	.772	20.8	15.8	.401
Smell loss/reduced taste	55.8	45.8	.211	30.6	**63.2**	**<.001**	55.3	49.1	.408
Cough	17.0	12.5	.446	**25.0**	12.6	**.016**	17.3	12.3	.368
Intraoperative pus*	10.5	20.8	.053	**19.4**	9.9	**.046**	7.5	**30.2**	**<.001**
Allergic mucin*	7.3	8.3	.814	1.5	**9.9**	**.027**	8.1	5.7	.559
CRSsNP	**Absence % (n = 96)**	**Presence % (n = 25)**	***P* value**	**Absence % (n = 55)**	**Presence % (n = 66)**	***P* value**	**Absence % (n = 88)**	**Presence % (n = 33)**	***P* value**
Sex (female)	53.1	**76.0**	**.039**	60.0	56.1	.662	55.7	63.6	.430
Headache/migraine	28.1	16.0	.216	14.5	**34.8**	**.011**	27.3	21.2	.496
Smell loss/reduced taste	33.3	36.0	.802	23.6	**42.4**	**.030**	35.2	30.3	.610
Pus*	11.4	**28.0**	**.040**	21.2	9.8	.094	8.5	**32.3**	**.002**
CRSwNP	**Absence % (n = 111)**	**Presence % (n = 23)**	***P* value**	**Absence % (n = 17)**	**Presence % (n = 117)**	***P* value**	**Absence % (n = 110)**	**Presence % (n = 24)**	***P* value**
Sex (female)	32.4	52.2	.072	23.5	37.6	.258	36.4	33.3	.779
Headache/migraine	15.5	8.7	.400	**41.2**	10.3	**.001**	15.6	8.3	.357
Smell loss/reduced taste	75.5	56.5	.065	52.9	75.0	.058	71.6	75.0	.734
Intraoperative pus*	9.7	13.0	.635	13.3	9.9	.683	6.7	**27.3**	**.004**

The *P* value was determined by the χ^2 test.
The values in bold indicate statistical significance of $P < .05$.
*All CRS: absence (n = 191) and presence (n = 48) of T1 endotype, absence (n = 67) and presence (n = 172) of T2 endotype, absence (n = 186) and presence (n = 53) of T3 endotype. CRSsNP, absence (n = 88) and presence (n = 25) of T1 endotype, absence (n = 52) and presence (n = 61) of T2 endotype, absence (n = 82) and presence (n = 31) of T3 endotype. CRSwNP, absence (n = 103) and presence (n = 23) of T1 endotype, absence (n = 15) and presence (n = 111) of T2 endotype, absence (n = 104) and presence (n = 22) of T3 endotype.

T1, T2, or T3 inflammation (single endotypes) (Figure 1). Among patients with CRSwNP, the overall frequency of any T1, T2, or T3 inflammation was 17%, 87%, and 18%, respectively, of which 0.7%, 62%, or 2.2% had only T1, T2, or T3 single inflammation (Figure 1). Twenty-six percent of patients with CRSsNP and 26% of patients with CRSwNP had a combination of T1, T2, and/or T3 inflammation and were thus referred to as having mixed endotypes. In contrast, 30% of patients with CRSsNP and 9% of patients with CRSwNP had no detectable elevations of T1, T2, or T3 inflammation and thus were referred to as having an untypeable (Tun) endotype (Figure 1). The frequency of T2 inflammation was significantly higher in patients with CRSwNP than in patients with CRSsNP ($P < .001$) and the frequency of T3 inflammation tended to be higher in patients with CRSsNP than in patients with CRSwNP ($P = .073$).

Differences in clinical presentation between patients with CRSsNP and patients with CRSwNP

We reviewed 16 clinical parameters, including 14 parameters in the clinical chart and 2 parameters in the surgical report, and examined whether there were any differences between patients with CRSsNP and patients with CRSwNP. We found that patients with CRSsNP had a higher prevalence of females compared with patients with CRSwNP (Table I). The frequency of asthma and atopy was significantly higher in patients with CRSwNP than in patients with CRSsNP (Table I), confirming our previous findings.[10,23] In regard to symptoms, we found that rhinorrhea, sinus pressure/pain, headache/migraine, fatigue/fever, and cough were more often reported by patients with CRSsNP than by patients with CRSwNP (Table I). In contrast, smell loss was more frequently reported by patients with CRSwNP. In addition, history of recurrent functional endoscopic sinus surgery and the presence of allergic mucin were more frequently found in patients with CRSwNP (Table I).

Inflammatory endotypes associate with clinical presentations in all patients with CRS

We examined whether specific clinical characteristics were associated with a particular inflammatory endotype (Table II). Among all patients with CRS, those with the T2 endotype were significantly more likely to have NPs, asthma, smell loss, and allergic mucin and were less likely to report rhinorrhea, cough, and pus (Table II). We also found that the T1 endotype was more common in females, and the presence of pus was significantly associated with the T3 endotype (Table II). Other features including atopy, nasal congestion, purulent nasal drainage, sinus pressure, headache, fatigue, ear fullness, ocular

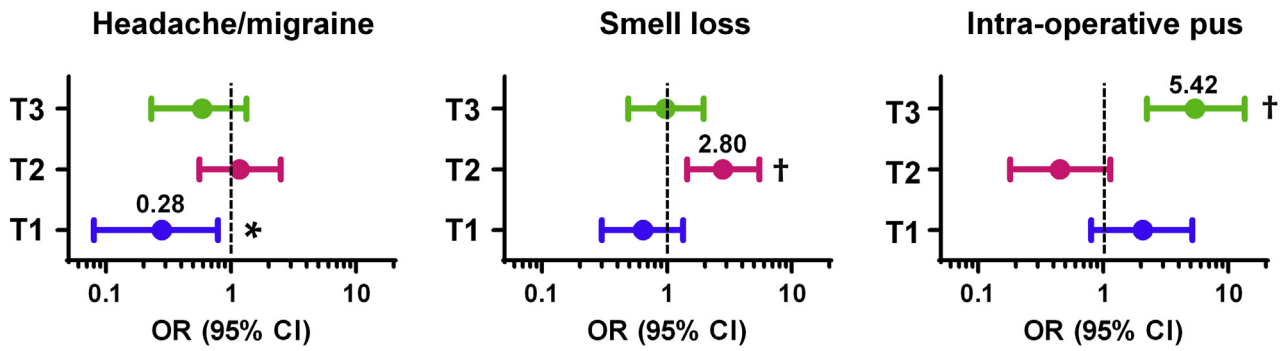

FIGURE 2. OR for clinical presentations within endotypes in all patients with CRS. Multivariate logistic regression analysis with predictor endotype controlling for age, sex, asthma, atopy, and NP and the corresponding OR, 95% CI, and *P* value for headache/migraine (n = 230), smell loss (n = 230), and intraoperative pus (n = 217) in patients with CRS. **P* < .05, †*P* < .01 by logistic regression analysis.

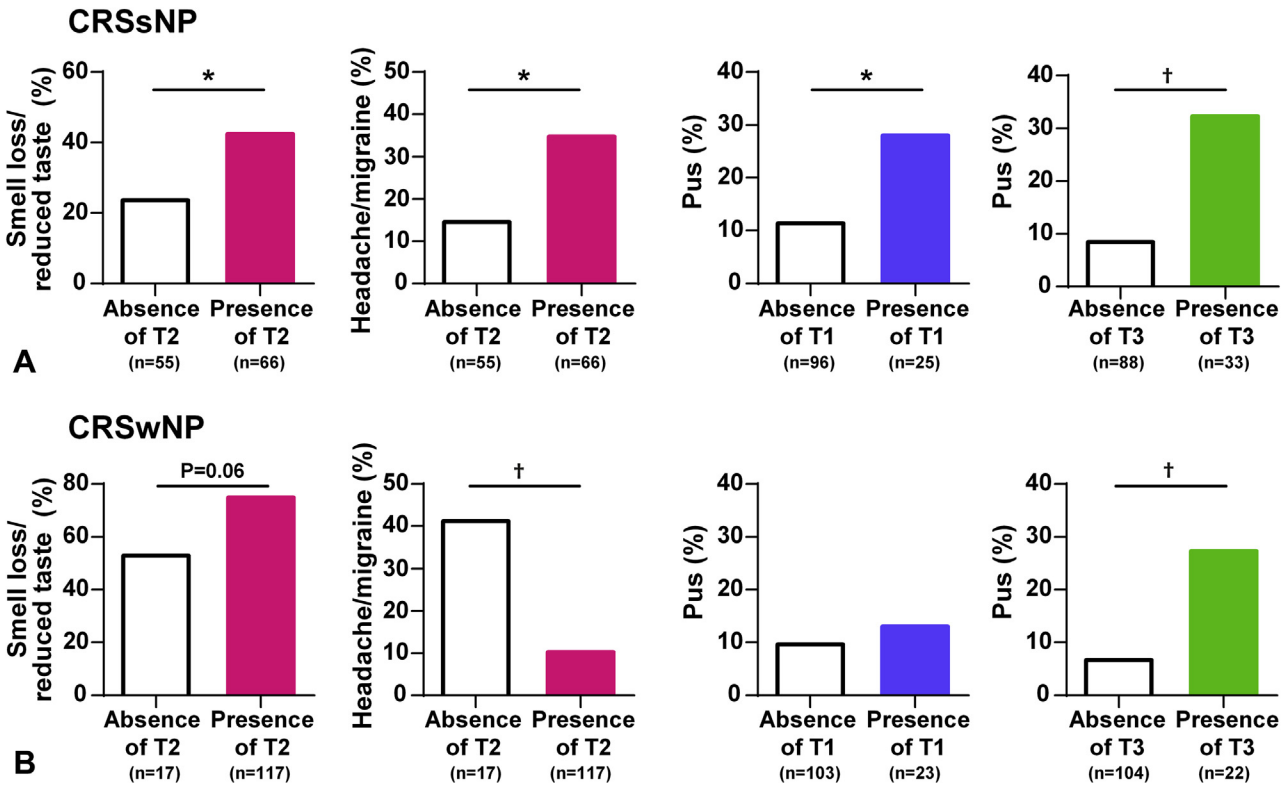

FIGURE 3. Endotype-phenotype associations in patients with CRSsNP and patients with CRSwNP. Association of clinical presentations with the absence and/or presence of all T1, T2, or T3 endotypes in **A,** patients with CRSsNP and **B,** patients with CRSwNP. **P* < .05, †*P* < 0.01 by the chi-square test.

symptoms, and history of functional endoscopic sinus surgery were not different among the 3 inflammatory endotypes (see Table E2 in this article's Online Repository at www.jaci-inpractice.org).

We also performed multivariate logistic regression analysis and found that smell loss was associated with T2 endotype (OR, 2.80; 95% CI, 1.45-5.51; $P < .01$) and intraoperative pus was associated with T3 endotype (OR, 5.42; 95% CI, 2.23-13.61; $P < .01$) while controlling for age, sex, NP, atopy, and asthma (Figure 2). In addition, headache/migraine was negatively associated with T1 endotype (OR, 0.28; 95% CI, 0.08-0.79; $P = .03$) (Figure 2). Other clinical factors were not significantly associated with any endotype when controlling for age, sex, NP, atopy, and asthma (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

Inflammatory endotypes associate with clinical presentations in patients with CRSsNP

Among patients with CRSsNP, we found that smell loss and headache/migraine were significantly associated with the presence of a T2 endotype (Figure 3, *A*; Table II). In addition, the presence of pus was significantly more common in T1 and T3

TABLE III. Comparisons of clinical presentations between single or mixed and untypeable CRS endotypes in all CRS

		Single or multiple endotype				
Characteristics	TunCRS % (n = 48)	T2CRS % (n = 124)	T3CRS % (n = 13)	T1/2CRS % (n = 23)	T1/3CRS % (n = 8)	T2/3CRS % (n = 22)
NP	25.0	**66.9**	23.1	47.8	12.5	**59.1**
P value		**<.001**	.886	.054	.438	**.006**
Asthma	25.0	**42.7**	15.4	43.5	50.0	36.4
P value		**.031**	.465	.115	.147	.329
Purulent nasal drainage	18.8	16.3	**53.8**	21.7	12.5	18.2
P value		.697	**.011**	.767	.669	.955
Smell loss/reduced taste	31.3	**65.9**	38.5	52.2	12.5	**63.6**
P value		**<.001**	.623	.089	.277	**.011**
Eye watering/itching	16.7	**6.5**	0.0	4.3	12.5	4.5
P value		**.040**	.114	.114	.766	.160
Intraoperative pus*	6.8	5.2	**50.0**	21.7	**50.0**	**26.3**
P value		.687	**<.001**	.074	**.001**	**.033**

TunCRS, Untypeable CRS.
TunCRS: undetectable elevations of T1, T2, or T3 inflammation.
The *P* value was determined by the χ^2 test compared with TunCRS.
The values in bold are significantly different statistically from the comparator at $P < .05$ level. The *P* values are in bold when <.05.
*TunCRS (n = 44), T2CRS (n = 116), T3CRS (n = 12), T1/2CRS (n = 23), T1/3CRS (n = 8), and T2/3CRS (n = 19).

endotypes (Figure 3, *A*; Table II). Other clinical factors were not different among the inflammatory endotypes in patients with CRSsNP (see Table E3 in this article's Online Repository at www.jaci-inpractice.org).

Inflammatory endotypes associate with clinical presentations in patients with CRSwNP

We next analyzed patients with CRSwNP and found that the T3 endotype was significantly associated with the presence of pus and the T2 endotype tended to be associated with smell loss ($P = .058$) (Figure 3, *B*; Table II). Interestingly, in contrast to patients with CRSsNP, headache/migraine was lower in the presence of the T2 endotype in patients with CRSwNP (Figure 3, *B*; Table II). Other clinical factors were not different among the inflammatory endotypes in patients with CRSwNP (see Table E4 in this article's Online Repository at www.jaci-inpractice.org).

Comparisons of clinical presentations between single, mixed, and untypeable CRS endotypes

Because 26% of patients with CRS had more than 1 endotype (eg, CRS with T1 and T2 endotypes; called T1/2CRS), we were able to test whether the presence of mixed endotypes may affect the endotype-phenotype associations. The single T1 CRS endotype was rare (1.8%, n = 3, Figure 1) and was not included in the analysis. We compared the clinical presentations between patients with untypeable CRS and patients with either a single endotype (T2 or T3) or mixed endotypes (T1/T2, T1/T3, or T2/T3) (Table III). We again found that the presence of NPs, asthma, and smell loss significantly associated with the presence of a single T2 endotype (T2CRS) (Table III). In contrast, ocular symptoms were negatively associated with T2CRS. The presence of pus and purulent nasal drainage was significantly associated with a single T3 endotype (T3CRS) (Table III). Other clinical factors were not different among the single inflammatory endotypes (see Table E5 in this article's Online Repository at www.jaci-inpractice.org).

In some instances, mixed endotypes shared similar phenotypes as single endotypes. For example, pus was present in T3CRS as well as T3 mixed endotypes (T1/3CRS and T2/3CRS) (Table III). Smell loss and NP were present in T2CRS as well as T2 mixed endotypes (T1/2CRS and T2/3CRS), although T1/2CRS ($P = .089$ and .054, respectively) did not reach significance (Table III). Similar to T2CRS, asthma tended to be associated with a T2 mixed endotype (T1/2CRS); however, this did not reach significance (Table III). In contrast, purulent nasal drainage was present in the T3 single endotype but not in T3 mixed endotypes (Table III). This suggests that the phenotype of mixed endotypes is not necessarily a simple combination of individual endotype-associated phenotypes in CRS.

Finally, we subdivided CRS into CRSsNP and CRSwNP and analyzed the relationships between clinical presentations and either single or mixed inflammatory endotypes in both populations. However, because of low patient numbers, T1 and T3 single endotypes were excluded from the CRSwNP analysis. Among patients with CRSsNP, those with a single T3 endotype (T3sNP) or a mixed T1/T3 endotype (T1/3sNP) were more likely to have pus (Figure 4, *A*). Among patients with CRSwNP, those with a mixed T2/3 endotype (T2/3wNP) but not with a single T2 endotype (T2wNP) were likely to have pus (Figure 4, *B*). In addition, smell loss was significantly associated with the single T2 endotype (T2wNP) as well as the mixed T2/T3 endotype (T2/3wNP) (Figure 4, *B*). A higher prevalence of asthma was found in the mixed T1/T2 endotype (T1/2wNP), with a trend toward being elevated in the single T2 endotype ($P = .066$) (Figure 4, *B*). Interestingly, headache and ocular symptoms were negatively associated with T2wNP and were most commonly associated with the untypeable CRSwNP endotype (Figure 4, *B*).

DISCUSSION

The division of CRS into 2 major phenotypes, CRSsNP and CRSwNP, is widely accepted, and the patterns of inflammatory endotypes in these 2 CRS phenotypes are known to be different.[7-9,11] Although associations between endotype and phenotype in asthma

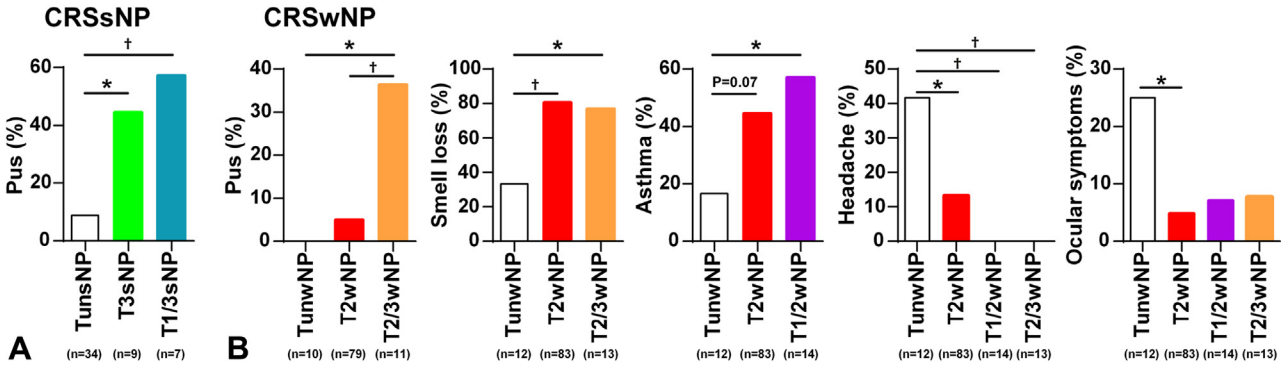

FIGURE 4. Endotype-phenotype association in single, mixed, and untypeable endotypes of patients with CRSsNP and patients with CRSwNP. Comparison of clinical presentations between untypeable, single, or mixed endotypes in **A**, patients with CRSsNP and **B**, patients with CRSwNP. $*P < .05$, $\dagger P < .01$ by the chi-square test.

have been well studied in the past decade,[16-21,24] these associations in CRS have only begun to be examined. Tomassen et al[8] found that the presence of T2 inflammation with *Staphylococcus aureus* enterotoxin–specific IgE was highly associated with CRSwNP and asthma. Likewise, Turner et al[22] found that T2 inflammation was associated with the presence of NPs and asthma. Although previous studies identified this association between T2 inflammation and presence of NPs and asthma, it was not known whether T2 inflammation was associated with other clinical presentations, or whether T1 and T3 inflammation were associated with other distinct clinical phenotypes. To our knowledge, this is the first study to report how T3 inflammation influences clinical presentations in CRS. Furthermore, we have identified new associations between T2 inflammation and clinical presentations in CRS.

In the present study, we first confirmed the published observations that T2 inflammation was associated with the presence of NPs and asthma comorbidity in CRS (Table II). This suggests that patients with CRS in this study were typical of the general CRS population in the United States. Interestingly, we also found that the T1 and T2 mixed endotype (T1/2wNP) showed the highest asthma comorbidity in patients with CRSwNP but not in patients with CRSsNP (Figure 4, *B*, and not shown). Although we did not investigate asthma phenotypes in the present study, CRSwNP with a mixed T1 and T2 endotype may correspond to a unique phenotype of asthma. Further studies will be required to identify the association between asthma and CRS phenotypes and endotypes as well as the endotype of asthma associated with CRS endotypes.

In addition to the presence of NP and asthma comorbidity, we identified that smell loss was strongly associated with the T2 endotype. We recently found that complaints of smell/taste loss were significantly higher in eosinophilic CRS (78% were patients with CRSwNP) and that expression of an eosinophil marker, CLC, in superior turbinate correlated with olfactory defect in patients with CRS.[25,26] These studies may suggest that T2 inflammation promotes smell loss in patients with CRS. However, smell loss is also well known to be associated with the presence of NPs,[1] and therefore it was not clear whether the T2 inflammation was just a marker of NPs or whether the T2 inflammation was instead more directly associated with smell loss. In our present study, we found that T2 inflammation was also associated with smell/taste loss in patients with CRSsNP (Figure 3). Furthermore, smell loss was still associated with T2 endotype while controlling for asthma and presence of NPs (Figure 2). These results suggest that the symptoms of smell/taste loss may be directly induced by T2 inflammation. It will be valuable to investigate how T2 inflammation mediates olfactory defects.

In contrast to the presence of asthma and olfactory defects, headaches and migraines were differentially reported in patients with CRSsNP and patients with CRSwNP with a T2 endotype. We found that the presence of T2 inflammation positively associated with headache and migraine in patients with CRSsNP whereas they negatively associated in patients with CRSwNP (Figure 3). This suggests that a subset of endotype-phenotype associations is affected by the presence (or absence) of NPs.

This study also provides the first evidence suggesting that T3 inflammation is associated with the presence of pus and purulent nasal drainage in patients with CRS. The intraoperative finding of pus was almost always associated with T3 inflammation in both patients with CRSsNP and patients with CRSwNP. Multivariate analysis also supported the direct link between T3 inflammation and pus in CRS (Figure 2). However, documentation of symptoms of purulent nasal drainage was only associated with the T3 single endotype (Table III). Because endoscopic sinus surgery facilitates the direct inspection of sinus contents, we believe it is a more sensitive measure of purulence than relying on the patient's ability to identify purulent nasal discharge and may explain why purulent nasal drainage was less strongly associated with T3 inflammation.

CRS is one of the diseases for which antibiotics are commonly prescribed and accounts for 7.1% of all primary diagnoses for ambulatory care visits with antibiotic prescriptions, despite limited evidence of efficacy.[27] This level of overuse may lead to the emergence of antibiotic-resistant bacteria. Importantly, T3 (T_H17) immunity is very important for protection against bacteria and fungi.[28,29] In addition, purulent nasal drainage and pus are common symptoms associated with bacterial infections, and we found that these symptoms were associated with the T3 endotype in CRS. Together, our findings may suggest that the T3 endotype in CRS is most strongly associated with bacterial

infection, and, importantly, that patients with T3CRS may be the most responsive to treatment with antibiotics. This possibility may generate a more precise and personalized medical strategy for this subset of patients with CRS. Several studies have suggested a central role for IL-17, T_H17 cells, and group 3 innate lymphoid cells in severe neutrophilic asthma, which is generally characterized by steroid insensitivity.[30] From this we can infer that T3CRS may also be characterized by neutrophilic inflammation in the sinonasal mucosa and be resistant to glucocorticoid treatments. Future study will be required to identify whether the T3 endotype is associated with bacterial infection in patients with CRS, whether patients with T3CRS are responsive to antibiotic treatment, and whether patients with T3CRS have neutrophilic inflammation with resistance to glucocorticoid treatments.

We found that 30% of patients with CRSsNP and 9% of patients with CRSwNP were untypeable using the current endotyping markers (Figure 1). Interestingly, we also found distinct clinical presentations in these untypeable patients, especially in patients with CRSwNP. Ocular tearing and pruritus were more common in patients with untypeable CRS compared with T2 and T3 single endotypes in all patients with CRS (Table II) and compared with T2 single and T2 mixed endotypes in patients with CRSwNP (Figure 4, *B*), although some comparisons did not reach significance. In addition, headache/migraine was significantly associated with untypeable CRSwNP (Figure 4, *B*). These results suggest that the untypeable group may have 1 or more unrecognized endotypes independent of T-cell—associated cytokines. Further study will be required to examine whether there are any biomarkers (such as non-T-cell—associated cytokines or chemokines) that could identify potential new endotypes in untypeable CRS.

Although we showed clear evidence that inflammatory endotypes are associated with distinct clinical presentations in patients with CRS, our present study has certain limitations. We have purposefully selected the method used for identification of endotypes in this study. In the case of published asthma studies, most investigators used periostin, CCL26, eosinophil numbers, and fractional exhaled nitric oxide level as biomarkers to identify T2 endotype, because the levels of T-cell—associated cytokines were not high in tissue.[31-33] In our present study however, we used eosinophil cationic protein and CLC, which are very sensitive markers of eosinophils, to determine the T2 endotype in patients with CRS and we were able to use the canonical T-cell—associated cytokines IFN-γ and IL-17A for the determination of T1 and T3 inflammation, respectively. It is possible that there are some false-negative calls in our data set, that is, patients whose disease was driven by T1 or T3 cytokines but were nonetheless assigned to the untypeable group. Future study is required to identify more sensitive biomarkers of T1 and T3 endotypes in patients with CRS to diminish the possibility of such false negatives. Another limitation is that the study was performed only in patients undergoing surgery, and we did not control for systemic or topical corticosteroids and antibiotic use perioperatively. These medications could have affected our findings. Future studies in a primary population of patients with CRS and studies on the effect of medications would be worthwhile.

In conclusion, we report that a subset of clinical presentations was directly associated with inflammatory endotypes in patients with CRS. Identification of inflammatory endotypes may help in the diagnosis of CRS phenotypic groups and may be useful for the future design of more precise and personal medicine strategies that effectively prevent or treat disease in patients with CRS.

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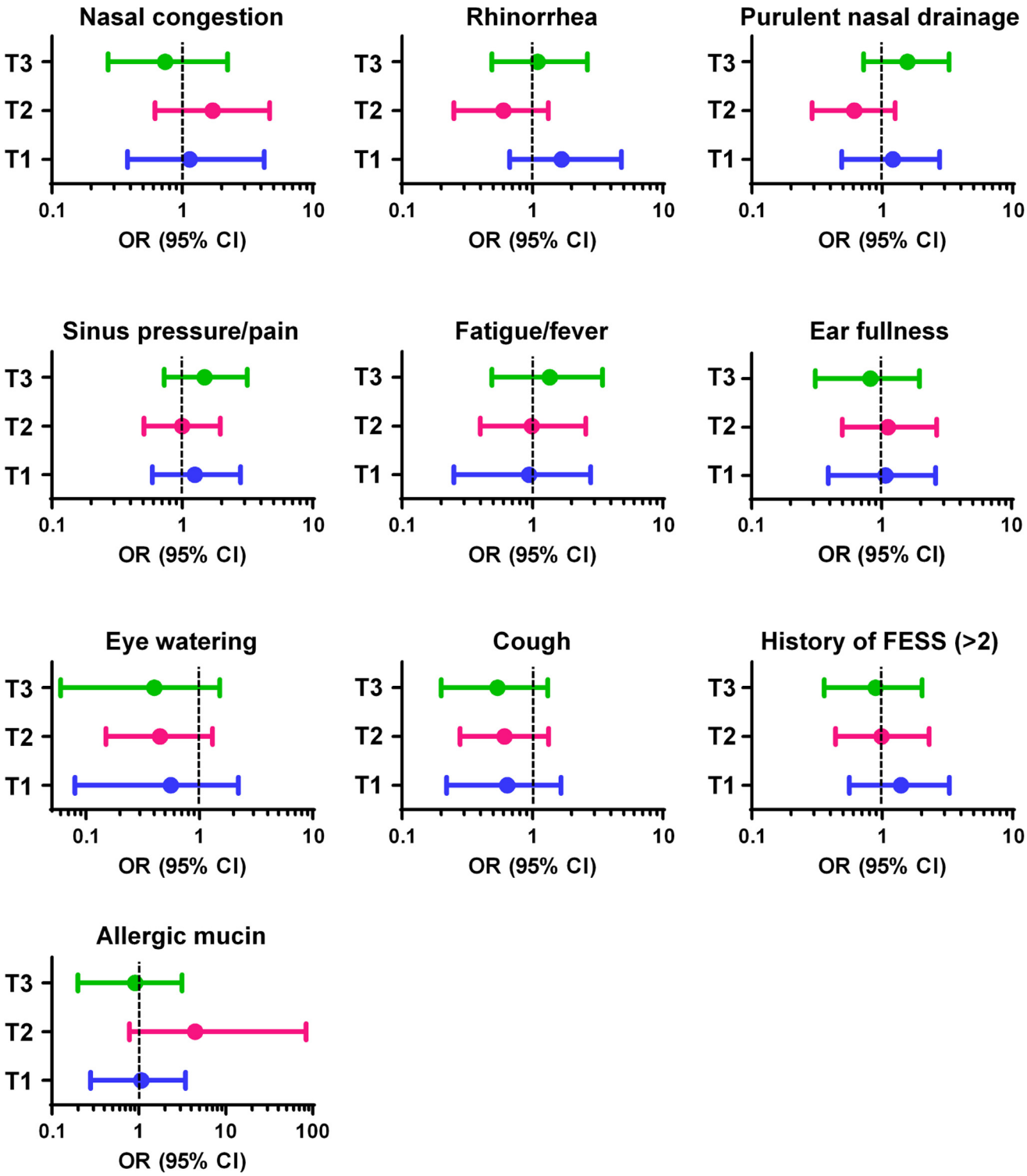

FIGURE E1. OR for clinical presentations within endotypes in all patients with CRS. Multivariate logistic regression analysis with predictor endotype controlling for age, sex, asthma, atopy, and NP and the corresponding OR, 95% CI, and *P* value for nasal congestion (n = 230), rhinorrhea (n = 230), purulent nasal drainage (n = 230), sinus pressure/pain (n = 230), fatigue/fever (n = 230), ear fullness (n = 230), eye watering (n = 230), cough (n = 230), history of FESS (n = 231), and allergic mucin (n = 217) in CRS. *FESS*, Functional endoscopic sinus surgery.

TABLE E1. Clinical characteristics of control patients

Characteristic	Control % (n = 46)
Age (y), median (range)	56 (22-75)
Sex (female)	58.7
Atopy	27.6
Current smoker	13.0

TABLE E2. Comparisons of clinical presentations and inflammatory endotypes in all patients with CRS

	T1 endotype			T2 endotype			T3 endotype		
Characteristics	Absence % (n = 207)	Presence % (n = 48)	*P* value	Absence % (n = 72)	Presence % (n = 187)	*P* value	Absence % (n = 198)	Presence % (n = 57)	*P* value
Atopy*	54.8	48.8	.480	47.9	56.3	.240	56.7	43.1	.087
Nasal congestion/obstruction/blockage	91.7	91.7	.985	87.5	93.4	.123	92.4	89.5	.482
Purulent nasal drainage	19.4	20.8	.824	25.0	17.6	.180	17.8	26.3	.153
Sinus pressure/pain	62.1	70.8	.259	66.7	62.6	.547	61.9	70.2	.254
Headache/migraine	21.4	12.5	.165	20.8	19.2	.772	20.8	15.8	.401
Fatigue/fever/feel poor	10.2	8.3	.697	12.5	8.8	.371	9.1	12.3	.483
Ear fullness/pain/popping	15.0	16.7	.779	15.3	15.4	.983	16.2	12.3	.465
Eye watering/itching	8.3	4.2	.333	12.5	5.5	.056	8.6	3.4	.187
History of FESS (>2)	21.7	22.9	.859	16.7	24.0	.200	23.2	17.5	.361

FESS, Functional endoscopic sinus surgery.
The *P* value was determined by the χ^2 test.
*Absence (n = 188) and presence (n = 43) of T1 endotype, absence (n = 71) and presence (n = 160) of T2 endotype, absence (n = 180) and presence (n = 51) of T3 endotype.

TABLE E3. Comparisons of clinical presentations and inflammatory endotypes in patients with CRSsNP

	T1 endotype			T2 endotype			T3 endotype		
Characteristics	Absence % (n = 96)	Presence % (n = 25)	*P* value	Absence % (n = 55)	Presence % (n = 66)	*P* value	Absence % (n = 88)	Presence % (n = 33)	*P* value
Atopy*	47.9	26.1	.058	48.1	40.0	.372	48.8	30.3	.068
Asthma	31.3	24.0	.480	25.5	33.3	.345	31.8	24.2	.417
Nasal congestion/obstruction/blockage	88.5	92.0	.619	85.5	92.4	.218	89.8	87.9	.765
Rhinorrhea/post−nasal drip/nasal drainage	85.4	80.0	.507	87.3	81.8	.412	84.1	84.8	.919
Purulent nasal drainage	21.9	12.0	.270	23.6	16.7	.338	18.2	24.2	.457
Sinus pressure/pain	71.9	80.0	.412	69.1	77.3	.310	72.7	75.8	.736
Fatigue/fever/feel poor	16.7	8.0	.278	12.7	16.7	.544	14.8	15.2	.958
Ear fullness/pain/popping	15.6	24.0	.325	16.4	18.2	.793	19.3	12.1	.352
Eye watering/itching	9.4	4.0	.385	10.9	6.1	.335	10.2	3.0	.200
Cough	26.0	20.0	.533	27.3	22.7	.564	27.3	18.2	.302
History of FESS (>2)	13.5	8.0	.454	12.7	12.1	.920	13.6	9.1	.499
Allergic mucin†	3.4	0.0	.349	0.0	4.9	.105	3.7	0.0	.280

FESS, Functional endoscopic sinus surgery.
The *P* value was determined by the χ^2 test.
*Absence (n = 96) and presence (n = 23) of T1 endotype, absence (n = 54) and presence (n = 65) of T2 endotype, absence (n = 86) and presence (n = 33) of T3 endotype.
†Absence (n = 88) and presence (n = 25) of T1 endotype, absence (n = 52) and presence (n = 61) of T2 endotype, absence (n = 82) and presence (n = 31) of T3 endotype.

TABLE E4. Comparisons of clinical presentations and inflammatory endotypes in patients with CRSwNP

	T1 endotype			T2 endotype			T3 endotype		
Characteristics	Absence % (n = 111)	Presence % (n = 23)	*P* value	Absence % (n = 17)	Presence % (n = 117)	*P* value	Absence % (n = 110)	Presence % (n = 24)	*P* value
Atopy*	62.0	75.0	.270	47.1	67.4	.108	63.8	66.7	.818
Asthma	40.5	60.9	.074	29.4	46.2	.194	43.6	45.8	.844
Nasal congestion/obstruction/blockage	94.5	91.3	.552	94.1	94.0	.980	94.5	91.7	.598
Rhinorrhea/post−nasal drip/nasal drainage	67.3	78.3	.299	76.5	68.1	.485	68.8	70.8	.846
Purulent nasal drainage	17.3	30.4	.351	29.4	18.1	.547	17.4	29.2	.423
Sinus pressure/pain	53.6	60.9	.526	58.8	54.3	.727	53.2	62.5	.408
Fatigue/fever/feel poor	4.5	8.7	.720	11.8	4.3	.438	4.6	8.3	.758
Ear fullness/pain/popping	14.5	8.7	.456	11.8	13.8	.819	13.8	12.5	.870
Eye watering/itching	7.3	4.3	.612	17.6	5.2	.056	7.3	4.2	.575
Cough	9.1	4.3	.453	17.6	6.9	.133	9.2	4.2	.420
History of FESS (>2)	28.8	39.1	.329	29.4	30.8	.910	30.9	29.2	.867
Allergic mucin†	10.7	17.4	.369	6.7	12.6	.505	11.5	13.6	.783

FESS, Functional endoscopic sinus surgery.
The *P* value was determined by the χ^2 test.
*Absence (n = 92) and presence (n = 20) of T1 endotype, absence (n = 17) and presence (n = 95) of T2 endotype, absence (n = 94) and presence (n = 18) of T3 endotype.
†Absence (n = 103) and presence (n = 23) of T1 endotype, absence (n = 15) and presence (n = 111) of T2 endotype, absence (n = 104) and presence (n = 22) of T3 endotype.

TABLE E5. Comparisons of clinical presentations between single or mixed and untypeable CRS endotypes in all patients with CRS

		Single or mixed endotype				
Characteristics	TunCRS % (n = 48)	T2CRS % (n = 124)	T3CRS % (n = 13)	T1/2CRS % (n = 23)	T1/3CRS % (n = 8)	T2/3CRS % (n = 22)
Atopy*	56.3	55.6	38.5	68.2	25.0	57.9
P value		.936	.255	.344	.102	.903
Nasal congestion/obstruction/blockage	87.5	94.3	92.3	95.5	87.5	86.4
P value		.131	.630	.303	1.0	.895
Rhinorrhea/post−nasal drip/nasal drainage	81.3	72.4	92.3	82.6	100.0	72.7
P value		.229	.339	.890	.181	.420
Sinus pressure/pain	66.7	59.3	61.5	69.6	87.5	68.2
P value		.377	.730	.807	.235	.90
Headache/migraine	27.1	20.3	7.7	8.7	0.0	22.7
P value		.340	.140	.076	.093	.699
Fatigue/fever/feel poor	12.5	8.9	23.1	4.3	0.0	4.5
P value		.485	.340	.281	.290	.303
Ear fullness/pain/popping	20.8	14.6	7.7	17.4	0.0	9.1
P value		.325	.274	.733	.154	.226
Cough	25.0	14.6	30.8	17.4	25.0	**4.5**
P value		.109	.675	.473	1.0	**.041**
History of FESS (>2)	16.7	24.2	15.4	30.4	12.5	22.7
P value		.286	.912	.184	.766	.545
Allergic mucin†	2.3	9.5	0.0	13.0	0.0	10.5
P value		.122	.598	.077	.667	.158

FESS, Functional endoscopic sinus surgery; *TunCRS*, untypeable CRS.
TunCRS: undetectable elevations of T1, T2, or T3 inflammation.
The *P* value was determined by the χ^2 test compared with TunCRS.
The values in bold are significantly different compared to TunCRS. The *P* values are in bold when <.05.
*TunCRS (n = 44), T2CRS (n = 108), T3CRS (n = 13), T1/2CRS (n = 22), T1/3CRS (n = 8), and T2/3CRS (n = 19).
†TunCRS (n = 44), T2CRS (n = 116), T3CRS (n = 12), T1/2CRS (n = 23), T1/3CRS (n = 8), and T2/3CRS (n = 19).