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# Malakoplakia Associated with Bladder Cancer: A Case Report

**Alessandro Vengjer [1,2,*], Eliel Júnior [2], Camille Colla [1], Dafne Ferreira [1], Renata Carvalho [1], Angelo Sementilli [1]**

[1] Metropolitan University of Santos (UNIMES), Santos, São Paulo, Brazil.
[2] Urology Department, Irmandade da Santa Casa da Misericórdia de Santos, Santos, São Paulo, Brazil.

* Correspondence: alvengjer@uol.com.br.

**Abstract:** Malakoplakia is a rare granulomatous inflammatory condition, frequently associated with *Escherichia coli* infection and immunosuppression, primarily affecting the urinary tract. We report the case of a 49-year-old woman with recurrent *E. coli* urinary tract infections and symptoms of overactive bladder, whose initial diagnosis of bladder malakoplakia was confirmed by biopsy. She received antibiotic prophylaxis, antimuscarinic therapy, intravesical botulinum toxin injections, and multiple transurethral resections; however, the lesions recurred. In 2023, a new biopsy revealed high-grade papillary urothelial carcinoma with squamous differentiation, representing a rare association not previously described in the literature. The patient underwent radical cystectomy with orthotopic ileal neobladder reconstruction, with good functional recovery and improved quality of life. This case illustrates the diagnostic challenge of malakoplakia due to its clinical and endoscopic similarity to bladder neoplasms and underscores the importance of rigorous follow-up in persistent cases. Periodic endoscopic surveillance and diagnostic reassessment in the presence of recurrent lesions are essential, considering the possibility of neoplasia even after a previous histological diagnosis of malakoplakia, in order to avoid treatment delays and optimize prognosis.

**Keywords:** Malakoplakia; Urinary bladder; Bladder tumor; Overactive bladder; Case reports.

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## 1. Introduction

Malakoplakia is an inflammatory condition believed to be caused by an abnormality in macrophage function. It generally occurs in immunocompromised patients and is considered a rare disease, with its true incidence remaining unknown. Leal et al. reported approximately 700 cases described in the literature up to 2017 [1,2]. Although its exact etiology remains unknown, *E. coli* is the organism most commonly associated with the condition [1]. This disorder primarily affects the urinary tract; however, it can involve almost any organ system.

In the excretory system, malakoplakia may lead to acute kidney injury, recurrent urinary tract infections, renal failure, and, rarely, death [1]. Within the urinary system, the most common site of malakoplakia is the bladder, followed by the renal parenchyma and, more rarely, the ureters. At these sites, the disease may manifest as nodules, plaques, or ulcers [3]. The age of disease onset is generally above 50 years, and its prevalence is four times higher in women [4]. Currently, there are no validated guidelines for treatment; oral antibiotics and/or surgical treatment may be administered [4].

In this case report, we discussed the clinical course of a patient who developed malakoplakia accompanied by symptoms of bladder overactivity and was subsequently diagnosed with high-grade urothelial carcinoma. To date, it is not possible to establish a direct causal relationship between malakoplakia and the development of neoplasia.

## 2. Case Report

A 49-year-old woman with a medical history of systemic lupus erythematosus, Raynaud syndrome, fibromyalgia, arterial hypertension, panic disorder, and smoking presented to the urology outpatient clinic in December 2021 (Table 1). Her medications included atenolol, hydrochlorothiazide, carbamazepine, duloxetine, amitriptyline, azathioprine, midazolam, clonazepam, and oxybutynin (Retemic). She complained of hypogastric pain, dysuria, urinary urgency, urge incontinence, and urinary frequency for more than 3 years, as well as recurrent urinary tract infections (UTIs), occurring more than six times per year and confirmed by urine cultures. All cultures were positive for E. coli, with a history of several hospitalizations for intravenous treatment.

**Table 1.** Timeline of the main clinical events in the case.

| Date/Period | Clinical Event |
|---|---|
| 2018–2021 | Recurrent *E. coli* UTIs |
| Dec 2021 | Initial urological evaluation |
| mar/22 | Cystoscopy – malakoplakia confirmed |
| jun/22 | First transurethral resection |
| jan/23 | Second transurethral resection + fulguration |
| jul/23 | Intravesical botulinum toxin (200 U) |
| Oct 2023 | Diagnosis of pT1 urothelial carcinoma |
| Dec 2023 | Radical cystectomy + orthotopic ileal neobladder |
| 2024 | Pelvic floor rehabilitation and clinical improvement |

During the investigation, urinary tract ultrasonography showed no abnormalities; however, the bladder was poorly distended, and postvoid residual volume could not be assessed. Urodynamic testing revealed detrusor overactivity due to uninhibited contractions beginning at an infused volume of 68 mL, with high amplitudes (78 $cmH_2O$), followed by painful sensation and loss of the entire infused volume. Therefore, the voiding phase could not be performed or assessed. The patient subsequently underwent two transurethral resections of bladder lesions. The first, performed in June 2022, was partial, and histopathological examination showed chronic cystitis compatible with bladder malakoplakia. The second was performed in January 2023, with complete fulguration of the lesions. During this period, the patient continued treatment with trimethoprim-sulfamethoxazole (Bactrim) and solifenacin.

During follow-up, magnetic resonance imaging of the abdomen and pelvis showed no abnormalities. Due to worsening symptoms, intravesical botulinum toxin (200 U) was administered. Because a follow-up urine culture demonstrated resistance to trimethoprim-sulfamethoxazole, antibiotic prophylaxis was changed to weekly fosfomycin, and solifenacin was replaced with trospium three times daily. The antimicrobial susceptibility profiles of the serial urine cultures are presented in Table 2. During cystoscopy performed for botulinum toxin administration in July 2023, lesions suggestive of malakoplakia were observed. Following the procedure, the patient experienced significant improvement in symptoms for 30 days, followed by subsequent worsening.

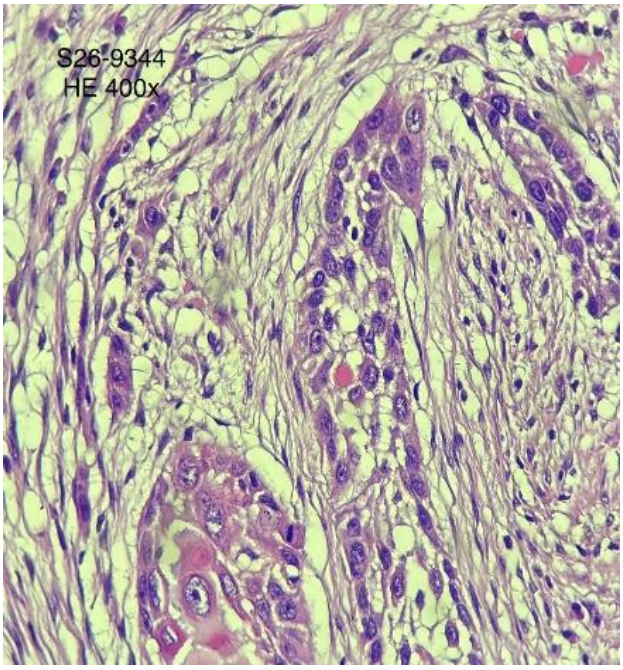
Due to clinical deterioration, another transurethral resection of the bladder was performed in October 2023, with partial resection of the lesions and complete fulguration of the remaining lesions, in addition to the administration of another 300 U of intravesical botulinum toxin. This time, histopathological examination revealed high-grade papillary urothelial carcinoma with areas of invasive squamous differentiation in the lamina propria (Figure 1). Segments of the muscularis propria showed no abnormalities, corresponding to stage pT1.

Additional treatment with intravesical gemcitabine was proposed; however, the patient was unable to tolerate it because of severe pain and worsening of symptoms. Given the prolonged and difficult-to-control clinical course, with progressive worsening of symptoms, radical cystectomy with orthotopic ileal neobladder reconstruction was performed using the Melchior technique, based on the surgeon's greater experience with this technique. The uterus and adnexa were preserved. Bilateral double-J ureteral stents were maintained and secured to a 16-Fr Foley catheter.

**Table 2.** Antimicrobial susceptibility profiles of urine cultures obtained during clinical follow-up.

| Date | Microorganism | Colony Count | Main Antimicrobial Susceptibility Findings |
|---|---|---|---|
| 15/07/2021 | *Escherichia coli* | 80,000 CFU/mL | Resistant to trimethoprim-sulfamethoxazole, nitrofurantoin, ampicillin, and ciprofloxacin; susceptible to fosfomycin and other antimicrobials tested. |
| 11/02/2022 | *Escherichia coli* | 100,000 CFU/mL | Persistent resistance to trimethoprim-sulfamethoxazole, nitrofurantoin, ampicillin, and ciprofloxacin; susceptible to fosfomycin. |
| 16/02/2022 | — | — | Negative urine culture, with no growth after 48 hours. |
| 24/04/2024 | *Enterococcus faecalis* | >100,000 CFU/mL | Susceptible to the antimicrobials tested, including nitrofurantoin and ampicillin. |

**Figure 1.** Histological section of the bladder lesion, stained with hematoxylin and eosin (H&E), at 400× magnification, showing high-grade urothelial carcinoma with squamous differentiation (arrow).




The patient remained in the intensive care unit for 2 days. A clear-liquid diet was initiated on postoperative day 3, with daily progression. Urine output through the catheter was adequate (1,200–2,000 mL/24 hours), with daily aspiration of mucus clumps. However, a significant increase in drain output was observed on postoperative day 6, accompanied by minimal urine output through the catheter. Conservative management with fluid restriction was chosen, followed by progressive reduction in drain output. The drain

was subsequently removed, and the patient was discharged from the hospital on postoperative day 14. On postoperative day 21, the Foley catheter was removed while the bilateral double-J stents remained in place. The patient received training in clean intermittent catheterization and was referred for pelvic floor rehabilitation.

Currently, the patient remains under regular follow-up at the urology outpatient clinic and continues pelvic floor rehabilitation. She performs clean intermittent catheterization twice daily, combined with voiding using the Credé maneuver, and uses a diaper at night. She has resumed physical activities that she had previously discontinued, with remission of symptoms and improved quality of life, according to her report, allowing her to fully return to her professional activities as a physical education teacher.

## 3. Discussion

Malakoplakia is a rare granulomatous inflammatory condition, first described by Michaelis and Gutmann in 1902 and histologically characterized by von Hansemann in 1903. It occurs more commonly in women, with a prevalence four times higher than in men, and generally manifests after 50 years of age [8]. This disorder is primarily associated with the urinary tract, particularly affecting the bladder [4]. Although its exact etiology remains unclear, it may be related to a defect in the phagocytic or degradative functions of histiocytes associated with infection by E. coli and Proteus, leading to a chronic inflammatory process. In addition to patients with previous E. coli infection, according to reported cases, the condition predominantly affects individuals with immunosuppression, diabetes, renal transplantation, or prolonged systemic corticosteroid therapy [4]. In the present case, the etiological factors identified were recurrent UTIs and the use of immunosuppressive medication for the treatment of lupus.

Clinically, malakoplakia may present with symptoms such as dysuria, urinary frequency, urinary urgency, and hematuria, which may mimic cystitis and bladder cancer [4]. The patient in the present case had compatible symptoms, including hypogastric pain, dysuria, urinary urgency, urge incontinence, and urinary frequency, for more than three years. In addition, the patient reported recurrent UTIs, occurring more than six times per year, all with urine cultures positive for E. coli, a bacterium associated with the pathogenesis of the disease. Cystoscopy performed in March 2022 revealed multiple sessile nodules suggestive of malakoplakia, as described above. However, during another transurethral resection performed in October 2023, histopathological examination identified high-grade papillary urothelial carcinoma. This finding demonstrates that the coexistence of malakoplakia and bladder cancer represents a significant diagnostic challenge due to the similarity between the lesions visualized on cystoscopy and those associated with malignant neoplasms, as well as between the clinical manifestations and imaging findings [3,4].

In addition to the diagnostic difficulty, the relationship between malakoplakia and bladder neoplasia remains poorly understood. Although malakoplakia is not recognized as a premalignant lesion, chronic inflammatory processes involving the urothelium may induce proliferative and metaplastic changes. In particular, keratinizing squamous metaplasia of the bladder is considered a recognized premalignant condition and has been associated with the development of squamous cell carcinoma in some patients. Similarly, intestinal metaplasia and cystitis glandularis have been investigated as possible precursor lesions, although current evidence suggests a low potential for malignant transformation in the absence of dysplasia. In the present case, the prolonged presence of chronic inflammation associated with recurrent E. coli urinary infections, immunosuppression, and multiple local recurrences may have contributed to microenvironmental changes favorable to the development of urothelial carcinoma, although a direct causal relationship between malakoplakia and bladder cancer remains unproven [5–7].

Another relevant aspect is the possibility of diagnostic anchoring bias. Following the initial diagnosis of malakoplakia, recurrent lesions were primarily interpreted as manifestations of the underlying inflammatory disease. However, the coexistence of neoplasia at an early stage or its presence within lesions previously classified as malakoplakia cannot

be completely excluded, reinforcing the need for serial histopathological reassessment in persistent cases. Additionally, the patient's history of smoking represents an important confounding factor. Smoking is the main risk factor for urothelial carcinoma and may have contributed significantly to the development of the neoplasm. Thus, although chronic inflammation, recurrent urinary infections, and immunosuppression may have promoted changes in the bladder microenvironment, a direct causal relationship between malakoplakia and bladder cancer cannot be established in this case.

The diagnosis of malakoplakia relies primarily on histopathological examination of a biopsy obtained from a visible mass during cystoscopy [2,3]. It typically appears as a small, soft, yellowish plaque or ulcer. The lesion is usually solitary but may be multiple or may even occur without any visible lesion [4,8]. Histologically, the diagnosis is mainly based on the presence of cells with abundant eosinophilic, foamy cytoplasm and Michaelis–Gutmann bodies [9]. As in the case reported above, cystoscopy revealed multiple sessile, yellowish, firm nodules, approximately 1 cm in diameter, involving all bladder walls. Histopathological examination of the biopsy specimens revealed bladder mucosa with a lamina propria containing a dense histiocytic infiltrate (Figure 2A), with eosinophilic cytoplasm and some spherical intracellular structures compatible with Michaelis–Gutmann bodies (Figures 2B and 2C). The findings were consistent with bladder malakoplakia, with no evidence of malignancy (Figure 2D).

Imaging studies, including ultrasonography, computed tomography, and intravenous pyelography, may be useful for identifying concomitant hydroureteronephrosis and detecting subtle abnormalities of the upper urinary tract, indicating its involvement. However, imaging techniques are unfortunately not sufficiently accurate to distinguish malakoplakia from neoplastic diseases or other inflammatory lesions [4,7], as demonstrated in the present case. Regarding treatment, because malakoplakia is rare, large prospective trials are lacking, and evidence regarding treatment success is largely anecdotal. Therefore, there are no standardized treatment guidelines [1]. General treatment principles include systemic antibiotics, surgical excision, and reduction of immunosuppression [1]. Medical treatment may often control the disease; however, as the disease progresses, surgical treatment may become necessary [1,6]. As in the present case, the patient underwent several transurethral resections of the bladder for lesion resection and fulguration.

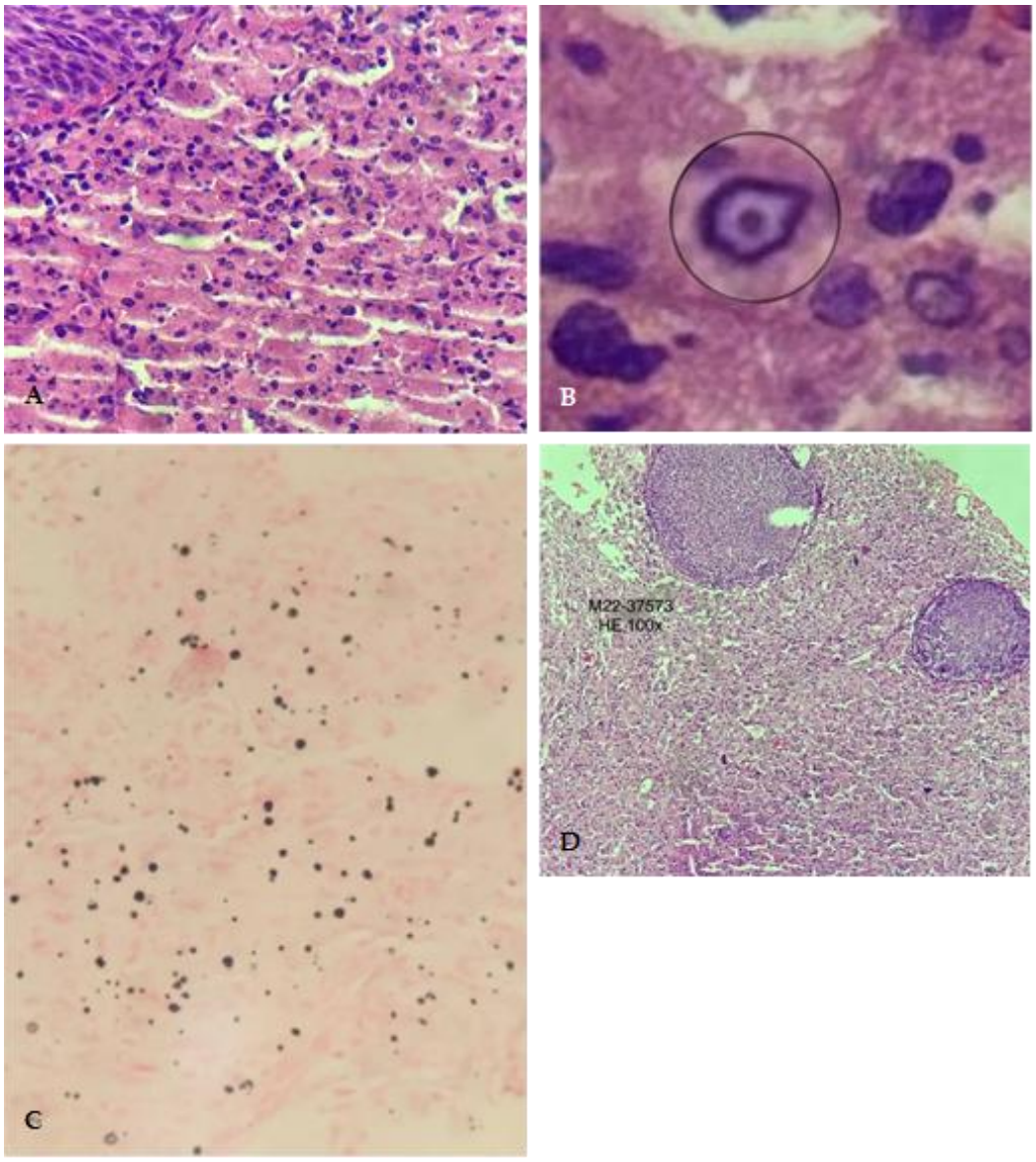
Quinolones, sulfamethoxazole, and rifampicin have been reported to be effective antibiotics for diseases involving intracellular organisms within macrophages [8,9]. Antibiotic therapy directed against Gram-negative bacteria combined with surgery offers a greater likelihood of cure [8,9]. The duration of treatment varies according to disease progression and its association with surgical intervention [9]. As described above, in 2022, the patient initiated antibiotic prophylaxis with trimethoprim-sulfamethoxazole (Bactrim F), in addition to solifenacin to treat symptoms caused by detrusor overactivity followed by incontinence. However, her symptoms worsened, and intravesical botulinum toxin was subsequently administered, without a sustained therapeutic effect. Quinolones, sulfamethoxazole, and rifampicin have been reported to be effective antibiotics for diseases involving intracellular organisms within macrophages [8,9]. Antibiotic therapy directed against Gram-negative bacteria combined with surgery offers a greater likelihood of cure [8,9]. In the present case, despite prolonged use of trimethoprim-sulfamethoxazole, documented bacterial resistance developed in follow-up urine cultures, prompting a switch to fosfomycin. This finding suggests difficulty in controlling chronic E. coli infection, a factor potentially associated with the persistence of bladder inflammatory activity observed during the clinical course.

## 4. Conclusion

The subsequent development of bladder neoplasia in patients with malakoplakia is exceptionally rare and has not been established as a direct consequence of the disease. However, persistent chronic inflammation, recurrent bladder lesions, and the potential

presence of metaplastic changes underscore the importance of rigorous endoscopic surveillance and periodic histopathological reassessment.

**Figure 2.** Histopathological examination stained with hematoxylin and eosin (H&E). A. Microscopic field demonstrating a histiocytic infiltrate consistent with malakoplakia. B. Higher magnification showing a rounded, basophilic intracellular structure compatible with a Michaelis–Gutmann body (circle). C. Von Kossa staining demonstrating microcalcifications and Michaelis–Gutmann bodies, identified by black staining, within the examined tissue. D. Bladder mucosa stained with hematoxylin and eosin (H&E), at 100× magnification, demonstrating extensive histiocytic infiltration of the lamina propria.




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**Conflicts of Interest:** All other authors declare no conflicts of interest.

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