Original Article

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Comparison of Prostate Specific Antigen and Neuropeptide Y Parameters in Patients with Prostate Cancer

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Abstract

Objective: Prostate cancer is a solid tumor that can be fatal in men. Early detection and proper management are essential for improving outcomes and reducing mortality rates associated with this disease. This study aimed to evaluate the potential of neuropeptide Y (NPY) as a biomarker to enhance the effectiveness of prostate specific antigen (PSA) testing in diagnosing and predicting prostate cancer prognosis. NPY, a well-known sympathetic neurotransmitter, possesses growth-promoting and angiogenic properties in various cell types, including those relevant to prostate cancer. Additionally, NPY has been linked to neuroendocrine differentiation of prostate cancer cells. By comparing the efficacy of PSA testing alone with the addition of NPY, this study aimed to determine whether NPY could offer additional predictive value for prostate cancer progression and prognosis.

Materials and Methods: This study involved 90 patients each diagnosed with localized prostate cancer (LPC), metastatic prostate cancer (mPC) at diagnosis, and metastatic castration-resistant prostate cancer (mCRPC) who visited our urology clinic between 2022 and 2023. Blood samples were collected from all participants between 08:00 and 09:00 after a 12 hour fast. In the LPC and mPC groups, samples were collected upon diagnosis, whereas in the mCRPC group, samples were collected upon development of treatment resistance. NPY levels in blood samples were analyzed using enzyme-linked immunosorbent assay method. Serum NPY levels were compared between the LPC, mPC, and mCRPC groups.

Results: PSA values were calculated as 12.6 (7.08-32.47) ng/L in the LPC group, 159 (73.1-405.2) ng/L in the mPC group, and 38.33 (18.4-132) ng/L in the mCRPC group, with a statistically significant difference between the groups ($p<0.001$). The average NPY values were 351.3±162.7 ng/L in the LPC group, 276.5±85 ng/L in the mPC group, and 272.13±94.7 ng/L in the mCRPC group. NPY values were found to be statistically significantly higher in the LPC group ($p=0.018$).

Conclusion: The serum NPY levels were notably elevated in the LPC group compared with the mPC and mCRPC groups. This finding implies a potential association between low NPY levels and mPC as well as mCRPC.

Keywords: Prostate cancer, PSA, NPY, neuropeptide-Y

Introduction

Prostate cancer is the prevailing form of solid tissue cancer among men in Western societies. Prostate specific antigen (PSA) testing and screening have led to higher rates of early detection and decreased incidences of metastasis and fatalities associated with the disease (1). PSA, while specific to the prostate, lacks specificity to prostate cancer and can be elevated in benign conditions like benign prostatic hyperplasia (BPH) and prostate infections. This highlights the necessity of identifying new biomarkers with higher specificity and sensitivity for prostate cancer diagnosis. These potential biomarkers must undergo rigorous validation to ensure their accuracy and effectiveness in the detection and monitoring of prostate cancer. These markers should aid in patient classification, enable personalized treatment planning, and prevent overdiagnosis and overtreatment of clinically insignificant prostate cancers, thus safeguarding patients' quality of life.

The neuropeptide Y (NPY) family comprises three peptides: NPY, polypeptide YY, and pancreatic polypeptide. The NPY plays an

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integral role in peripheral organs, including vasoconstriction and food intake regulation. In humans, NPY exerts its effects through four G protein coupled receptors: Y1, Y2, Y4, and Y5. NPY1, Y2, and Y5 receptors play crucial roles in oncogenesis and angiogenesis (2).

The relationship between NPY levels and cancer progression is complex and somewhat controversial. Although active NPY is primarily known for its roles in appetite stimulation, vasoconstriction, and stress behavior regulation, its involvement in cancer progression is multifaceted. NPY is strongly linked to the development of certain tumors, including neural crest-derived tumors, breast cancer, and prostate cancer. It appears to promote cancer progression by facilitating processes such as proliferation, invasion, metastasis, and angiogenesis (3). The precise mechanisms governing the role of NPY in the development and progression of cancer are still unclear. Further research is essential to comprehensively assess its influence on tumor biology.

NPY and other neuroendocrine modulators have been identified in prostate cancer, suggesting a potential role for neuroendocrine signaling pathways in the development of the disease (4). In addition to its critical role in regulating several physiological processes, NPY promotes cell proliferation and has been implicated as a growth-promoting factor in several malignancies, including prostate cancer (5,6). Indeed, it has been suggested that NPY is synthesized at higher levels in cancerous prostate tissue than in benign prostate tissue and cancerous tissues from other organs (4-7). Despite the available data, the precise effect of NPY on prostate cancer diagnosis and progression remains unclear. Further research is needed to fully elucidate the role of NPY in the development and progression of prostate cancer and its potential use as a biomarker or therapeutic target in the management of prostate cancer.

This study demonstrated the potential of NPY levels as a new marker for predicting the risk of prostate cancer. To achieve this goal, we compared serum PSA levels with serum NPY levels in patients with prostate cancer. Early diagnosis, treatment effectiveness, and prevention of recurrence and progression are crucial aspects of prostate cancer management. Therefore, clinicians need to identify specific and sensitive markers for early diagnosis. By assessing the utility of NPY values alongside PSA levels, we sought to enhance risk stratification in patients with prostate cancer and improve clinical decision-making during their management.

Materials and Methods

The study involved 90 patients each diagnosed with localized 30 prostate cancer [localized prostate cancer (LPC)], 30 metastatic prostate cancer (mPC) at diagnosis, and 30 metastatic castration-resistant prostate cancer (mCRPC) who visited the urology clinic between 2022 and 2023.

All participants provided informed verbal and written consent before participation. Age, PSA levels, digital rectal examination (DRE) findings, and pathological findings were systematically collected and recorded for each participant. Clinical staging was conducted following the 2017 tumor, lymph node, metastasis classification, considering DRE findings and imaging results. Pathological staging was based on pathological reports, and Gleason scores from prostate biopsy and radical prostatectomy specimens were graded using the 2014 International Society of Urological Pathology (ISUP) grading system. Additionally, patients were classified according to the D'Amico risk classification, considering serum PSA levels, Gleason scores, and clinical stages. Venous blood samples were collected from all participants between 08:00 and 09:00 a.m. following a 12 hour fast. Blood samples were collected upon diagnosis in the LPC and mPC groups and upon treatment resistance in the mCRPC group. After centrifugation at 3000 rpm for 15 minutes, serum samples were separated and stored at -80 °C in the Biochemistry Laboratory of Sivas Cumhuriyet University Faculty of Medicine Health Services Application and Research Hospital for analysis. NPY levels in serum samples were determined using enzyme-linked immunosorbent assay (ELISA) method. Absorbance was measured at 450 nm using an ELISA reader (Thermo Scientific Multiskan FC). Serum NPY levels were measured using a Human NPY ELISA Kit (Bioassay Technology Laboratory) after dilution at a ratio of 1:5, following the procedures specified in the kit package insert. The kit has a sensitivity of 2.36 ng/L and a measurement range of 5-2000 ng/L, with an inter-assay precision coefficient of variability of less than 10%.

Statistical Analysis

The data were analyzed using the SPSS software (SPSS Inc., Chicago, IL). Parametric tests were used for data evaluation when the assumptions, such as the normal distribution assessed using the Kolmogorov-Smirnov test, were satisfied. ANOVA followed by Tukey's post-hoc test was used to compare measurements from more than two independent groups. Non-parametric tests, such as the Kruskal-Wallis test and Mann-Whitney U test, were used to compare measurements from more than two independent groups when the assumptions for parametric tests were not met. Additionally, the chi-square test was employed with assurance to analyze the count data. The significance level was set at a confidence level of 0.05.

All subjects provided informed consent for study participation before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Sivas Cumhuriyet University Ethics Committee (decision no: 2022-01/02, date: 11.01.2022).

Results

In our study, the mean age of the LPC group was 67.6±6.4, while the mean ages of the mPC and mCRPC groups was 73.1±9.1 and 72.7±7.9, respectively. The LPC group was significantly older than the other two groups (p=0.013) (Table 1).

PSA values were calculated for the patient groups as follows: 12.6 (7.08-32.47) ng/L in the LPC group, 159 (73.1-405.2) ng/L in the mPC group, and 38.33 (18.4-132) ng/L in the mCRPC group. A statistically significant difference was found between the groups (p<0.001). NPY values were also calculated for the patient groups: 351.3±162.7 ng/L in the LPC group, 276.5±85 ng/L in the mPC group, and 272.13±94.7 ng/L in the mCRPC group. The LPC group had significantly higher NPY values (p=0.018) (Table 1).

Table 1. Comparing age, PSA, NPY, PNI, and ISUP grades among groups				
	LPC (n=30)	mPC (n=30)	mCRPC (n=30)	p-value
Age (years)	67.6±6.4[a]	73.1±9.1[b]	72.7±7.9[b]	0.013
PSA (ng/L)	12.6 (7.08-32.47)[a]	159(73.1-405.2)[b]	38.33(18.4-132)[c]	<0.001
NPY (ng/L)	351.3±162.7[a]	276.5±85[ab]	272.13±94.7[b]	0.018
PNI	15 (50%)[a]	15 (50%)[a]	29 (96.7%)[b]	<0.001
ISUP 1	11 (36.7%)	0 (0%)	0 (0%)	
ISUP 2	7 (23.3%)	2 (6.7%)	0 (0%)	
ISUP 3	5 (16.7%)	6 (20%)	4 (13.3%)	
ISUP 4	6 (20%)	9 (30%)	10 (33.3%)	
ISUP 5	1 (3.3%)	13 (43.3%)	16 (53.3%)	
PSA: Prostate specific antigen, NPY: Neuropeptide Y, PNI: Perineural invasion, ISUP: International Society of Urological Pathology, LPC: Localized prostate cancer, mPC: Metastatic prostate cancer, mCRPC: Metastatic castration-resistant prostate cancer				

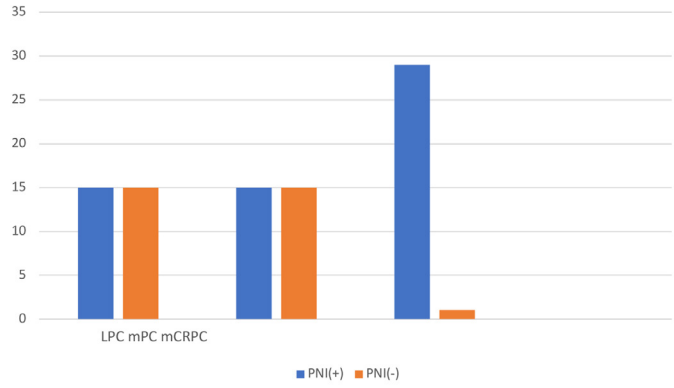

Figure 1. Distribution of PNI positivity between groups

PNI: Perineural invasion, LPC: Localized prostate cancer, mPC: Metastatic prostate cancer, mCRPC: Metastatic castration-resistant prostate cancer

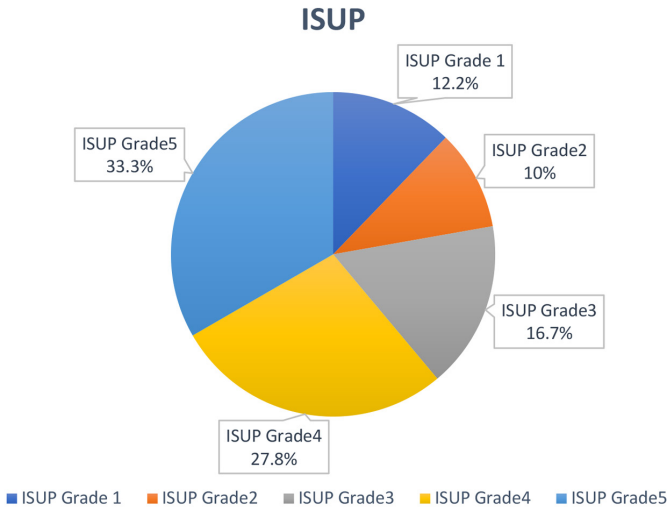

Figure 2. ISUP grade distribution in all patients

ISUP: International Society of Urological Pathology

Perineural invasion (PNI) was present in 50% of LPC patients, 50% of mPC patients, and 96.7% of mCRPC patients. The mCRPC group demonstrated a statistically significant increase in PNI compared with the other two groups (p<0.001) (Table 1, Figure 1).

A comprehensive evaluation of all patients according to ISUP grade revealed the following distribution: ISUP grade 1 (11.2%), ISUP grade 2 (10%), ISUP grade 3 (16.7%), ISUP grade 4 (27.8%), and ISUP grade 5 (33.3%) (Table 2, Figure 2).

There were no statistically significant differences between the patients in terms of ISUP Grade scores and NPY values (p=0.193) (Table 2). However, pairwise comparisons indicated a statistically significant difference between ISUP grades 1 and 2, as well as between ISUP grades 1 and 5 (p=0.031 and p=0.047, respectively) (Figure 3).

When the LPC and mPC patient groups were compared, PSA values were found to be significantly higher in the mPC group (p<0.001). NPY values were found to be statistically significantly higher in the LPC group (p=0.031) (Table 3, Figure 4).

When the LPC and mCRPC patient groups were compared in terms of NPY, the NPY values were found to be significantly higher in the LPC group (p=0.026) (Table 4, Figure 4).

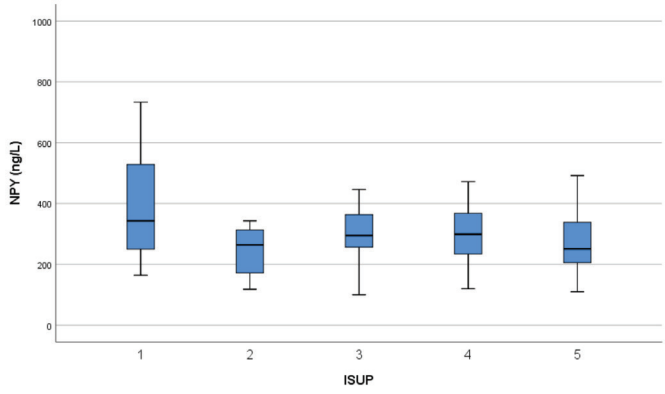

Figure 3. Relationship between ISUP Grade and NPY (box-plot graph)

ISUP: International Society of Urological Pathology, NPY: Neuropeptide Y

Table 2. Comparing ISUP Grade scores and NPY levels among all patients						
ISUP grade	**1**	**2**	**3**	**4**	**5**	**p-value**
N	11 (12.2%)	9 (10%)	15 (16.7%)	25 (27.8%)	30 (33.3%)	
NPY	343 (244-557)	264 (171-313.5)	295 (251-367)	299 (233-370)	251 (203-343)	0.193
NPY: Neuropeptide Y, ISUP: International Society of Urological Pathology						

Table 3. Comparison of age, PSA, NPY, and ISUP grades between the LPC and mPC groups			
	LPC (n=30)	**mPC (n=30)**	**p-value**
Age (years)	67.6±6.4	73.1±9.1	0.009
PSA (ng/L)	12.6 (7.08-32.47)	159 (73.1-405.2)	<0.001
NPY (ng/L)	351.3±162.7	276.5±85	0.031
ISUP 1	11 (36.7%)	0 (0%)	<0.001
ISUP 2	7 (23.3%)	2 (6.7%)	
ISUP 3	5 (16.7%)	6 (20%)	
ISUP 4	6 (20%)	9 (30%)	
ISUP 5	1 (3.3%)	13 (43.3%)	
PSA: Prostate specific antigen, NPY: Neuropeptide Y, ISUP: International Society of Urological Pathology, LPC: Localized prostate cancer, mPC: Metastatic prostate cancer			

Table 4. Comparison of NPY levels between the LPC and mCRPC patient groups			
	LPC (n=30)	**mCRPC (n=30)**	**p-value**
NPY (ng/L)	351.3±162.7	272.13±94.7	0.026
NPY: Neuropeptide Y, LPC: Localized prostate cancer, mCRPC: Metastatic castration-resistant prostate cancer			

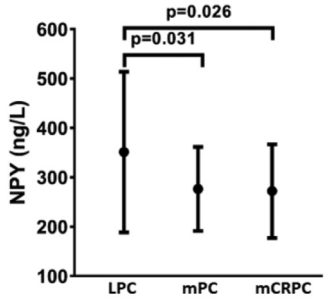

Figure 4. Relationship between LPC, mPC, and mCRPC and NPY

LPC: Localized prostate cancer, mPC: Metastatic prostate cancer, mCRPC: Metastatic castration-resistant prostate cancer, NPY: Neuropeptide Y

Discussion

Prostate cancer is a significant health challenge for men worldwide, with 81.4 million cases of the second most frequently diagnosed cancer in men reported in 2020 (8). Studies indicate that approximately one in every seven men will receive a prostate cancer diagnosis during their lifetime (9). Presently, screening for prostate cancer is a risk-based approach. While PSA and DRE serve as primary screening tools, the limitations of PSA, as it is organ-specific rather than cancer-specific and can increase in non-cancerous conditions, restrict its clinical utility. Consequently, numerous studies aim to enhance the sensitivity and specificity of PSA and to identify new, more ideal markers for prostate cancer diagnosis. The NPY family comprises three peptides: NPY, polypeptide YY, and pancreatic polypeptide. In addition to its vital role in regulating various physiological functions like vasoconstriction and food intake stimulation, NPY has been implicated in stimulating cell proliferation and acting as a growth-promoting factor in several malignancies (5,6). A study examining 400 pathology samples across different organs observed predominant staining for pro-NPY in prostate cancer. NPY has been implicated in the development of certain tumors, including neural crest-derived tumors, breast cancer, and prostate cancer, by promoting processes such as proliferation, invasion, metastasis, and angiogenesis (4). However, there is a paucity of studies investigating the relationship between PSA and NPY in prostate cancer. Recent studies have highlighted the expression of the Y1-R gene and protein in prostate cancer cells, suggesting the involvement of NPY in the regulation of tumor growth (10,11). Therefore, data on NPY levels in patients with prostate cancer at various stages are warranted. In this study, we investigated the relationship between PSA and NPY levels in serum samples collected from prostate cancer patients at various clinical and pathological stages.

PNI is a frequent indicator of tumor metastasis and can be identified in various malignancies, including prostate cancer (12). The presence of PNI is associated with an increased risk of extraprostatic spread. Although PNI defines PSA recurrence following radical prostatectomy, it has been suggested that it does not influence the preoperative Gleason score, irrespective of PSA levels and clinical stage (13). Passavanti et al. (14) evaluated radical prostatectomy specimens from 94 patients and reported a PNI positivity rate of 53%. Moreover, their research did not reveal any statistically significant correlation between PSA and

PNI (14). In a study involving 364 patients who underwent radical prostatectomy, PNI positivity was observed in 287 individuals (79%). Interestingly, the study results indicated no significant relationship between PNI and preoperative PSA levels (p=0.96) (15). In line with these findings, our study evaluated patients in the LPC group, and the PNI positivity rate was 50%. Similar to previous studies, no statistically significant relationship was identified between PSA and PNI in these patients (p=0.148). In this study, no statistically significant relationship was observed between NPY levels and PNI in the LPC group (p=0.222). Although there may be differences in tissue characteristics, the results of our study are supported by Alshalalfa et al. (16), who studied both localized and mPC patients. Based on these findings, it appears that there is no significant association between NPY and PNI, suggesting that NPY can independently predict the negative features of prostate cancer regardless of PNI status.

In a study conducted by Niu et al. (17) involving 402 patients with prostate cancer, significant differences were observed in the expression of the NPY gene across various T stages and Gleason scores (17). In our study, we divided 90 patients according to ISUP Grade scores. However, when comparing NPY scores across ISUP grades, we did not find a significant difference between ISUP grades (p=0.193). In pairwise comparisons, we found a statistically significant difference between ISUP grade 1 and ISUP grade 2, and between ISUP grade 1 and ISUP grade 5 (p=0.031 and p=0.047, respectively). Our findings suggest that low NPY values in prostate cancer are correlated with high-grade disease. Therefore, patients with low NPY values may require closer monitoring for tumor aggressiveness.

Accumulating evidence suggests that NPY plays a role in aging and determining lifespan (18). It is known that NPY levels decrease with age. However, determining this decline solely by age is not sufficient to evaluate tumor aggressiveness in patients with prostate cancer. Indeed, it has been observed that as the ISUP grade increases, NPY levels decrease. This indicates that NPY is an independent biomarker of tumor aggressiveness in prostate cancer.

The study, conducted in localized and mPC patients, found that although NPY expression was generally higher than that in other solid tumors, low NPY expression may serve as a negative predictor of aggressive disease and progression in prostate cancer. In the Gleason score-matched groups, lower NPY expression was correlated with more aggressive disease phenotypes. In addition, tumors with the lowest decile of NPY expression had significantly higher rates of metastasis (16). In the same study, low NPY expression was linked to shorter metastasis-free survival and progression-free survival (PFS). Additionally, the study revealed lower NPY expression in castration-resistant mPC than in primary tumors. A gradual decrease in NPY expression was observed in correlation with castration and neuroendocrine developmental status.

In a study involving patients with castration-resistant prostate cancer, those who tested positive for NPY were found to have a 4.2 times higher risk of treatment failure (p<0.01) and a 3.2 times shorter PFS (p<0.001) compared with those who tested negative (19). In our study, patients were categorized into LPC, mPC, and mCRPC groups. Significant differences in NPY values were observed between the LPC and mPK and mCRPC groups. Specifically, NPY levels were higher in the LPC group than in the mPC and mCRPC groups. Based on these findings, we observed lower NPY values in advanced stage and mPC, which aligns with existing literature. We propose that low NPY levels during prostate cancer diagnosis may serve as a predictor of metastatic disease. Therefore, patients with low NPY levels that are not initially metastatic should undergo detailed examination to assess the risk of progression to metastatic disease.

Study Limitations

Despite our efforts, several limitations were encountered in our study. These include the heterogeneity among patient groups, the relatively small sample size compared with other studies in the literature, and the absence of a BPH or healthy control group for comparison. Additionally, while most studies in the literature utilize cell or tissue samples, our study employs serum samples, which may introduce differences in the results due to sample type. However, despite these limitations, the results of our study are consistent with existing literature, and we believe that they contribute valuable insights that can enhance current knowledge and guide future research endeavors in this field. We believe that our study will contribute to our national data regarding the classification of prostate cancer and its relationship with NPY.

Conclusion

In conclusion, prostate cancer remains a significant global health concern, prompting extensive research into its diagnosis and treatment. Many studies have focused on improving the sensitivity and specificity of PSA as well as identifying biomarkers such as NPY. Unlike previous studies, our research examined serum NPY levels using a faster and less invasive method applicable to clinical practice. Our findings revealed lower serum NPY levels in patients with metastatic and castration-resistant mPC than in those with localized disease. Additionally, higher NPY levels were observed in patients with lower ISUP grades, suggesting a potential role for NPY in both clinical and pathological staging of prostate cancer.

Although our study highlights the potential utility of NPY in prostate cancer diagnosis and its association with disease progression, serum PSA levels remain more sensitive indicators of tumor burden and pathological staging. Therefore, we propose that NPY may complement PSA for predicting metastatic disease rather than serving as a standalone agent. Some prostate cancers do not produce significant levels of PSA, which can result in false-negative results. Furthermore, patients with mCRPC may exhibit low PSA levels because of the effects of castration. In light of these considerations, a more comprehensive view of the patient's condition can be obtained using the use of both biomarkers to monitor disease progression and response to treatment. This approach can facilitate more informed clinical decisions, more effective and personalized patient care, and more accurate patient stratification. We anticipate that our findings will stimulate further research into the use of NPY as a diagnostic marker for prostate cancer, encouraging more comprehensive studies with larger sample groups in the future.

Footnote

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Informed Consent: All participants provided informed verbal and written consent before participation.

Authorship Contributions

Surgical and Medical Practices: A.Ö., H.S., A.A., İ.E.E., E.Ko., Concept: A.Ö., H.S., A.A., İ.E.E., E.K., E.Ko., Design: A.Ö., H.S., A.A., S.B., İ.E.E., E.K., Data Collection or Processing: A.Ö., S.B., İ.E.E., E.K., Analysis or Interpretation: A.Ö., S.B., E.K., E.Ko., Literature Search: A.Ö., H.S., A.A., E.Ko., Writing: A.Ö., H.S., S.B., E.Ko.

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