

Clinicopathologic Features of Genitourinary Malakoplakia and Analytical Utility of the MetaPath Assay

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Purpose: To describe the clinicopathological spectrum of genitourinary malakoplakia (MPL) and to evaluate the feasibility and clinical impact of metagenomic pathogen detection (MetaPath) performed on archival formalin-fixed paraffin-embedded (FFPE) tissue.

Patients and Methods: Clinical imaging, histopathology, immunohistochemistry, special stains and MetaPath results were retrospectively analysed in five MPL cases diagnosed between January 2019 and August 2025.

Results: The cohort comprised four men and one woman with a median age of 65.4 years. Four lesions arose in the prostate and one in the bladder. Histology showed chronic granulomatous inflammation with numerous eosinophilic histiocytes containing 5–10 µm targetoid Michaelis–Gutmann bodies. CD68 and CD163 were diffusely positive; PAS and iron stains highlighted the inclusions. MetaPath identified pathogens in 3/5 (60%) FFPE specimens (*Escherichia coli* in two, *Pseudomonas aeruginosa* in one). Antibiotic regimens were adjusted according to MetaPath results. After a median follow-up of 6 months (range 4–8) all patients remained symptom-free.

Conclusion: MPL is frequently misdiagnosed as malignancy. MetaPath can reliably detect pathogens in archival tissue and guide targeted antimicrobial therapy, representing a valuable adjunct to conventional culture.

Keywords: malakoplakia, Michaelis–Gutmann body, malakoplakia concurrent with prostate cancer, metagenomic pathogen detection technology, special stains

Introduction

Malakoplakia (MPL) is a rare chronic granulomatous disorder that most frequently involves the genitourinary tract.¹ Since its first description by Michaelis and Gutmann in 1902 the pathognomonic Michaelis–Gutmann (M-G) body has remained the histological cornerstone of diagnosis.² The aetiology is incompletely understood; impaired macrophage killing of Gram-negative bacteria—especially *Escherichia coli*—is considered central.^{3–5} Consequently, demonstration of the causative organism would strengthen both diagnostic certainty and therapeutic precision.

Conventional urine or blood cultures often fail to identify the responsible pathogen, particularly when antibiotics have been administered or when only archival tissue is available. Metagenomic next-generation sequencing (mNGS) has recently been applied to fresh clinical samples, but its sensitivity in formalin-fixed paraffin-embedded (FFPE) tissue is limited because of human DNA over-representation and DNA fragmentation.^{6–8} MetaPath is a novel capture-based metagenomic assay that enriches microbial reads and depletes host nucleic acids, thereby allowing pathogen detection from FFPE specimens.^{9–11}

We report the largest single-centre genitourinary MPL series to date and provide the first proof-of-concept that MetaPath can reliably identify pathogens in FFPE lesions, guiding targeted antibiotic therapy.

Materials and Methods

Study Cohort

After Institutional Review Board approval (2020105) we retrieved all MPL cases diagnosed at Chengdu Second People's Hospital between January 2019 and August 2025. Inclusion required (i) typical histology with M-G bodies, (ii) archived FFPE tissue and (iii) available clinical follow-up.

Histopathology, Special Stains and Immunohistochemistry

Sections (4 µm) were stained with H&E, PAS and iron. Immunohistochemistry was performed on an automated Leica Autostainer Link 48 using antibodies against CD68, CD163, PCK, PSA, NKX3.1, p63, 34βE12, P504S, S100, ALK, Langerin, CD1a and Ki67 (Maixin Biotech, Fuzhou, China). Appropriate positive and negative controls were included. All slides were independently reviewed by two experienced pathologists.

MetaPath Workflow

DNA was extracted from five 4 µm FFPE curls as previously described.⁹ Libraries were prepared by mechanical fragmentation (350 bp), end-repair, adapter ligation and eight-cycle PCR. Pools were enriched with the MetaPath capture panel (KingCreate, China) targeting 3,125 clinically relevant pathogens. Sequencing (100-bp single-end) aimed at ≥300,000 reads per sample was performed on an Illumina MiniSeq. Raw reads were demultiplexed (bcl2fastq v2.20), quality-filtered (Fastp; Q ≥20) and mapped to GRCh38 to remove human sequences. Remaining reads were aligned to an in-house NCBI pathogen database. A pathogen was called when ≥3 unique genomic regions were covered at ≥10 RPM. Results were visually confirmed with IGV.

Results

Baseline characteristics are summarised in Table 1. Median age was 65.4 years; four patients presented with voiding difficulty and one with left flank pain. Pre-operative PSA ranged 1.0–10.8 ng/mL. Imaging suggested bladder tumour (n = 1) or prostatic hyperplasia/cancer (n = 4).

Histology

All specimens showed sheets of eosinophilic histiocytes with abundant granular cytoplasm and extracellular 5–10 µm targetoid M-G bodies (Figure 1A and B). Background infiltrates included sparse lymphocytes, plasma cells and neutrophils. Histiocytes showed diffuse positivity for CD68 (Figure 1C) and CD163, low Ki67 index, and were negative for S100 (Figure 1D), PCK, PSA, NKX3.1, p63, 34βE12, P504S, ALK, Langerin and CD1a. Epithelial, neuroendocrine and Langerhans markers were negative. PAS and iron stains confirmed M-G bodies (Figure 1E and F).

MetaPath Findings

Pathogens were identified in 3 of 5 cases (60%): *Escherichia coli* in Cases 1 (66,671 RPM, 96.9% relative abundance; Figure 1G) and 5 (6,358 RPM, 80.4% relative abundance), and *Pseudomonas aeruginosa* in one case (1,158 RPM, 29.2% relative abundance). No clinically relevant fungi, viruses, or parasites were detected. Cases 2 and 3 showed only low-level skin commensals below the detection threshold.

Concordance with Cultures

Pre-operative mid-stream urine was positive for *E. coli* in 3/4 patients (75%). Blood culture yielded *E. coli* in case 4. MetaPath and urine culture were concordant in 2/3 positive cases; case 4 displayed mixed organisms (*E. coli* in blood vs *P. aeruginosa* in tissue), suggesting polymicrobial infection.

Treatment and Outcome

Antibiotic regimens were adjusted according to MetaPath and resistance genes (Table 1). All patients received antimicrobials that achieve high intracellular concentration (ceftazidime, cefoperazone-sulbactam or amikacin). After 4–8

Table 1 Clinicopathological Summary of the Five Genitourinary Malacoplakia Patients

Variable	Case 1	Case 2	Case 3	Case 4	Case 5
Sex/age (yrs)	F/58	M/69	M/73	M/70	M/57
Chief complaint	Left flank dull pain for 2 mo	Dysuria for 2 yrs + PSA elevation	Dysuria for 6 yrs + PSA elevation	Dysuria for 6 mo + acute retention and fever for 6 days	Dysuria for 2 yrs + acute retention for 4 days
Site	Bladder	Prostate	Prostate	Prostate	Prostate
Pre-operative suspicion	Bladder mass: malignancy?	BPH with PSA elevation	BPH with PSA elevation	BPH with PSA elevation	BPH with PSA elevation
Imaging	CT: 1.2×1.5 cm nodular thickening at bladder neck/trigone protruding into lumen (Figure 1H)	External CT: BPH	MRI: 4.8 cm prostate, right-TZ nodule, mild DWI restriction	MRI: 6.2 cm prostate, diffuse PZ hypointensity, patchy DWI restriction	CT: 6.6 cm transverse prostate, normal density
t-PSA/f-PSA (ng/mL)	/	6.96/0.60	10.83/1.02	31.46/3.56	10.72/0.24
Pre-op culture	<i>E. coli</i> urine	Not done	<i>E. coli</i> urine	Blood <i>E. coli</i> ; urine sterile	Sterile
MetaPath (pathogens /RPM/relative abundance)	<i>E. coli</i> /66671/96.94%	Neg	Neg	<i>P. aeruginosa</i> /1158/29.20%	<i>E. coli</i> /6358/80.40%
Pathology	Bladder malacoplakia	Prostatic malacoplakia	Acinar adenocarcinoma + malacoplakia	Prostatic malacoplakia	Prostatic malacoplakia
Treatment	Ceftazidime + sulbactam–cefoperazone; transurethral resection + PCNL	Transrectal prostate biopsy + Ceftazidime and Moxifloxacin	Transrectal prostate biopsy revealed prostatic acinar adenocarcinoma and malacoplakia, followed by Amikacin therapy and radical prostatectomy	Transrectal prostate biopsy + Ceftazidime and Sulperazon; due to persistent severe urethral obstruction, transurethral resection of the prostate was performed	Transrectal prostate biopsy +Ceftazidime
Follow-up	8 mo, recurrence-free	8 mo, symptom-free, PSA normal	5 mo, recurrence-free, PSA normal	5 mo, symptom-free, PSA normal	5 mo, symptom-free, PSA normal

Abbreviations: PSA, prostate-specific antigen; BPH, benign prostatic hyperplasia; CT, Computed Tomography; MRI, Magnetic Resonance Imaging; TZ, Transition Zone; PZ, Peripheral Zone; DWI, Diffusion Weighted Imaging; RPM, Reads Per Million; PCNL, Percutaneous Nephrolithotomy; Neg, Negative.

months' follow-up all remained symptom-free; PSA normalised in the four prostate cases and imaging showed no residual mass.

Discussion

Clinical presentation of malacoplakia varies by site. Bladder lesions typically appear as solitary yellowish plaques or nodules mimicking malignancy, producing abdominal pain, abdominal mass, or irritative voiding symptoms;¹² case 1 showed a nodular mass at the bladder neck/trigone (Figure 1H) and was pre-operatively suspected of cancer. Prostatic malacoplakia usually presents with dysuria;¹³ cases 2–5 all had dysuria and elevated PSA, raising pre-operative concern for prostate cancer. Histologically, all specimens showed eosinophilic histiocytic infiltrates forming non-necrotising granulomas; many histiocytes contained 5–10 µm spherical inclusions (M–G bodies) with targetoid lamination. PAS and iron stains confirmed their presence, and immunohistochemistry excluded other disorders, fulfilling diagnostic criteria for malacoplakia.

Malacoplakia is classically linked to Gram-negative bacteria, especially *Escherichia coli*, that reach the tissue via the urinary or gastrointestinal tract and trigger a localized inflammatory response.⁴ Although urine cultures can document

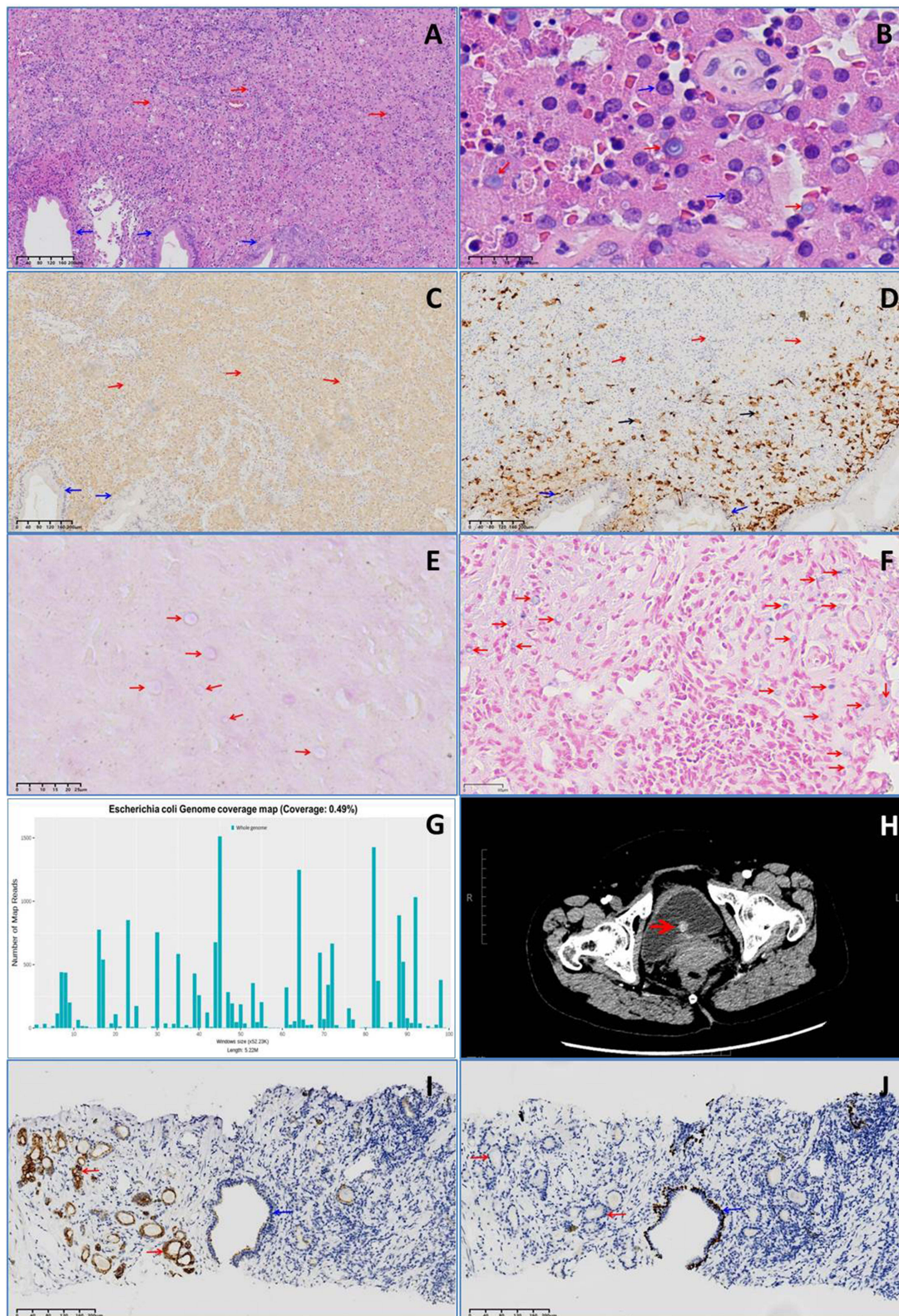


Figure 1 Representative images of case 1 and 3 (bladder and prostate malakoplakia). **(A)** Diffuse infiltrate of eosinophilic histiocytes (H&E) (red arrow); overlying bladder mucosa (blue arrow). **(B)** Targetoid Michaelis–Gutmann bodies (red arrow), histiocyte nuclei and nucleoli (blue arrows). **(C)** CD68 diffusely positive (red arrow); bladder mucosa (blue arrow). **(D)** S100 negative (red arrow) in histiocytes bladder mucosa (blue arrow). Antigen-presenting or inflammatory mediator cells positive (black arrows). **(E)** PAS staining (red arrow). **(F)** Iron staining (red arrow). **(G)** MetaPath coverage plot for *Escherichia coli*. *E. coli*, 66,671 reads, relative abundance 96.87%, coverage 0.49% (25,543/5,223,257 bp), with uniform genome-wide distribution. **(H)** CT showing nodular thickening of the bladder neck (red arrow). **(I)** Concurrent prostatic adenocarcinoma (P504S staining) (red arrow); normal prostatic glands exhibit weak cytoplasmic staining (blue arrows). **(J)** Concurrent prostatic adenocarcinoma (p63 staining) (red arrow); basal cells of normal glands positive (blue arrows).

urinary infection, defining the species, burden and resistance profile of the pathogens provides more direct insight into disease pathogenesis and therapy. In 2021, Yan Z¹⁴ reported the first renal allograft malakoplakia verified by both histopathology and metagenomic detection of *E. coli* sequences in urine and graft tissue; however, metagenomic identification of pathogens directly within lower urinary-tract or prostatic malakoplakia lesions has not previously been described.

MetaPath identified pathogens in 3/5 cases (60%): *E. coli* in two (66,671 and 6,358 RPM; 96.9% and 80.4% relative abundance) and *P. aeruginosa* in one (1,158 RPM; 29.2% relative abundance). The 10-fold higher bacterial load in case 1 versus case 5 suggests a correlation between microbial burden and lesion severity. Although the read count for *P. aeruginosa* in case 4 was low, the assignment confidence was 99%. Cases 2 and 3 yielded only skin commensals, likely introduced during transperineal biopsy; advanced fibrosis may also reduce organism numbers, causing false negatives. MetaPath delivered results within 2–3 days and, by targeting lesional tissue, provided direct evidence of intralesional organisms; however, contamination and commensal overgrowth must be excluded. Mid-stream urine cultures were positive for *E. coli* in 3/4 patients (75%). Concordance with MetaPath was complete for case 1. In case 4, blood culture grew *E. coli* whereas MetaPath detected *P. aeruginosa*, indicating polymicrobial infection with a dominant and a residual pathogen. Case 5 had negative urine culture but *E. coli* was recovered by MetaPath, underscoring its superior sensitivity for low-density infections. Therapy guided by species and resistance-gene predictions achieved microbiological and clinical cure without adverse events. Combining meticulous micro-dissection with histological validation minimises misinterpretation.

Prostatic malakoplakia (PM) concurrent with prostate cancer (PCa) is exceedingly rare. Only 25 cases have been reported; five remained recurrence-free, one progressed at 3 years, one progressed without surgery, and 18 were lost to follow-up. Five men developed sepsis or sudden prostatic enlargement ≥ 2 weeks after biopsy, implying PM may be a rare post-biopsy complication, yet its impact on PCa prognosis remains undefined.^{15–17} In case 3, biopsy revealed both PCa (Figure II and J) and PM; radical specimen showed bilateral cancer, whereas PM was confined to the apex, indicating topographically distinct coexistence. Two preceding catheterisations for urinary retention likely precipitated PM. All four prostatic PM cases presented with elevated PSA; imaging and clinical findings could not distinguish PM from PCa, and definitive diagnosis required histopathology. PSA normalised in every case after targeted therapy. Persistently elevated or rebound PSA after treatment should prompt exclusion of concomitant PCa.

Differential Diagnoses of Malakoplakia

1) Urothelial carcinoma: Painless gross haematuria; cystoscopy shows frond-like or nodular masses. Cytologically atypical, disordered urothelial cells invade stroma; positive for GATA-3/uropilin III. Malakoplakia lacks epithelial atypia and consists of sheets of histiocytes. 2) Xanthogranulomatous cystitis: Polypoid masses; lipid-laden foamy histiocytes, lymphocytes, plasma cells, occasional multinucleated giant cells and follicles; no M–G bodies. 3) Tuberculosis: Caseating granulomas with Langerhans giant cells; no eosinophilic histiocytic granules or M–G bodies; acid-fast bacilli positive. 4) Rosai–Dorfman disease: Emperipolesis present; S100-positive histiocytes; negative CD1a/Langerin; no M–G bodies. 5) Langerhans cell histiocytosis: Children; lytic bone lesions, rarely bladder. Reniform nuclei; CD1a⁺/Langerin⁺ histiocytes; no M–G bodies. 6) Granular-cell tumour: Polygonal cells with abundant eosinophilic granules, small nuclei, perivascular lymphocytes; CD68+/PAS+, S100+/CD56+/NSE+; no M–G bodies. 7) Malakoplakia with concurrent malignancy: Both lesions coexist; abundant histiocytes must not obscure co-existing epithelial or mesenchymal malignancy (illustrated in case 3).

Malakoplakia carries a favourable prognosis but a high relapse rate. No multicentre randomised trials exist; management is therefore tailored to site, severity and symptoms. Antibiotics that accumulate intracellularly within macrophages—eg β -lactams (cephalosporins) or trimethoprim–sulfamethoxazole—are first-line and achieve high cure rates.¹⁸ For multidrug-resistant isolates, abscess formation or sepsis, MetaPath profiling or blood-culture data guide pathogen-specific and resistance-guided therapy.¹⁹ Among our patients, case 5 harboured aminoglycoside-resistance genes (amikacin, gentamicin, tobramycin, streptomycin); the remaining four lacked definitive resistance determinants. Case 3 received amikacin; the others ceftazidime or cefoperazone–sulbactam, with rapid clinical response. When mass effect persists or antibiotics fail, combined surgical excision and antimicrobial therapy improves outcome.²⁰ Cases 1, 3, 4 and 5 underwent complete resection followed by targeted antibiotics and remain recurrence-free with durable symptom relief.

Conclusion

Malakoplakia is frequently misdiagnosed as neoplasia. Histomorphology, special stains and immunohistochemistry provide the diagnostic cornerstone, while MetaPath rapidly identifies FFPE-resident pathogens and tailors antibiotic therapy, representing a valuable adjunct to conventional assays.

Data Sharing Statement

All data generated or analysed during this study are included in this published article. Raw sequencing reads are available from the corresponding author on reasonable request and under institutional data-transfer agreement.

Ethics Approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Chengdu Second People's Hospital (Approval No. 2020105).

Consent to Participate

Written informed consent to participate in this study was obtained from all individual participants.

Consent to Publish

Patients signed informed consent regarding publishing their data and images.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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