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ORIGINAL ARTICLE

Inflammatory endotype of odontogenic sinusitis

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Abstract

Background: Odontogenic sinusitis (ODS) is distinct from non-odontogenic rhinosinusitis with regard to clinical features as well as diagnostic and therapeutic approaches. While numerous studies have explored immune profiles of chronic rhinosinusitis, very few studies have explored the inflammatory endotype of ODS.

Methods: Odontogenic sinusitis was diagnosed by confirming infectious sinusitis adjacent to infectious maxillary odontogenic pathology. Maxillary sinus cultures and mucosal biopsies were obtained during endoscopic endonasal surgery in ODS and control patients. Controls were patients undergoing endoscopic skull base surgery with no sinus disease. Specimens were snap frozen in liquid nitrogen and stored at −80°C. Analysis was performed using a multiplex assay to measure Th-1 (TNFα, IFNγ, IL-2,12,18), Th-2 (IL-4,5,9,13), Th-17 (IL-17A,17F,22), and innate (CCL5,CXCL9,CXCL10, IL-6,8,10,12,23,27) immune pathways. Groups were compared via independent sample *t*-tests; if assumptions were violated, nonparametric Wilcoxon ranked sum tests were performed.

Results: Specimens from 22 ODS patients were compared to nine controls. ODS mucosal tissue was sampled in the setting of the following dental pathologies: post-dental extraction ($n = 15$), untreated apical periodontitis ($n = 2$), apical periodontitis after root canal therapy ($n = 2$), and maxillary sinus bone grafting with or without dental implantation ($n = 3$). The following cytokines were significantly elevated in ODS compared to controls: IFNγ, TNFα, IL-6, 8, 10, 27, and CXCL9. IL-17 levels were similar in both ODS and controls. Therefore, ODS demonstrated heightened innate and Th1 immune activity.

Conclusion: ODS demonstrated both innate immune and Th1 inflammatory endotypes. Further studies are needed to explore ODS immunopathobiology and its potential impact on ODS management.

KEYWORDS
odontogenic sinusitis, chronic rhinosinusitis, maxillary sinusitis, apical periodontitis, dental implant, oroantral fistula

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1 | INTRODUCTION

Odontogenic sinusitis (ODS) refers to bacterial maxillary sinusitis, with or without extension to other paranasal sinuses, secondary to either adjacent infectious maxillary dental pathology, or following complications from dental procedures.[1,2] ODS is therefore distinct from other types of primary rhinosinusitis,[3] and should be approached differently both diagnostically and therapeutically.

Odontogenic sinusitis may account for 25%−40% of all chronic maxillary sinusitis,[4,5] occurs unilaterally most commonly,[6–14] and represents 45%−75% of unilateral maxillary sinus opacification on computed tomography (CT).[6–8,15] Unfortunately, due to low publication volumes and quality,[16] ODS has been underrepresented in recent rhinosinusitis guidelines or position statements.[3,17–19] Over the last few years, ODS publication volume and evidence levels have been increasing, but these studies have largely focused on diagnosis and management. Publications on ODS pathophysiology have largely centered on dental and sinus microbiology[20–22] and histopathology,[23,24] but little has been studied with regard to ODS endotyping.

There has been increased recognition of multiple distinct and overlapping chronic rhinosinusitis (CRS) endotypes based on inflammatory cytokines identified in both CRS patients' sinus mucosa and mucus, representing Th1, Th2, Th17, and innate immune pathways.[25,26] However, previous CRS endotype studies have not discussed an ODS endotype. Only one study to date has explored the ODS endotype, but only three cytokines were assessed across nine ODS patients.[27] The purpose of this study was to describe in more detail the inflammatory endotype of ODS patients.

2 | MATERIALS AND METHODS

An analysis was conducted on consecutive ODS patients presenting to and undergoing endoscopic sinus surgery (ESS) by one fellowship-trained rhinologist (JRC) from September 2020 through February 2022. Institutional Review Board approval was obtained.

The study group was comprised of adult ODS patients diagnosed by having confirmed infectious sinusitis adjacent to confirmed infectious dental pathology.[1] Dental pathology was confirmed by endodontists or oral surgeons depending on the suspected pathology and patients' desires for different dental interventions. Endodontists assessed intact dentition for apical periodontitis (AP, endodontic infection), and oral surgeons assessed for oroantral fistula (OAF) or complications after prior maxillary sinus bone grafting (sinus augmentation) or dental implants. Some patients had ODS after dental extraction but no OAF at the time of evaluation, so those patients had ODS diagnosed in one of two ways. First, if pre-extraction cone beam CT showed maxillary sinus opacification adjacent to confirmed infectious maxillary dental pathology, that was considered ODS. Second, if there was no pre-extraction imagi , patients' maxillary sinus bacterial cultures had to demonstrate oral or odontogenic organisms. If these criteria were not met, patients were excluded.

The following demographic and clinical data were collected: age, gender, ethnicity, medical comorbidities, and ODS clinical features (sidedness, symptom duration, dental pathologies at the time of ESS, nasal endoscopy findings in the middle meatus and maxillary sinus, and sinus CT opacification patterns).

Odontogenic sinusitis patients with treatable dental pathologies were offered either primary dental treatment or ESS, and they decided which intervention to pursue. If patients elected primary dental treatment and failed, they underwent ESS. If patients elected primary ESS, they were always followed by dental specialists to ensure appropriate subsequent dental treatment. Patients who had ODS but no treatable dental pathology underwent ESS only (e.g., ODS after dental extraction and no OAF, or ODS after maxillary sinus bone graft or dental implant but no infectious dental source). Patients never received systemic antibiotics, steroids, antihistamines, or antileukotrienes within a month of ESS. Other exclusion criteria included prior ESS on the side of ODS; patients requiring allergy immunotherapy perioperatively; patients on chemotherapy or other immunomodulating therapies; concurrent non-odontogenic inflammatory, bacterial, or fungal rhinosinusitis; sinus neoplasia; primary or acquired immunodeficiency; and autoimmune disease.

The control group was comprised of patients without infectious or inflammatory sinusitis, who underwent endoscopic skull base tumor resections or cerebrospinal fluid leak repairs.

All patients in the study underwent ESS which included at least a wide maxillary antrostomy. Maxillary sinus purulent secretions were collected in a sterile fashion and sent for aerobic and anerobic bacterial cultures according to previously reported methods.[20] For cytokine and chemokine analysis, maxillary sinus mucosa was sampled in all ODS and control patients. In two control patients, some mucosa was also sampled from the lamina papyracea adjacent to the maxillary sinus to ensure adequate tissue for analysis. Sampled tissue was immediately snap frozen in liquid nitrogen then stored at −80°C. Individual 100 μg tissue samples were incubated with 2 ml of protein extraction buffer containing protease inhibitors (Thermo Fisher Scientific, Waltham, MA). Samples were then homogenized using a tissue homogenizer for 2 min

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at room temperature and then centrifuged in a microcentrifuge at 10,000 × *g* for 5 min at room temperature. Cleared supernatants were carefully removed and stored at −80°C. Supernatants were then assayed in duplicate with Milliplex MAP Human Cytokine/Chemokine Kits per manufacturer's instructions (Millipore/MilliporeSigma, Burlington, MA) using a Bio-Plex 200 System (BioRad Life Science Research, Hercules, CA). Analyte concentrations were reported in pg/ml. Clarified supernates were analyzed for the following cytokines and chemokines: TNFα, IFNγ, IL-2, IL-4, IL-5, IL6, IL-8, IL-9, IL-10, IL-12, IL-13, IL-17A, IL-17F, IL-18, IL-22, IL-27, CCL5 (RANTES), CXCL9 (MIG), and CXCL10 (IP-10). For each analyte, sample values below the concentration of the lowest standard were assigned a concentration equal to half the lowest standard. Concentrations were calculated from standard curves using vendor software (Bioplex Manager v6.2, BioRad Life Science Research). Cytokines and chemokines were then categorized into Th1 (TNFα, IFNγ, IL-2,12,18), Th2 (IL-4,5,9,13), Th17 (IL-17A,17F,22), and innate (CCL5; CXCL9; CXCL10; IL-6, 8, 10, 12, 23, 27) immune pathways according to literature standards.[26,28]

O ther sinus tissue was also collected separately during ESS in specimen collection traps and placed in formalin for routine processing. Formalin-fixed and paraffin-embedded tissue blocks were created and used to cut 5-μm thick sections, which were stained with hematoxylin and eosin. A pathologist with subspecialty expertise in head and neck pathology (CK) then generated structured histopathology reports.[29]

All statistical calculations were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC) and R Studio version 4.0.4 (R Foundation, Vienna). Groups were compared via independent samples *t*-tests and summarized as means ± standard deviations. If assumptions were violated, nonparametric Wilcoxon ranked sum tests were substituted for *t*-tests and summarized as medians and interquartile ranges. *P*-values less than 0.05 were considered statistically significant.

3 | RESULTS

When comparing the 22 ODS and nine control group patients, Table 1 shows there were no significant differences in age, gender, ethnicity, or medical comorbidities that might affect mucosal inflammatory cytokines concentrations. Table 2 shows the frequencies of clinical features in the ODS group. First, all ODS cases were unilateral with equal proportions of left- and right-sided disease, and patients universally presented with chronic symptoms (median, 6.5 months). On preoperative endoscopy all patients had purulence, 73% had edema, and 27% had polyps in the middle meatus. Intraoperatively, all patients had papillary edematous or polypoid mucosa in their maxillary sinuses (Figure 1). On CT, 77% of patients had extramaxillary sinus opacification, with 41% having frontal sinus opacification.

Regarding dental pathologies causing ODS, note that 68% of patients (15/22) had undergone dental extraction prior to ESS (median 16 months from extraction to ESS, IQR = 6, 32). Of these post-extraction patients, four had maxillary sinus opacification on CT plus confirmed maxillary molaAP prior to extraction. The other 11 patients had sinusitis symptom onset after dental extraction. Technically, the dental pathologies in these 11 post-extraction patients cannot be known with certainty because they could have had asymptomatic ODS caused by infectious dental pathologies, or ODS due to the extraction itself.

TABLE 1 Demographic data for odontogenic sinusitis (ODS) and control group patients

	ODS *n*/22 (%)	Control *n*/9 (%)	*p*-value
Age (years) (mean [SD])	59.3 (15.7)	55.3 (13.8)	0.513
Gender			
Male	11 (50.0)	6 (66.7)	0.456
Female	11 (50.0)	3 (33.3)	
Ethnicity			
White	15 (68.2)	6 (66.7)	1.000
Black	6 (27.3)	3 (33.3)	
Asian	1 (4.6)	0 (0.0)	
Comorbidities			
Allergic rhinitis			
Yes	4 (18.2)	2 (22.2)	1.000
No	18 (81.8)	7 (77.8)	
Asthma			
Yes	1 (4.55)	1 (11.1)	0.503
No	21 (95.5)	8 (88.9)	
Diabetes mellitus			
Yes	6 (27.3)	2 (22.2)	1.000
No	16 (72.7)	7 (77.8)	
Active smoker			
Yes	2 (9.1)	0 (0.0)	1.000
No	20 (90.9)	9 (100.0)	
Former smoker			
Yes	2 (9.1)	2 (22.2)	0.560
No	20 (90.9)	7 (77.8)	
Active marijuana smoker			
Yes	1 (4.6)	1 (11.1)	0.503
No	21 (95.5)	8 (88.9)	

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TABLE 2 Clinical features of odontogenic sinusitis (ODS) patients

Variables	Frequencies *n*/22 (%)
Side of ODS	
Left	11 (50.0)
Right	11 (50.0)
Symptom duration (months, median, IQR)	6.5 [5, 22]
Endoscopic findings in middle meatus	
Purulence	22 (100)
Edema	16 (72.7)
Polyps	6 (27.3)
Endoscopic findings in maxillary sinus	
Purulence	22 (100)
Papillary edema	22 (100)
Distribution of sinus opacification	
Maxillary, anterior ethmoid, frontal	9 (40.9)
Maxillary, anterior ethmoid	6 (27.2)
Maxillary only	5 (22.7)
Pan-sinus	2 (9.1)
Dental pathologies	
Post-extraction	15 (72.7)
Apical periodontitis, no dental treatment before ESS	2 (9.1)
Apical periodontitis, root canal therapy before ESS	2 (9.1)
Maxillary sinus bone grafting related	2 (9.1)
Dental implant related	1 (4.5)

Abbreviations: ESS, endoscopic sinus surgery; IQR, interquartile range.

Note that all 11 patients grew bacteria from their sinuses consistent with oral or odontogenic bacteria. Similarly, the infectious dental sources in the three patients with ODS after maxillary sinus bone grafting or dental implants could not be determined because the grafts and implants were not infected. Therefore, the ODS ensued either from previous dental disease or prior dental extraction. Again though, all three of these patients demonstrated oral or odontogenic bacteria in sinus cultures, reinforcing that these were ODS cases.

Table 3 shows comparisons of the median cytokine concentrations in ODS versus control patients, with cytokines categorized under their representative inflammatory pathways. Overall, ODS patients demonstrated both an innate immune and Th1 inflammatory endotype, with no Th2 or Th17 inflammatory markers.

Table 4 shows ODS tissue histopathology results. About 80% of ODS patients had severe chronic inflammation, with all cases having predominantly lymphoplasmacytic infiltrates. Patients also frequently demonstrated varying degrees of eosinophils and neutrophils in tissue, but these cells never predominated over lymphoplasmacytic cells (Figure 2). ODS patients never demonstrated eosinophilic aggregates and Charcot–Leyden crystals. ODS patients had basement membrane thickening and fibrosis in 86% of cases. Most ODS patients had normal respiratory epithelium, but 24% demonstrated squamous metaplasia. Lastly, no ODS patients had fungal elements identified histopathologically.

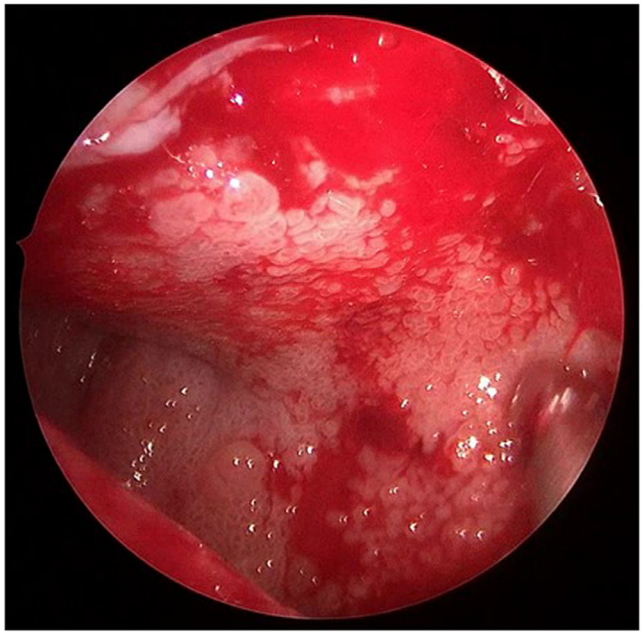

FIGURE 1 Seventy-degree endoscopic view of the right maxillary sinus, demonstrating the papillary edema of the sinus walls that was seen in every odontogenic sinusitis patient in this study

Table 5 shows maxillary sinus bacterial culture results, demonstrating high rates of anaerobic (77.3%) and oral alpha-hemolytic streptococcal species (81.8%). Of note, 20/22 (90.9%) of ODS cultures demonstrated polymicrobial bacterial growth, often growing both odontogenic and nonodontogenic organisms concurrently.

4 | DISCUSSION

Odontogenic sinusitis is distinct from rhinosinusitis, as it is infectious sinusitis secondary to a dental source, generally with no primary sinonasal inflammation. Supporting this infectious distinction, sinus purulence containing oral bacteria has been shown to be more likely in ODS than in CRS.[20–22] It is therefore possible that the inflammatory endotype of ODS could be unique from other forms of CRS. However, prior rhinosinusitis studies have often either categorized ODS as a subtype of CRS without nasal polyps

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TABLE 3 Median cytokine concentrations compared between odontogenic sinusitis (ODS) and control group patients

Immune pathways and cytokines	ODS pg/ml, median (IQR)	Controls pg/ml, median (IQR)	*p*-value
Th1			
TNFα	18.3 [12.26, 21.88]	3.2 [3.2, 3.2]	**<0.001**
IFNγ	21.5 [12.95, 27.59]	6.12 [3.14, 11.47]	**<0.001**
IL-2	0.32 [0.32, 0.32]	0.32 [0.32, 0.32]	1.000
IL-12	1.6 [1.6, 1.6]	1.6 [1.6, 1.6]	1.000
IL-18	52.45 [38.98, 80.95]	34.09 [17.19, 82.68]	0.317
Th2			
IL-4	0.32 [0.32, 0.32]	0.32 [0.32, 0.32]	1.000
IL-5	0.32 [0.32, 0.32]	0.32 [0.32, 0.32]	1.000
IL-9	4.16 [3.48, 5.54]	4.17 [2.52, 5.36]	0.725
IL-13	3.2 [3.2, 3.2]	3.2 [3.2, 3.2]	0.522
Th17			
IL-17A	9 [1.18, 15.59]	9.01 [0.64, 13.5]	0.645
IL-17F	16 [16, 16]	16 [16, 16]	0.179
IL-22	6.4 [6.4, 6.4]	6.4 [6.4, 6.4]	0.540
Innate			
IL-6	391.04 [243.35, 912.12]	6.51 [5.21, 11.62]	**<0.001**
IL-8 (CXCL8)	3499.62 [2415.11, 4499.98]	124.83 [117.5, 304.2]	**<0.001**
IL-10	28.59 [17.75, 34.71]	1.28 [1.28, 1.28]	**<0.001**
IL-12	1.6 [1.6, 1.6]	1.6 [1.6, 1.6]	1.000
IL-23	18.4 [8.4, 63.2]	54.1 [4.8, 75.6]	0.542
IL-27	1102.01 [930.73, 1534.99]	117.77 [87.33, 200.62]	**<0.001**
CCL5 (RANTES)	14794.5 [12303.7, 20850.9]	13001.3 [6247.1, 16294.6]	0.192
CXCL9 (MIG)	4350.3 [3601.0, 5433.8]	2429.5 [1986.5, 4439.1]	**0.026**
CXCL10 (IP-10)	124.2 [90.9, 156.6]	196.5 [87.9, 290.3]	0.459

Abbreviation: IQR, interquartile range.

(CRSsNP) or have not separated ODS from other CRS cases for subgroup analyses. Categorizing ODS as a CRS phenotype is problematic not only because it is inaccurate pathophysiologically, but also because ODS can present with or without nasal polyps.[6,30] Establishing an ODS inflammatory endotype should facilitate further differentiation of ODS from other forms of rhinosinusitis, which should benefit both research efforts and clinical care.

The current study showed that ODS patients largely demonstrated innate and Th1 immune responses to dental infectious sources. While perhaps intuitive that these immune pathways would be involved in this chronic purulent sinusitis phenotype, the results were actually discrepant from a prior ODS endotype study and should be considered when an prior CRS endotype studies.

Zhang et al. published the only ODS endotype study to date, by performing cytokine mRNA analysis on nine Chinese ODS patients. They assessed three cytokines and categorized cases as Th1, Th2, and Th17 immune responses based on the presence of IFNγ, IL-5, and IL-17, respectively. They did not assess for innate immunity markers. ODS patients only demonstrated a Th17 endotype with elevated IL-17 and with no elevations in IFNγ or IL-5. They also demonstrated predominantly lymphocytes and plasma cells, with minimal to no neutrophils or eosinophils.[27] These results were discrepant from the current study which showed elevations in IFNγ, but not IL-17. Additionally, while the current study also showed predominantly lymphoplasmacytic inflammation in ODS, neutrophils and eosinophils were also identified to varying degrees. One explanation for the difference in immune profiles between studies could be regional and ethnic differences in ODS populations. For example, CRS patients of Asian descent have demonstrated higher IL-17 levels[31] and less eosinophilic inflammation.[32] Note there was only one Asian ODS patient in the current study. Future research is necessary to explain the differences between these two studies. Specifically, studies could explore mechanisms behind the eosinophilic inflammation seen in some ODS patients[23] and how ethnicity affects immune profiles.

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TABLE 4 Structured histopathology results from odontogenic sinusitis (ODS) patients

Variables in ODS patients ($n = 21$)	Frequencies $n/21$ (%)
Degree of inflammation	
Severe	17 (81.0)
Moderate	4 (19.0)
Mild	0 (0.0)
Predominant inflammatory cell[a]	
Lymphocytic	10 (47.6)
Lymphoplasmacytic	8 (38.1)
Plasma cell	3 (14.3)
Eosinophil	0 (0.0)
Neutrophil	0 (0.0)
Number eosinophils per HPF	
>10	12 (57.1)
5–10	3 (9.5)
<5	7 (33.3)
Neutrophil infiltrate	
>10	7 (33.3)
5–10	13 (61.9)
<5	1 (4.8)
Basement membrane thickening	
Present	18 (85.7)
Absent	3 (14.3)
Fibrosis	
Present	18 (85.7)
Absent	3 (14.3)
Squamous metaplasia	
Present	5 (23.8)
Absent	16 (76.2)
Mucosal ulceration	0 (0.0)
Eosinophil aggregates	0 (0.0)
Charcot–Leyden crystals	0 (0.0)
Fungal elements	0 (0.0)

Note: One patient did not have histopathology recorded; hence the 21-patient sample.

[a]The predominant inflammatory cell refers to the cell type seen in greatest frequency in the high-powered field (HPF). Therefore, while eosinophils and neutrophils were often present in tissue to varying degrees, they never predominated over lymphoplasmacytic cells.

Considering that the Th17 pathway is important in fighting bacterial infection,[33] and that IL-17A has been shown to be elevated in purulent CRSsNP and CRS with nasal polyps (CRSwNP),[34] it was surprising to see no IL-17A or IL-17F elevations in the current study. IL-17 promotes neutrophil-dominant inflammation by stimulating neutrophil recruitment and promoting antimicrobial protein synthesis.[34,35] However, IL-17 has also been shown to recruit neutrophils through IL-8 chemokine (CXCL8) release.[36] In the current study, not only was IL-8 elevated in ODS, multiple other proneutrophilic cytokines were elevated as well, suggesting that other inflammatory cascades were at play.

The prominent Th1 signature in ODS patients in this study was also interesting to see in concert with an elevated innate immune response. This was presumably due to the chronicity of both the dental and sinus infections, with patients having an average 6.5 months of sinusitis symptoms. One potential, but speculative, explanation for the combined Th1 and innate immune profile could be that ongoing dental, oral, and sinus luminal infections are continuously being attacked by the mucosal innate immune system, while the adaptive Th1 pathway is stimulated and maintained chronically. Future studies could explore how the immune rechanges over time in ODS from acute to chronic stages.

Some interesting correlations can also be drawn from the dental literature. A significant body of literature exists for the immune profiling of AP with periapical lesions. AP is one of the most common causes of ODS, stemming from endodontic infection of the pulp chamber that spreads into the periapical tissues.[37] Interestingly, AP studies have demonstrated a nearly identical innate immune and Th1 response to endodontic infection as was shown in the current ODS study, with a similar presence of lymphocytes, macrophages, and neutrophils in periapical tissues.[38] Note that while some ODS patients in this study had untreated AP, the majority of patients had dental extractions prior to ESS, so the mucosal environment was potentially different from AP alone. Regardless, there is now evidence that the sinus mucosal immune response in ODS mirrors that of the periapical tissue immune response AP, suggesting common immune pathways between ODS and odontogenic infections.

With regard to CRS endotypes, multiple large studies from China, Europe, and the United States have shown CRS populations to harbor distinct inflammatory clusters, with isolated or overlapping Th1, Th2, and Th17 inflammatory profiles.[34,39–41] However, of these studies, only the study by Turner et al. excluded ODS patients from analyses.[41] By potentially including ODS patients in these studies, some of the inflammatory endotypes of both CRSsNP and CRSwNP phenotypes could have been skewed toward an ODS endotype. Future CRS endotype studies should separate out or exclude ODS patients from their study populations to avoid potential confounding effects.

One of the main limitations of the current study was the small sample size, similar to prior ODS histopathology and endotype studies. A second important limitation was the lack of assessment for fungi on either culture or next-generation sequencing. While fungal elements were

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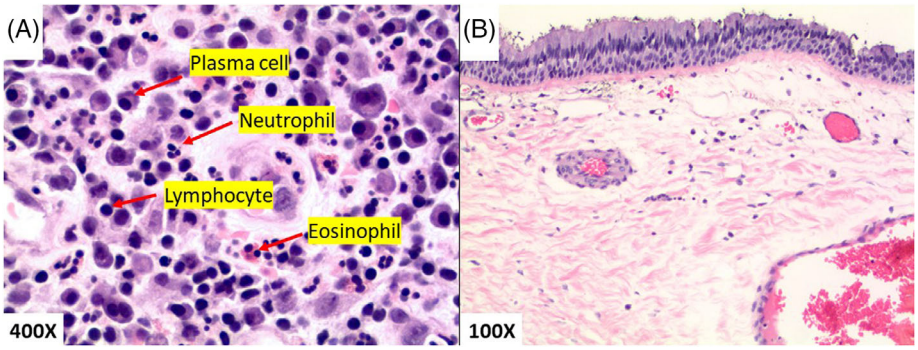

FIGURE 2 Representative examples of histopathologic views demonstrating (A) odontogenic sinusitis with significant numbers of inflammatory cells in the stroma (400X) and (B) a control patient with no significant stromal inflammatory cell infiltrate (100X). Lymphocytes or plasma cells always predominated in odontogenic sinusitis, but eosinophils and neutrophils were also often identified in varying amounts (cell types labeled)

TABLE 5 Groups and individual bacteria cultured from maxillary sinuses purulence in odontogenic sinusitis (ODS) patients

Bacteria	ODS *n*/22 (%)
Anaerobes (obligate)	17 (77.3)
Mixed anaerobes	4 (18.2)
Fusobacterium nucleatum	4 (18.2)
Prevotella spp.	3 (13.6)
Gram-negative bacilli, nonspeciated	3 (13.6)
Micromonas micros (formerly *Peptostreptococcus micros*)	2 (9.1)
Finegoldia magna (formerly *Peptostreptococcus magnus*)	1 (4.6)
Bacteroides fragilis	1 (4.6)
Parvimonas micra	1 (4.6)
Cutibacterium acnes (formerly *Propionibacterium acnes*)	1 (4.6)
Aerobes (grampositive)	
Alpha-hemolytic streptococci	18 (81.8)
Streptococcus intermedius	5 (22.7)
Streptococcus anginosus	3 (13.6)
Streptococcus constellatus	8 (36.4)
Streptococcus sanguinis	1 (4.6)
Alpha-hemolytic streptococcus	1 (4.6)
Staphylococcus aureus	2 (9.1)
Coagulase-negative staphylococcus	9 (40.9)
Corynebacterium spp.	4 (18.2)
Staphylococcus epidermidis	3 (13.6)
Aerobes (gram-negative)	
Moraxella nonliquiefans	1 (4.6)
Klebsiella aerogenes (formerly *Enterobacter aerogenes*)	1 (4.6)

Note: 20/22 (90.9%) of ODS cultures demonstrated polymicrobial bacterial growth, often growing both odontogenic and nonodontogenic organisms concurrently.

not identified on histopathology, it is still possible that fungal species contributed to the sinus microbiome and mucosal immune response. Future studies are necessary to understand the role of fungi in ODS and their effects on the inflammatory endotype. Another limitation common to other endotype studies is that only a limited number of cytokines could be studied at once. Many other inflammatory mediators that could be important were not assessed. Future studies can build on this study by casting a wider net of inflammatory markers. However, this study provides preliminary data demonstrating the inflammatory endotype of ODS, one that should help build a stronger pathophysiologic understanding of ODS.

5 | CONCLUSION

In this preliminary study, ODS demonstrated both innate immune and Th1 inflammatory endotypes. Further in-depth studies are needed to explore ODS immunopathobiology and its potential impact on ODS management.

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