Weber's gland immune/histopathology in pediatric recurrent tonsillitis and obstructive tonsillar hypertrophy cases

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Abstract. – OBJECTIVE: Recurrent tonsillitis and obstructive tonsillar hypertrophy are very common in childhood and constitute the two major causes of tonsillectomy in this age group. There is no study in the literature on the immune/histopathological changes in the recurrent and obstructive tonsillar hypertrophy of Weber's glands. In this study, we aimed to histopathologically and immunohistochemically examine the Weber's glands of pediatric patients with recurrent.

PATIENTS AND METHODS: A total of 63 patients, with 31 patients aged 6-9 who had surgery for recurrent tonsillitis, and 32 patients aged 6-11 years who had surgery for obstructive tonsillar hypertrophy, were included in the study. The removed Weber's glands were included in the obstructive tonsillar hypertrophy or recurrent tonsillitis group according to the patient's clinical diagnosis. All specimens were coded with a numbering method, where only the surgeon knew which patient was in which group. All specimens were evaluated in the same histology center and by the same histologist, unaware of the clinical diagnosis of the patients (blind).

RESULTS: The comparison of Weber's gland immunohistochemical parameter scores of the groups revealed that the scores of the RT group were significantly higher for all three parameters (VEGF: t=6.777; p<0.001), (EGFR: t=4.386; p<0.001), (IL-6: t=5.072; p<0.001). The comparison of the groups in terms of inflammation, basement membrane thickening, myoepithelial cell and glycoprotein accumulation revealed significantly higher Weber's gland evaluation scores in the RT group for all four parameters. (inflammation: t=7.794; p<0.001), (basement membrane thickening: t=6.582; p<0.001), [myoepithelial cell: t=3.693; p<0.001), (glycoprotein accumulation: t=5.287; p<0.001)].

CONCLUSIONS: Histopathological and immunohistochemical examination of Weber's gland in pediatric recurrent tonsillitis and obstructive tonsillar hypertrophy cases revealed inflammatory changes in both disease groups. As expected, inflammatory manifestations were more common in the recurrent tonsillitis group. Besides, inflammatory changes detected in Weber's glands of obstructive tonsillar hypertrophy cases without a history of tonsillitis may contribute to the Weber's gland hypothesis, which attempts to explain the etiology of peritonsillar abscess.

Key Words:
  Weber gland, VEGF, EGFR, IL-6, Tonsil, Recurrent tonsillitis, Obstructive tonsillar hypertrophy.

Introduction

Weber's glands, a group of minor salivary glands, were first described by Ernst Heinrich Weber in 1927. Roy Harvey Parkinson referred to the anatomy of the tonsillar fossa and Weber's glands in his book "Tonsils and Allied Problems" published in 1951[1]. Despite the initial emphasis on their localization close to the upper pole of the tonsil, Kraitrakul et al[2] reported that Weber's glands are located throughout the peritonsillar region and have a ductal system that penetrates the tonsillar capsule and opens into the tonsil crypts with a ductal system. Thanks to this ductal system, the saliva secreted from Weber's glands reaches the tonsil crypts and contributes to the cleaning of food residues, etc[3]. Several studies have emphasized the role of Weber's glands in the etiology of peritonsillar abscess[4]. Despite the lack of definitive histopathological evidence, some studies indicate that after infecting the tonsillar mucosa, pathogenic bacteria spread to the peritonsillar space via the salivary gland duct system and form abscesses[5]. On the other hand, scarring or anatomical changes in the tonsils or Weber's glands due to an infection in the palatine tonsils or peritonsillar tissues are thought to be associat-

ed with an increased risk of recurrent tonsillitis. Vascular endothelial growth factor (VEGF) is a protein that increases neovascularization, which is important in the pro-angiogenesis of endothelial cells (ECs)[6]. Activation of Epidermal growth factor receptor (EGFR) has been reported to lead to a phosphorylation cascade mediated by tyrosine kinases that promote proliferation, invasion, angiogenesis, and metastatic spread in the PI3K–PTEN–AKT, MAPK, ERK, and Jak/STAT pathways[7]. IL6 synthesis and secretion is induced proinflammatory during inflammatory conditions such as cell receptor stimulation[8].

Recurrent tonsillitis and obstructive tonsillar hypertrophy are very common in childhood and constitute the two major causes of tonsillectomy in this age group[9]. While recurrent tonsillitis has a clinical course that manifests itself mostly with recurrent infective symptoms, obstructive tonsillar hypertrophy displays symptoms such as obstruction-induced fatigue, poor school performance, and sleep problems rather than an infectious manifestation[10,11]. Although clinical criteria have been established for these two diseases, which are very common in childhood and are thought to affect children in many ways such as psychosocial status, quality of life, and sleep quality, the etiopathogenesis of these two different morphological and pathophysiological diseases has still not been fully elucidated[11-13]. There is no study in the literature on the immune/histopathological changes in the recurrent and obstructive tonsillar hypertrophy of Weber's glands, which are the structures closest to the palatine tonsillar tissue, and whether they play a role in the etiopathogenesis of recurrent tonsillitis. In this study, we aimed to histopathologically and immunohistochemically examine the Weber's glands of pediatric patients with recurrent tonsillitis and obstructive tonsillar hypertrophy who underwent tonsillectomy.

Patients and Methods

This cross-sectional study includes patients who underwent tonsillectomy due to recurrent tonsillitis and obstructive tonsillar hypertrophy between May 2022 and June 2022. The study was approved by the Ethics Committee of Mardin Artuklu University (Document date and number: 13/05/2022-53581) and conducted in accordance with the principles of the Declaration of Helsinki. A total of 63 patients, with 31 patients aged 6-9 who had surgery for recurrent tonsillitis, and 32 patients aged 6-11 years who

had surgery for obstructive tonsillar hypertrophy, were included in the study. Patients were divided into two groups according to tonsil size and clinical infection history. The criteria for the recurrent tonsillitis group were having a history of 3 or more tonsillitis attacks per year in the last 3 years, 5 or more attacks per year in the last two years, and 7 or more attacks in the last year and having Stage 0 and Stage 1 tonsillar size according to the Brodsky scale[14]. The criteria for the obstructive tonsillar hypertrophy group were having Stage 3 or Stage 4 tonsillar size and sleep apnea symptoms, and not having a history of recurrent tonsillitis[15]. Exclusion criteria from the study were as follows: 1. Showing symptoms of acute infection or having received antibiotic therapy for an infection one month ago; 2. Having chronic diseases such as malignancy, immunodeficiency, diabetes mellitus; 3. Patients with salivary gland involvement or other diagnosed autoimmune disorders; 4. Having a history of peritonsillar abscess.

The patients were operated on in two centers, and the cold dissection technique was used for all patients to avoid tissue degranulation due to possible heat damage. After tonsillectomy, tonsils were examined under a surgical microscope. If detected on the side of the tonsils facing the peritonsillar region, this salivary gland tissue was excised. If a salivary gland was detected in the specified region in both removed tonsils, only one side was included in the study and the larger Weber's gland was preferred. For standardization, the Weber's gland located in the upper pole of the tonsil was studied for all cases. The removed Weber's glands were included in the obstructive tonsillar hypertrophy or recurrent tonsillitis group according to the patient's clinical diagnosis. All specimens were coded with a numbering method, where only the surgeon knew which patient was in which group. All specimens were evaluated in the same histology center and by the same histologist, unaware of the clinical diagnosis of the patients (blind).

Tissue Collection, Processing, and Histological Staining

Postoperatively, Weber's gland tissue samples were placed in a 10% neutral buffered formalin solution, passed through an ascending alcohol series, and then incubated in xylene and paraffin. Sections of 5 µm thickness were cut from the blocks using a microtome (catalog No: Leica RM2265, Wetzlar, Germany). Specimens were stained by Hematoxylin-eosin (HE) staining, Periodic acid Schiff staining and immunohistochemical staining[16,17].

Table I. Patient distribution by gender.

		RT (n) (%)	OTH (n) (%)	χ^2	p
Gender	**Female**	13 (41.9%)	14 (43.8%)		
	Male	18 (58.1%)	18 (56.3%)	0.021	0.543
	Total	31 (100%)	32 (100%)		

RT: recurrent tonsillitis, OTH: obstructive tonsillar hypertrophy. *p*: Pearson chi-square test. *X²:* Test value.

Immunohistochemical Staining

Sections were brought into distilled water and immersed in EDTA buffer solution (pH: 8.0, catalog no: ab93680, Abcam, Cambridge, CA, USA) for epitope uptake in a microwave oven at 700 Watts for 10 minutes. For endogenous peroxidase blocking, hydrogen peroxide solution (catalog no: TA-015-UB, Thermo Fisher, Fremont, CA, USA) was dropped onto the sections and left for incubation for 20 minutes. After blocking the solution, sections were incubated overnight with 1/100 diluted IL-6 (Interleukin-6) (catalog no: sc-32296, Santa Cruz Biotechnology, Santa Cruz, CA, USA), EGFR (epidermal growth factor receptor) (catalog no: 374255 Santa Cruz Biotechnology, Santa Cruz, CA, USA), and VEGF-A anti-VEGF-A (Vascular endothelial growth factor), (catalog no:sc-53463; Santa Cruz Biotechnology, Santa Cruz, CA, USA) antibodies. Diaminobenzidine (DAB) (catalog no: TA-001-HCX, Thermo Fischer, Fremont, CA, USA) was used as chromogen. After counterstaining with Harris hematoxylin, sections were mounted with Entellan (catalog no:107961, Sigma-Aldrich, St. Louis, MO, USA) and analyzed with Zeiss Imager A2 (Germany) using Zen 3.2 lite software[18,19].

For histopathological examination, statistical analysis was performed on the measurements of the cells, basement membrane thickness, and periductal and/or interlobular lymphocytic/lymphoplasmacytic inflammatory cell infiltrations in the connective tissue in the interlobular area among the acinar structures in 10 different regions of glandular mass in the lobular area.

For immunohistochemical expression analysis, expressions in acinar cells, myoepithelial cells, endothelial cells, and inflammatory cells in the connective tissue area were evaluated in 10 different areas in the lobular area.

The results of immunohistochemical staining were evaluated using a scoring system. The presence and prevalence of each parameter were scored and recorded according to staining intensity (0=no expression, 1=mild expression, 2=moderate expression, 3=intense expression, and 4=very intense expression)[20].

Statistical Analysis

IBM SPSS 21.0 (IBM Corp., Armonk, NY, USA) statistical package program for Windows was used for the statistical analysis of our study data. Measured variables were presented as mean ± standard deviation (SD), and categorical variables were given in numbers and percentages (%). An independent samples *t*-test was completed to compare the two groups. Chi-square (χ^2) test was used to compare qualitative variables. The hypotheses were tested bilaterally, and *p<0.05* was considered statistically significant.

Results

Of the 63 patients included in the study, 31 were operated for recurrent tonsillitis and 32 for obstructive tonsillar hypertrophy. There was no statistical difference between the patient groups in terms of gender (Table I). The mean age of the OTH group (8.28±1.59 years) was significantly higher than the mean age of the RT group (7.32±0.94 years) (*p*=0.005).

Immune/Histopathological Findings of Weber's Glands in Recurrent Tonsillitis and Obstructive Tonsillar Hypertrophy Cases

Immune/histopathological findings of Weber's glands in recurrent tonsillitis cases are shown in Figure 1, Figure 2, Figure 3, Figure 4, and Figure 5. Immune/histopathological findings of Weber's glands in obstructive tonsillar hypertrophy cases are shown in Figure 6, Figure 7, Figure 8, Figure 9, and Figure 10. Inflammatory changes were more common in Weber's glands in cases of recurrent tonsillitis.

Statistical Immunohistochemical and Histopathological Data

The comparison of Weber's gland immunohistochemical parameter scores of the groups revealed that the scores of the RT group were significantly higher for all three parameters (VEGF: *t*=6.777; *p<0.001*), (EGFR: *t*=4.386; *p<0.001*),
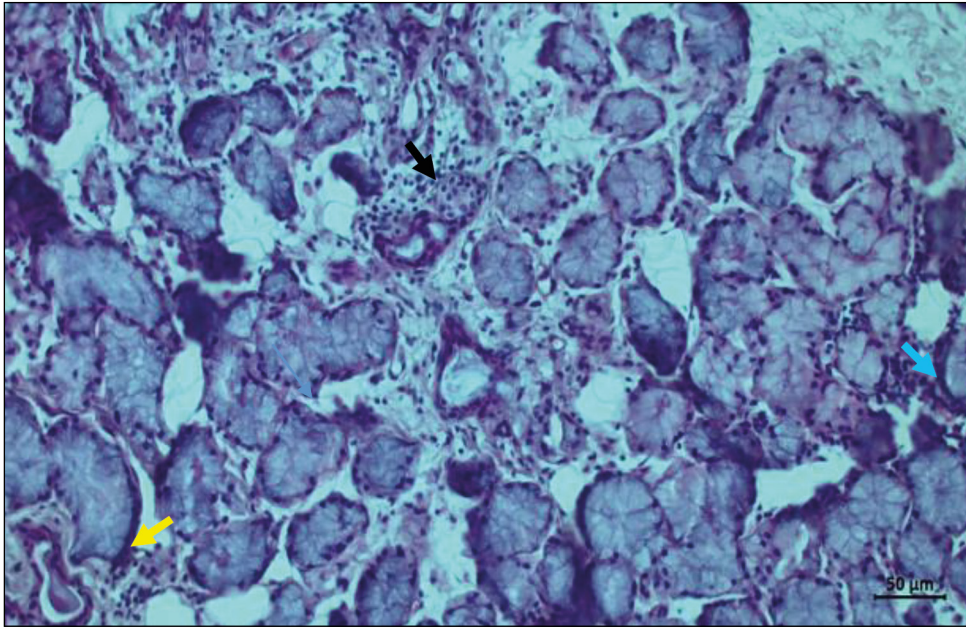
Figure 1. Weber's gland cross-section (H&E staining, 20X) of a recurrent tonsillitis case. Local thickenings (yellow arrow) in the basement membrane structure of Weber's glands and degenerative changes in myoepithelial cells. Inflammation (black arrow) mostly in the outer part of Weber's glands, where the ducts and sub-glands are located within the interlobular space. Leukocyte structures increased particularly in areas with myoepithelial cells (blue arrow).

(IL-6: t=5.072; p<0.001) (Table II). The comparison of the groups in terms of inflammation, basement membrane thickening, myoepithelial cell and glycoprotein accumulation revealed significantly higher Weber's gland evaluation scores in the RT group for all four parameters (inflammation: t=7.794; p<0.001), (basement membrane thickening: t=6.582; p<0.001), (myoepithelial cell: t=3.693; p<0.001), (Glycoprotein accumulation: t=5.287; p<0.001) (Table II) 4).
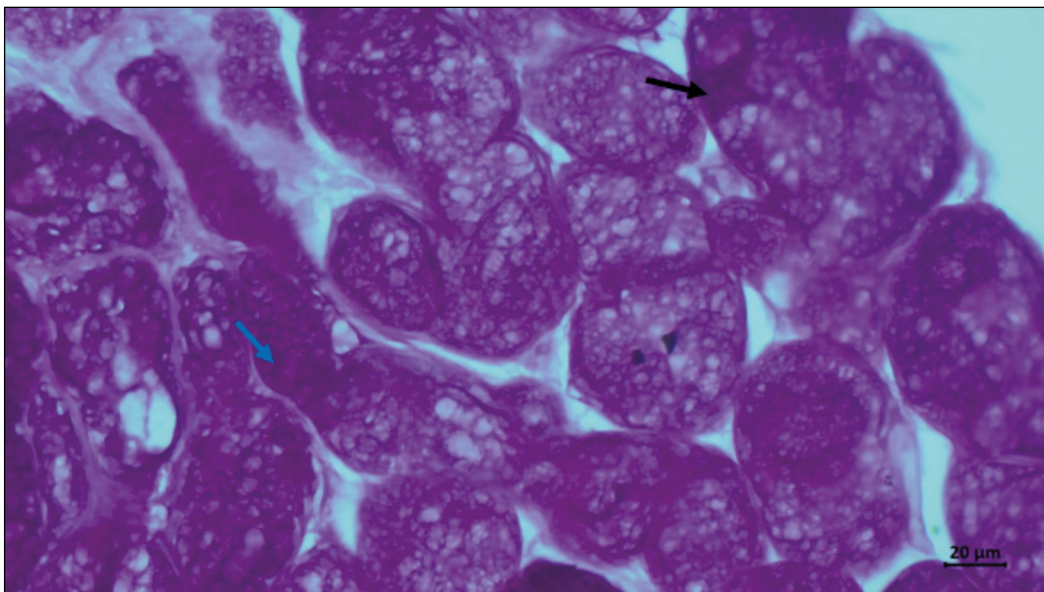

Figure 2. Weber's gland cross-section of a recurrent tonsillitis case (PAS staining, 40X). Intense PAS positivity in areas with significant glycoprotein accumulation (black arrow). PAS positivity (blue arrow) was observed in areas with leukocyte density.
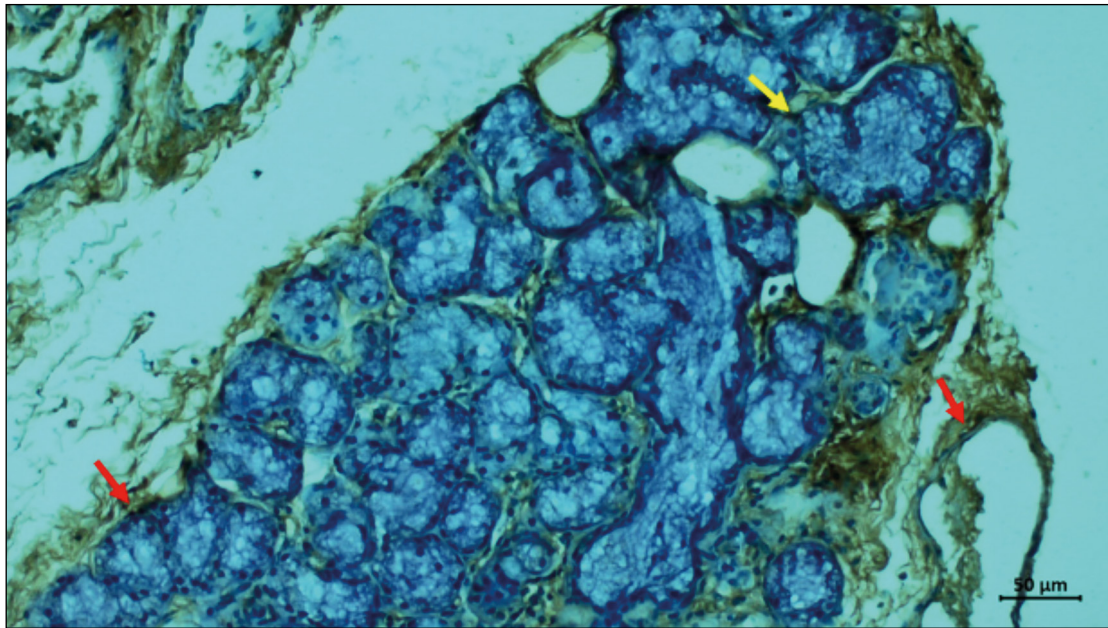
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Figure 3. Weber's gland cross-section of a recurrent tonsillitis case (IL-6 immunostaining, 20X). Inflammatory cell infiltration in the basement membrane around the duct and around the glands and positive IL-6 reaction (red arrow), and IL-6 positive reaction in myoepithelial cells (yellow arrow).

Discussion

Although clinical diagnostic criteria have been established for both recurrent tonsillitis and obstructive tonsillar hypertrophy, the pathophysiology of these two diseases has still not been fully elucidated[11]. Therefore, there is still a need to uncover disease-specific objective data for these two clinical diagnoses. In this study, inflammatory changes were detected in immunohistochemical
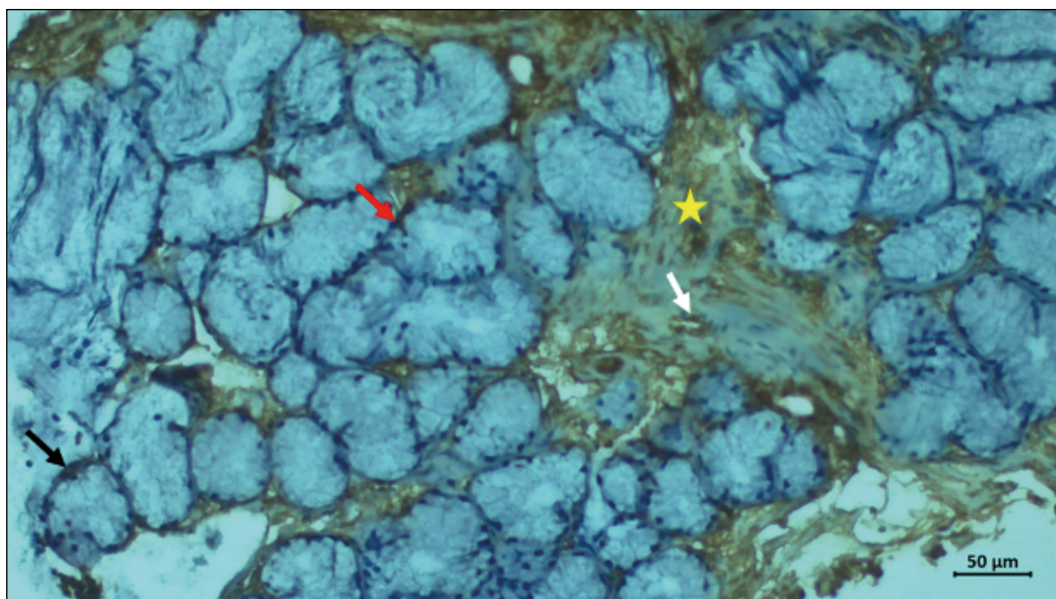

Figure 4. Weber's gland cross-section of a recurrent tonsillitis case (EGFR immunostaining, 20X). Positive EGFR reaction (red arrow) in both myoepithelial cell and mucous secreting glands, Positive EGFR reaction (black arrow) in nuclei pushed to baseline depending on secretion density, Positive EGFR reaction in connective tissue (yellow star) and vascular endothelial cells (white arrow).
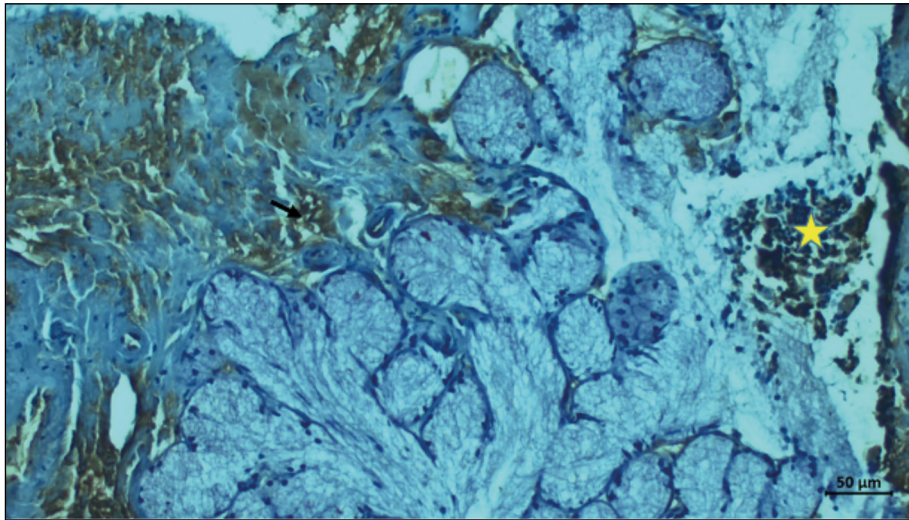
Figure 5. Weber's gland cross-section of a recurrent tonsillitis case (VEGF immunostaining, 20X). Intense VEGF positivity (yellow star) in the inflammation site in the connective tissue, significant increase in inflammatory cells, and VEGF positive reaction (black arrow) around the vessel and outside the basement membrane.

and histopathological examinations of Weber's gland in both recurrent tonsillitis and obstructive tonsillar hypertrophy cases. Weber's gland inflammation scores were statistically significantly higher in recurrent tonsillitis cases than in obstructive tonsillar hypertrophy cases.

Before Passy's study on the role of Weber's gland in the etiology of peritonsillar abscess, there were no clinical studies on Weber's glands in the literature. After this article, studies on Weber's glands began to be published, albeit in limited numbers. Yet, most of these studies are related to the role of Weber's glands in the etiology of peritonsillar abscess[3-5]. Our study, unlike the literature, examines Weber's glands immunohistochemically in cases of pediatric recurrent tonsillitis and pediatric obstructive tonsillar hypertrophy, and is the first study in the literature in this respect.
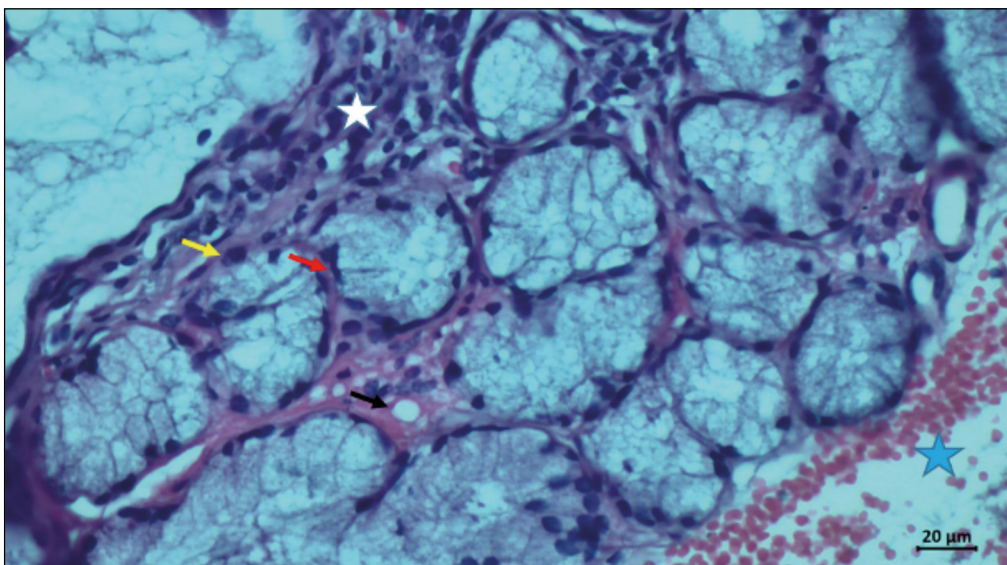

Figure 6. Weber's gland cross-section of an obstructive tonsillar hypertrophy case (H&E staining, 40X). Myoepithelial cell degeneration (red arrow), Hypertrophic area (yellow arrow) in secretory cells. Infiltration of few solitary and aggregated inflammatory cells around the basement membrane (white arrow). Apparent hemorrhagic area and free erythrocytes (blue arrow). Distinct vacuoles in connective tissue areas (black arrow).
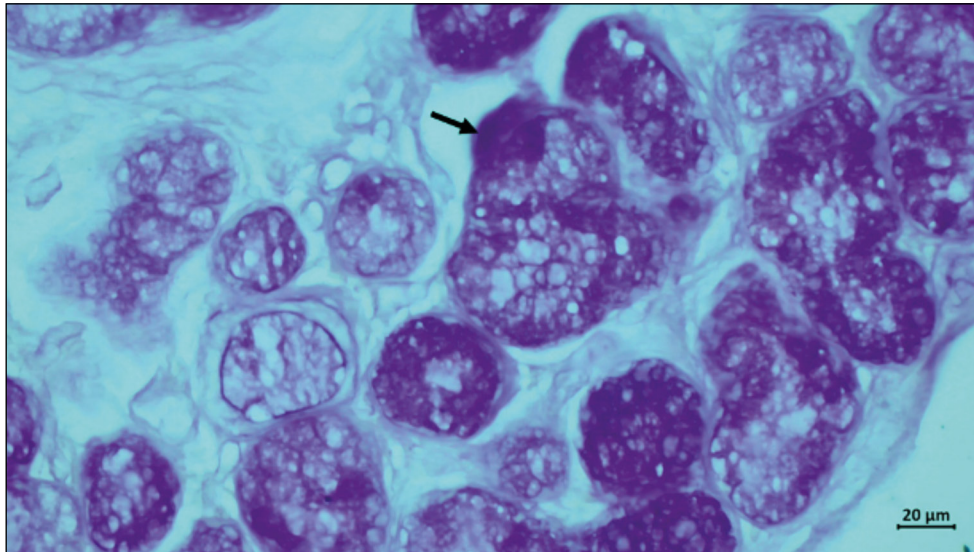
Figure 7. Weber's gland cross-section of an obstructive tonsillar hypertrophy case (PAS staining, 40X). PAS positive reaction in mucous glands.

In their study on Weber's glands in recurrent tonsillitis, chronic tonsillitis and peritonsillar abscess patients over the age of 18, Kaltiainen et al[4] emphasized that there were inflammatory changes in Weber's glands in all three patient groups and that inflammation was more intense in those located closer to the tonsil surface. Therefore, in our study, we evaluated Weber's glands, which are close to the tonsil surface and only detected in the upper pole, so that their immunohistochemical and histopathological findings can be subjected to a standard evaluation.

According to Klug et al[5] fibrotic changes in the ductal system of Weber's gland and the inflammatory processes that occur afterwards may result from recurrent tonsillitis attacks. On the other hand, disruption of the ductal system of Weber's glands opening to the tonsillar crypts may cause these glands to fail to function, not cleaning the tonsillar crypts, and perhaps more tonsillitis at-
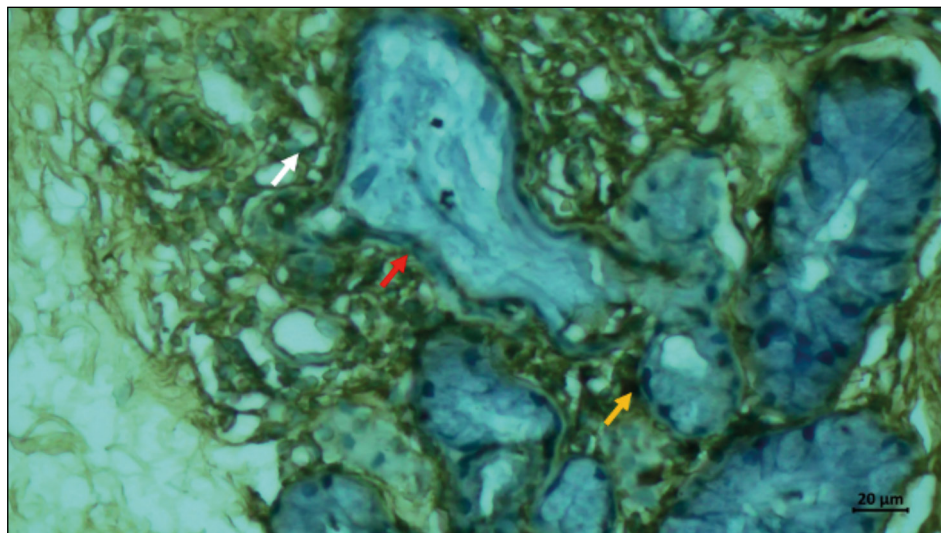

Figure 8. Weber's gland cross-section of an obstructive tonsillar hypertrophy case (IL-6 immunostaining, 40X). Positive IL-6 reaction in basement membrane subdivisions (red arrow) and inflammatory cells (yellow arrow) and vascular endothelium (white arrow). Positive IL-6 reaction in some connective tissue cells, mostly plasma cells and lymphocyte structures within the increasing fibrous tissue.
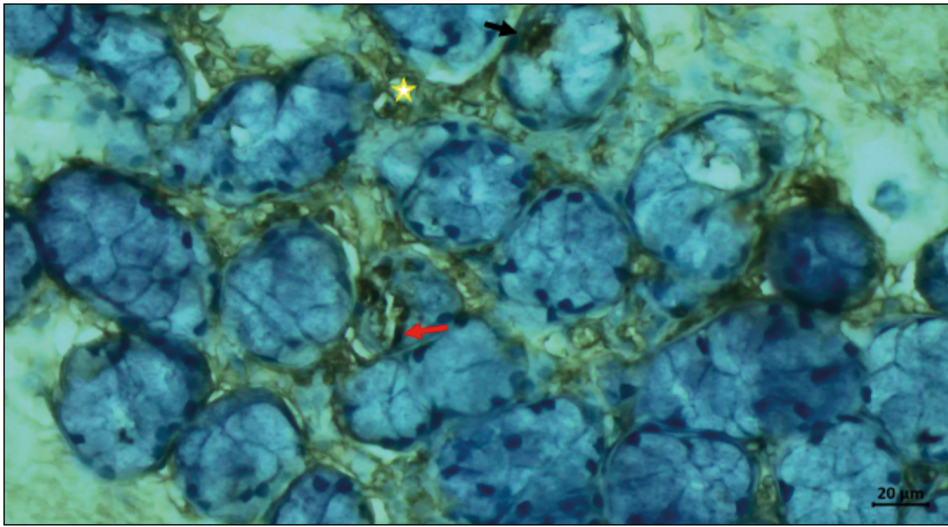
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Figure 9. Weber's gland cross-section of an obstructive tonsillar hypertrophy case (EGFR immunostaining, 40X). Positive EGFR reaction in myoepithelial cells and some secreting mucous cells (black arrow) and endothelial cells (red arrow) in Weber's glands. Positive EGFR reaction in connective tissue areas (yellow asterisks).

tacks later on. The presence of a higher incidence of pathological and inflammatory changes in Weber's gland structures of the recurrent tonsillitis group compared to the obstructive tonsillar hypertrophy group in our study supports these arguments.

In cases of obstructive tonsillitis, degeneration of myoepithelial cells in Weber's glands and gland hypertrophy in more limited areas, as well as solitary distribution of inflammatory cells may mean that in-

flammatory changes are less in these cases compared to cases of recurrent tonsillitis, and Weber's gland functions are partially preserved. The fact that glycoprotein accumulation and glandular hypertrophy are more common in recurrent tonsillitis cases compared to the obstructive tonsillar hypertrophy group can be explained by the salivary retention due to possible damage to Weber's gland ductal system by previous tonsillitis attacks. The increase in IL-6 expression in inflammatory cells around the basement membrane
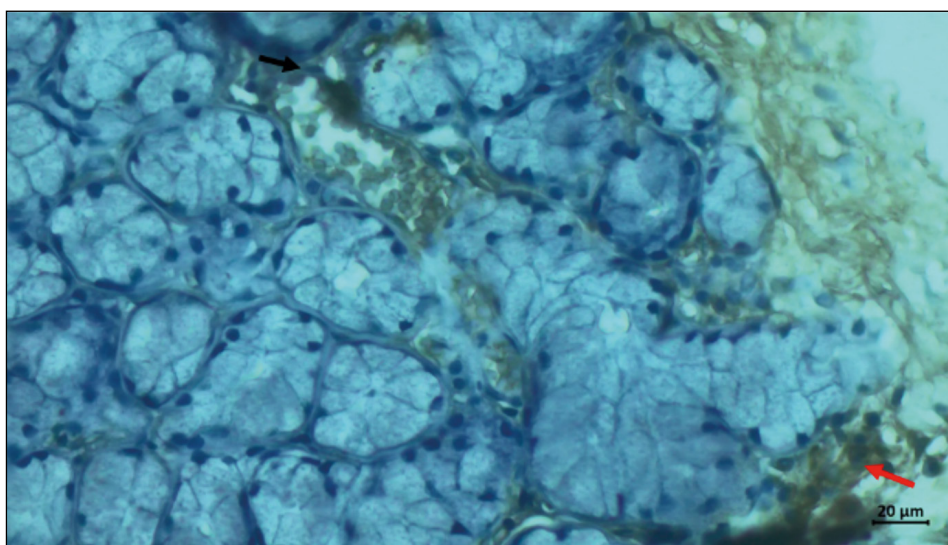

Figure 10. Weber's gland cross-section of an obstructive tonsillar hypertrophy case (VEGF immunostaining, 40X). Positive VEGF reaction in vascular endothelium (black arrow) and connective tissue cells (red arrow).

Table II. Comparison of immunohistochemical and histopathological examination scores of Weber's glands between recurrent tonsillitis and obstructive tonsillar hypertrophy cases.

Parameter	Diagnosis	N	X	SD	df	t	p
VEGF	RT	31	3.29	0.69	61	6.777	<0.001
	OTH	32	1.88	0.94			
EGFR	RT	31	3.00	0.82	61	4.386	<0.001
	OTH	32	2.06	0.88			
IL-6	RT	31	3.26	0.82	61	5.072	<0.001
	OTH	32	2.25	0.76			
Inflammation	RT	31	3.39	0.72	61	7.794	<0.001
	OTH	32	1.94	0.76			
Basement membrane thickening	RT	31	3.06	0.63	61	6.582	<0.001
	OTH	32	1.88	0.79			
Myoepithelial cell	RT	31	2.77	0.181	61	3.693	<0.001
	OTH	32	1.94	0.98			
Glycoprotein accumulation	RT	31	3.35	0.71	61	5.287	<0.001
	OTH	32	2.53	0.51			

VEGF: Vascular endothelial growth factor, EGFR: epidermal growth factor receptor, IL-6: Interleukin 6, RT: recurrent tonsillitis, OTH: obstructive tonsillar hypertrophy, N: number, X: mean, SD: Standard deviation, df: degrees of freedom, *t*: Independent *t*-test value. *p*: statistical significance value.

along with degeneration in gland cells and myoepithelial cells can be attributed to the cytokine-induced defense against the existing situation in cases of recurrent tonsillitis. In cases of obstructive tonsillar hypertrophy, immune signaling of IL-6 in inflammatory cells residing between connective tissue cells in the gland interlobular area may have caused the initiation of apoptotic process in some cells and angiogenetic regulation in the vascular endothelium. EGFR protein positivity in gland cells and myoepithelial cells suggests an action towards stimulating functional remodeling of the gland. EGFR activity in endothelial cells may also be associated with the induction of angiogenesis. Macrophage activity and VEGF expression in endothelial cells, together with increased inflammation intensity, indicate induction of angiogenic signaling. Although immunohistochemical evaluations of Weber's glands showed positive staining for all three parameters in both recurrent tonsillitis and obstructive tonsillar hypertrophy cases, IL-6, EGFR and VEGF scores were significantly higher in recurrent tonsillitis cases.

In our study, although it seems inconsistent with the clinical diagnosis, it can be thought that the inflammatory changes detected in Weber's glands, especially in the obstructive tonsillar hypertrophy group, were actually caused by bacterial agents in the tonsil flora and resulted from a subclinical inflammatory process that progressed backwards with the ductal system of Weber's glands. Indeed, Jeonng et al[21] found similar bacterial agents in both

clinical diagnoses in the culture from tonsil tissue in the study where pediatric patients who had more than five tonsillitis attacks in a year were included in the recurrent tonsillitis group, and patients with tonsillar hypertrophy but no tonsillitis history were included in the tonsillar hypertrophy group. Another study also reported that similar bacterial agents were grown in tonsil specimen cultures of patients who underwent tonsillectomy due to velopharyngeal insufficiency (normal tonsil tissue) and patients who underwent tonsillectomy for recurrent tonsillitis[22]. In other words, bacterial agents still exist even in tonsils with clinically normal appearance.

The acute tonsillitis hypothesis, which attempts to explain the etiology of peritonsillar abscess, advocates the idea that peritonsillar abscess occurs after an acute tonsillitis attack, but it cannot explain how bacteria penetrate the tonsillar capsule and spread to the peritonsillar region. The Weber's gland hypothesis, on the other hand, argues that only a small portion of peritonsillar abscess cases have a history of tonsillitis, and most of them do not have acute tonsillitis findings. This hypothesis proposes that a suppurative salivary gland infection leads to a peritonsillar abscess after obstruction of the ductal system of Weber's glands. It has also been suggested that duct obstruction may be secondary to recurrent tonsillitis or other inflammatory processes[5]. The increase in EGFR signaling, IL-6 and VEGF activation in Weber's glands in patients with recurrent tonsillitis and chronic tonsillitis can be explained by the increase

of inflammatory reaction and the alteration of many biological events, including the change of angiogenesis and their chronic onset and progression through the cell cycle. Our study may support the Weber's gland hypothesis in one respect. Indeed, we detected inflammatory changes in the immunohistochemical examination of Weber's gland in patients with obstructive tonsillar hypertrophy without a history of recurrent tonsillitis. Accordingly, these findings support the view that a suppurative inflammatory process originating from Weber's gland may occur in the peritonsillar region when the necessary conditions are met in an individual without a history of tonsillitis.

Limitations

The main limitation of the study was the absence of a control group of completely normal tonsils. Because in the otolaryngology practice, there are limited number of diagnoses in which tonsils are normal, but tonsil surgery is performed. This limitation could have been overcome if the control group consisted of patients who were operated for velopharyngeal insufficiency and underwent tonsillectomy even though their tonsils were normal, as in the study of Brook and Foote[22]. Such a design can be adopted in future studies on this subject.

Conclusions

Histopathological and immunohistochemical examination of Weber's gland in pediatric recurrent tonsillitis and obstructive tonsillar hypertrophy cases revealed inflammatory changes in both disease groups. As expected, inflammatory manifestations were more common in the recurrent tonsillitis group. Besides, inflammatory changes detected in Weber's glands of obstructive tonsillar hypertrophy cases without a history of tonsillitis may contribute to the Weber's gland hypothesis, which attempts to explain the etiology of peritonsillar abscess.

Conflicts of Interest

The authors declare no conflict of interest.

Ethics Approval

The study was approved by the Ethics Committee of Mardin Artuklu University (Document date and number: 13/05/2022-53581) and conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent

Consent was obtained from each patient who agreed to participate in the study. Written and verbal information about the study was given to the participants. The patients were informed that they could withdraw from the study at any stage if they want to.

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