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Clinicopathological Features of Nephrogenic Adenomas Mimicking Malignancy

Maligniteyi Taklit Edebilen Nefrojenik Adenomların Klinikopatolojik Özellikleri

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Abstract: Nephrogenic adenoma (NA) is a rare benign lesion of the urinary tract with diverse clinical and histopathological features that may mimic malignancy. This study aimed to evaluate the clinicopathological features, histological patterns, and associated conditions in a single-center cohort, and to emphasize the differential diagnosis from other malignant entities that may pose diagnostic challenges. A retrospective analysis was performed on 49 biopsy specimens from 39 patients diagnosed with NA. Clinical data, cystoscopic findings were recorded. The median patient age was 68 years, with a male predominance (76.9%). The most common presenting symptoms were hematuria and dysuria (28.2% each). The bladder was the most frequent site of involvement (79.5%). Histologically, flat (67.3%) and tubular (59.2%) patterns were predominant, and most cases exhibited multiple coexisting patterns. Accompanying neoplasia was identified in 71.8% of the cases, most commonly invasive urothelial carcinoma (53.8%). Recurrence occurred in a subset of patients. NA demonstrates marked histologic heterogeneity and is frequently coexists with urothelial neoplasia. Awareness of its diverse morphology and frequent coexistence with malignancy is essential to avoid diagnostic pitfalls and ensure appropriate clinical management.

Keywords: Nephrogenic adenoma, nephrogenic metaplasia, fibromyxoid, renal pelvis, bladder

Ethics statement / Compliance with Ethical Standards: This study was approved by the Institutional Ethics Committee of Ondokuz Mayıs University Hospital (protocol number 2026/242, approval date: 29.04.2026).

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

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Özet: Nefrojenik adenom (NA), maligniteyi taklit edebilen çeşitli klinik ve histopatolojik özelliklere sahip, idrar yollarının nadir görülen benign bir lezyonudur. Bu çalışma, tek merkezli bir kohortta klinikopatolojik özellikleri, histolojik paternleri ve ilişkili durumları değerlendirmeyi; ayrıca tanısal açıdan karışabileceği diğer malign durumlarla ayırıcı tanıyı vurgulamayı amaçlamıştır. NA tanısı konulan 39 hastadan alınan 49 biyopsi örneği üzerinde retrospektif bir analiz yapılmıştır. Klinik veriler, sistoskopik bulgular kaydedilmiştir. Hastaların medyan yaşı 68 olup, erkeklerde daha sıktır (%76.9). En sık görülen belirtiler hematüri ve dizüri (%28.2) olmuştur. En sık etkilenen bölge mesane (%79.5) olmuştur. Histolojik olarak düz (%67.3) ve tübüler (%59.2) paternler baskın olup, vakaların çoğunda birden fazla birlikte görülen patern mevcuttu. Vakaların %71.8'inde eşlik eden neoplazi tespit edildi, en sık görülen ise invaziv ürotelyal karsinomdu (%53.8). Hastaların bir alt grubunda nüks meydana geldi. NA, belirgin histolojik heterojenite gösterir ve sıklıkla ürotelyal neoplazi ile birlikte görülmektedir. Çeşitli morfolojisinin ve malignite ile sık birlikte görülmesinin farkında olmak, tanısal tuzaklardan kaçınmak ve uygun klinik yönetimi sağlamak için önemlidir.

Anahtar Kelimeler: Nefrojenik adenom, nefrojenik metaplazi, fibromiksoid, renal pelvis, mesane

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1. Introduction

Nephrogenic adenoma (NA) is a rare, benign epithelial lesion of the urinary tract that arises from renal tubular epithelial cells (1). According to the inflammation theory, chronic inflammation and urothelial stimulation cause metaplasia of urothelial cells into nephrogenic cells. The embryologic theory suggests that NA arises from residual mesonephric tissue in the bladder. In contrast, the implantation theory proposes that NA develops from shed renal tubular cells implanted into damaged mucosa. Common predisposing factors include genitourinary trauma, chronic inflammation, prior surgery, chronic catheterization, intravesical therapy, renal calculi, anatomical anomalies, and pelvic radiation (1,2,3). Environmental factors such as cigarette smoking may also contribute to its development (4).

It occurs mostly in adults, between the ages of 4 and 81 (5). The clinical presentation or cystoscopic appearance is not specific. A wide range of morphological patterns, including tubular, papillary, microcystic, fibromyxoid, and flat patterns, have been reported in NA (6). Follow-up is essential for all patients with NA, particularly given the documented potential for recurrence and the need to monitor for any possible malignant transformation (7). Despite various reports in the literature, there are very few large series to comprehensively assess clinical behavior and optimal management strategies, and no clear consensus guidance on follow-up protocols exists. This study aims to characterize the clinicopathological features and histological patterns of NA in our patient group, and to investigate specific relationships between histological patterns and cellular features and the frequency of concomitant urothelial neoplasia in our cohort, contributing to the existing body of knowledge.

2. Material and methods

2.1. Patient selection and histopathological evaluation

This retrospective study included 49 biopsy specimens taken at different times from 39 patients diagnosed with NA between 2021 and 2026 at Ondokuz Mayıs University. Clinical data, including demographic characteristics, potential predisposing factors (such as prior urological interventions, recurrent urinary tract infections, ureteral stent placement, and urolithiasis), presence of accompanying neoplasia, recurrence status, and cystoscopic findings, were retrieved from the hospital information management system. All available histological slides corresponding to NA were retrieved from pathology archives and their histopathological features were examined by 2 pathologists.

Two units of analysis were used throughout the study. Patient-level data (n = 39) were used for demographic characteristics, presenting symptoms, predisposing factors, treatment history, recurrence and follow-up. Specimen-level data (n = 49) were used for lesion size, cystoscopic findings, specimen type, histological patterns and cellular features. The denominator is stated explicitly for every reported proportion.

2.2. Statistical analyses

Statistical analyses were performed using Jamovi software (version 2.6.26). Descriptive statistics for numerical variables were presented as mean ± standard deviation and median (minimum-maximum); for categorical data, they were expressed as frequencies and percentages. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. A p-value of <0.05 was considered statistically significant. This study was approved by the Institutional Ethics Committee of Ondokuz Mayıs University Hospital (protocol number 2026/242, approval date: 29.04.2026) and was performed in accordance with the tenets of the Declaration of Helsinki.

3. Results

Forty-nine biopsies were analyzed from 39 patients in this retrospective study. The female-to-male ratio was 3:10 (23.1% vs. 76.9%). The median age of the patients was 68 years (range, 11–88 years; mean, 69 ± 16.7). Among the study population, 17 patients (43.6%) were smokers. Pack-year data were available for 14 patients, with missing data in 3 cases, with a median exposure of 30 pack-years (range, 6–100). The most common presenting symptoms were hematuria and dysuria (28.2% each), followed by pollakiuria/nocturia (25.6%). Incontinence was less frequent (10.3%), whereas flank pain and obstructive symptoms were rare (2.6% each; Table 1).

Table 1. Distribution of presenting symptoms (n = 39)

Symptoms	n (%)
Hematuria	11 (28.2%)
Dysuria	11 (28.2%)
Pollakiuria / Nocturia	10 (25.6%)
Incontinence	4 (10.3%)
Flank pain	1 (2.6%)
Obstructive symptoms	1 (2.6%)
Asymptomatic	4 (10.3%)

Cystoscopic size data was available for 22 NA. The mean tumor size was 7.2±10.8mm, with a median of 1.5mm (1-40mm). Lesion localization was generally consistent within the same patient; however, one patient presented with synchronous lesions involving both the ureter and bladder. Given this overlap, localization frequencies were primarily evaluated on a per-patient basis (n=39). The bladder was the most common site (n=31, 79.5%), followed by the urethra (n=4, 10.3%), the ureter (n=3, 7.69%), and the renal pelvis (n=1, 2.6%). Bladder lesion localization analysis revealed that the posterior wall was the most frequently involved site (n=7, 22.6%), followed by diffuse involvement of the bladder (n=6, 19.4%). The trigone and left lateral walls were affected at similar rates (n=5, 16.1% each), while the anterior wall was involved in 12.9% of the cases (n=4). The dome and bladder neck were less commonly affected (n=2, 6.5% each). For completeness, lesion-based analysis (n=49) showed a similar distribution, with the majority of lesions located in the bladder (n=39, 79.6%), followed by the urethra (n=5, 10.2%), ureter (n=4, 8.2%), and renal pelvis (n=1, 2.0%). The most common cystoscopic finding was hyperemia (n=19, 38.8%), followed by papillary lesion (n=13, 26.5%) (Table 2).

Table 2. Cystoscopic characteristics of the lesions (n = 49)

Cystoscopic findings	n	%
Hyperemia	19	38.8%
Papillary lesion	13	26.5%
Mass	3	6.1%
Flattening	2	4.1%
Polypoid	2	4.1%
Hemorrhage	1	2.0%
Scar	1	2.0%
Edema	1	2.0%
Ulcer	1	2.0%
Cyst	1	2.0%
N/A	5	10.2%
Total	49	100%

Specimens in which an NA diagnosis was given were most frequently transurethral resection (TUR) specimens (n=29, 59.2%). This was followed by punch biopsies (n=19, 38.8%) and, less frequently, radical cystoprostatectomy specimens (n=1, 2.0%). Concomitant neoplasia was defined as urothelial or non-urothelial malignancy histologically confirmed in the sample diagnosed with NA or in a separate sample previously obtained from the same patient. Accompanying neoplasia was identified in 28 patient (71.8%) of the 39 patients. Invasive urothelial carcinoma was the most common (n=21, 53.8%), followed by non-invasive papillary urothelial carcinoma (n=4, 10.3%). Less commonly, prostatic adenocarcinoma infiltrating the bladder, urothelial carcinoma in situ, clear cell adenocarcinoma and endometrial adenocarcinoma were each observed in one case (2.6% each). No accompanying neoplasia was present in 11 cases (28.2%). BCG therapy was administered to 21 patients (53.8%), while chemotherapy and radiotherapy were administered to 10 (25.6%) and

four (10.3%) patients, respectively. A history of ureteral stent placement was present in 3 patients (7.69%), while urinary stones and urinary tract infection were identified in 2 (5.12%) and one (2.56) patients, respectively. Follow-up information was available for 37 of 39 patients, with a mean follow-up time of 47.5 ± 56.1 months and a median of 29 months (3–204). Recurrence was documented in 6 patients, representing 15.4% (6/39) of the entire cohort and 16.2% (6/37) of patients with available follow-up information. These 6 patients caused a total of 9 relapses: one patient recurred three times, one patient twice, and four patients once. Time to recurrence was defined as the time elapsed since the initial NA diagnosis. The mean time to recurrence was 22.2 monhts in the 6 cases, with a median of 15 months (8–48 months).

Histological analysis of the 49 NA biopsies revealed that the most frequent patterns were flat (n=33, 67.3%) and tubular (n=29, 59.2%), followed by microcystic (n=23, 46.9%) and papillary (n=15, 30.6%) patterns. The fibromyxoid pattern was rare, observed in only one case (2.0%) (Figure 1). Multi-pattern analysis demonstrated notable heterogeneity. The most frequent pairwise combination was tubular with flat (n=20, 40.8%), and the most frequent triad was tubular + flat + microcystic (n=11, 22.4%), which was also the single largest group in the series. The fibroid pattern was seen in only one biopsy (2.0%) (Figure 2) (Table 3). Most NA biopsies displayed multiple coexisting histological patterns, whereas single-pattern lesions were relatively uncommon, highlighting the frequent histological heterogeneity within individual specimens.

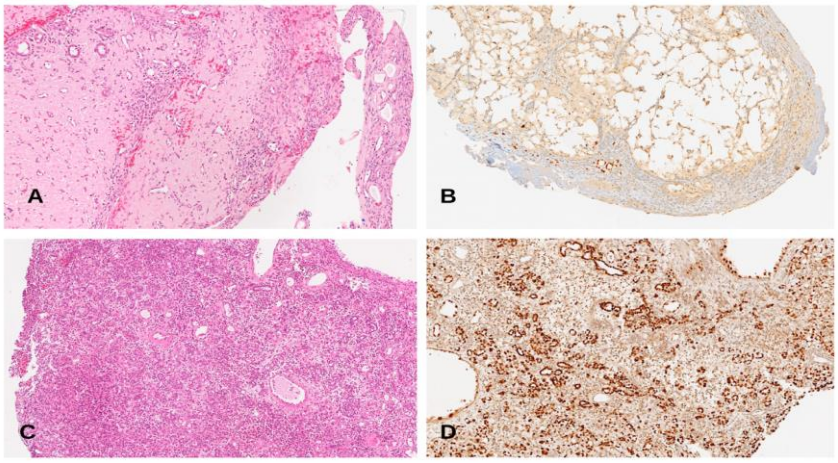


Figure 1. Nephrogenic adenoma with fibromyxoid pattern (1A: H&E; 80x). PAX8 positivity in fibromyxoid nephrogenic adenoma (1B: DAB; 80x). Nephrogenic adenoma with tubular pattern in renal pelvis (1C: H&E; 60x). PAX8 positivity in nephrogenic adenoma in renal pelvis (1D: DAB; 60x)

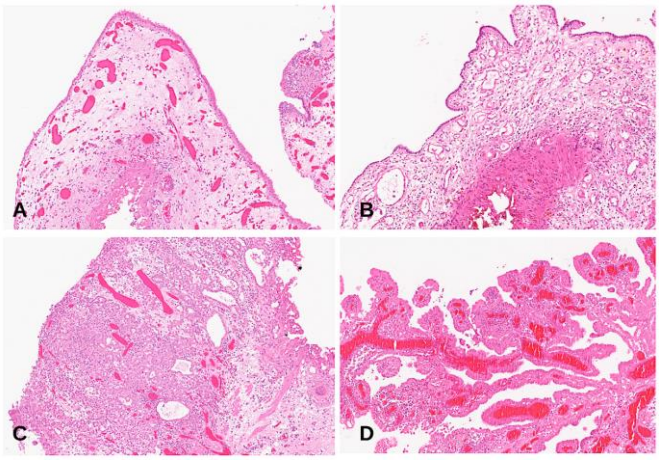


Figure 2. Flat pattern in nephrogenic adenoma (2A: H&E; 80x). Clear cell change in nephrogenic adenoma with flat pattern (2B:H&E; 100x). Nephrogenic adenoma with tubular and microcystic pattern (2C: H&E; 80x). Papillary pattern 2D: H&E; 80x)

Table 3. Distribution of histological pattern combinations in nephrogenic adenoma biopsies n = 49

Pattern Combination	n	%
Tubular + flat + microcystic	11	22.4
Flat only	7	14.3
Tubular + flat	5	10.2
Tubular only	4	8.2
Papillary only	3	6.1
Papillary + flat	3	6.1
Papillary + tubular + flat	3	6.1
Flat + microcystic	2	4.1
Microcystic only	2	4.1
Tubular + microcystic	2	4.1
Papillary + tubular + microcystic	2	4.1
Other rare combinations	5	10.2
Total	49	100

Clear cell features were observed in 2 cases (4.1%), luminal secretion in 5 cases (10.2%), and a hobnail pattern in 3 cases (6.1%). All luminal secretions were basophilic, except for one. Nucleoli were observed in 29 cases (59.2%). Inflammation was common, with 43 biopsies (87.8%). When we examined the relationship between cellular changes and patterns, clear cell changes were observed in only 2 patients with papillary and flat patterns (p=0.08, p=1). All biopsies with a hobnail pattern had a tubular pattern. Two showed a papillary, tubular, and flat pattern. No statistically significant correlation was found in any of them (p=0.2, p=0.2, p=1). Prominent nucleoli were significantly more frequent in biopsies showing a microcystic pattern than in those without it (18/23, 78.3% vs. 11/26, 42.3%; p = 0.011), whereas no significant association was found with the papillary, tubular, or flat patterns. No significant associations were observed with papillary (p = 0.580), tubular (p= 0.093), or flat patterns (p = 0.362). No significant associations were observed between histologic patterns (Table 4). PAX8 was administered to twenty-two patients diagnosed with NA. Three patients were administered GATA3, and two were administered NKX3.1, with negative results.

Table 4. Association between histologic patterns and cellular features or inflammation n = 49

Feature	Papillary (n=15, 30.6%)		Tubular (n=29, 59.2%)		Flat (n=33, 67.3%)		Microcystic (n=23, 46.9%)		Fibromyxoid (n=1, 2.0%)	
	n (%)	p-value	n (%)	p-value	n (%)	p-value	n (%)	p-value	n (%)	p-value
Clear cell feature	1 (2.0%)	0.080	0	0.162	1 (2.0%)	1.000	0	0.491	0	1.000
Luminal secretion	1 (2.0%)	1.000	0	0.636	0	0.313	4 (8.2%)	0.018	0	0.102
Hobnail pattern	2 (4.1%)	0.200	3 (6.1%)	0.260	2 (4.1%)	0.200	0	0.594	0	1.000
Nucleoli present	8 (16.3%)	0.580	20 (40.8%)	0.093	21 (42.9%)	0.362	18 (36.7%)	0.011	0	1.000
Inflammation present	15 (30.6%)	0.159	26 (53.1%)	0.677	30 (61.2%)	0.377	19 (38.8%)	0.400	1 (2.0%)	0.122

Percentages are calculated based on the total number of cases (n=49). Multiple histologic patterns may be present in a single case. Statistical analysis for the fibromyxoid pattern is limited due to small sample size (n=1)

4. Discussion

NA is a benign proliferative lesion of the urinary tract with a broad spectrum of clinical and histopathological presentations. In the present study, we provide a comprehensive clinicopathologic evaluation of NA, highlighting its morphological diversity, frequent association with urothelial neoplasia, and specific histologic correlations that may have diagnostic implications. While similar single-center studies have revealed variable patient populations, our study contributes to the literature as a series with a rare localization and histological pattern (2,3,8). The male predominance and mean age in our series are consistent with previously reported demographic data; although, the male-to-female ratio varies among some studies (2,3). Although a high proportion of patients were smokers, this likely reflects underlying urothelium pathology or chronic irritation rather than a direct risk factor for NA. Inflammation was present in most cases. The presence of inflammation and previous urological interventions (e.g., intravesical BCG treatment and ureteral stenting) in most cases supports the reactive/metaplastic nature of NA.

In line with the literature, patients most frequently presented with hematuria and dysuria, and the bladder was the most frequently affected area, consistent with previous studies (3,6). Less frequently, it can also occur anywhere in the lower urinary system, such as the urethra, ureters, and renal pelvis (1,2,5,6,9). Renal pelvis localization, reported in approximately 20 cases to date, was observed in 1 patient in our series (4,6,7,8). The polypoid tumor we observed in the renal pelvis had a rich appearance of tubular structures, and due to its rarity, it was more likely to be mistaken for malignancy.

From a cystoscopic perspective, hyperemia and papillary formations were the most common findings in our cohort. These features are nonspecific and may overlap with urothelial carcinoma or inflammatory conditions, further emphasizing the importance of histological confirmation. Macroscopically, as in our study, NA typically presents as small lesions (1-2 cm). Histologically, it consists of a surface covered with a single mitotically inactive layer of flat, cuboidal, or spike-head cells and papillary structures containing small tubular components in the subepithelial space (6). Our findings confirm the morphological diversity of NA, with flat and tubular patterns being the most common, followed by microcystic and papillary architectures. Multiple patterns frequently coexist, consistent with previous studies. In some comparable series, the dominant pattern is mixed, followed by papillary and polypoid patterns; in another, tubular pattern, mixed tubular and papillary, and less frequently flat lesions were documented in most cases (1,2,8). In those with a mixed pattern, the most frequent association is between tubulocystic and flat lesions, as in our study (9).

Fibromyxoid NA is a rare variant characterized by sparse tubular structures within a stroma composed of well-circumscribed myxoid or spindle cells (1,2,6). If the presence of the fibromyxoid variant is detected, special attention is required to differentiate it from malignant spindle cell lesions to avoid misdiagnosis and overtreatment (10).

We also identified nominally significant associations between certain histological features. Microcystic pattern was significantly associated with the presence of nucleoli. Although other associations, such as those involving clear cell changes or hobnail morphology, were not statistically significant, these features may still pose diagnostic challenges, particularly in distinguishing NA from malignant mimickers, such as clear cell carcinoma.

Another notable finding is the high frequency of accompanying neoplasia, particularly invasive urothelial carcinoma. Most specimens in our series were transurethral resections or biopsies performed because of a clinically or cystoscopically suspected bladder tumour, and NA was in most instances an incidental finding in tissue sampled for another indication. The observed co-occurrence therefore largely reflects the selection and sampling characteristics of a surgical pathology cohort; it provides no evidence of a causal relationship between NA and urothelial neoplasia, and it should not be taken to indicate an increased risk of malignant transformation of NA. The relevance of this coexistence is diagnostic rather than prognostic: It can resemble clear cell adenocarcinoma, endocervicosis, prostatic adenocarcinoma of the bladder, and papillary urothelial carcinoma (2,3,4,7,11). The coexistence of NA with malignant lesions may lead to diagnostic confusion, especially in small biopsies, underscoring the importance of careful histopathological evaluation.

The immunophenotype of NA is well-defined; consistent PAX8 and CK7 positivity supports a distal tubular renal origin, as well as p63, PSA, and NKX3.1 negativity (1,4,6,8). This

immunophenotype is particularly useful in differentiating NA from urothelial and prostatic malignancies in challenging cases (8). PAX8, however, is a marker of renal-tubular and Müllerian differentiation rather than a specific marker of NA: it is also expressed in clear cell adenocarcinoma of the bladder and urethra, in Müllerian-type lesions and in renal cell carcinoma, and it therefore cannot by itself distinguish NA from its most important malignant mimic. PAX8 should accordingly be interpreted with the morphological findings, in particular the absence of significant cytological atypia, of mitotic activity and of destructive stromal invasion. In addition, napsin is a highly sensitive marker, and staining with GATA3 has been reported in 40% of cases (7).

Treatment typically involves transurethral resection (7). Despite its benign nature, NA has a tendency to recur, with reported recurrence rates ranging from 10% to 63% (2,3,8). Recurrence is common in childhood and is reported in up to 80% of cases (3,5,7). Some patients in our study group experienced recurrence, highlighting the importance of follow-up. Malignant transformation of NA is exceptionally rare and has been documented mainly in isolated case reports. In one such report, the transformed component showed CEA and p53 immunoreactivity together with an elevated Ki-67 index (11). These findings emphasize the importance of careful histopathologic examination and, when clinically warranted, immunohistochemical assessment for proliferation markers to exclude malignant transformation.

First, NA should be considered in the differential diagnosis of bladder and upper urinary tract lesions, particularly in patients with prior instrumentation or chronic irritation. Second, long-term follow-up is warranted to monitor the rare possibility of recurrence or malignant transformation, despite the benign biological behavior that is typically observed.

This study, being a retrospective analysis, has inherent limitations, such as relying on existing medical records, which may lead to incomplete clinical data. Ten of the 49 samples were repeat biopsies from patients who had previously provided another sample; therefore, sample-level observations were not entirely independent. This could be considered one of the study's limitations. Furthermore, small case numbers for specific rare histological patterns or localizations may limit the statistical power to detect subtle associations and affect the generalizability of our findings to larger populations. Future prospective studies with larger, multicenter cohorts are needed to confirm our findings, particularly regarding the prevalence of specific histological patterns and their association with neoplasia, and to establish standardized follow-up protocols.

5. Conclusion

NA is a benign but heterogeneous lesion with variable clinical and morphological features. The demographic profiles, clinical presentations, histopathologic patterns, immunohistochemical findings, and recurrence patterns observed by us are consistent with those reported in comparable studies, supporting the understanding of NA as a benign reactive lesion that requires careful diagnosis and judicious long-term follow-up. Even if cohort selection has an effect, the high frequency of concomitant neoplasms, particularly invasive urothelial carcinoma, is a significant finding. This association has been reported in previous studies and highlights a potential diagnostic pitfall. Therefore, careful histopathological evaluation is essential to avoid misinterpretation, particularly in cases with atypical features or complex architectural patterns.

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