Case Report

Prostatic Malakoplakia Presenting as PI-RADS Score 5 Lesion Which was Down-Scored after Treatment: A Case Report and Review Literatures

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Background: Malakoplakia is a rare, granulomatous disorder that is typically triggered by infections in immunocompromised patients and most commonly affects the bladder. Herein, we report the seventy-fourth case of prostatic malakoplakia in the world literatures and the first case reported in Thailand. The paper will also be the first to compare the multiparametric (mp) magnetic resonance imaging (MRI) of malakoplakia before and after treatment, for differentiating the combined concurrence of malakoplakia and prostatic adenocarcinoma.

Case Report: A case of prostatic malakoplakia in a 70-year-old Thai man with a history of recurrent urinary tract infections who presented with acute urinary retention and prostatitis. An mpMRI study showed a Prostate Imaging- Reporting and Data System (PI-RADS) 5 lesion. His serum prostate specific antigen level (PSA) had risen to be 47.53 ng/mL. All findings strongly indicated prostate cancer. The patient underwent MRI-TRUS (Transrectal ultrasound) fusion-guided prostate biopsy and pathology slides revealed, microscopically, macrophages known as von Hansemann cells with scattered targetoid intracytoplasmic inclusions known as Michaelis-Gutmann bodies. He underwent transurethral resection of the prostate combined with antibiotic therapy. There was no longer any evidence of the PI-RADS 5 lesion by mpMRI six months after the treatment.

Conclusion: We reported that prostatic malakoplakia can present as prostatitis and a PI-RADS score 5 lesions. This awareness can prevent misdiagnosis and overtreatment of such a rare but benign condition. Combined surgical excision and antibiotic courses were effective in the treatment, and the importance of long-term follow-up of the patient is emphasized.

Keywords: Malakoplakia; Michaelis-Gutmann bodies; Prostate; Multiparametric magnetic resonance imaging

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Malakoplakia is a rare, granulomatous disorder that is related to defective macrophage response to bacterial infection in immunocompromised patients[1]. Malakoplakia can only be diagnosed by pathological examination. Although malakoplakia has been known for over 119 years, many cases were initially and frequently misinterpreted as carcinoma[2].

The mechanism of malakoplakia is not fully understood. It has been postulated that microorganisms play a role in the pathogenesis. It is believed that the cause of malakoplakia is an unusual response to bacterial infection in which macrophages fail to phagocytose them properly[3]. The original theory was that malakoplakia's etiology of the urinary tract was exclusively ascribed to the presence of *Escherichia coli*[4]. However, the patient linked to prostatitis which co-existed with *E. coli* and *Klebsiella pneumoniae* infection. The patient was consistent with a previous report that 80 to 90% of patients' urine cultures predominately involve *E. coli* and *K. pneumoniae*[5]. Combination antibiotic therapy for a prolonged duration may be required in the treatment of malakoplakia.

In 1989, more than 200 cases of malakoplakia had been reported in the literatures, and only 11 involved the prostate[6]. Three years later, a total of 29 cases involving the prostate had been reported in the literature[7]. To our knowledge, at the present (2020) there are only 73 previous reports of prostatic malakoplakia. In this paper, we describe the first case of malakoplakia of the prostate gland in a Thai patient, and this represents the seventy-fourth case of malakoplakia of the prostate reported in the world literature. The patient also suffered from diabetes and hypertension.

In addition, our paper confirmed that the diagnosis of malakoplakia is able to be established by MRI-TRUS

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fusion biopsy of the prostate gland[8,9] and is the first to compare the multiparametric magnetic resonance imaging (mpMRI) of malakoplakia before and after treatment to rule out combined concurrence of malakoplakia and prostatic adenocarcinoma. Finally, we reviewed the literature to compare the patient with the previously reported cases in view of the pertinent clinical and pathological data in the literature.

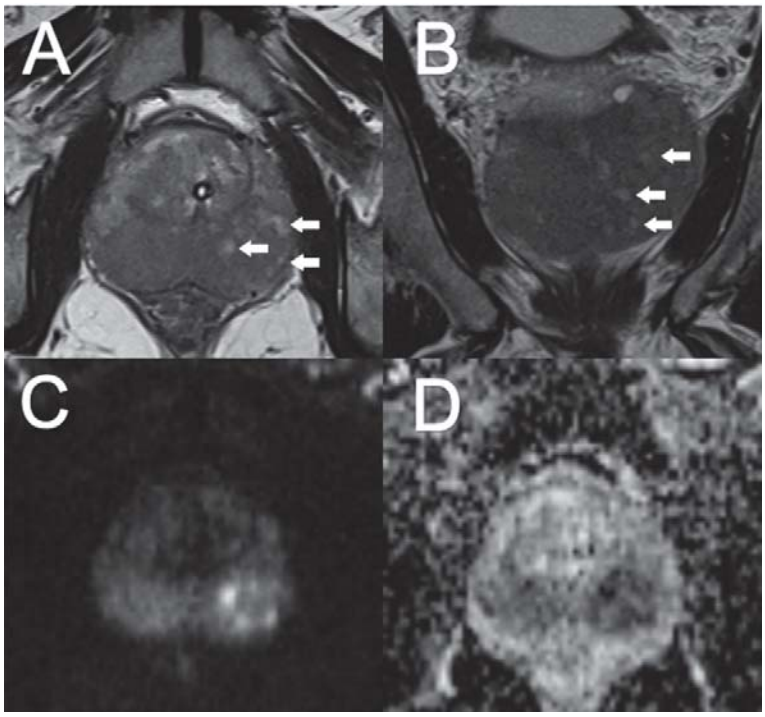
Case Report

A 70-year-old Thai man, presented to our urology outpatient clinic with complaints of lower urinary tract symptoms for approximately one month. His current medical history included uncontrolled diabetes and hypertension. He had no family history of prostate cancer. On clinical examination, digital rectal examination (DRE) of the prostate gland was normal. His urine analysis showed pyuria and bacteriuria and his serum prostate specific antigen (PSA) level was 9.6 ng/mL. The diagnosis was chronic prostatitis and the patient was treated as an outpatient with ciprofloxacin, tamsulosin and finasteride.

A few weeks later, he came back with inability to urinate and without fever. Three hundred milliliters of residual urine were found. The patient underwent retaining Foley Catheter treatment. Both *E. coli* and *K. pneumoniae* were grown in his urine culture. They were resistant to ciprofloxacin but were susceptible to sulfamethoxazole/trimethoprim. His serum PSA level had risen to 47.53 ng/mL. He had poorly controlled diabetes mellitus (Hb_{A1C} 7.29%, fasting blood glucose 244 mg/dl). We prescribed medicine to control his blood sugar level.

Diagnosis

The patient underwent imaging with mpMRI as shown in Figure 1(A-D). The mpMRI of the prostate was performed using a 3-Tesla scanner with a phased array body surface coil. T2-weighted imaging mpMRI of the prostate was performed by using a 1.5-Tesla scanner with a phased-



According to PI-RADS version 2.1 assessment, these findings were suggestive of a PI-RADS 5 observation

Figure 1. A and B) Axial and coronal T2-weighted images demonstrated a large T2 hypointense observation, 5.7x1.9x3.6 cm in dimensions, in bilateral peripheral zones of the prostate and internal small T2 hyperintense locules (arrows) in left peripheral zone. C and D) The observation was markedly hyperintense on the high b-value (b=1,500) diffusion-weighted imaging (DWI) and markedly hypointense on apparent diffusion coefficient map (ADC map). It should be noted that those small T2 hyperintense locules in left peripheral zone also showed markedly hyperintense on DWI and markedly hypointense on ADC map and no enhancement (image not shown).

array body surface coil. The prostate size was 5.3x6.5x5.3 cm in dimensions, with an estimated volume of 94.9 cc. The calculated PSA density was 0.48 ng/mL/cc.

The T2-weighted images demonstrated a large, 5.7x1.9x3.6 cm in dimensions, hypointense observation in bilateral peripheral zones from base to apex of the prostate. The observation demonstrated marked hyperintensity on high-b value (b = 1,500) diffusion weighted imaging (DWI) and marked hypointensity on the apparent diffusion coefficient (ADC) map. After gadolinium administration, the observation demonstrated a positive enhancement pattern on dynamic-contrast enhancement (DCE). Note that there were several small T_2 hyperintense locules in the left peripheral zone observation which showed marked hyperintensity on DWI and marked hypointensity on the ADC map, but no enhancement. Similar observations were seen in bilateral transition zones. According to PI-RADS version 2.1 assessment, these findings were suggestive of a PI-RADS 5 observation.

Later, the patient underwent MRI-TRUS fusion-guided prostate biopsy and histopathological examination of the biopsy revealed diffuse infiltration of the prostate with polygonal cells with pink granular cytoplasm (von Hansemann cells) (Figure 2A) with positive Periodic acid-Schiff (PAS) stain (Figure 2B). Several of these cells showed intracytoplasmic concentrically layered basophilic inclusions (Michaelis-Gutmann bodies) with black color by von Kossa silver method indicating the presence of calcium (Figure 2C). Immunohistochemical staining revealed strong immune reactivity of these histocytes for CD68 (Figure 2D). Immunohistochemical staining for AE1/AE3, HMW-CK, P504s and PSA were negative and prostatic adenocarcinoma could be ruled out.

For the treatment, sulfamethoxazole/trimethoprim therapy was administered instead of ciprofloxacin for an addition month. Four months after receiving alpha blocker and 5-alpha reductase inhibitor, the patient could not void and finally underwent transurethral resection of the prostate (TURP). The absolute surgical indication of the case were urinary retention (intractable) and failure of medical therapy. The postoperative course was uneventful. The final pathological diagnosis from TUR-P was focal malakoplakia which verified by positive CD 68, Von Kossa, and PAS in small clusters of inflammation. Malakoplakia is still seen in the prostate tissue.

During his first follow-up appointment after TURP

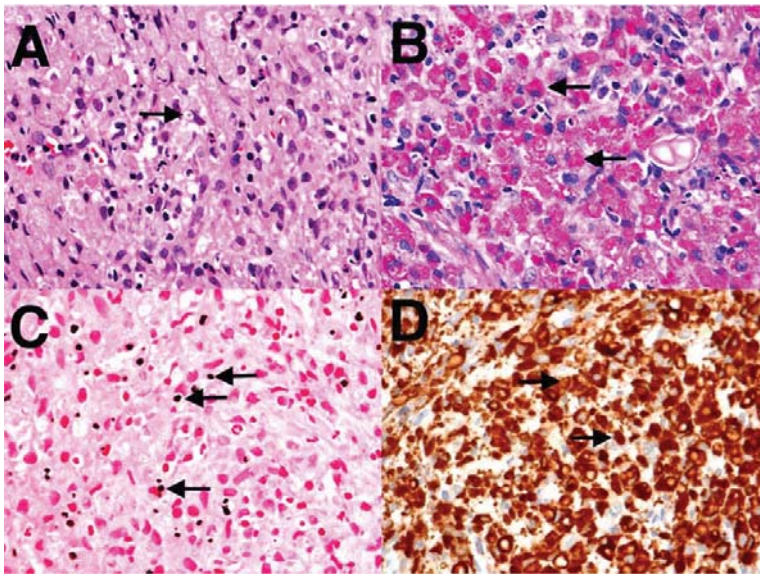


Figure 2. A) Hematoxylin and eosin stained histopathologic section demonstrating the Michaelis-Gutmann body as scattered targetoid intracytoplasmic inclusions of macrophages which is pathognomonic for prostatic malakoplakia (x400). B) Histopathologic section revealed predominantly sheets of macrophages known as von Hansemann cells with positive Periodic acid-Schiff stain (PAS) (x400). C) The patient's prostatic tissue showing positive von Kossa stain with black color of intracytoplasmic inclusion (Michaelis-Gutmann bodies) of macrophages as a defective intraphagolysosomal digestive activity of macrophages and containing calcium salts, iron, and bacterial glycolipid (x400). D) Immunohistochemical staining demonstrated diffuse strong positive immune reactivity of macrophage/histiocyte for CD68 with brown color appearance in the cytoplasm to rule out other cell types such as epithelial cells (x400).

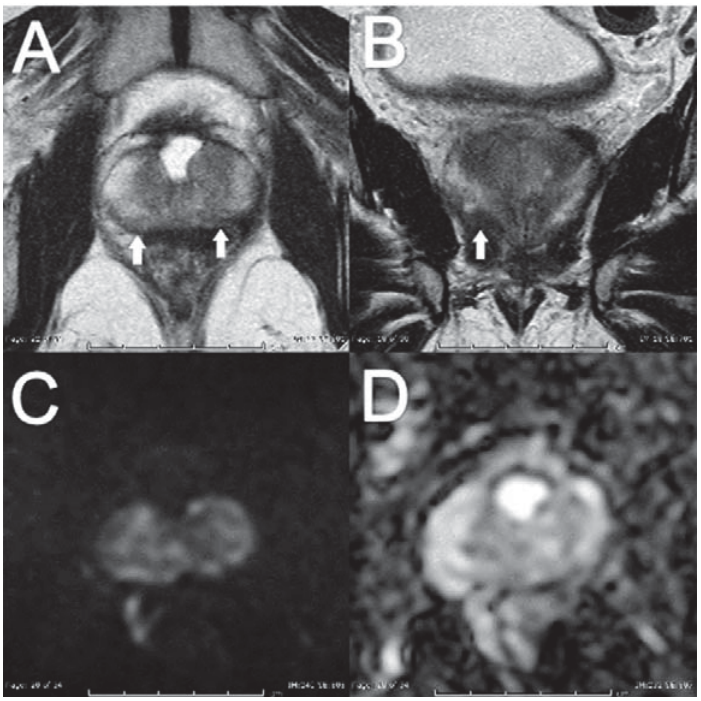
with urology, 1 month later, his urinary tract infection (UTI) symptoms had resolved, and PSA was 5.8 ng/mL. The antibiotics were prolonged to 2 months which is suggested to prevent a relapse when the antibiotics were discontinued after more than 1 month as in other reports[5]. Ten months later he displayed as normal, while no residual urine was found. PSA was decreased to 1.28 ng/mL. The mpMRI demonstrated PI-RADS 2 and there was no longer any evidence of the PI-RADS 5 lesion (Figure 3). The present study was approved by the Ethics committee of the institutions (No. MURA2020/1105).

Discussion

In malakoplakia disease, Professor von Hanseman first defined histologically von Hansemann histiocytes in 1901 and then 1 year later, Michaelis and Gutmann reported a pathognomonic sign for malakoplakia named "Michaelis-Gutmann bodies" in 1902[10]. Malakoplakia is an inflammatory process related to defective macrophage response to bacterial infection and characterized by the presence of plaques with macrophages containing inclusion bodies. Malakoplakia is commonly observed in immuno-compromised patients, or after infection and systemic illness which are suspected causative factors contributing to the development of this entity[11]. We explore the role of uncontrollable diabetes mellitus in the pathogenesis of malakoplakia.

Infact, malakoplakia involvement of the prostate was firstly reported by Carruthers, et al[12], and to date, this location is considered extremely rare to be reported to present. Arena et al present a case of prostatic malakoplakia presenting as a prostatic and seminal vesicle abscess in a patient with diabetes[12]. Guner, et al also suggested malakoplakia could be a complication after transrectal prostatic needle biopsy[13]. In addition, Chang, et al reported severe complication of malakoplakia of the prostate forming a fistulous tract to the rectum[14].

Malakoplakia sometimes mimics neoplasia and many cases were initially mistaken for carcinoma[2].



According to PI-RADS version 2.1 assessment, the final assessment was a PI-RADS 2 category (down scored after treatment)

Figure 3. A and B) Axial and coronal T2-weighted images (follow-up at 6 months) demonstrated significantly decreased prostate size and no longer evidence of PI-RADS 5 lesions in peripheral and transition zones. There were wedge-shaped T2 hypointense observations in bilateral peripheral zones (arrows). Noted a small defect at transition zone post transurethral resection of the prostate. C and D) The observations were iso-intense on the high *b*-value (*b* 1500) diffusion-weighted imaging (DWI) and mild hypointense on apparent diffusion coefficient map (ADC map) and negative enhancement (image not shown).

Interestingly, combined concurrence of malakoplakia and prostatic adenocarcinoma was also reported by Repassay, et al[15] and Gidwani, et al[16], Medlicott, et al[17]. Therefore, the importance of long-term follow-up of the patient is emphasized to rule out malignancy. In this paper, we demonstrated that there was no evidence of the PI-RADS 5 lesion by mpMRI six months after the treatment. It means that there was no significant risk of concurrent malakoplakia and prostatic adenocarcinoma in this case according to the previous report[18].

Malakoplakia may cause relevant diagnostic confusion for both clinicians and pathologists, since the lesions could be mistaken for malignancy. Therefore, careful tissue diagnosis with histochemical and immunohistochemical tests is recommended to avoid unnecessary radical surgery for this type of tumor-like lesion, and to avoid delay in management, is critically needed[19].

PI-RADS helps provide a standardized probabilistic approach for identifying clinically significant prostate cancer[20] and can be used as a mpMRI evaluation system in the selection of prostate biopsy. The rate of increase of prostate cancer detection on the first targeted biopsy core, with higher PI-RADS scores 5, was 87 to 89.4%[21-23]. In addition, the cut-off point of PSA at 4 ng/mL, is considered to indicate an increasing risk of prostate cancer. Therefore, the PI-RADS score 5 and high PSA suggested that this case was too urgent for active surveillance, as significant cancer was very likely. MRI-TRUS fusion guided prostate biopsy needed to be the next step.

The diagnosis of malakoplakia relies on histological examination, showing the presence of von Hansemann's cells and Michaelis-Gutmann bodies. However, Michaelis et al[2] reported malakoplakia without the pathognomonic that can be absent in early and late phases of the inflammatory reaction and after culture-directed antibiotics. Herein, we presented that prostatic malakoplakia can be diagnosed by clinically prostatitis, PI-RADS 5 lesion and MRI-TRUS fusion-guided prostate biopsy.

Once malakoplakia was discovered, the treatment was based on active and long-term antibiotics[5]. Antibiotics, ideally, should be culture specific and targeted against intracellular bacteria, possibly associated with surgery[24]. In addition, drugs that easily permeate the macrophages appear to be the best choice[25]. In the drug combination of trimethoprim sulfamethoxazole therapy, trimethoprim enhanced the killing of the viable undigested bacteria inside the malakoplakia macrophages. Sulfamethoxazole penetrates into the macrophage and proves useful for patients with advanced malakoplakia[26].

Generally, malakoplakia of the prostate can be treated successfully by antibiotic therapy. TUR-P is uncommon treatment for this condition. However, if conservatory treatment proves to be insufficient, TURP is necessary. In the paper we demonstrated that although, ciprofloxacin is an antibiotic with the ability to penetrate histiocytes, it may be unsuitable. In addition, a cholinergic agonist, such as bethanechol chloride, is used in combination with antibiotics to correct lysosomal defects[27,28]. However, we did not use a cholinergic agonist in our particular patient. Finally, we demonstrated combined trimethoprim sulfamethoxazole therapy and TURP, appear to have the highest success rate as in previous reports[25]. Our case presented as a PI-RADS score 5 lesion which down scored after treatment.

Conclusion

Prostatic malakoplakia is an unexpected diagnosis in patients suspected of having malignancy or prostatitis. If the patients present with prostatitis and PI-RADS 5 lesion, we emphasize maintaining a high index of suspicion for malakoplakia to avoid possible unnecessary radical surgery as further tests may prevent its confusion with prostatic carcinoma. However, we could not postpone prostate biopsy or repeat MRI before undergoing MRI-TRUS fusion biopsy.

What is already known in this topic?

Our paper confirmed that prostatic malakoplakia can be diagnosed by clinically prostatitis, PI-RADS 5 lesion and MRI-TRUS fusion-guided prostate biopsy.

What this study adds?

The paper is the first to compare the multiparametric (mp) magnetic resonance imaging (MRI) of malakoplakia before and after treatment, for differentiating the combined concurrence of malakoplakia and prostatic adenocarcinoma.

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Potential onflicts of interest

The authors declare no conflict of interest.

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