THE ROLE OF FINE-NEEDLE ASPIRATION BIOPSY IN THE DIAGNOSIS OF SALIVARY GLAND LESIONS: A COMPARATIVE HISTOPATHOLOGICAL STUDY

TÜKÜRÜK BEZI LEZYONLARININ TANISINDA İNCE İĞNE ASPİRASYON BİYOPSİNİN YERİ: HİSTOPATOLOJİK KARŞILAŞTIRMALI ÇALIŞMA

Selma Sengiz ERHAN [1]✉ Caglar CAKIR[1] Pinar Ozay NAYIR[1] Elis KANGAL[2] Serkan ARIBALI[3] Ziya SALTURK[4]

1. *Department of Pathology, Istanbul Prof. Dr. Cemil Tascioglu City Hospital, Istanbul, Turkey*
2. *Department of Pathology, Kars Harakani Public Hospital, Kars, Turkey*
3. *Department of Radiology, Istanbul Prof. Dr. Cemil Tascioglu City Hospital Istanbul, Turkey*
4. *Anatolia Health Center, Department of Otorhinolaryngology, Kocaeli, Turkey*

ORCID: *0000-0001-8810-8806, 0000-0002-6403-1442, 0000-0003-3827-1466, 0000-0002-5373-7212, 0000-0002-0338-2652, 0000-0001-6722-7865*
E-mail*: selmaserhan@hotmail.com*

Received/Geliş Tarihi	Accepted/Kabul Tarihi	Published/Yayın Tarihi
29.05.2023	22.08.2023	31.08.2023

To cite this article / Bu makaleye atıfta bulunmak için:
Erhan SS, Cakir C, Nayir PO, Kangal E, Aribali S, Salturk S. The role of fine-needle aspiration biopsy in the diagnosis of salivary gland lesions: a comparative histopathological study. Atatürk Üniversitesi Tıp Fakültesi Cerrahi Tıp Bilimleri Dergisi. 2023; 2(2):78-84

Abstract

Objective: As the treatment of neoplastic and non-neoplastic lesions of salivary gland differs, their differentiation in preoperative period is crucial. Fine-needle aspiration biopsy (FNAB) is among the common diagnostic methods for this purpose. We intended to compare the cytological-histopathological diagnosis of salivary gland lesions, and evaluate sensitivity, specificity, predictive value (PV) and diagnostic accuracy of the FNAB results. **Methods:** 156 cases examined in our department, having FNAB and excision material, were compared with their cytological-histopathological diagnosis. **Results:** Lesions were localized in parotid gland in 132 cases, in submandibular gland in 22 cases, and in minor salivary gland in 2 cases. FNABs were categorized based on their cytomorphological results into nondiagnostic (7.05%), benign (78.21%), suspicious (7.05%) and malignant (7.69%) groups. When the cytological-histopathological diagnosis of cases was compared, the diagnosis of 12 cases among malignant lesions (100%, 12/12) and 121 among benign lesions (99.2%, 121/122) were found to be compatible. One false negative case (0.8%) (warthin tumor→mucoepidermoid carcinoma) was detected, but no false positive (0%) was the case. Histopathological examinations of three cases among suspicious lesions resulted in diagnosis of ectopic thyroid tissue, sialadenitis and pleomorphic adenoma. Results of sensitivity, specificity, positive PV, negative PV and accuracy analysis examinations were respectively 92.3%, 100%, 100%, 99.2% and 99.3%. **Conclusion:** Evaluating FNABs with sufficient sampling minimizes false positive/negative results, leading to accurate diagnosis in preoperative period. Wide range of salivary gland lesions and overlapping cytomorphological findings should also be minded.

Keywords: Salivary gland, fine-needle aspiration biopsy, pleomorphic adenoma, mucoepidermoid carcinoma

Özet

Amaç: Tükürük bezi non-neoplastik ve neoplastik lezyonlarının tedavileri farklılık gösterdiği için, preoperatif dönemde ayrımlarının yapılması önemlidir. İnce iğne aspirasyon biyopsisi (İİAB) bu amaçla en yaygın kullanılan tanı yöntemlerinden biridir. Burada tükürük bezi lezyonlarının sitolojik-histopatolojik tanılarının karşılaştırılması, İİAB sonuçlarının sensitivite, spesifite, prediktif değer (PV) ve tanısal doğruluğunun değerlendirilmesi amaçlandı. **Materyal ve metod:** Bölümümüzde incelenen İİAB ve eksizyon materyali olan 156 olgu sitolojik-histopatolojik tanıları ile karşılaştırıldı. **Bulgular:** Lezyonlar 132 (%84.6) olguda parotis bezinde, 22 (%14.1) olguda submandibuler bezde ve 2 (%1.3) olguda minör tükürük bezinde lokalizeydi. İİAB'lerin sitomorfolojik sonuçlarına göre % 7.05'i (n=11) nondiagnostik, %78.21'i (n=122) benign, % 7.05'i (n=11) kuşkulu ve % 7.69'u (n=12) malign olarak sınıflandırıldı. Olguların sitolojik-histopatolojik tanıları karşılaştırıldığında; malign lezyonlar içinde 12 olgunun (12/12; %100) ve benign lezyonlar içinde 121 olgunun (121/122; %99.2) tanıları uyumluydu. False negatif bir olgu (%0.8) (warthin tümör→mukoepidermoid karsinom) saptandı. False pozitif olgu saptanmadı (%0). Kuşkulu lezyonlar içinde üç olgunun histopatolojik incelemeleri ektopik tiroid dokusu, sialadenit ve pleomorfik adenom tanıları ile sonuçlandı. Sensitivite, spesifite, pozitif PV, negatif PV ve doğruluk analizi değerlendirmesinde sırasıyla % 92.3, % 100.0, % 100.0, % 99.2 ve % 99.3 sonuçları elde edildi. **Sonuç:** İİAB'lerinde yeterli örnekleme ile birlikte değerlendirmelerindeki deneyim, çalışmamızda olduğu gibi false pozitif/negatif sonuçları en aza indirgeyecek ve preoperatif dönemde doğru tanıya ulaştıracaktır. Bununla birlikte tükürük bezi lezyonlarının geniş yelpazesi ve örtüşebilecek sitomorfolojik bulguların varlığı da akılda tutulmalıdır.

Anahtar Kelimeler: Tükürük bezi, ince iğne aspirasyon biyopsisi, pleomorfik adenom, mukoepidermoid karsinom.

1. INTRODUCTION

Salivary gland lesions including a wide variety of tumor-like lesions and tumor types have a broad morphological pattern (1,2). It is important to distinguish neoplastic and non-neoplastic lesions in the preoperative evaluation due to the fact that neoplastic lesions are usually excised surgically, while non-neoplastic lesions are treated conservatively with clinical follow-up (3).

Fine needle aspiration biopsy (FNAB) is one of the most widely used first-stage diagnostic methods for this purpose. FNAB is a method that can provide rapid morphological evaluation in determining the origin (salivary gland or not), nature (benign or malignant), and possible grade (low or high) of the lesions (1,4,5). However, there are also limitations of FNAB (1,5-7). Sampling errors, presence of cystic components, lesions with morphological heterogeneity and overlapping cytomorphological findings are among the related limitations which lead to a wide range of sensitivity (81-100%) and specificity (90-100%) in cytological diagnosis (4,8-12).

In our study, we aimed to compare the cytological and histopathological diagnoses of salivary gland lesions, and to evaluate the sensitivity, specificity, predictive value as well as diagnostic accuracy of the FNAB results.

2. MATERIAL AND METHOD

This study was found ethically appropriate according to the local ethical committee with its decision number 2019-1137.

2.1. FNAB and histopathological data of the patients:

The FNAB samples and excision material of patients with lesions located in the salivary gland (parotid, submandibular and minor salivary glands) which were sent to our department between 2014-2019 were evaluated with their clinical information. All the FNABs were performed with real-time ultrasound guidance. Demographic characteristics (age, gender) of the patients, the localization of the FNABs, cytomorphological findings and diagnoses of FNABs were recorded.

The FNAB results according to the cytomorphological findings were classified into four groups as nondiagnostic, benign, suspicious for malignancy, and malignant. Insufficient, acellular or hypocellular smears, cyst contents consisting of only macrophages without diagnostic cells or smears containing elements of peripheral blood were interpreted as nondiagnostic. When characteristic cytomorphological findings of benign epithelial and mesenchymal neoplasia of the salivary gland (pleomorphic adenoma, warthin tumor, etc) were observed, it was interpreted as benign. On the other hand, it was interpreted as malignant when significant malignancy findings such as atypical cells with increased nuclear/cytoplasmic ratio, pleomorphic and hypercromatic nucleus which forms sheets or three-dimensional groups, and frequent mitosis, necrotic background and specific findings for malignant tumor type (for example matrix globules and basal cells for adenoid cystic carcinoma) were in question. Although suggestive of malignancy, smears that did not meet all the criteria for specific diagnoses were interpreted as suspicious for malignancy.

Histopathological diagnoses of excision materials were classified into three groups as non-neoplastic, benign and malignant.

2.2. Evaluation of compliance between FNAB and histopathological diagnoses:

The histopathological diagnoses of excision materials and FNAB diagnoses were compared in order to evaluate the cytological-histopathological compatibility. The obtained true negative and true positive, and false negative and false positive results were evaluated.

When evaluated together with histopathological results, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy rates were analyzed for the FNAB findings. Analyzes were made in two separate groups. In the first group, patients with nondiagnostic results and suspicious for malignancy were not included. While nondiagnostic patients were not included in the second group, patients suspicious for malignancy were included in the malignant group and evaluated. All the analyses were evaluated separately and totally based on the localizations of the lesions (parotid and submandibular gland). Due to two patients with minor salivary gland lesions, they were not included in the analysis performed based on localization but were evaluated in the total group.

2.3. Statistical analysis

The data were transferred to IBM SPSS Statistics 23 package program. While evaluating the study data, frequency distribution (number, percentage) for categorical variables and descriptive statistics (mean, standard deviation) for numerical variables were given. Chi-square test was used to examine the relationship between gender and localization, and cytological and histological categories. By comparing the FNAB results with the histopathology results, sensitivity, specificity, PPV, NPV and accuracy values were calculated.

3. RESULTS

3.1. FNAB findings of the lesions:

One hundred fifty-six patients with excision material out of 417 patients whose FNAB was examined were included in the study. 85 (54.5%) of the patients were

male, whereas 71 (45.5%) were female, with the male/female (M/F) ratio being 1.2: 1. The mean age was 52.65 ± 14.21.

The lesions were localized in the parotid gland in 132 (84.6%) patients, in the submandibular gland in 22 (14.1%) patients, and in the minor salivary gland in 2 (1.3%) patients.

Of the lesions of the patients, 7.05% were in the nondiagnostic group, 78.21% in benign group, 7.05% in suspicious for malignancy group, and 7.69% in malignant group (Table 1).

3.2. Histopathological findings of the lesions:

Of the lesions in the nonneoplastic diagnosis group (12.2%), 68.4% were located in the parotid gland and 31.6% were in the submandibular gland. Among this group, sialadenitis was the most common etiology (47.4%).

Of the patients with benign neoplasia (73.1%), 93% of the lesions were located in the parotid gland, 6.1% were in the submandibular gland and 0.9% were in the minor salivary gland. Pleomorphic adenoma was the most common benign neoplasia (55.3%).

Of the lesions in the malignant group (14.7%), 56.5% were located in the parotid gland, 39.1% in the submandibular gland and 4.4% in the minor salivary gland. Mucoepidermoid carcinoma (MEC) was the most common primary malignant neoplasia (21.7%). Other tumors were acinic cell carcinoma (ACC), lymphoma, poorly differentiated carcinoma, undifferentiated carcinoma, adenoid cystic carcinoma (AdCC), carcinoma ex pleomorphic adenoma, lymphoepithelial carcinoma, and leiomyosarcoma. MEC showed moderate differentiation in three patients, while it was of low or high grade in the other patients. High-grade transformation was not detected in all three patients with a diagnosis of ACC. The carcinoma component detected in the patient with carcinoma ex pleomorphic adenoma was high grade squamous cell carcinoma (SCC). Both patients with a diagnosis of lymphoma were of high grade. Leiomyosarcoma was well differentiated. SCC metastasis was the most common among the metastatic tumors in this group. Others were renal cell carcinoma, malignant melanoma and breast carcinoma metastases. While primary carcinoma and metastasis diagnoses were made simultaneously in two patients with SCC, the time to occurrence of the metastatic lesion varied between 12 and 72 months in other patients.

While benign lesions in the parotid gland were detected at a higher rate than malignant lesions, the rate of malignant lesions in the submandibular gland was higher than the rate of benign lesions ($p=0.000$). There was no statistically significant relationship between gender and benign and malignant lesions ($p> 0.05$).

The distribution of histopathological diagnoses based on the localizations of the lesions is given in Table 2.

3.3. Compatibility of cytological and histopathological diagnoses of the lesions:

When cytological and histopathological diagnoses were compared in the study, 12 true positive results (100%), 121 true negative results (99.2%) and one false negative result were found (0.8%). The false negative one was benign cytologically (warthin tumor), being localized in the parotid gland and diagnosed as malignant tumor (MEC) as a result of the histopathological examination (Figure 1). No false positive results were found in the study (0%).

Incompatibility between cytological and histopathological diagnoses was detected in three patients in the suspicious for malignancy group. As a result of the histopathological examination, two of the patients were diagnosed as having non-neoplastic lesions (ectopic thyroid tissue (Figure 2) and sialadenitis) and one was diagnosed as having benign tumor (pleomorphic adenoma).

Sensitivity, specificity, PPV, NPV and accuracy analysis results are included in Table 3

Table 1: The distribution of the cytological-histopathological categories of the cases

FNAB categories	Histopathological categories			
	Nonneoplastic (N,%)	**Benign (N,%)**	**Malignant (N,%)**	**Total (N,%)**
Nondiagnostic	2 (1.28)	7 (4.49)	2 (1.28)	11 (7.05)
Benign	15 (9.62)	106 (67.95)	1 (0.64)	122 (78.21)
Suspicious	2 (1.28)	1 (0.64)	8 (5.13)	11 (7.05)
Malignant	0	0	12 (7.69)	12 (7.69)
Total (N,%)	19 (12.18)	114 (73.08)	23 (14.74)	156 (100)

Table 2: The distribution of the histopathological diagnosis of the cases based on their localizations

Parotid gland	**N (%)**	**Submandibular gland**	**N (%)**	**Minor salivary gland**	**N (%)**
Nonneoplastic lesion		***Nonneoplastic lesion***			
Sialadenitis	5 (3.2)	Sialadenitis	4 (2.6)		0 (0)
Granulomatous infl.	2 (1.3)	Branchial cyst	1 (0.6)		
Lymphoepithelial cyst	2 (1.3)	Ectopic thyroid tissue	1 (0.6)		
Necrotizing SM	1 (0.6)				
Oncocytosis	1 (0.6)				
Sjögren syndrome	1 (0.6)				
Epidermoid cyst	1 (0.6)				
Benign		*Benign*		*Benign*	
PA	56 (35.9)	PA	6 (3.8)	PA	1 (0.6)
Warthin tumor	45 (28.8)	Lipoma	1 (0.6)		
Basal cell adenoma	2 (1.3)				
Lipoma	2 (1.3)				
Canalicular adenoma	1 (0.6)				
Malignant		*Malignant*		*Malignant*	
MEC	3 (1.9)	MEC	2 (1.3)	Leiomyosarcoma	1 (0.6)
ACC	3 (1.9)	Lymphoma	2 (1.3)		
Ca-ex-PA	1 (0.6)	Poorly diff. carcinoma	2 (1.3)		
Undifferentiated carcinoma	1 (0.6)	AdCC	1 (0.6)		
SCC metastasis	2 (1.3)	Lymphoepithelial carcinoma	1 (0.6)		
RCC metastasis	1 (0.6)	SCC metastasis	1 (0.6)		
BC metastasis	1 (0.6)				
MM metastasis	1 (0.6)				
Total	132 (84.6)		22 (14.1)		2 (1.3)

Table 3: Sensitivity, specificity, PPV, NPV and accuracy results

	Sensitivity	Specificity	PPV	NPV	Accuracy
*Total	92.3%	100%	100%	99.2%	99.3%
Parotid gland	87.5%	100%	100%	99.1%	99.2%
Submandibular gland	100%	100%	100%	100%	100%
**Total	95.2%	97.6%	87%	99.2%	97.2%
Parotid gland	91.7%	99.1%	91.7%	99.1%	98.4%
Submandibular gland	100%	80%	81.8%	100%	89.5%

PPV: Positive predictive value, NPV: Negative predictive value.
*: The group in which nondiagnostic and suspicious for malignancy in FNABs were not included
**: The group in which nondiagnostic FNABs were not included

4. DISCUSSION

Due to the findings that can overlap between non-neoplastic, benign and malignant salivary gland lesions, it is sometimes difficult to make a definitive diagnosis in the histopathological examination (5-7). The traps at the diagnosis stage in the FNABs may also be due to sampling errors that may cause false negative results (5,11,12). False negative results can be observed in mostly small lesions, tumors with cystic components such as pleomorphic adenoma, Warthin tumor or low grade MEC, and tumors such as sialadenitis or Warthin tumor with regenerative epithelial hyperplasia and squamous metaplasia (11,13). In the literature, false negative rates are reported up to 37% (11,14,15). In our study, the false negative rate was 0.8%. The low false negative rate compared to the literature may be related to the increasing experience in this regard with adequate sampling and increased use of FNAB in salivary gland.

The histopathological examination of the patient with a lesion localized in the parotid gland whose FNAB was interpreted as Warthin tumor resulted in the diagnosis of MEC. There are studies in the literature reporting false-negative results with similar diagnoses (6,16-18). MEC is one of the lesions that is difficult to diagnose accurately with FNAB. Diagnostic cytological findings are a dirty background of mucus and debris with intermediate cells, mucin-producing cells, and squamous epithelial cells. However, in about 20% of these tumors, oncocytic cells, the presence of many lymphocytes on the background with cystic debris, may be misinterpreted as a Warthin tumor. Moreover, mucinous differentiation may be seen in Warthin tumor, which may further complicated differentiate from mucoepidermoid carcinoma (8).

The false positive rate reported in the literature is lower than the false negative rate, and this varies between 0-10% (14,15). In our study, we did not have a false positive result, and accordingly PPV was high (100%), which is consistent with the rates reported in the literature (6,10,11).

The diagnostic accuracy rates evaluated in two separate groups in our study were 99.3% and 97.2%, respectively. Wide ranged rates are reported in studies for sensitivity (81-100%) and specificity (90-100%) (4,6,8-11,18). Our findings were consistent with those reported in the literature. In particular, the specificity was higher than the sensitivity, and the result obtained above 95% showed us that the accuracy rate of FNAB in the diagnosis of benign lesions was high. When we evaluated the parotid gland and submandibular gland separately, it was observed that the sensitivity rate in the submandibular gland was higher than the rate found in the parotid gland (100% vs 87.5% -91.7%). This finding showed us that FNAB was more reliable in detecting the malignant lesions in the submandibular gland. This reliability may also be the case since the lesions observed in the submandibular region are more malignant (1,19).

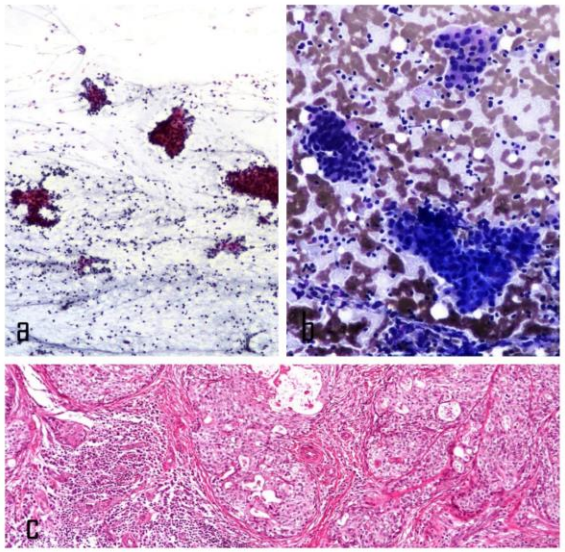

Figure 1: In the patient who was diagnosed as Warthin tumor cytologically, MEC was found as a result of resection. a-b: Epithelial cell groups with oncocytoid appearance on a background containing lymphoid cells (PAP, x100; MGG, x200), c: Tumor tissue consisting of squamoid islands containing keratinous material in their lumen and lymphoid cell infiltration around it (H&E, x100).

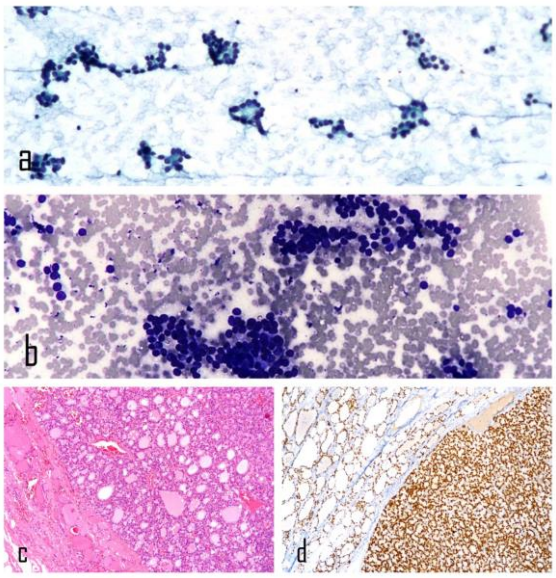

Figure 2: In the patient who was diagnosed as suspicious for malignancy group cytologically, ectopic thyroid tissue was found as a result of resection. a-b: Cellular smears containing microfollicle-like structures consisting of cells in uniform appearance (PAP, x200; MGG, x200), c: Adenoma with normal thyroid tissue (H&E, x100), d: TTF-1 positivity in surrounding the thyroid tissue and adenoma (x100).

For FNAB, which is widely used in the diagnosis of salivary gland lesions, it is important that FNAB is sufficient and of good quality, besides the experience of the evaluating pathologist (20). Nondiagnostic cytology in FNAB is generally reported with a rate varying between 2-34% in the literature (14,15,20,21). Nondiagnostic cytologies that do not contain sufficient cellular elements may depend on the experience of the person performing the procedure, the cytomorphological character of the lesion such as bleeding, necrosis, or low cellularity, as well as the location of the lesion. The rate we found in this group in our study was compatible with the one in the literature, and it was 7.05%.

Studies have reported that 30-60% of lesions suspicious for malignancy are found malignant in histopathological examinations (8,22,23). In our study, this rate was 73%, which was above the rate in the literature. However, histopathological examinations of two lesions originating from the submandibular gland in this group resulted in the diagnosis of ectopic thyroid tissue and sialadenitis, while the lesion originating from the parotid gland was also diagnosed as pleomorphic adenoma. Ectopic thyroid tissue localized in the submandibular region may not be clinically differentiated from the other pathologies such as salivary gland tumors or cysts, as in our study (24).

In the FNAB of sialadenitis, which is one of the non-neoplastic lesions, ductal epithelial cell groups and mononuclear inflammatory cells as well as mucous and squamous metaplastic cells can be observed (8). These metaplastic cells play an important role in the misinterpretation of FNAB, and low-grade MEC should primarily be kept in mind in the differential diagnosis of sialadenitis, as it was the case in our patient (11,13,25). Pleomorphic adenoma is the parotid gland tumor that we encounter most frequently and diagnose in FNAB (2,8,19). Ductal epithelial cells, myoepithelial cells and mesenchymal matrix are observed in varying proportions in smears. Due to the different components, AdCC from matrix-producing tumors, epithelial/myoepithelial carcinoma, solid variant AdCC in the presence of highly cellular smear without matrix, and low-grade MEC when it contains a mucoid matrix may be included in the differential diagnosis (1,8).

Of salivary gland tumors, 60-80% are localized in the parotid gland. Most of the tumors are benign and the most common benign tumor is pleomorphic adenoma. Malignant tumors are in the submandibular gland at a rate of 45% and in the sublingual gland at a rate of 90%. They are observed less frequently (%30) in the parotid gland. The most common malignant tumor is MEC (1,2,5,19,26). The findings of higher rate of benign tumors in the parotid gland and higher rate of malignant tumors in the submandibular gland in our study were consistent with those in the literature. Pleomorphic adenoma was the most common benign tumor, and MEC was the most common among the malignant tumors.

5. CONCLUSION:

The high sensitivity and specificity results we obtained in our study showed that FNAB was a reliable diagnostic tool in salivary gland lesions. However, the wide spectrum of salivary gland lesions and the presence of overlapping cytomorphological findings should also be kept in mind and taken into consideration.

Funding: No financial support was received for the study.

Conflict of interest: None

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