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Bladder Tumor or Not? When Nephrogenic Metaplasia Masquerades as Recurrence: A Case Report

Mohammed Amine ELAFARI[1*], Mohammed Amine BIBAT[1], Ayoub MAMAD[1], Siham MESMOUDI[2], Zineb ZIRIAB[2], Kaoutar ZNATI[2], Pr Amine SLAOUI[1], Pr Tariq KARMOUNI[1], Pr Abdelatif KOUTANI[1], Pr Khalid ELKHADER[1]

[1]Urology B Department, IBN SINA Hospital, University Hospital Center IBN SINA, University Mohammed V, Rabat, Morocco.
[2]Pathology Department, IBN SINA Hospital, University Hospital Center IBN SINA, University Mohammed V, Rabat, Morocco.

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***Corresponding author:** Mohammed Amine ELAFARI
Urology B Department, IBN SINA Hospital, University Hospital Center IBN SINA, University Mohammed V, Rabat, Morocco.

Abstract | **Case Report**

Nephrogenic adenoma (NA) is an uncommon benign lesion of the urinary tract that arises from the proliferation of implanted renal tubular cells in areas of urothelial injury. This condition has the capacity to clinically and histologically mimic urothelial carcinoma, thereby posing a significant diagnostic challenge. The following report details the case of a 55-year-old male patient with a medical history of high-grade pT1 non–muscle-invasive bladder cancer (NMIBC), which was resected six years prior. The patient presented with recurrent gross hematuria, pollakiuria, and dysuria. Contrast-enhanced computed tomography (CT) revealed a suspicious posterior bladder wall lesion. Transurethral resection of the bladder tumor was performed, and histopathological examination revealed tubular and microcystic structures lined by bland cuboidal to flattened cells. Immunohistochemistry revealed strong positivity for PAX8 and negativity for GATA3, thereby confirming a diagnosis of nephrogenic adenoma. No recurrence was observed at 12 months of follow-up. This case underscores the significance of immunohistochemical analysis in distinguishing nephrogenic adenoma from urothelial carcinoma, particularly in patients with a prior history of bladder malignancy.

Keywords: nephrogenic adenoma, urinary bladder, urothelial carcinoma, PAX8, GATA3, immunohistochemistry.

INTRODUCTION

Nephrogenic adenoma (NA) is a rare benign lesion of the urinary tract that results from the displacement, implantation, and proliferation of exfoliated renal tubular cells in areas of urothelial injury and denudation [1,2]. First described by Davis in 1949, NA most commonly occurs in the urinary bladder (approximately 80% of cases), though it may arise anywhere along the urinary tract from the renal pelvis to the urethra [1,3].

NA predominantly affects males, with a male-to-female ratio of approximately 3:1, and a mean age at diagnosis ranging from 55 to 66 years [1,2]. Recognized predisposing factors include prior urologic surgery, transurethral resection, intravesical therapy (including Bacillus Calmette–Guérin [BCG]), chronic urinary tract infections, urolithiasis, renal transplantation and prolonged catheterization [1,4,5]. The most prevalent clinical antecedent is a history of urothelial carcinoma, which has been documented in up to 43% of cases [2].

Clinically, NA may manifest with symptoms such as hematuria or lower urinary tract symptoms, or it may be detected incidentally [1]. On cystoscopy and imaging modalities, it can closely resemble urothelial carcinoma, manifesting as a papillary, polypoid, or sessile lesion [1,6]. Histologically, NA exhibits a wide spectrum of architectural patterns, including tubular, tubulocystic, papillary, flat, and fibromyxoid variants, which may simulate malignancy [3,4]. Accurate diagnosis necessitates the integration of morphological features with immunohistochemical analysis, particularly the expression of renal lineage markers such as PAX8 and PAX2, and the absence of urothelial markers such as GATA3 and p63 [2,7,8].

We present the case of a patient with a remote history of high-grade non–muscle-invasive bladder

cancer (NMIBC) who developed a bladder lesion clinically suspicious for tumor recurrence, ultimately diagnosed as nephrogenic adenoma.

CASE PRESENTATION

A 55-year-old male, presented to our department with a three-month history of intermittent gross hematuria associated with pollakiuria and dysuria. His past medical history was significant for a high-grade pT1 non–muscle-invasive urothelial carcinoma of the bladder (NMIBC), resected by transurethral resection six years prior. Intravesical BCG therapy had been planned at the time of initial diagnosis; however, the patient was subsequently lost to follow-up and did not receive adjuvant treatment.

The patient reported continued tobacco use, estimated at 25 pack-years. He denied weight loss, fever, or flank pain. No other significant comorbidities were reported.

On physical examination, the patient was in good general condition. Abdominal examination revealed no palpable masses or tenderness. External genital examination was unremarkable. Digital rectal examination demonstrated a normal-sized prostate with regular contours, elastic consistency, and no palpable nodules.

Laboratory investigations were within normal limits. Complete blood count showed no anemia or leukocytosis. Serum creatinine and electrolyte levels (sodium, potassium, chloride) were within normal ranges. Urinalysis confirmed hematuria without leukocyturia. Urine culture was sterile.

Contrast-enhanced computed tomography (CT) of the abdomen and pelvis revealed focal budding thickening of the posterior bladder wall measuring approximately 18 mm in maximal thickness, with enhancement after contrast administration (Figure 1).

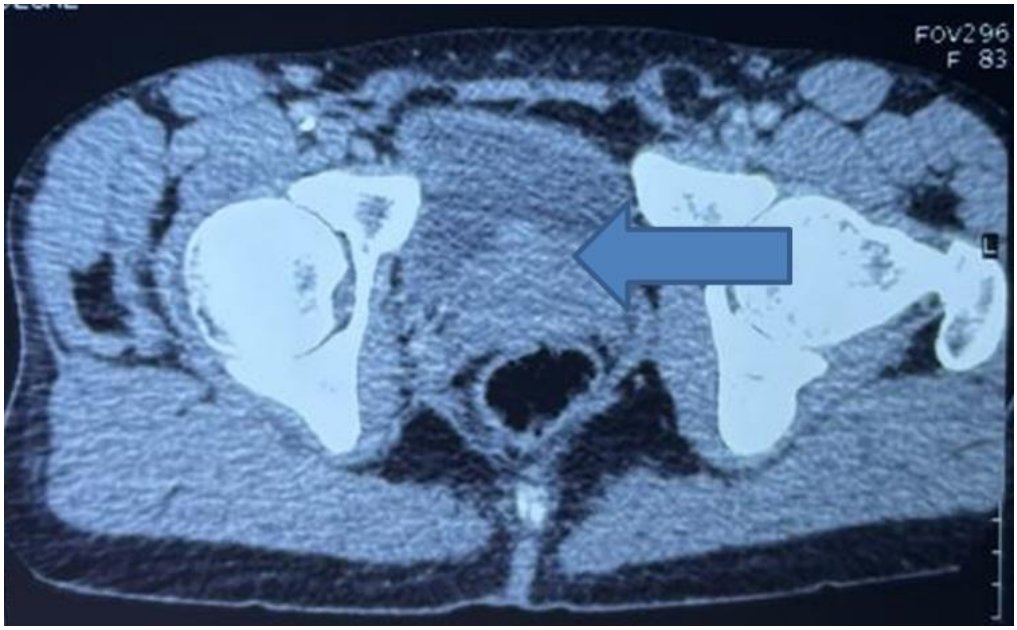

Figure 1: Contrast-enhanced computed tomography of the pelvis

Axial view showing a focal, contrast-enhancing endophytic lesion on the posterior bladder wall (blue arrow), measuring approximately 18 mm. These findings were initially concerning for a recurrence of the patient's known urothelial carcinoma.

These findings were highly suspicious for tumor recurrence. No upper urinary tract abnormalities, lymphadenopathy, or distant metastases were identified.

The patient underwent transurethral resection of the bladder tumor (TURBT) with deep resection of the lesion, including the underlying detrusor muscle, to ensure adequate staging.

Microscopic examination of the resected specimens revealed numerous tubulars and microcystic structures lined by a single layer of cuboidal to flattened cells. The cells exhibited no cytological atypia, nuclear pleomorphism, or mitotic activity. The surrounding stroma showed mild edema and scattered chronic inflammatory infiltrate. No evidence of urothelial carcinoma, either invasive or in situ, was identified.

Immunohistochemical staining demonstrated strong and diffuse nuclear positivity for PAX8 in the lesional cells. GATA3 staining was negative. These findings were consistent with a renal tubular cell origin and excluded a urothelial lineage, supporting a final diagnosis of nephrogenic adenoma (Figure 2).

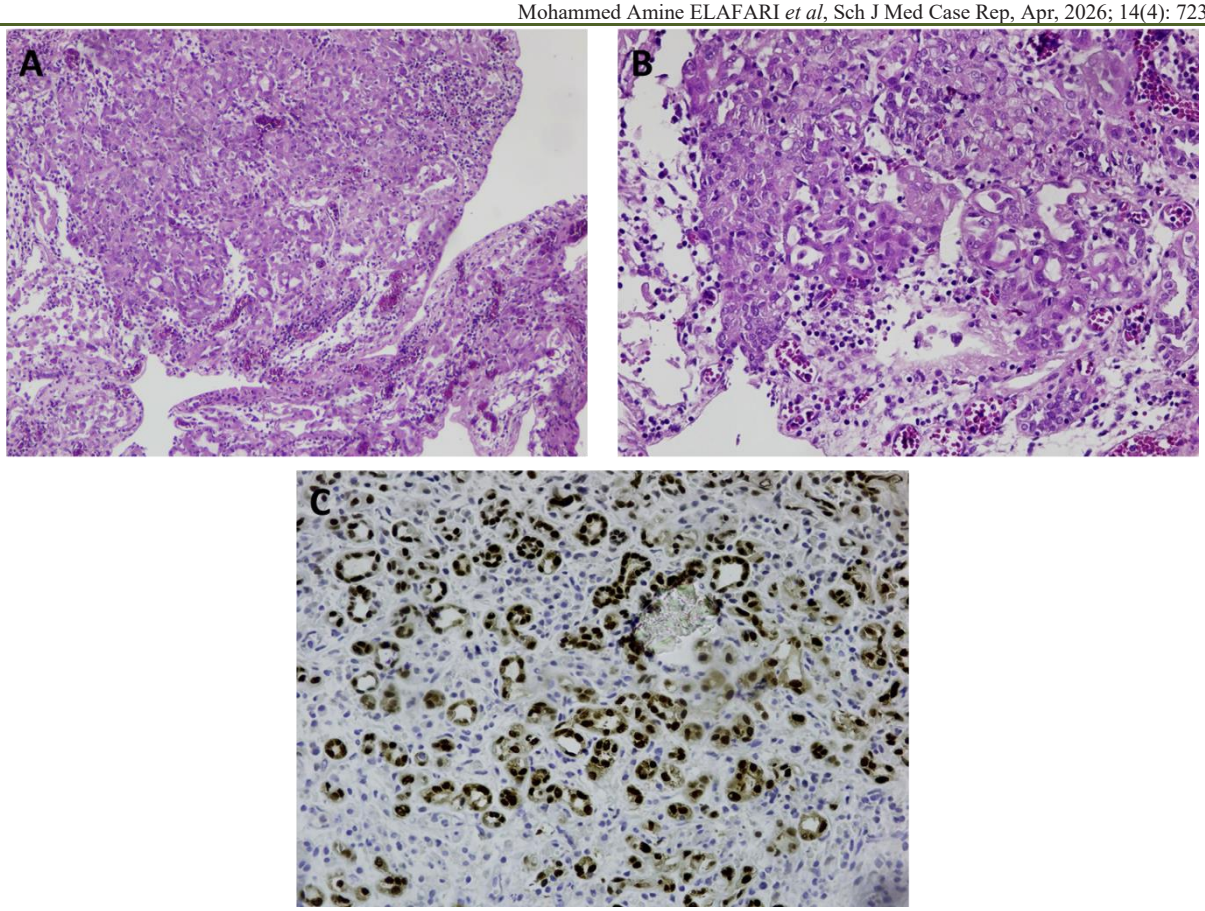

Figure 2: Histopathological and immunohistochemical features of the bladder lesion.
(A) Hematoxylin and Eosin (H&E), 100x: Proliferation of small tubular and microcystic structures within an edematous stroma.
(B) Hematoxylin and Eosin (H&E), 400x: High-power view demonstrating the tubules lined by a single layer of bland, cuboidal to flattened cells without cytologic atypia or mitotic activity.
(C) PAX8 Immunohistochemistry, 200x: Strong and diffuse nuclear positivity for PAX8 in the lesional cells, confirming a renal tubular cell origin.

The patient was placed on a structured surveillance protocol. Urinary cytology and cystoscopic evaluation performed at 3, 6, and 12 months postoperatively showed no evidence of recurrence of either nephrogenic adenoma or urothelial carcinoma.

DISCUSSION

This case exemplifies the diagnostic challenges posed by nephrogenic adenoma in a patient with a substantial history of high-grade non–muscle-invasive bladder cancer. The patient's clinical presentation, which included recurrent hematuria and lower urinary tract symptoms, in conjunction with imaging findings suggestive of a bladder mass, raised suspicion for urothelial carcinoma recurrence. The definitive diagnosis of NA was only established subsequent to meticulous histopathological and immunohistochemical evaluation.

A number of aspects of this case call for deliberation. First, the patient exhibited a multitude of acknowledged risk factors for the development of NA, including prior TURBT and a medical history marked by urothelial carcinoma. In the most extensive published series of 134 cases, López *et al.,* reported that urothelial carcinoma was the most prevalent clinical antecedent, present in 43.2% of cases, and the average time lapse between the pathological antecedent and the discovery of NA was 32 months [2]. In the present case, the interval was approximately six years, which is longer than the reported average but consistent with the wide range described in the literature, emphasizing that nephrogenic adenoma can manifest as a late-onset complication of urothelial injury. It is noteworthy that although BCG therapy was planned, it was never administered. However, prior TURBT alone constitutes a sufficient predisposing insult to the urothelium [4].

Secondly, the histological pattern observed in this case, tubular and microcystic structures lined by bland cuboidal to flattened cells, is among the most commonly reported morphological patterns of NA. Turcan *et al.,* reported that mixed patterns were the most frequent (71.4%), with tubulocystic and flat patterns being particularly common [3]. The tubular pattern alone

was identified in 14.3% of cases and was the most frequent pure pattern in the series by López *et al.,* (40%) [2]. The absence of cytological atypia and mitotic activity in our case is characteristic of NA and helps distinguish it from malignant mimickers [1,3].

Thirdly, the immunohistochemical profile was critical for establishing the diagnosis. PAX8, a transcription factor expressed in renal tubular cells, has been demonstrated to be positive in 100% of nephrogenic adenomas in a multitude of studies [2,7,9]. Tong *et al.,*established that PAX8 was detected in all 35 nephrogenic adenomas tested but was absent in urothelial carcinoma (0/48), prostate adenocarcinoma (0/100), and normal urothelium, thereby establishing it as a highly sensitive and specific marker for NA [7]. However, recent evidence suggests that PAX8 positivity may be observed in a subset of conventional urothelial carcinomas (approximately 10%) and in up to 56% of nested variant urothelial carcinomas, underscoring the importance of interpreting PAX8 in the context of a broader immunohistochemical panel [10,11].

GATA3 is a well-established marker of urothelial differentiation and is routinely used in the diagnosis of urothelial carcinoma [12]. In our case, GATA3 negativity argued against a urothelial origin. However, it should be noted that GATA3 expression has been reported in a variable proportion of nephrogenic adenomas, ranging from 25% to 59% depending on the study [8,13,14]. McDaniel *et al.,* found GATA3 expression in 40% of NAs, while Sharifai *et al.,* reported positivity in 58% of cases [8,13]. Therefore, GATA3 positivity alone does not exclude NA, and its absence, as in the present case, provides additional support for the diagnosis when combined with PAX8 positivity.

The combination of PAX8 positivity and GATA3 negativity, in conjunction with the characteristic bland morphology and absence of p63 expression (a marker consistently negative in NA), provides a robust immunohistochemical profile for distinguishing NA from urothelial carcinoma [2,7,8]. Additional markers that may be useful in challenging cases include napsin A, which has been shown to be positive in 100% of classic NAs and is negative in pure urothelial carcinomas and prostatic adenocarcinomas [8].

In the realm of urological management, transurethral resection continues to be the prevailing treatment modality for NA [1,6]. The lesion in question has been classified as benign, with no documented potential for malignant transformation [6]. However, it is noteworthy that recurrence rates have been documented, with reported incidences ranging from approximately 27% in non-transplant populations to up to 80–88% in renal transplant recipients [1,5,15,16]. In the case study presented, no recurrence was observed at the 12-month follow-up stage. Nevertheless, ongoing surveillance is recommended, given the documented tendency for recurrence and the patient's underlying history of urothelial carcinoma.

The significance of long-term follow-up in this patient cannot be overstated. Beyond monitoring for NA recurrence, the patient's history of high-grade pT1 urothelial carcinoma without adjuvant BCG therapy and with six years of absent surveillance places him at elevated risk for urothelial carcinoma recurrence or progression. Consequently, the ongoing cystoscopic surveillance accompanied by urinary cytology is imperative for both indications.

CONCLUSION

Nephrogenic adenoma is a benign lesion that can closely mimic urothelial carcinoma both clinically and histologically, particularly in patients with a prior history of bladder malignancy. This case underscores the critical role of immunohistochemistry—specifically, PAX8 positivity and GATA3 negativity—in establishing the correct diagnosis and avoiding unnecessary aggressive treatment. Clinicians and pathologists are advised to maintain a high index of suspicion for NA in patients with predisposing factors, such as prior urologic surgery. Furthermore, when the histological findings are ambiguous, a comprehensive immunohistochemical panel should be employed. Long-term cystoscopic surveillance is recommended to monitor for both NA recurrence and potential urothelial carcinoma.

Declaration

Conflicts of Interest

The authors declare that they have no competing interests.

Sources of Funding

There are no funding sources to be declared.

Ethical Approval

Ethics approval has been obtained to proceed with the current study

Ethical approval for this study (Ethical Committee N009-24) was provided by the Ethical Committee Ibn University Hospitals, Rabat Morocco on 22 January 2024

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the
Editor-in-Chief of the journal.

Guarantor of Submission

The corresponding author is the guarantor of submission.

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Availability of Data and Materials
Supporting material is available if further analysis is needed.

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