Current Bladder Dysfunction Reports
https://doi.org/10.1007/s11884-024-00748-4

REVIEW

The Clinical Reality of Granulomatous Prostatitis

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Accepted: 5 February 2024

Abstract

Purpose of Review Granulomatous prostatitis is a rare inflammatory disease of the prostate. It is challenging for the clinician because it mimics prostate cancer and cannot be distinguished from prostate cancer clinically, biochemically, or radiologically. Granulomatous prostatitis can only be diagnosed by histopathological examination. To prevent overdiagnosis and overtreatment, it is an important disease to recognize.

Recent Findings There are multiple case reports and studies describing granulomatous prostatitis.

Summary This review aims to give an overview regarding the epidemiology, etiology, clinical presentation, diagnosis, and treatment of granulomatous prostatitis using (recent) literature.

Keywords Granulomatous prostatitis · Prostate cancer · Histopathology

Introduction

Granulomatous prostatitis (GP) is a rare inflammatory disease of the prostate. It is an important confusing disease because it mimics prostate cancer (PCa), given its similar clinical, biochemical, and radiological presentation [1]. Although a different pathological entity, PCa may be concomitantly present in up to 36% of patients with GP [2••].

While GP is often incidentally diagnosed on histological examination, patients might be referred to a urological practice with abnormal digital rectal examination (DRE) or increased serum prostate-specific antigen (PSA) levels for suspected PCa [3•]. Clinical presentation ranges from asymptomatic to complaints of lower urinary tract symptoms (LUTS), hematuria, fever, and chills [4••]. Both transrectal ultrasound (TRUS) and multiparametric magnetic resonance imaging (mpMRI) GP and PCa are difficult to distinguish [5••]. Ultimately, the diagnosis is made histopathologically with the presence of epithelioid granulomas [6].

GP is classically divided into specific (including infections), non-specific (NSGP), post-surgical, and allergic (sometimes deemed "secondary") causes [7]. Other classifications and additional subcategories have been proposed with the inclusion of systemic granulomatous diseases such as granulomatosis with polyangiitis (GPA) [8] and xanthogranulomatous prostatitis, a distinct histological subgroup [9•].

In this review, we give an overview of the most recent literature on GP with a focus on its diagnosis and distinction with PCa.

Epidemiology

GP is rarely encountered in urological practice. It is histologically present in 0.65–1.5% of prostate specimens derived from needle biopsy, transurethral resection of the prostate (TURP) or, prostatectomy [4••, 10]. Some authors suggest a rising incidence given the more widespread use of bacillus Calmette-Guerin (BCG) installations for non-muscle invasive bladder carcinoma (NMIBC) and increase of endourological surgery [3•, 5••].

More recently, Torà et al. reported an incidence of 1.06% ($n=39$) in 3651 men with histopathological prostate specimens (including those from cystoprostatectomy) from a tertiary urological center [2••]. The mean age was 68 years, which is roughly similar to recent case series, which reported mean ages of 61, 66, and 68 years upon diagnosis [5••, 6, 11]. Most patients with GP are over 50 years of age and a

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Published online: 28 February 2024

substantial portion present in their seventh decade of life [5••, 6, 11].

Urinary tract infection is often regarded as a risk factor, with a history of recent urinary tract infection (UTI) present in 71% of patients in the largest case series to date ($n = 200$) [12]. Recently, a retrospective case series by Lee et al. reported that 75% of patients with GP had antibiotics for suspect UTI [13], while other studies describe 30–35% of GP patients with dysuria or a history of UTI, respectively [2••, 11]. Other risk factors are intravesical BCG instillations, systemic tuberculosis infection, and prostate interventions. Lastly, smoking and hypertension are also proposed [2••].

Etiology

The etiology of GP is diverse, and the different causes are highlighted in Table 1. An identifiable cause is not present (i.e., non-specific) in up to 45–53% of patients with GP [2••, 4••]. These rates seem to decline compared to older studies, reporting rates of 69–77% [12, 14], possibly due to the rise in incidence of specific causes for GP. The most widely proposed mechanism for NSGP involves an auto-immune inflammatory response to alterations of prostatic secretions caused by obstruction due to BPH or urinary reflux [15•].

Prostate interventions such as fine needle biopsy, TURP, and open adenectomy can all cause GP [12]. In a recent case series of 27 patients with histopathologically confirmed GP, 11% (3) of cases were related to prostate interventions [4••]. Presumably, GP arises from the deposition of small metal fragments, mostly from diathermy instruments, causing inflammation and granuloma formation [16].

Specific pathogens can cause GP, ranging from bacterial, viral, and fungal to parasitic infections [17••]. BCG-related GP is probably the most encountered infective etiology of GP [3•], resulting from urinary reflux to the urethra prostatica after bladder installations [18]. While its (symptomatic) incidence is suggested to range between 0.8 and 3.3% [19•], a recent paper showed that BCG-related GP was present in 81.5% of post-cystoprostatectomy samples [18], possibly suggesting a higher (asymptomatic) incidence than previously reported [20•]. *Mycobacterium tuberculosis*–causing GP is rare, and the prostate involvement is usually secondary to another tuberculosis (TB) focus [21]. Interestingly, TB can cause osteolytic vertebral lesions similarly seen in PCa [22].

Seldom, fungal infections such as cryptococci and endemic mycosis cause GP, with a recent study reporting an incidence of 0.0066% of fungal GP in 105,600 prostate biopsies [23•]. Viral GP due to herpes simplex virus infection has been reported [6].

Malakoplakia is an infrequent cause of GP and is caused by an acquired disorder of the bactericidal function of histiocytes and macrophages. Although more commonly present in the bladder, Acosta et al. reported a multi-center series of 49 patients with prostate malakoplakia. Of note, concomitant malignancies (including prostate cancer) were present in 49% of the cases [24•].

Xanthogranulomatous prostatitis, histologically distinct by foamy macrophages forming granulomas [9•], accounts for 7–29% of GP cases [4••, 6]. Lastly, systemic granulomatous diseases such as GPA and rheumatoid arthritis are etiologies for GP [17••]. Interestingly, psoriatic arthritis was recently described as a new cause of GP [25•].

Symptoms and Signs

The clinical presentation of GP varies. Presumably, a large proportion of patients are asymptomatic [3•], which might especially be the case for patients receiving intravesical BCG therapy [3•]. LUTS are present in 48.7–67% of patients in recent case series, with primarily complaints of frequency, urgency, and obstructive micturition [2••, 4••]. Dysuria, hematuria, and pyuria are

Table 1 Causes of granulomatous prostatitis

Non-specific (idiopathic)	- Specific granulomatous prostatitis - Xanthogranulomatous prostatitis
Infective	- Bacterial (bacillus Calmette-Guerin related, tuberculosis, brucellosis, syphilis) - Fungal (coccidiomycosis, cryptococci, blastomycosis, histoplasmosis, paracoccidioidomycosis) - Parasitic (schistosomiasis, echinococcosis, enterobiasis) - Viral (herpes simplex virus)
Post-surgical	- Needle biopsy - Transurethral resection of the prostate - Open adenectomy
Systemic granulomatous disease associated	- Sarcoidosis, rheumatoid arthritis, psoriatic arthritis - Granulomatosis with polyangiitis - Polyarteritis nodosa, Churg-Strauss syndrome

less commonly reported. Sometimes patients present with fever and chills, as seen in acute prostatitis [1]. Seldom, acute urinary retention is observed [4••].

Upon DRE, a firm to hard fixed nodule is frequently present, which can be mistaken for PCa [3•]. Sometimes, the prostate is diffusely enlarged and might be painful upon palpation [1]. PSA is elevated in the majority of cases, with mean PSA levels of 5.67, 8.74, and 15.8 ng/ml reported in recent studies [5••, 6, 26]. Elevated PSA is associated with intravesical BCG therapy but is also present in NSGP, although the mean PSA might be lower in the latter group [5••].

Diagnosis

Imaging

The diagnosis of GP is challenging given the diagnostic similarities with PCa, both on TRUS and mpMRI. On TRUS, focal hypoechogenic lesions, suspect for PCa, might be observed [4••, 11].

mpMRI remains the image modality of choice for the assessment of prostate lesions, which are commonly reported according to the prostate imaging reporting and data system (PI-RADS) guidelines. When comparing histopathological outcomes in 105 patients with PI-RADS 5 suspected lesions on mpMRI, Pepe et al. found a 5.7% incidence of GP [27].

A recent narrative review by Gaudiano et al. highlighted the most common features of GP on mpMRI [17••]. NSGP usually presents as a nodular and circumscribed hypo-intense lesion on T2-weighted sequences (T2w) and hyperintense on diffusion-weighted imaging (DWI) with low apparent diffusion coefficient (ADC) values. The lesion is rarely over > 3.5 cm in size and is usually limited to the peripheral zone (PZ). Transitional zone (TZ) involvement is infrequent [5••].

On the contrary, infective causes of GP commonly give heterogeneous and diffuse lesions of the PZ with frequent extension into the TZ [17••]. Multiple solid-looking nodules are seen, often more than 1.5 cm, which are hypo-intense on T2w and iso-intense on T1-weighted images (T1w) compared to the obturator muscle [17••]. Both nodular and cystic lesions can occur in case of infective GP, with latter resulting from central necrosis in case of TB-related GP, portraying as hyperintense on T2w sequences [3•].

Granulomatous disease-associated GP often has a nodular appearance on mpMRI and can involve both the PZ and TZ [17••].

Differentiating PCa and GP

PCa and GP cannot be distinguished by clinical presentation or imaging; therefore, the diagnosis can only be made by histopathological examination.

As previously described, the most common form of GP is NSGP. Histologically, NSGP is defined as noncaseating prostate granulomas, composed of epithelioid histiocytes, giant cells, lymphocytes, plasma cells, and polynuclear cells in the absence of previous diagnostic and surgical interventions of the prostate or systemic granulomatous disease [7, 11, 15•].

A retrospective review by Dikov et al. investigated the histopathology of NSGP, in particular, the looking at eosinophilic metaplasia (EM). EM is characterized by the presence of eosinophilic cytoplasmic granules filling the apical cytoplasm in benign prostatic epithelium, which can be used to differentiate PCa of NSGP since EM was not observed in mimics of PCa (areas of atrophy and cribriform hyperplasia). EM is frequently more present in prostate tissue from adenomectomies and TURP with BPH rather than in needle biopsies and radical prostatectomies. It varies from 12 to 23% in prostatic needle biopsies and 20% in total prostatectomies. Additionally, the presence of EM might serve as additional diagnostic finding to support NSGP, since other types of GP do not show EM. Moreover, immunohistochemistry can also be used to differentiate between PCa and GP, since histiocytes of NSGP are cytokeratin negative and show CD68 expression, while PCa is cytokeratin positive [15•].

Another recent study by Dikov described the difficulties of recognizing epithelioid granulomatous inflammation by conventional histological observation alone. Therefore PD-L1 expression was studied in 17 GP cases and 10 PCa cases [28••]. PD-L1 (programmed death ligand-1) is a protein that can be found on the surface of cells. Expression of PD-L1 may be a result of genetic events or response to a T cell infiltrate. Cancer cells may be PD-L1 negative because it has no T cell infiltrate [29]. All GP cases showed PD-L1 expression, while all PCA specimens were PD-L1 negative. Thus, staining with PD-L1 can also help to diagnose GP and distinguish it from PCa immunohistochemically [28••].

XGP is a rare and histologically distinct form of GP, characterized by the presence of foamy macrophages forming granulomas. Lymphocytes and plasma cells may be present, but this also occurs in other chronic inflammatory prostatic conditions [9•].

Treatment and Prognosis

Clinical presentation of GP varies between patients, and treatment is only necessary in case of symptoms. The cause of GP will determine the treatment.

Most BCG-induced GP are asymptomatic and do not require any treatment. Patients diagnosed with symptomatic BCG-induced GP need to stop BCG instillation and need to be treated with quinolones and antituberculotics. A case report of Yao et al. described a successful treatment with isoniazid, rifapentine, ethambutol and levofloxacin. BCG instillation was replaced by epirubicin. Follow-up after 10 months showed no tumor recurrence or symptoms of tuberculosis. If oral therapy is ineffective, surgery such as TURP can be performed [20•].

XGP is often associated with an enlarged prostate resulting in lower urinary tract obstruction [30]. Therefore, TURP can also be performed in these cases [9•].

NSGP is mostly self-limiting. Kumbar et al. described nine cases of NSGP that were all self-limiting with an uneventful follow-up period [6]. However, there were several case reports of symptomatic NSGP being treated with different oral therapy. A case report by Komeda et al. described a successful treatment with chlormadinone acetate. After treatment, the patient was asymptomatic for 29 months [31]. Another case report showed improvement of symptoms and regression of granuloma after oral prednisolone therapy. The following dose schedule was used: 30 mg in 3 divided doses for 4 days, 20 mg in 3 divided doses for 4 days, 15 mg in 3 divided doses for 4 days, 10 mg in 2 divided doses for 4 days, and then 5 mg daily for 2 months. All symptoms disappeared within 1 week, but therapy was continued until digital rectal examination was normal. The patient had an uneventful follow-up period of 4 months after finishing steroid therapy [32].

The last case report showed a favorably result on combination therapy with antimicrobial agent and hydrocortisone. The patient was treated with 200 mg levofloxacin three times a day and 20 mg hydrocortisone two times a day. Patient responded well to this treatment in 2 weeks [33].

It is important to distinguish NSGP from other GP as it is self-limiting while others require treatment depending on the cause [6, 11].

Conclusion

GP is a rare inflammatory disease of the prostate which can mimic PCa. Clinical presentation varies from asymptomatic to symptoms of LUTS, fever, or hematuria. The diagnosis can only be made by histopathological examination with the presence of epithelioid granulomas. Clinical presentation or imaging cannot distinguish GP from PCa. In approximately 50% of patients with GP, no cause is present. Furthermore, it can be caused by, for example, specific pathogens, BCG instillation, or after surgery. If GP requires treatment, it will be dictated by the cause. Most patients respond well to antimicrobial agents and corticosteroids. Surgical intervention such as TURP can be performed if oral therapy is not effective.

Author contributions C.V. and A.H. are considered first author. All authors reviewed the manuscript.

Funding No funding was received for this article.

Declarations

Competing interests The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Uzoh CC, Uff JS, Okeke AA. Granulomatous prostatitis. BJU Int. 2007;99(3):510–2.
2.•• Coello Torà I, de la Cruz Ruiz M, Carrillo García P, Carmelo Pieras Ayala E. Carmelo Pieras Ayala E Epidemiological study of granulomatous prostatitis in a tertiary hospital: associated risk factors and relationship with prostate cancer. Urol J. 2022;89(2):257–60. **This study described risk factors and symptoms of GP**.
3.• Crocetto F, Barone B, De Luca L, Creta M. Granulomatous prostatitis: a challenging differential diagnosis to take into consideration. Future Oncol. 2020;16(13):805–6. **Granulomatous prostatitis: a challenging differential diagnosis to take into consideration**.
4.•• Suteri P, Ahuja A, Sen AK, Goel H, Bhardwaj M, Chauhan DS, et al. Granulomatous prostatitis: a clinico-pathological series of 27 cases. Journal of Clinical Urology. 2022;15(2):141–8. **Patient characteristics of cases diagnosed with GP**.
5.•• Bertelli E, Zantonelli G, Cinelli A, Pastacaldi S, Agostini S, Neri E, et al. Granulomatous prostatitis, the great mimicker of prostate cancer: can multiparametric MRI features help in this challenging differential diagnosis?. Diagnostics. 2022;12(10):2302. **This study highlights GP features based on clinical findings and mpMRI characteristics**.

6. Kumbar R, Dravid N, Nikumbh D, Patil A, Nagappa KG. Clinicopathological overview of granulomatous prostatitis: an appraisal. J Clin Diagn Res. 2016;10(1):Ec20-3.
7. Epstein JI, Hutchins GM. Granulomatous prostatitis: distinction among allergic, nonspecific, and post-transurethral resection lesions. Hum Pathol. 1984;15(9):818–25.
8. Miralles TG, Gosalbez F, Menendez P, Perez-Rodriguez A, Folgueras V, Cabanilles DL. Fine needle aspiration cytology of granulomatous prostatitis. Acta Cytol. 1990;34(1):57–62.
9.• A AN, Karzoun MZ, Abdelfattah O, Ibrahim T. Granulomatous and xanthogranulomatous prostatitis: a case report. Urol Case Rep. 2022;40:101887. **Case report describing a specific form of GP.**
10. Shanggar K, Zulkifli MZ, Razack AH, Dublin N. Granulomatous prostatitis: a reminder to clinicians. Med J Malaysia. 2010;65(1):21–2.
11. Shukla P, Gulwani HV, Kaur S. Granulomatous prostatitis: clinical and histomorphologic survey of the disease in a tertiary care hospital. Prostate Int. 2017;5(1):29–34.
12. Stillwell TJ, Engen DE, Farrow GM. The clinical spectrum of granulomatous prostatitis: a report of 200 cases. J Urol. 1987;138(2):320–3.
13. Lee SM, Wolfe K, Acher P, Liyanage SH. Multiparametric MRI appearances of primary granulomatous prostatitis. Br J Radiol. 2019;92(1098):20180075.
14. Oppenheimer JR, Kahane H, Epstein JI. Granulomatous prostatitis on needle biopsy. Arch Pathol Lab Med. 1997;121(7):724–9.
15.• Dikov D, Koleva M, Boivin J-F, Lisner T, Belovezhdov V, Sarafian V. Histopathology of nonspecific granulomatous prostatitis with special reference to eosinophilic epithelial metaplasia: pathophysiologic, diagnostic and differential diagnostic correlations. Indian J Pathol Microbiol. 2020;63(5):34–40. **This retrospective review investigated the presence of eosinophilic metaplasia in NSGP**.
16. Henry L, Wagner B, Faulkner MK, Slater DN, Ansell ID. Metal deposition in post-surgical granulomas of the urinary tract. Histopathology. 1993;22(5):457–65.
17.•• Gaudiano C, Renzetti B, De Fino C, Corcioni B, Ciccarese F, Bianchi L, et al. Multiparametric magnetic resonance imaging for the differential diagnosis between granulomatous prostatitis and prostate cancer: a literature review to an intriguing diagnostic challenge. Front Oncol. 2023;13. **A study describing the difficulties of indentifying GP on mpMRI.**
18. Butel R, Ball R. The distribution of BCG prostatitis: a clue for pathogenetic processes? Prostate. 2018;78(15):1134–9.
19.• Lee S, Oh YT, Kim HM, Jung DC, Hong H. Imaging patterns of bacillus Calmette–Guérin-related granulomatous prostatitis based on multiparametric MRI. Korean J Radiol. 2022;23(1):60–7. **The role of mpMRI in BCG-related GP.**
20.• Yao Y, Ji JJ, Wang HY, Sun LJ, Zhang GM. Granulomatous prostatitis after bacille Calmette-Guérin instillation resembles prostate carcinoma: a case report and review of the literature. World J Clin Cases. 2023;11(9):2051–9. **Important characteristics of BCG-induced GP.**
21. Mishra KG, Ahmad A, Singh G, Tiwari R. Tuberculosis of the prostate gland masquerading prostate cancer; five cases experience at IGIMS. Urol Ann. 2019;11(4):389–92.
22. Joshi PV, Shewalkar B, George T, Sahasrabudhe S, Joshi S, Kulkarni M. The great mimicker—tuberculosis involving prostate and vertebrae posing as metastatic prostate carcinoma on FDG PET/CT. Clin Nucl Med. 2020;45 (3).
23.• Takada-Owada A, Fuchizawa H, Kijima T, Ishikawa M, Takaoka M, Nozawa Y, et al. Cryptococcal prostatitis forming caseous and suppurative granulomas diagnosed by needle biopsy: a case report. Int J Surg Pathol. 2022;30(5):586–9. **Case report of a very rare form of prostatitis.**
24.• Acosta AM, Sangoi AR, Maclean F, Trpkov K, Osunkoya AO, Collins K, et al. Prostatic malakoplakia: clinicopathological assessment of a multi-institutional series of 49 patients. Histopathology. 2022;81(4):520–8. **An infrequent cause of GP.**
25.• De Luca L, Crocetto F, Barone B, Creta M, Pesce S, Aveta A, et al. Granulomatous prostatitis mimicking prostate cancer in a patient with psoriatic arthritis: a case report. Future Sci OA. 2020;6(7):Fso591. **Psoriatic arthritis as new cause of GP.**
26. Wang Z, Han C, Xu Y, Yu X, Kang W, Xiang Y, et al. The role of prostate-specific antigen and multiparametric magnetic resonance imaging in the diagnosis of granulomatous prostatitis induced by intravesical bacillus Calmette–Guérin vaccine therapy in patients with nonmuscle invasive bladder cancer. J Cancer Res Therapeutics. 2021;17(3).
27. Pepe P, Pennisi M. Negative biopsy histology in men with PI-RADS score 5 in daily clinical practice: incidence of granulomatous prostatitis. Clin Genitourin Cancer. 2020;18(6):e684–7.
28.•• Dikov D, Koleva M, Mollova A, Fakirova A. Strong PD-L1 expression in granulomatous prostatitis. Prostate. 2023;83(13):1285–9. **A recent study investigating PD-L1 expression in GP.**
29. Ribas A, Hu-Lieskovan S. What does PD-L1 positive or negative mean? J Exp Med. 2016;213(13):2835–40.
30. Demeter J, Deshmukh A, Salari B, Sindhwani P, Khan O. An improbable trifecta: occurrence of xanthogranulomatous prostatitis, prostate cancer, and prostatic abscess in a single patient. Urol Case Rep. 2021;35:101526.
31. Komeda H, Takeuchi T, Yamada S, Shinoda I, Ban Y, Kawada Y. A case report of non-specific granulomatous prostatitis: successful treatment with chlormadinone acetate. Hinyokika Kiyo. 1988;34(10):1815–7.
32. Saha PK, Hyakutake H, Nomata K, Yushita Y, Kanetake H, Saito Y. Non-specific granulomatous prostatitis treated with steroids. Hinyokika Kiyo. 1991;37(8):927–30.
33. Ohkawa M, Yamaguchi K, Kobayashi M. Non-specific eosinophilic granulomatous prostatitis responded favorably to an antimicrobial agent and a hydrocortisone. Int J Urol. 2001;8(10):578–80.