7-25-2022

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## Recommended Citation

Acosta AM, Sangoi AR, Maclean F, Trpkov K, Osunkoya AO, Collins K, Miyamoto H, Hirsch MS, Chan E, Tretiakova M, Mohanty SK, Kaushal S, Cornejo KM, Aron M, Quiroga-Garza G, Arora K, Nguyen JK, Williamson SR, Epstein JI, and Matoso A. Prostatic malakoplakia: clinicopathological assessment of a multi-institutional series of 49 patients. Histopathology 2022.

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Histopathology

*Histopathology* 2022 DOI: 10.1111/his.14729

# Prostatic malakoplakia: clinicopathological assessment of a multi-institutional series of 49 patients

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Date of submission 31 May 2022
Accepted for publication 20 July 2022
Published online *Article Accepted* 25 July 2022

Acosta A M, Sangoi A R, Maclean F, Trpkov K, Osunkoya A O, Collins K, Miyamoto H, Hirsch M S, Chan E, Tretiakova M, Mohanty S K, Kaushal S, Cornejo K M, Aron M, Quiroga-Garza G, Arora K, Nguyen J K, Williamson S R, Epstein J I & Matoso A
(2022) *Histopathology*. https://doi.org/10.1111/his.14729

## Prostatic malakoplakia: clinicopathological assessment of a multi-institutional series of 49 patients

Prostatic malakoplakia (MP) is rare, with only case reports and small series (< five patients) available in the literature. In this study we analysed an international multi-institutional series of 49 patients with prostatic MP to more clearly define its clinicopathological features. The median age was 67 years and the median serum prostate-specific antigen (PSA) was 7.5 ng/ml. MP was clinically manifest in most cases (28 of 45 patients with data available, 62%). Of 43 patients with detailed clinical history available, 21 (49%) had concurrent or metachronous malignancies (including prostate cancer). Diabetes or insulin

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resistance was present in 11 patients (26%). Additionally, three patients had a history of solid organ transplantation and one had HIV. Of note, six of 34 patients (18%) without concurrent prostate cancer had an abnormal digital rectal examination and/or lesions on magnetic resonance imaging (MRI) with prostate imaging reporting and data system (PIRADS) scores 4–5. The initial diagnosis was made on core biopsies (25 of 49, 51%), transurethal resection specimens (12 of 49, 24%), radical prostatectomies (10 of 49, 20%), Holmium-laser enucleation (one of 49, 2%) and cystoprostatectomy (one of 49, 2%). Tissue involvement was more commonly diffuse or multifocal (40 of 49, 82%). Von Kossa and periodic acid-Schiff stains were positive in 35 of 38 (92%) and 26 of 27 lesions (96%), respectively. Of note, two cases were received in consultation by the authors with a preliminary diagnosis of mesenchymal tumour/tumour of the specialised prostatic stroma. The present study suggests that prostatic MP is often associated with clinical findings that may mimic those of prostate cancer in a subset of patients. Moreover, MP may be found incidentally in patients with concurrent prostate cancer.

Keywords: genitourinary, granulomatous prostatitis, malakoplakia, prostate, urinary infection

## Introduction

Malakoplakia (MP) is a rare chronic inflammatory disorder thought to be caused by an acquired impairment of the phagolysosomal function of histiocytes and macrophages that leads to the accumulation of intracellular bacteria.[1,2] Undigested bacteria and bacterial components aggregate within the cytoplasm, forming inclusions that can be seen with light microscopy.[1] These inclusions (Michaelis–Gutmann bodies) contain mucopolysaccharides, calcium and iron and can therefore be highlighted with histochemical stains such as periodic acid-Schiff (PAS), von Kossa and Perls Prussian blue, respectively.

MP is most commonly diagnosed in the genitourinary and gastrointestinal tract, but may involve virtually any organ.[3] In the genitourinary system, the urinary bladder is most frequently affected, followed by the ureters, pelvicalyceal system and kidneys.[3–5] Prostatic MP is rare, with a limited number of reports of individual cases or small series (less than five patients) available in the literature.[6] In this study, we present a large multi-institutional series of prostatic MP, to further describe the clinicopathological associations of this rare disease.

## Materials and methods

This research was performed with the approval of the Institutional Review Boards of Brigham and Women's Hospital (BWH) (MGB Insight version 4.0) and the remaining institutions (when applicable).

The databases of the participating pathology departments and personal consultation files of the authors were queried to identify cases of prostatic MP. Histopathological data were obtained by review of pathology reports and archival pathology slides (when available). Clinical and demographic data were extracted from pathology reports, consultation letters and electronic medical records. The following data were collected for each case: age at diagnosis, serum prostate-specific antigen (PSA) levels prior to the diagnosis, clinical presentation (incidental versus clinically manifest), results of special stains (PAS and von Kossa), presence of lower urinary tract symptoms (LUTS), type of LUTS, relevant clinical and oncological history, results of urine cultures, type of specimen in which the diagnosis was made, extent of disease on the pathology specimen (focal versus multifocal/diffuse), presence of synchronous prostate cancer and accuracy of the initial diagnosis (correct diagnosis versus misdiagnosis). Tissue involvement was considered focal if there was only a discrete lesional focus seen at intermediate magnification, and multifocal or diffuse if there were two or more discrete foci or extensive (i.e. non-discrete) disease. The diagnosis was considered incidental if it was made on (1) a specimen with concurrent prostate cancer, obtained to diagnose or treat prostate cancer, (2) prostate biopsies performed during active surveillance or (3) specimens obtained to evaluate or treat another concurrent disease (e.g. cystoprostatectomy performed for bladder cancer). Diffuse or multifocal MP on transurethral resection specimens performed to treat LUTS was not considered incidental, because MP may contribute to the symptomatology and benign prostatic hyperplasia is almost invariably present in elderly men. Additionally, MP was considered

clinically manifest if it there were clinical findings known to be associated with MP (e.g. recurrent urinary tract infections) in the absence of criteria for incidental diagnosis described above. Of note, MP was considered clinically manifest if it was associated with abnormal digital rectal examination (DRE) findings and/or lesions on magnetic resonance imaging (MRI) with prostate imaging reporting and data system (PIRADS) scores 4–5.

Clinicopathological data were originally reviewed by the submitting authors at their corresponding institutions and subsequently compiled and re-reviewed at BWH.

## Results

### CLINICAL FEATURES

The series comprised 49 patients with a median age of 67 years (range = 38–77 years) (Table 1). Serum PSA levels were available for 31 patients (31 of 49, 63%), with a median PSA of 7.5 ng/ml (range = 0.7–49.1 ng/ml). Two additional patients had elevated serum PSA levels per clinical records, but the exact values were unavailable. In the remaining 16 patients, there was no information on serum PSA values prior to the diagnosis of MP. Information about clinical presentation was available for 45 patients (45 of 49, 92%). Presentation was considered incidental in 17 patients (17 of 45, 38%) and clinically manifest in 28 (28 of 45, 62%). Information about the presence or absence of LUTS was evaluated separately and was available for 42 patients (42 of 49, 86%). Of these, 30 (30 of 41, 71%) had one or more LUTS and 12 (12 of 42, 29%) had no reported LUTS. Obstructive LUTS were present in 13 patients (13 of 30, 43%), with one or more episodes of acute urinary retention in six of them (six of 30, 20%). Irritative LUTS were present in 15 patients (15 of 30, 50%), the most common being dysuria (seven of 30 patients, 23%). In eight patients with LUTS (eight of 30, 27%), the specific symptoms were not described. Nineteen patients with LUTS (19 of 30, 63%) had positive urine cultures, with the remaining 11 having either negative cultures (five of 30, 17%) or no cultures available (six of 30, 20%).

Additional medical and oncological history was available for 43 patients (43 of 49, 88%). The most commonly associated medical problem was diabetes mellitus and/or insulin resistance, which was present in 11 patients (11 of 43, 26%). More specifically, eight patients had Type 2 diabetes, two patients had diabetes of unspecified type and one patient had glucose intolerance/insulin resistance. Twenty-one patients (21 of 43, 49%) had synchronous or metachronous malignancies, including prostate cancer in 16 patients (16 of 43, 37%; 15 synchronous and

**Table 1.** Clinical characteristics of 49 patients with prostatic malakoplakia

| | Median (range) | *n* (%) |
|---|---|---|
| Age | 67 years (38–77 years) | |
| PSA | 7.5 ng/ml (0.7–49.1 ng/ml) | |
| Elevated[a] | | 29 (94) |
| Clinical presentation | | |
| Clinically manifest | | 28 (57) |
| Incidental | | 17 (35) |
| Not available | | 4 (8) |
| LUTS | | |
| Present | | 30 (61) |
| Absent | | 12 (24) |
| Not available | | 7 (14) |
| Abnormal DRE findings | | |
| Yes | | 6 (12) |
| No/not available | | 43 (88) |
| History of comorbidities | | |
| Malignant neoplasms[b] | | 5 (10) |
| Solid organ transplantation | | 3 (6) |
| Diabetes/insulin resistance[c] | | 11 (22) |
| Urine culture | | |
| Positive | | 22 (45) |
| *Escherichia coli*[d] | | 14 (64) |
| Other[d] | | 8 (36) |
| Negative | | 10 (20) |
| Not performed/not available | | 17 (35) |

DRE, digital rectal examination; LUTS, lower urinary tract symptoms; PSA, prostate-specific antigen.
[a]Denotes cases with serum PSA ≥ 4 ng/ml. The percentage was calculated using the number of cases with PSA information available.
[b]Other than prostate cancer.
[c]Includes nine cases with diabetes and one patient with glucose intolerance/insulin resistance.
[d]These percentages were calculated using the number of positive cases as the denominator.

one metachronous) and clear cell renal cell carcinoma, squamous cell carcinoma of the lung and hepatocellular carcinoma, central nervous system lymphoma (not otherwise specified), chronic lymphocytic leukaemia/small lymphocytic lymphoma and bladder cancer (not otherwise specified) in one patient each (one of 43, 2%). Other relevant comorbidities were present in six patients (six of 43, 14%), including solid organ transplantation in three patients (one kidney, one liver and one lung) and HIV, Gitelman syndrome and aplastic anaemia in one patient each.

Nine of 29 patients (nine of 29, 31%) with elevated serum PSA levels (≥ 4 ng/dl) had concurrent prostate cancer, while the remaining 20 patients (20 of 29, 69%) had only MP. Of note, among 34 patients without concurrent prostate cancer, six patients (six of 34, 18%) had an abnormal DRE and/or a PIRADS ≥ 4 lesion on MRI. More specifically, five patients had an abnormal DRE, one of whom also had a PIRADS 4 lesion on MRI, and the remaining patient had a PIRADS 5 lesion. Thirty-two patients (32 of 49, 65%) had urine cultures performed around the time of diagnosis of MP available for review. Twenty-two (22 of 32, 69%) were reported positive and 10 (10 of 32, 31%) were reported negative. Among the former, 14 were positive for *Escherichia coli* (14 of 22, 64%, including one case positive for both *E. coli* and *Corynebacterium glucuronolyticum*), three were positive for *Klebsiella* (three of 22, 14%; two *Klebsiella pneumoniae*, one Klebsiella not further specified), one was positive for *Pseudomonas aeruginosa* (one of 22, 5%) and four were positive for Gram-negative bacilli, not further specified (four of 22, 18%).

Twenty of the 28 patients (20 of 28, 71%) with clinically manifest MP had LUTS. Among the remaining eight patients, three had an abnormal DRE (three of 28, 11%; one with concurrent haematuria), one (4%) presented with acute pyelonephritis and four (14%) had no specific urinary symptoms, but the diagnosis was considered clinically manifest based on other unspecified clinical findings. Ten of 17 (10 of 17, 59%) patients with an incidental diagnosis of MP had LUTS, with the remaining seven (seven of 17, 41%) having no symptoms (four) or no information available (three). Fifteen of the 17 patients (15 of 17, 88%) with incidental diagnosis of MP had concurrent prostate cancer. In the remaining two patients (two of 14, 11%), the diagnosis of MP was made on a Holmium-laser enucleation performed for obstruction in the context of a prior prostatic abscess and on a cystoprostatectomy performed for bladder cancer, respectively.

## PATHOLOGICAL FEATURES

The initial diagnosis of MP was made on core biopsies in 25 patients (25 of 49, 51%), transurethral resection specimens in 12 patients (12 of 49, 24%), radical prostatectomies in 10 patients (10 of 49, 20%), Holmium-laser enucleation in one patient (one of 49, 2%) and cystoprostatectomy in one patient (one of 49, 2%) (Table 2). In this series, MP did not demonstrate a preference for any zonal or topographic distribution. More specifically, there was no preferential distribution around glands or ducts, and both the transition zone and peripheral zone were frequently involved. The extent of tissue involvement was diffuse or multifocal in 40 patients (40 of 49, 82%: 29 of 49, 59% diffuse, 11 of 49, 22% multifocal), focal in eight patients (eight of 49, 16%) and not specified in one patient (one of 49, 2%). Among 15 biopsies with information on the number of cores involved and/or slides available for review, the median number of cores involved by MP was five (range = one to 12 cores). Of note, different sampling methods were used depending on where and when the biopsies were performed. In one patient with grade group 2 pT3b prostate cancer treated with radical prostatectomy, MP extended beyond the prostate, reaching the right pelvic sidewall. Among the six patients presenting with abnormal DRE and/or PIRADS ≥ 4 lesions and no concurrent prostate cancer, five had diffuse/multifocal MP. The two patients with PIRADS ≥ 4 lesions had diffuse/multifocal MP, with disease present in the areas corresponding to the PIRADS ≥ 4 foci seen on MRI. One patient presented with a discrete nodule on DRE (unspecified location) and had focal MP involving the right prostatic base.

Fifteen patients (15 of 49, 31%) had concurrent prostate cancer in the same specimen. Among these, the tumour was grade group 1 in five patients (five of 15, 33%), grade group 2 in six patients (six of 15, 40%), grade group 3 in one patient (one of 15, 7%), grade group 5 in two patients (two of 15, 13%), and not graded due to prior androgen deprivation therapy (ADT) in one patient (one of 15, 7%). One additional patient was diagnosed with grade group 2 prostate cancer 3 years after the diagnosis of MP. Cases with available information on bladder status did not demonstrate concurrent involvement of this organ by MP. Von Kossa histochemical stain for calcium was performed in 38 specimens (38 of 44, 86%), being positive in 35 (35 of 38, 92%) and negative in three (three of 38, 8%). Periodic acid-Schiff histochemical stain for polysaccharides was performed in 27 lesions (27 of 49, 55%), being positive in 26 (26 of 27,

**Table 2.** Pathological characteristics of 49 patients with prostatic malakoplakia

| | Median (range) | *n* (%)[a] |
|---|---|---|
| Type of specimen | | |
| Prostate biopsies | | 25 (51) |
| TURP | | 12 (24) |
| Radical prostatectomy | | 10 (20) |
| HoLEP | | 1 (2) |
| Cystoprostatectomy | | 1 (2) |
| Disease extent | | |
| Diffuse/multifocal | | 40 (82) |
| Focal | | 8 (16) |
| Not specified | | 1 (2) |
| Number of cores involved[b] | 5 (1–12) | |
| PAS stain | | |
| Positive | | 26 (53) |
| Negative | | 1 (2) |
| Not performed/not available | | 22 (45) |
| Von Kossa stain | | |
| Positive | | 35 (71) |
| Negative | | 3 (6) |
| Not performed/not available | | 11 (22) |
| Concurrent prostate cancer | | |
| Yes | | 15 (31) |
| GG1[c] | | 5 (33) |
| GG2[c] | | 6 (40) |
| GG3[c] | | 1 (7) |
| GG5[c] | | 2 (13) |
| Not graded[c] | | 1 (7) |
| No | | 34 (69) |

GG, grade group; HoLEP, holium laser enucleation of the prostate; TURP, transurethral resection of the prostate.

[a]Percentages were rounded to integer values; therefore, they may not add up to 100% in some categories.

[b]Based of 15 prostate biopsies with information on the number of cores involved by malakoplakia and/or archival slides available for review.

[c]These percentages were calculated using the number of cases with concurrent prostate cancer as the denominator.

96%) and negative in one (one of 27, 4%). The three lesions negative for von Kossa were positive for PAS and the only case negative for periodic acid-Schiff was positive for von Kossa.

Forty-two cases (42 of 44, 95%) were diagnosed correctly. The remaining two cases (two of 44, 5%; one radical prostatectomy and one prostate biopsy) were received in consultation by the authors with a preliminary diagnosis of spindle cell neoplasm/tumour of the specialised prostatic stroma. The radical prostatectomy with a suspected mesenchymal tumour had been performed for grade group 2 prostate cancer; therefore, the diagnosis of MP was considered incidental. Both cases demonstrated diffuse involvement of the prostate parenchyma by sheets of epithelioid and spindled histiocytes. Nuclear pleomorphism was absent and Michaelis–Gutmann bodies highlighted by Von Kossa and PAS histochemical stains were readily identifiable (Figures 1 and 2). Selected slides of the prostatectomy specimen were available for re-review at the time of this study, revealing minimal mitotic activity (one mitosis per 10 high-power fields) and frequent entrapment of benign and malignant prostatic glands. One additional patient with multifocal MP and concurrent grade group 2 prostate cancer on radical prostatectomy had a prior diagnosis of grade group 5 prostatic adenocarcinoma on outside prostate biopsies. As MP was not mentioned in the outside biopsy report, we speculate that it may had been misdiagnosed as high-grade prostate cancer. However, this could not be confirmed because the original biopsies were not available for re-review.

## Discussion

MP is a rare chronic inflammatory disorder that preferentially affects the genitourinary and gastrointestinal systems but may involve virtually any organ.[3] Affected sites demonstrate focal to extensive infiltration by histiocytes, with frequent giant cells and granulomas. An acquired impairment of the bactericidal activity of histiocytes and macrophages seems to underlie the pathogenesis of this disorder.[1,7] This defect confers susceptibility especially for Gram-negative organisms, leading to intracytoplasmic accumulation of undigested bacteria in tissues colonised or susceptible to infection by these organisms.[2] The undigested bacteria form intracytoplasmic inclusions that can be seen with light microscopy, termed Michaelis–Gutmann bodies. Michaelis–Gutmann bodies are basophilic and often have a targetoid

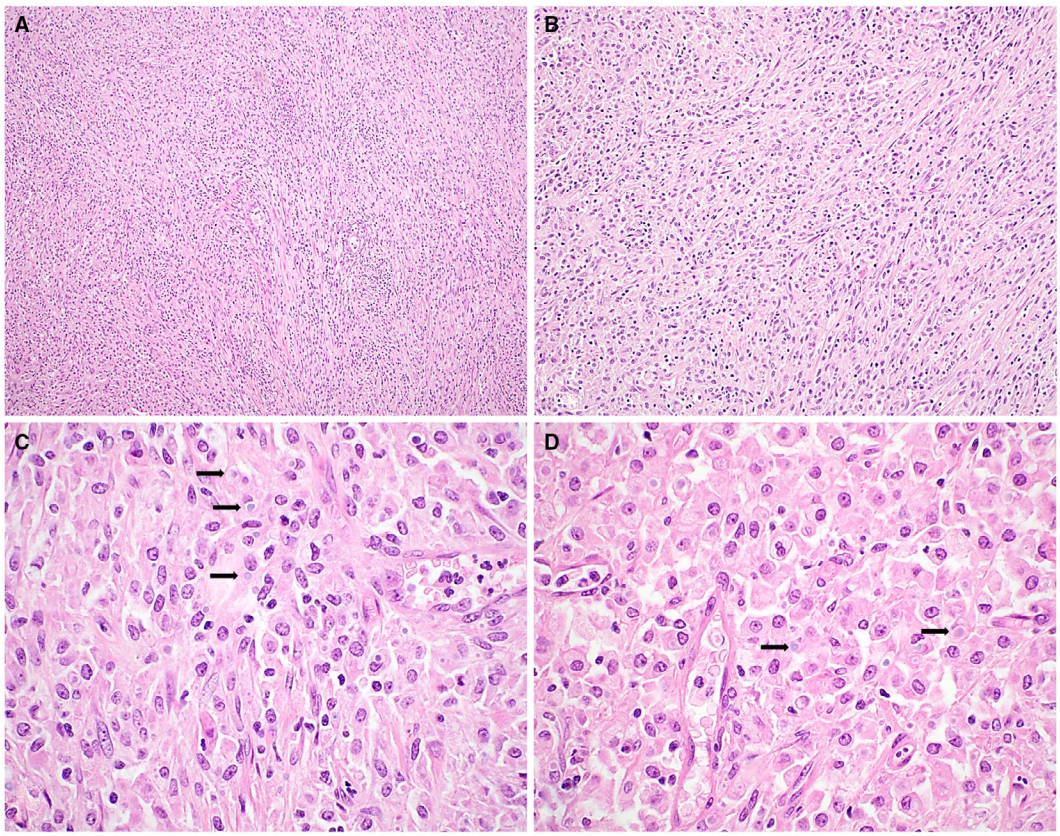


**Figure 1.** Prostatic malakoplakia mimicking a mesenchymal tumour of the prostate. **A,B,** Low and intermediate magnification micrographs of a radical prostatectomy (performed for grade group 2 prostate cancer) diffusely involved by malakoplakia with spindle cell morphology. **C, D,** Michaelis–Gutmann bodies (arrows) were present in spindled histiocytes (**C**) as well as in histiocytes with more typical morphological features (**D**).

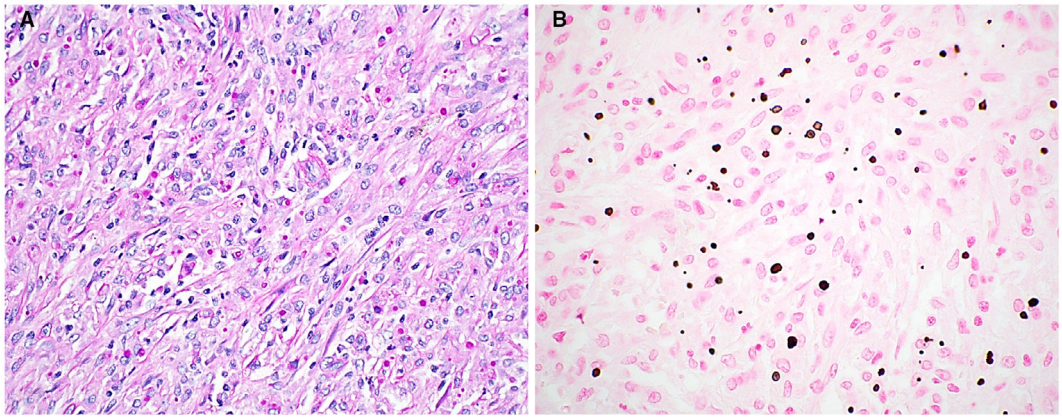


**Figure 2.** Prostatic malakoplakia mimicking a mesenchymal tumour of the prostate, histochemical stains. **A,B,** Periodic acid-Schiff (**A**) and von Kossa (**B**) stains performed on the case shown in Figure 1 highlight numerous Michaelis–Gutmann bodies.

appearance, being highlighted by PAS, von Kossa and Perls Prussian blue histochemical stains. In the present study, PAS was slightly more sensitive than von Kossa stain (96 versus 92%), likely because the former stains intracellular Michaelis–Gutmann bodies that lack calcium deposits. However, in this study,

cases that were negative for von Kossa were positive for PAS and vice versa, suggesting that these stains are probably best used in combination.

MP has a predilection for patients with baseline immunosuppression and can be frankly symptomatic or clinically silent and diagnosed incidentally during the evaluation of other medical conditions.[8] Symptomatology is highly dependent upon the organ system involved, but presentation as a mass mimicking malignancy has been well described at multiple anatomical sites.[9–13] Although local recurrences may occur, MP usually follows an indolent clinical course, with good response to a combination of antibiotic therapy, surgical resection and/or reduction of immunosuppression.[14,15] However, exceptionally rare aggressive cases with fatal outcomes have been documented previously, mainly prior to the availability of newer antimicrobials.[16–18]

In the genitourinary tract, MP commonly affects the urinary bladder and the upper urinary tract (ureters/pelvicalyceal system).[5,6] Prostatic MP is rare, and most of the literature on this entity consists of individual case reports and small series (less than five patients).[6] Therefore, the clinicopathological spectrum of this disease remains incompletely described. The present study demonstrated that prostatic MP is more often clinically manifest, being frequently associated with LUTS and increased serum PSA levels. Given the retrospective nature of this study and the frequent co-occurrence of MP and BPH, a causal relationship between MP and LUTS cannot be established with certainty. Therefore, we decided to use the term 'clinically manifest' rather than 'non-incidental' to indicate that MP was associated with LUTS (albeit not necessarily causing them). Incidental MP is mainly diagnosed in patients undergoing diagnostic evaluation or treatment for prostate cancer. The association of prostatic MP with prostate cancer was previously thought to be rare.[6] However, in our series > 30% of the patients had concurrent prostate cancer in the same specimen (Figure 3). We hypothesise that this is probably an underestimation, as focal or multifocal MP may go unnoticed in specimens with a concurrent malignant neoplasm. This association is most probably coincidental (i.e. random), considering that prostate cancer is common in men within the age group of the patients with MP in this series.

Like prior studies of MP, this series found a relatively high frequency of multiple concurrentconditions associated with impaired immunity, such as organ transplantation, HIV or malignancies other than prostate cancer (nine of 43 patients with available clinical and oncological history, 21%). Disorders of glucose metabolism were also frequent (11 of 43, 26%), including manifest diabetes in 10 patients and glucose intolerance in one patient. In patients with positive urine cultures (22 of 32 patients with urine cultures available, 69%), the isolated bacteria invariably included Gram-negative rods (22 of 22, 100%), with a clear predominance of *E. coli*.

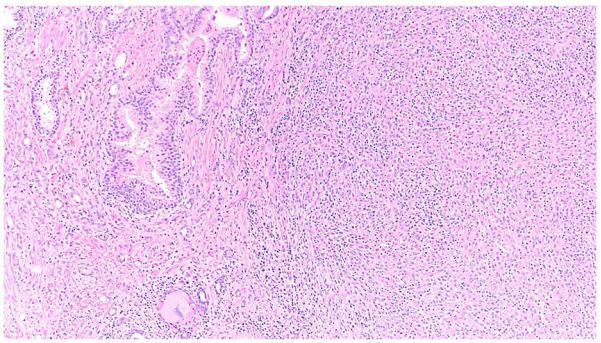

**Figure 3.** Prostatic malakoplakia with concurrent prostatic adenocarcinoma. The histiocytic infiltrate (right) is immediately adjacent to a benign gland (upper centre-left) and small glands of prostatic adenocarcinoma (left).

Prior case reports have documented that MP can mimic prostate cancer both clinically and on multiparametric MRI.[19–21] In this study, six patients with MP and absence of concurrent prostate cancer presented with abnormal DRE findings and/or PIRADS ≥ 4 lesions on MRI. Additionally, 15 patients without abnormal DRE or MRI findings and absence of concurrent prostate cancer had elevated PSA levels. Therefore, 21 of the 34 patients without concurrent prostate cancer (21 of 34, 62%) had a clinical presentation suggestive of malignancy.

In most patients, MP was diagnosed correctly based on its characteristic histopathological features (i.e. Michaelis–Gutmann bodies), with or without the help of histochemical stains. However, two cases were seen in consultation by the authors with a preliminary diagnosis of a mesenchymal neoplasm/tumour of the specialised prostatic stroma. Of note, one was an incidental finding in a radical prostatectomy performed for grade group 2 prostate cancer. Both cases demonstrated diffuse involvement of the prostatic parenchyma by a histiocytic infiltrate that included spindle cell areas. These infiltrates entrapped prostatic glands akin to mesenchymal tumours of the prostate.[22] Therefore, it might be worth considering MP in the differential diagnosis of spindle cell lesions of the prostate, especially in patients with a history of immunosuppression, urinary infections and/or positive urine cultures.

The differential diagnosis of prostatic MP includes inflammatory conditions such as non-specific granulomatous prostatitis and bacillus Calmette–Guérin

(BCG)-associated granulomatous inflammation. The distinction between MP and these entities can be difficult, especially because Michaelis–Gutman bodies may be absent or sparse in MP. Notwithstanding its name, non-specific granulomatous prostatitis (NSGP) is a defined entity characterised by a mixed inflammatory infiltrate centered around prostatic ducts. The early lesions of NSGP are characterised by dilated glandular spaces filled with foamy histiocytes, lymphocytes, plasma cells, neutrophils and eosinophils. This leads to destruction of ducts and acini with formation of lobular areas of dense inflammation rich in histiocytes and multinucleated giant cells. With time, such lesions may become less cellular and more fibrotic.[23] BCG-induced inflammation of the prostate consists of well-formed caseating and/or non-caseating granulomas with a peri-glandular location.[24]

This study has limitations that should be acknowledged. First, despite being the largest series to date, the number of cases is still somewhat limited. Second, this is a retrospective study that included cases seen in consultation by multiple authors; therefore, meaningful disease-specific follow-up data were not available for most patients. Finally, it is likely that some cases of MP were missed, since a re-review of cases diagnosed as 'granulomatous prostatitis' in the absence of an obvious cause (e.g. intravesical BCG therapy) was not performed. In spite of these shortcomings this represents, to our knowledge, the largest compilation of cases of prostatic MP to date.

In conclusion, the present study demonstrates that prostatic MP is often clinically manifest. Importantly, its clinical manifestations overlap with those of prostate cancer and benign prostatic hyperplasia. Also, approximately a third of prostatic MP cases can be found incidentally in patients with concurrent prostate cancer. Microscopically, rare cases can be confused with mesenchymal neoplasms, suggesting that MP should be considered in patients with spindle cell lesions of the prostate and a history of immunosuppression, repeated urinary infections or positive urine cultures.

## Conflicts of interest

The authors declare that they have no conflicts of interest.

## Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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