• Clinical Research •

Contiguous orbital inflammation from paranasal sinus abnormalities in etiology of thyroid-associated ophthalmopathy

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Abstract

● **AIM:** To define the prevalence and anatomical patterns of paranasal sinus abnormalities (PSA) in thyroid-associated ophthalmopathy (TAO) and to test the hypothesis that TAO is partially driven by contiguous orbital inflammation rather than systemic autoimmunity or generalized orbital pressure.

● **METHODS:** Data included ophthalmic assessments and a panel of thyroid function and autoimmune biomarkers. Blinded radiological analysis of orbital computed tomography (CT) scans was performed to quantify sinus abnormalities and extraocular muscles (EOMs) involvement. Patients were categorized into two groups based on CT findings, those with no radiological evidence of sinus abnormalities (non-PSA control group) and those with identifiable PSA. Furthermore, ethmoid sinus mucosal biopsies from a subset of TAO patients and non-inflammatory controls were subjected to histopathological analysis.

● **RESULTS:** Totally 121 TAO patients (mean age 42.4±12.8y, range 10-78y), male:female=42:79, were included. PSA was identified in 44.6% (*n*=54) of patients, with a distribution anatomically restricted to the maxillary (50.0% isolated) and ethmoid sinuses (18.5% isolated; 29.6% combined). Compared to the non-PSA group (*n*=67), patients with PSA were significantly older (45.1±11.8 *vs* 40.3±13.2y; *P*=0.040) and were more likely to be male (55.6% *vs* 17.9%; *P*<0.001). They also had significantly higher proptosis (22.1±3.2 *vs* 20.7±2.9 mm; *P*<0.001). Medial/inferior rectus involvement was most frequent (88.4% *vs* 89.3%). Histopathological analysis of sinus mucosa from PSA patients provided direct evidence of pathology, revealing a dense, chronic lymphoplasmacytic infiltrate and submucosal edema, validating the radiological findings as a true inflammatory process. No significant correlation was found with systemic autoimmune markers, including thyroid-stimulating hormone (TSH) receptor antibodies (TRAb, median 4.86 *vs* 2.71 IU/L, *P*=0.104).

● **CONCLUSION:** TAO is associated with a high prevalence of PSA in a pattern consistent with the orbital anatomy. The correlation with ipsilateral muscle thickening combined with the lack of association with proptosis laterality or systemic biomarkers lend strong support to a model of contiguous inflammation over systemic autoimmunity, a hypothesis that warrants further validation through longitudinal and mechanistic studies.

● **KEYWORDS:** thyroid-associated ophthalmopathy; paranasal sinus abnormalities; proptosis; orbital inflammation

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INTRODUCTION

Thyroid-associated ophthalmopathy (TAO), also known as Graves' ophthalmopathy, is an organ-specific autoimmune inflammatory disorder characterized by orbital soft tissue involvement, eyelid retraction, proptosis, and in severe cases, compressive optic neuropathy[1-4]. While the pathogenesis of TAO is complex and not fully elucidated, it is widely accepted that orbital fibroblasts are the primary target cells in this condition[5]. In response to autoantibodies against the thyroid-stimulating hormone receptor (TSHR) and signaling from activated T-cells and B-cells, these cells differentiate into myofibroblasts and adipocytes, leading to the overproduction of hydrophilic glycosaminoglycans, predominantly hyaluronan, and promotes de novo adipogenesis and resulting in extraocular muscle (EOM) enlargement and orbital fat expansion[6-8]. While classically defined as an organ-specific disease confined to the orbit, this paradigm fails to account for emerging clinical evidence suggesting a frequent co-occurrence of disease in the adjacent paranasal sinuses.

The anatomical interface between the orbit and the paranasal sinuses provides a plausible conduit for pathological processes, particularly where the ethmoid and maxillary sinuses are separated from orbital contents by bone as thin as 0.5 mm[9-10]. Despite this clear anatomical linkage, systematic investigation has been absent, leaving the evidence base fragmentary and reliant on case reports[11]. The most direct, albeit dated, evidence comes from a case series by Kremer *et al*[12], which documented infiltration of periorbital sinuses in two patients with dysthyroid orbitopathy. More recently, Abazari *et al*[13] described three patients whose stable TAO acutely worsened following sinus inflammation, suggesting a potential for bidirectional inflammatory crosstalk[14]. However, these reports lack the systematic cohort data needed to establish prevalence, define anatomical patterns, or test mechanistic hypotheses. The fundamental gap in understanding has led to several competing, non-exclusive theories, one posits a mechanical etiology *via* obstruction of sinus ostia, while another suggests a contiguous inflammatory process, where mediators diffuse across the thin bony partitions or traffic through shared vascular networks[15-17]. Disentangling these possibilities is important but has remained an unresolved question in the field. Therefore, the present study was designed to systematically address this critical knowledge gap. Our primary aim was to define the prevalence and precise anatomical patterns of paranasal sinus abnormalities (PSA) in a large, consecutive cohort of TAO patients. We sought to test the central hypothesis that sinus involvement is driven by contiguous orbital inflammation rather than being a secondary consequence of systemic autoimmunity or generalized orbital pressure by integrating detailed radiological analysis of both orbital and sinonasal structures with comprehensive clinical and serological data to deconstruct the relationship between these interconnected anatomical sites.

PARTICIPANTS AND METHODS

Ethical Approval The study protocol was approved by the Ethics Committee of Beijing Tongren Hospital, Capital Medical University [approval number: TRECKY2018-056-GZ (2022)-07], and written informed consent was obtained from all participants. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Study Design and Participants The cross-sectional observational study was conducted at the Beijing Tongren Hospital between November 2021 and September 2022. We enrolled 121 consecutive TAO patients. The diagnosis of TAO was established based on consensus criteria, requiring the presence of characteristic orbital signs, proptosis, eyelid retraction, and restrictive extraocular myopathy, in confirmed thyroid dysfunction or a positive thyroid autoantibody status. Exclusion criteria for all participants included any known history of chronic sinus disease, prior orbital or sinus surgery, or significant facial trauma. Patients were then categorized into two groups based on computed tomography (CT) findings, those with no radiological evidence of sinus abnormalities (non-PSA control group, n=67) and those with identifiable PSA (n=54).

Clinical and Ophthalmologic Evaluation All participants underwent a standardized ophthalmologic evaluation, including assessment of best-corrected visual acuity, measurement of intraocular pressure, and slit-lamp biomicroscopy. Proptosis was quantified for each eye using a Hertel exophthalmometer. EOM involvement was evaluated through a two-step process. A clinical assessment of ocular motility deficits was performed first. Subsequently, the presence and anatomical pattern of EOM enlargement were definitively confirmed and characterized by orbital CT analysis, which identified specific involvement of the medial, lateral, superior, or inferior rectus muscles.

Computed Tomography Image Acquisition and Analysis All participants underwent high-resolution, non-contrast CT of the orbits and paranasal sinuses using a standardized institutional protocol on a 256-slice scanner (Revolution,

GE Healthcare). Axial and coronal plane images were acquired with a layer thickness of 0.625 mm. Datasets were reconstructed using both standard soft-tissue and high-resolution bone algorithms for optimal visualization of all relevant structures. All CT datasets were independently analyzed in a randomized order by two board-certified radiologists. The reviewers were blinded to all clinical information and participant group allocation. Any discrepancies in interpretation were resolved by a consensus review.

The paranasal sinuses were systematically evaluated for the presence and nature of pathological findings. Sinus abnormalities were documented based on their anatomical location (maxillary, ethmoid, frontal, sphenoid) and classified according to specific features, including mucosal thickening (>3 mm), partial or complete opacification, the presence of air-fluid levels, or evidence of bony remodeling or erosion. For morphometric analysis of EOMs, measurements were performed on the coronal reconstructions. The maximum diameter of each rectus muscle (medial, lateral, superior, and inferior) was measured perpendicular to its longitudinal axis. Pathological muscle enlargement was defined as a maximum diameter exceeding 4.5 mm, a threshold based on established normative data for defining myopathic changes in TAO.

Histopathological Analysis of Ethmoid Sinus Mucosa To obtain direct evidence of mucosal inflammation, we prospectively collected ethmoid sinus mucosal biopsies from a representative subset of 5 TAO patients undergoing endoscopic orbital apex decompression. Control sinonasal mucosal samples were obtained from patients undergoing endoscopic dacryocystorhinostomy for primary acquired nasolacrimal duct obstruction. The cohort was chosen because nasolacrimal duct obstruction is a localized, predominantly non-inflammatory fibrotic process. Biopsies were taken from the lateral nasal wall, anatomically distinct from the posterior ethmoid and maxillary sinus mucosa in the TAO cohort, minimizing potential confounding from locoregional inflammation. Tissue samples were immediately fixed in 10% neutral-buffered formalin for 24h, followed by standard processing through graded ethanol dehydration and xylene clearing, and were then embedded in paraffin wax. Serial 4-μm thick sections were cut using a microtome. For morphological assessment, sections were deparaffinized, rehydrated, and stained with hematoxylin to visualize cell nuclei and counterstained with eosin to visualize cytoplasm and extracellular matrix. The stained slides were independently evaluated by two board-certified pathologists blinded to the patient's diagnosis. The analysis focused on identifying key features of inflammation, including epithelial integrity, submucosal edema, the density and composition of the inflammatory cell infiltrate (distinguishing between lymphocytes, plasma cells, eosinophils, and neutrophils), and evidence of mucosal remodeling such as goblet cell hyperplasia and glandular changes.

Serological and Autoimmune Marker Analysis Venous blood samples were obtained from all participants at the time of their initial clinical assessment. Serum was isolated by centrifugation (at 1500×g for 10min at 4°C) and stored at -80°C until analysis. A panel of biomarkers was quantified to assess thyroid pathology. Thyroid functional status was evaluated by measuring serum levels of thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), total triiodothyronine (TT3), and total thyroxine (TT4). The associated autoimmune response was characterized by quantifying serum concentrations of TSH receptor antibodies (TRAb), thyroglobulin antibodies (TgAb), and thyroid peroxidase antibodies [TPOAb/thyroglobulin microsomal antibodies (TMA)], following the manufacturer's validated protocols.

The serum concentration of FT3, FT4, T3, T4, and TSH was analyzed using an ADVIA Centaur XP Immunoassay (Siemens Diagnostics, Germany). The levels of thyroperoxidase antibody (TPOAb/TMA), anti-TgAb, and TRAb were assayed by electrochemiluminescence immunoassay using Cobas e601 (Roche Diagnostics, Germany). The established reference intervals (normal ranges) were, TSH 0.4-6 mIU/L, FT3 3-6.5 pmol/L, FT4 7.5-15 pmol/L, TT3 1.33-2.64 nmol/L, TT4 75-150 nmol/L, TRAb 0-1.75 IU/L, TgAb 0-4 IU/L, and TMA 0-9 IU/L.

Statistical Analysis Statistical analysis was performed using SPSS version 26.0. Normally distributed data are presented as mean±standard deviation and were compared using the independent samples *t*-test. Variables that were not normally distributed were compared between groups using the Mann-Whitney *U* test and are presented as median and interquartile range (IQR). Categorical variables were analyzed using the Chi-squared test or Fisher's exact test, as appropriate. A *P*-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Correlations between variables were assessed using Pearson's or Spearman's correlation coefficient as appropriate. A $P<0.05$ was considered statistically significant.

RESULTS

Demographic and Clinical Characteristics The study enrolled 121 consecutive patients with the diagnosis of TAO, 54 with PSA and 67 without PSA. The demographic and clinical characteristics of this cohort are detailed in Table 1. The mean age was 42.4±12.8y, with a significant female predominance (65.3%; *n*=79). Compared to the non-PSA group, patients with PSA were significantly older (45.1±11.8 *vs* 40.3±13.2y; *P*=0.040) and were more likely to

Table 1 Demographic and clinical characteristics

Characteristics	Total (*n*=121)	Absence of sinus abnormalities (*n*=67)	Presence of sinus abnormalities (*n*=54)	*P*
Age (y), mean±SD	42.4±12.8	40.3±13.2	45.1±11.8	0.040
Sex, *n* (%)				<0.001
Female	79 (65.3)	55 (82.1)	24 (44.4)	
Male	42 (34.7)	12 (17.9)	30 (55.6)	
Proptosis measurement (mm), mean±SD				
Right	21.2±3.1	20.6±3.0	22.1±3.2	0.003
Left	21.2±3.0	20.6±3.0	22.1±3.0	0.002

be male (55.6% *vs* 17.9%; *P*<0.001). The clinical phenotype was characteristic of moderate-to-severe TAO, with substantial mean proptosis of 21.2 mm in both eyes. The pattern of EOM involvement was consistent with the established hierarchy in TAO, with the inferior rectus (89.3%) and medial rectus (88.4%) being the most frequently affected.

Ocular Manifestations Clinical examination revealed bilateral disease in all 121 patients. Proptosis was substantial and highly symmetric between eyes, with a mean measurement of 21.2±3.1 mm for the right eye and 21.2±3.0 mm for the left. EOM involvement was extensive and followed the characteristic distribution for TAO, the inferior rectus (*n*=108, 89.3%) and medial rectus (*n*=107, 88.4%) were the most frequently affected, followed by the superior rectus (*n*=88, 72.7%). The lateral rectus was rarely involved (*n*=7, 5.8%). The high burden of myopathy in this cohort was further evidenced by the fact that a vast majority of patients (*n*=101, 83.5%) demonstrated involvement of three or more EOMs (Figure 1).

Prevalence and Anatomical Distribution of Paranasal Sinus Abnormalities The prevalence of PSA was 44.6% (54/121). The anatomical distribution of these abnormalities within the affected TAO patients was highly localized to sinuses contiguous with the orbit. Among the 54 patients with sinus disease, pathology was observed in the maxillary sinus alone (*n*=27, 50.0%), the ethmoid sinus alone (*n*=10, 18.5%), or a combination of both (*n*=16, 29.6%). Pathological changes were not observed in the frontal or sphenoid sinuses. To further test the hypothesis that sinus disease is related to generalized orbital pressure, we assessed the relationship between disease laterality and proptosis in the 107 patients with asymmetric exophthalmos. A McNemar's test revealed no significant association between the side of greater proptosis and the presence of ipsilateral sinus abnormalities (*P*=1.0). The lack of association was reflected in the distribution of discordant pairs, with an equal number of cases where sinus abnormalities occurred exclusively on the more proptotic side (*n*=12) as on the less proptotic side (*n*=12).

Histopathological Findings Confirm Mucosal Inflammation in TAO-Associated Sinus Abnormalities To validate that the radiological findings corresponded to true tissue-level inflammation, we performed histopathological

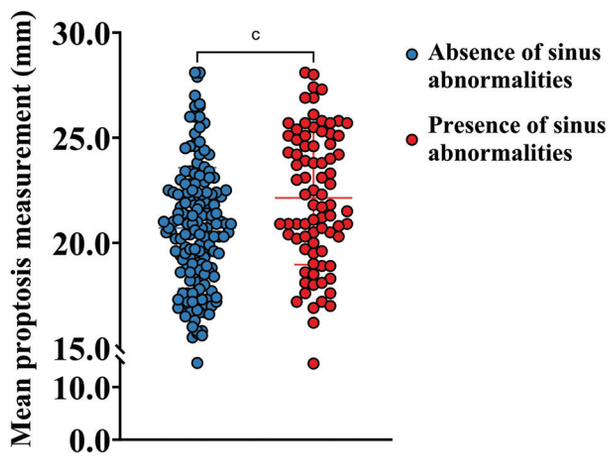

Figure 1 Increased proptosis is associated with the presence of paranasal sinus abnormalities A scatter plot comparing the distribution of mean proptosis measurements in patients with thyroid-associated ophthalmopathy, stratified by the absence (blue dots) or presence (red dots) of paranasal sinus abnormalities. Each dot represents the measurement from an individual patient. The central horizontal lines indicate the mean value for each cohort. [c]*P*<0.001.

analysis on ethmoid sinus mucosa. In control subjects, the mucosa displayed a normal architecture, characterized by a pseudostratified ciliated columnar epithelium overlying a quiescent submucosa with minimal resident immune cells. In contrast, all samples from TAO patients exhibited marked pathological changes consistent with a chronic inflammatory process (Figure 2). The most prominent features included significant submucosal edema and a dense, mixed inflammatory infiltrate. The infiltrate was predominantly composed of lymphocytes and plasma cells, with scattered eosinophils also noted, a composition suggestive of an immune-mediated, non-infectious inflammation. Furthermore, we observed significant epithelial remodeling, including pronounced goblet cell hyperplasia and luminal accumulation of mucus, which directly corroborates the mucosal thickening and opacification seen on CT scans. These findings provide definitive histological evidence that PSA in TAO patients are characterized by an active, chronic inflammatory state.

Association Between Extraocular Muscle Thickening and Ipsilateral Sinus Abnormalities A primary analysis revealed a significant anatomical correlation between EOM thickening

Table 2 Sinus abnormalities and EOM involvement in TAO patients *n* (%)

EOM enlargement	Total (*n*=121)	Absence of sinus abnormalities (*n*=67)	Presence of sinus abnormalities (*n*=54)	*P*
No	36 (29.8)	3 (4.5)	33 (61.1)	<0.001
Yes	85 (70.2)	64 (95.5)	21 (38.9)	

EOM: Extraocular muscle; TAO: Thyroid-associated ophthalmopathy.

Table 3 Thyroid biomarker profile of TAO patients stratified by the presence of paranasal sinus abnormalities

Variables	Total (*n*=54)	Absence of sinus abnormalities (*n*=27)	Presence of sinus abnormalities (*n*=27)	Statistic *Z*	*P*
TRAb, IU/L	4.12 (1.96, 9.04)	2.71 (1.56, 7.08)	4.86 (2.38, 9.71)	-1.63	0.104
TT3, nmol/L	1.59 (1.38, 1.90)	1.47 (1.34, 1.75)	1.70 (1.44, 1.97)	-1.81	0.071
TT4, nmol/L	122.95 (108.70, 141.57)	116.50 (103.75, 138.05)	130.90 (114.05, 145.20)	-1.57	0.115
FT3, pmol/L	5.25 (4.70, 5.90)	5.10 (4.65, 5.55)	5.50 (4.95, 6.18)	-1.92	0.055
FT4, pmol/L	11.70 (10.60, 13.38)	11.30 (10.62, 12.80)	11.90 (10.55, 14.15)	-1.13	0.257
TSH, mIU/L	1.68 (0.66, 2.72)	1.55 (0.79, 2.76)	1.74 (0.67, 2.53)	-0.64	0.525
TgAb, IU/mL	0.40 (0.10, 13.93)	0.60 (0.10, 24.00)	0.40 (0.10, 2.85)	-0.54	0.589
TMA, IU/mL	12.10 (1.33, 55.93)	17.40 (2.60, 62.50)	3.40 (0.95, 25.20)	-1.29	0.197

Data is presented as median (interquartile range). *P*-values were calculated using the Mann-Whitney *U* test. TSH: Thyroid-stimulating hormone; TRAb: TSH receptor antibodies; FT3: Free triiodothyronine; FT4: Free thyroxine; TT3: Total triiodothyronine; TgAb: Thyroglobulin antibodies; TMA: Thyroglobulin microsomal antibody; TAO: Thyroid-associated ophthalmopathy.

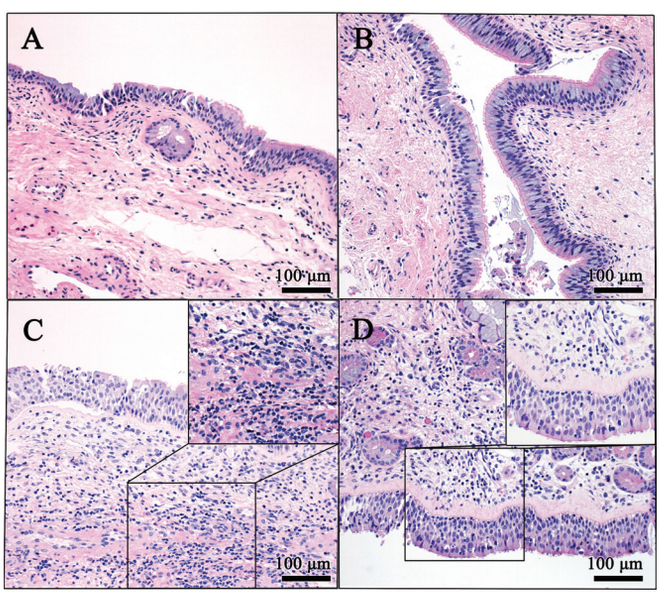

Figure 2 Histopathological comparison of ethmoid sinus mucosa from a control subject and a patient with TAO A, B: Representative sections of normal ethmoid sinus mucosa from a control subject; C, D: Sections from TAO patient with paranasal sinus abnormalities show evidence of significant inflammatory changes. Scale bar=100 μm. TAO: Thyroid-associated ophthalmopathy.

and ipsilateral sinus pathology (P<0.001; Table 2). Among the cohort of patients with documented sinus abnormalities, 38.9% (21 of 54) exhibited concurrent thickening of an adjacent EOM on the same side. Furthermore, the presence of sinus abnormalities was associated with more severe proptosis. Patients with sinus abnormalities had a mean Hertel exophthalmometry value of 22.1±3.2 mm, which was significantly greater than the mean of 20.7±2.9 mm recorded in patients without sinus abnormalities (P<0.001; Figure 3).

Association Between Thyroid Function and Sinus Abnormalities To determine if systemic thyroid status correlated with sinus pathology, we analyzed thyroid function parameters in the 54 patients for whom these data were available (Table 3). The primary analysis revealed no statistically significant differences in the mean serum concentrations of TT4, FT4, TSH, TgAb, or TMA between patients with and without sinus abnormalities. However, a trend was observed for triiodothyronine levels. Patients with documented sinus abnormalities exhibited higher mean concentrations of TT3 and FT3 compared to those without. However, these differences did not reach the pre-specified threshold for statistical significance (P=0.071, 0.055, respectively).

DISCUSSION

Our study establishes a significant association between TAO and the presence of PSA. The prevalence of PSA in the TAO cohort was nearly double that of higher than in the age- and sex-matched control group. The interpretation of our finding, however, requires an analysis of the specific patterns of association, which collectively point toward a shared, localized inflammatory mechanism rather than a systemic effect or a simple mechanical consequence of generalized orbital pressure[18-19]. The predilection for maxillary and ethmoid sinus involvement is noteworthy and provides the first line of evidence for our hypothesis. These sinuses are separated from the orbit by the thinnest bony partitions, the ethmoid sinuses by the lamina papyracea adjacent to the medial rectus, and the maxillary sinus by the orbital floor, underlying the inferior rectus[9]. The anatomical proximity creates a potential conduit for the bidirectional transmission of inflammatory mediators[20], explaining why these two sinuses are predominantly affected

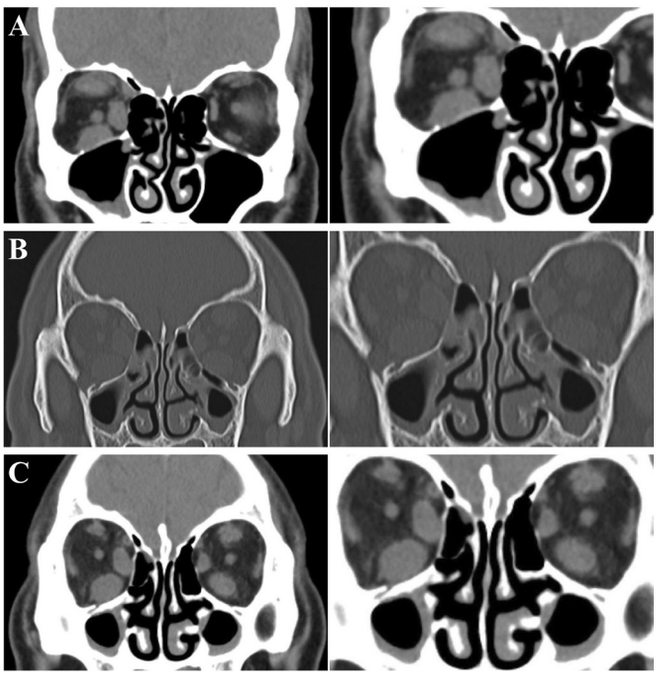

Figure 3 Representative coronal CT images demonstrating EOM enlargement and concurrent paranasal sinus abnormalities in patients with thyroid-associated orbitopathy (higher magnifications are shown on the right) A: Coronal bone window CT image shows unilateral enlargement of the superior, medial, and inferior rectus muscles, accompanied by soft-tissue opacification in the ipsilateral maxillary sinus; B: Coronal soft-tissue window CT image reveals bilateral rectus muscle enlargement, with soft-tissue opacification in the ethmoid and maxillary sinuses; C: Coronal bone window CT image demonstrates bilateral rectus muscle enlargement alongside soft-tissue opacification in the ethmoid and maxillary sinuses. CT: Computed tomography; EOM: Extraocular muscle.

while the more distant frontal and sphenoid sinuses are spared. The evidence supporting a direct pathophysiological link is the observed correlation between EOM involvement and ipsilateral sinus abnormalities. The association suggests two non-exclusive possibilities. Enlarged EOMs, particularly the medial and inferior recti, may mechanically compromise the drainage ostia of the adjacent ethmoid and maxillary sinuses, leading to secondary inflammation. We postulate that orbital fibroblasts, the primary effector cells in TAO, play a central role in this process. Activated orbital fibroblasts (OFs) are potent sources of pro-inflammatory cytokines [*e.g.*, interleukin (IL)-6, IL-8, tumor necrosis factor (TNF)-α] and chemokines [*e.g.*, C-C motif chemokine ligand 2 (CCL2)][21-22], which are known to recruit and activate immune cells. A high local concentration gradient of these mediators could readily traverse the thin bony lamina to incite an inflammatory response in the adjacent sinus mucosa[11,23]. Furthermore, this strong anatomical linkage invites speculation on a shared antigenic landscape or molecular mimicry between orbital and sinonasal tissues, which could render the sinus mucosa susceptible to the same autoimmune insult.

Our analysis revealed that patients with PSA exhibited a lower incidence of EOM enlargement compared to the non-PSA group, while simultaneously presenting with more severe proptosis. We propose this observation refines our central hypothesis by pointing to the established pathophysiological heterogeneity of TAO. TAO is understood to manifest along a spectrum of phenotypes, including predominantly myopathic and predominantly adipogenic forms. Proptosis itself is a composite measure of increased orbital volume and can be driven by either mechanism. Our findings suggest the cohort of patients who developed PSA may be enriched with individuals whose disease is primarily driven by the adipogenic phenotype. In these individuals, inflammation, edema, and adipogenesis within the orbital fat compartment would be the principal cause of severe proptosis and orbital pressure. Because the orbital fat possesses an extensive anatomical interface with the thin bony partitions of the sinuses, such as the lamina papyracea, a highly active, fat-predominant inflammatory process provides a direct and sufficient pathway for inflammatory mediators to affect the contiguous sinus mucosa. The interpretation reconciles the data by suggesting the key driver for PSA is the overall magnitude of locoregional orbital inflammation, with the adipose tissue compartment acting as a significant source of that inflammation. The model is further supported by our finding that there was no association between the side of greater proptosis and the side of sinus disease in asymmetric cases, which argues against the hypothesis that generalized orbital pressure is the primary driver and reinforces the concept that sinus pathology co-localizes with a specific inflammatory source.

Synthesizing our findings points toward a model for sinonasal involvement in TAO that must balance strong locoregional evidence with subtle systemic influences. The tight anatomical correlation between EOM enlargement and ipsilateral sinus disease suggests a core hypothesis of contiguous inflammation, whereby orbital inflammation may extend into or lower the threshold for inflammation in the adjacent sinus mucosa. The locoregional picture, however, must also account for a more complex pattern, a dissociation from the canonical autoimmune marker TRAb, yet a trend toward higher TT3 and FT3 levels, which reflect metabolic state. The sub-analysis may lack sufficient statistical power to detect subtle differences, which is particularly relevant for the observed trends in TT3 and FT3 levels. To reconcile these observations, we propose an expansion of the concept into a speculative two-hit conceptual framework. In this framework, anatomical contiguity and a high orbital inflammatory burden serve as the first hit, while a permissive systemic environment, such

as a hyperthyroid metabolic state, may act as the second hit to amplify or sustain the process. Because the framework arises from cross-sectional observations, it cannot itself confirm the directionality of inflammation, nor can it exclude contributions from other potential factors like a shared vascular supply or a common genetic predisposition. Its primary value, therefore, is to generate testable hypotheses for future longitudinal and mechanistic studies to clarify the crosstalk between local and systemic factors.

An additional noteworthy finding from our demographic analysis is the significant association of PSA with both older age and male sex. The predisposition in older individuals may reflect the influence of age-related factors on local tissue susceptibility. For instance, age-related immunosenescence could lead to a less effectively regulated inflammatory response, while cumulative, lifelong exposure to low-grade environmental irritants may diminish mucosal resilience. Furthermore, age-related decline in mucociliary clearance could impair the sinuses' ability to manage an increased inflammatory load originating from the orbit. The higher prevalence in males is intriguing, particularly as TAO itself is more common in females. Our observation may suggest that sex-specific factors influence the disease phenotype. While speculative, it is possible that hormonal factors, for example the complex immunomodulatory role of androgens, could shape the inflammatory response towards a pattern more likely to involve adjacent structures. Alternatively, the finding may align with observations in other autoimmune conditions where males, though less frequently affected, can present with severe or distinct disease courses. These demographic variables should likely be considered as potential modifiers that lower the threshold for developing sinonasal complications in orbital inflammation.

From a clinical perspective, awareness of the high prevalence of sinus abnormalities in TAO patients has several actionable implications. It suggests that a low-threshold for sinus evaluation, potentially with CT imaging, is warranted in TAO patients, particularly those presenting with disproportionate enlargement of the medial or inferior rectus muscles or with otherwise unexplained sinonasal symptoms[24-26]. Our findings advocate an integrated management strategy. In patients with TAO refractory to standard immunosuppression, for example, occult chronic rhinosinusitis could be a confounding factor, and its treatment may be a prerequisite for achieving orbital disease. In surgical planning, the preoperative identification of significant sinus pathology is critical, as it directly influences the choice of orbital decompression technique, for example, a balanced or lateral wall approach may be favored over a medial wall resection in the presence of severe ethmoiditis[27]. Furthermore, this raises the question of whether orbital decompression surgery, particularly procedures involving the medial wall or floor, might concurrently alleviate co-existing sinus pathology[28-29]. Collectively, these considerations highlight the importance of a multidisciplinary approach involving ophthalmologists, endocrinologists, and otolaryngologists in the management of complex TAO cases with sinonasal manifestations.

A primary limitation is the cross-sectional design, which precludes definitive conclusions about causality in the observed association between orbital inflammation and PSA. While our primary hypothesis posits that orbital inflammation extends into contiguous sinuses, the alternative hypothesis, that pre-existing or concurrent sinus inflammation could act as an adjuvant that exacerbates the orbital autoimmune process, potentially mediated through shared drainage pathways creating a regional inflammatory feedback loop, cannot be dismissed. Future longitudinal studies are required to definitively elucidate the temporal and causal relationship between these co-localized inflammatory conditions. Furthermore, our radiological analysis was based on morphological changes. Future investigations should employ functional imaging techniques, such as dynamic contrast-enhanced magnetic resonance imaging (MRI)[30-31], to quantify and correlate active inflammation in both orbital and sinonasal tissues. The concurrent intraoperative biopsy of orbital and sinonasal tissue for comparative molecular and cellular profiling, which would provide definitive evidence for or against the contiguous inflammation hypothesis by mapping cytokine signatures and immune cell populations. The role of the sinonasal microbiome in modulating local immunity represents an unexplored frontier, investigating whether dysbiosis correlates with TAO activity could uncover new pathogenic mechanisms and therapeutic targets.

In conclusion, our study demonstrates a high prevalence of PSA in patients with TAO, with a distinct pattern affecting the maxillary and ethmoid sinuses. The correlations between sinus abnormalities and ipsilateral EOM involvement contrasted with the lack of association with proptosis laterality or systemic autoimmune markers, supporting for a model of contiguous inflammation that requires definitive validation through future longitudinal and mechanistic investigations.

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