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Original Article

Granulomatous prostatitis: Clinicopathological overview and review of the literature.

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Abstract

Introduction and objectives

It is challenging to rule out granulomatous prostatitis (GP), an uncommon inflammatory condition of the prostate, from prostate cancer. This study aims to characterize the clinical presentation, diagnostic evaluation and available treatment options for patients who present with GP.

Methods

This is a retrospective descriptive analysis of GP cases presented to a tertiary care urological referral center in Sri Lanka over a period of five years. Their demographic data, clinical presentation, examination findings, biochemical investigations, imaging and histopathological findings were collected from the patients' records.

Results

Nine pathologically confirmed GP cases were found among the 1568 prostate specimens examined. They had an age range of 43–75 years, with a median age of 59 years. The majority of patients presented with acute urinary retention and found hard nodular prostates in a digital rectal examination (DRE). Their prostate-specific antigen (PSA) level ranged from 0.2 - 77.1 ng/ml, with a mean value of 30.66 ng/ml. Biochemical and histological evaluation revealed non-specific GP (NSGP) in five patients, suppurative GP in two patients, tubercular GP in one patient, and allergic GP in one patient.

Conclusions

GP is an uncommon condition in urological practice. Its presentation can mimic prostate cancer and is inevitably a diagnostic challenge for urologists, radiologists, and pathologists. Proper clinicopathological evaluation is the cornerstone of preventing overtreatment.

Key words: Granulomatous prostatitis, Genitourinary tuberculosis, Prostate cancer

Introduction

GP is a rare inflammatory disorder of the prostate that we encounter in urological surgical practice in Sri Lanka and throughout the world. About 3.3% of all benign inflammatory diseases of the prostate are caused by GP (1, 4). Despite its rarity, its management remains unclear and controversial.Tanner and McDonald were the first to describe GP in 1943 (3, 4). It refers to any inflammatory disease of the prostate in which granulomas are found

histopathologically. GP can affect both normal and nodular hyperplastic prostate glands, as well as carcinomatous prostates (2, 5). In the majority of instances, it is asymptomatic and is discovered by chance during a histological examination. Less frequently, it is symptomatic and needs additional evaluation and treatment (4, 6).

Clinicaly,biochemicaly,ultrasonographicall y,radiologicaly and in rare cases, histopathologically, GP closely resembles prostate cancer. As a result, it poses a significant diagnostic problem and, in the majority of instances, can result in overtreatment. Due to increased transurethral resection, prostate needle biopsy, and Bacille Calmette-Guérin (BCG) instillation in non-muscle invasive bladder cancer (NMIBC), GP is now detected more commonly despite its rarity, benign nature, and spontaneous resolution (4, 7). The vast majority of GP cases resolve on their own without the need for treatment. However, a small percentage of patients require medical and surgical therapy to keep their disease under control.

The research on the care of patients with GP in Sri Lanka are not well documented. According to the author's understanding, this is the first publication on the GP to be published in Sri Lanka. In this study, we describe the clinical presentation, diagnostic evaluation, and specific management of patients diagnosed with GP in a tertiary care urological surgery referral center in Sri Lanka. We feel that this article will add to the current body of information on the management of GP patients.

Materials and Methods

The Departments of Urology and Histopathology at Colombo South Teaching Hospital, Kalubowila, conducted this retrospective descriptive analysis on GP. The study comprised 1568 prostatic specimens from the histopathology department during a five-year period (January 2017 to December 2021), which included needle prostate biopsies, transurethral resection of prostate (TURP) chips, and prostatectomy specimens. Inadequate and poorly preserved prostate specimens were excluded from the study. Cases with histopathologically diagnosed GP were obtained, and retrospective data from the patients' records were gathered. Age, clinical presentation, DRE findings, serum PSA level, transrectal ultrasound scan (TRUS) and radiological imaging (MRI/CT) findings, the existence of prostate cancer in histological specimens and history of intravesicular BCG instillations were all examined in this data. All cases with GP were further subdivided based on these findings, using the classification proposed by Epstin and Hutchins.

Results

This study included 1568 prostate specimens. Nine pathologically confirmed GP cases were found among the 1568 specimens, representing a 1.2% incidence rate. The vast majority of them were needle prostate biopsy specimens. The patients ranged in age from 43 - 75 years, with a median age of 59 years. The majority of the patients had acute urinary retention, and subsequently revealed that they had a history of obstructive lower urinary tract symptoms. Almost all of the patients had a hard nodular prostate on DRE. These individuals' PSA levels ranged from 0.2 - 77.1 ng/ml, with a mean of 30.66 ng/ml. Only one patient had a positive genitourinary tuberculosis (GU TB) work-up. TRUS indicated hypoechoic lesions in the peripheral zone in the majority of the patients, which is more typical of prostate cancer. Three individuals received an MRI prostate scan, with two of them showing

prostate imaging reporting and data system (PIRADS) 3 and 4 lesions. As a result, clinically, prostate cancer was considered in the majority of instances, and none of these cases were suspected of being GP on a clinical basis. Table.1 summarizes the clinical characteristics of all GP patients.

Granulomata were present in all nine cases, according to histology. NSGP was detected in five of the nine patients. They had granulomata consisting of epithelioid histiocytes and Langerhans multinucleated giant cells (Figure 1). The patient whose work-up was positive for GU TB had tubercular GP comprising granulomas with foci of caseous necrosis surrounded by epithelioid cells, histiocytes, plasma cells, and multinucleated giant cells (Figure 2). Two patients had suppurative GP, containing granulomas with large amount of neutrophil infiltration combined with surrounding histiocytes, lymphocytes, plasma cells, multinucleated giant cells, and eosinophils (Figure:3). An allergic GP was diagnosed in one patient who had granulomas containing a large number of eosinophils infiltrating the prostatic stroma (Figure.4). In all the cases, Ziehl Neelsen staining for acid-fast bacilli and Grocott staining for fungi were negative. The histopathological features of these patients are summarized in Table 2.

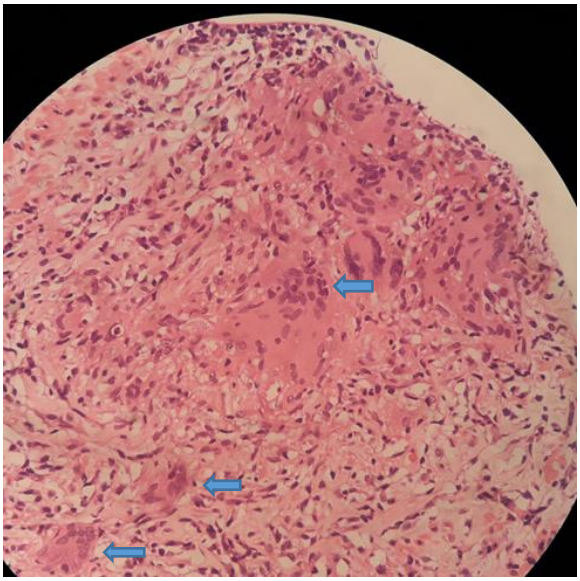

Fig 1. *Non-specific GP with granulomata containing epithelioid histiocytes and Langhan multinucleated giant cells (Black arrows). (H&E, X 400)*

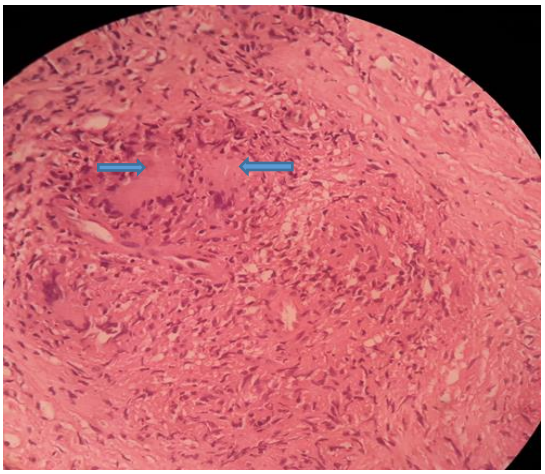

Fig 2. *Tubercular GP with granulomas containing foci of caseous necrosis (Black arrows) surrounded by epithelioid cells, histiocytes, plasma cells and multinucleated giant cells. (H&E, X400)*

Table 1. *Summary of patient characteristics*

Patient	Age (yrs)	Main symptoms	DRE	PSA (ng/ml)	MRI / CT	Urine AFB	Urine for TB culture	GeneXpert
A	47	Acute urinary retention	Hard irregular surface	35.5	Not done	Negative	Negative	Negative
B	43	Abdominal pain Uraemia	Hard nodular surface	0.2	Bilateral Hydronephrosis. No focal lesions in prostate	Positive on two occasions	Positive	Not done
C	55	Acute urinary retention	Hard area in one lobe	36.7	Three PIRADS IV nodules seen	Negative	Negative	Negative
D	62	Frequency Urgency	Suspicious firm nodule	2.5	One PIRADS IV nodule and one PIRADS III nodule	Negative	Negative	Not done
E	61	Left upper abdominal pain	Hard nodular surface	55.7	Not done	Negative	Negative	Negative
F	63	Acute urinary retention	Hard nodule on right lobe	36. 0	Not done	Negative	Negative	Negative
G	64	Acute urinary retention	Hard nodular surface	26.4	Not done	Negative	Negative	Negative
H	61	Acute urinary retention	Hard nodular surface	77.1	Not done	Negative	Negative	Negative
I	75	Dysuria, Frequency	Hard nodular surface	5.81	Not done	Negative	Not done	Not done

Table 2. *Summary of histopathological features*

Patient	Prostate specimen	Histological Features	Type of GP
A	TURP chips	Granulomata with epithelioid histiocytes and Langhan multinucleated giant cells Ziehl-Neelsen and Grocott stains negative	NSGP
B	TRUS biopsy	Granulomas with foci of caseous necrosis surrounded by epithelioid cells, histiocytes, plasma cells and multinucleated giant cells Ziehl-Neelsen and Grocott stains negative	Tubercular GP
C	TRUS biopsy	Granulomata with Langhan multinucleated giant cells Ziehl-Neelsen, PAS, Wade-Fite and Grocott stains negative	NSGP
D	TRUS biopsy	Granulomata with foci of epithelioid histiocytes with few lymphocytes Pan CK is negative and CD-68 is positive in epithelioid histiocytes	NSGP
E	TRUS biopsy	Foci with poorly defined granulomas composed of epithelioid histiocytes and multinucleated giant cells	NSGP
F	TURP chips	Granulomas with large area of neutrophil infiltration surrounded by histiocytes, lymphocytes, plasma cells, multinucleated giant cells and eosinophils, Ziehl-Neelsen and Grocott stains negative, No prostate cancer or high-grade prostatic intraepithelial neoplasia (PIN)	Suppurative GP
G	TRUS biopsy	Granulomata with epithelioid histiocytes, eosinophils and occasional foreign body type multinucleated giant cells, No high-grade PIN or prostate cancer	Allergic GP
H	TRUS biopsy	Granulomata with epithelioid histiocytes and multinucleated giant cells Ziehl-Neelsen and Grocott stains negative	NSGP
I	TRUS biopsy	Granulomata with neutrophils infiltrating the prostatic stroma and surrounded by histiocytes, lymphocytes, plasma cells, multinucleated giant cells and eosinophils, Ziehl-Neelsen and periodic acid Schiff negative for AFB and fungi	Suppurative GP

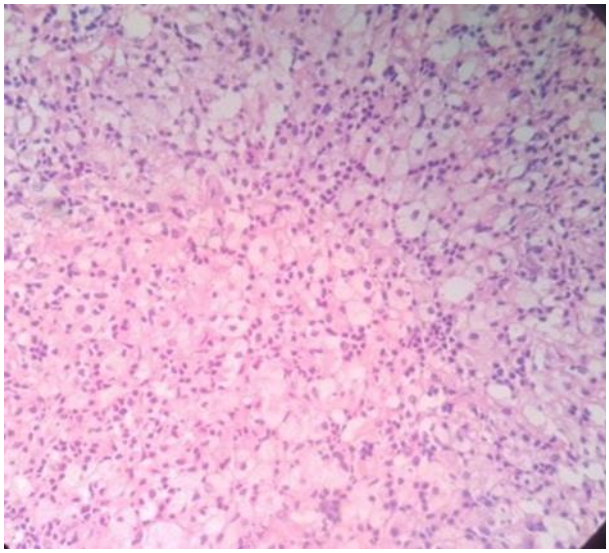

Fig 3. *Suppurative GP with granulomas containing large amount of neutrophil infiltration. (H&E, X400)*

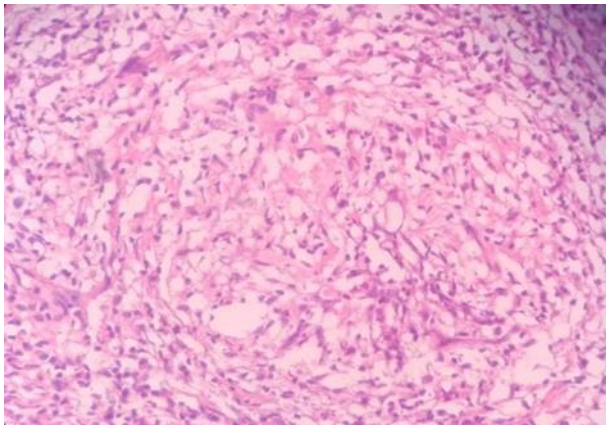

Fig 4. *Allergic GP with granulomas containing eosinophils infiltrating the prostatic stroma. (H&E, X400*)

Discussion

GP refers to any inflammatory condition of the prostate in which granulomas are present histologically. It is rarely encountered in urologic practice and often detected incidentally on histopathology. The reported incidence from South Asian countries like India and Pakistan is 1.5% (1, 4, 5). In our study, the reported incidence is 1.2% which is slightly lower than these countries. As eported by Shanggar K. et al from Malaysia, the mean age of occurrence is 59.5 years which is similar to mean age of occurrence in our study (59 years) also (80. But, Shukla P. et al and Mohan H. et al from India report a mean age of 61 years and 62.85 years respectively which is slightly higher than the Sri Lanka and Malaysia (4, 9).

Patients with GP can present with a range of symptoms. Storage and voiding lower urinary tract symptoms (LUTS), hematuria, pyuria, fever with chills and acute urinary retention are the most common presentations. Some patients can remain asymptomatic and therefore it is essentially an incidental diagnosis after a longer period (3, 7). Majority of patients in our cohort presented with acute urinary retention which is quite different from India where Kumbar R. et al and Mohan H. et al report increased frequency, urgency, dysuria with or without obstructive LUTS as their commonest presentations (2, 9).

In DRE, prostate glands with GP may feel firm to hard in consistency. Majority (08) of patients in our study had focal or diffuse area of induration with hard and fixed feel on DRE mimicking prostate cancer. This was true for other studies as well. Serum PSA level in GP patients can be normal or high. Shanggar K. et al from Malaysia report a PSA range of 0.88 – 19.22 ng/ml. Studies done in India by Kumbar R. et al and Mohan H. et al revealed a PSA range of 2.8 – 28.8 ng/ml and 2.2 – 18.6 ng/ml respectively (2,4,9). Interestingly, in our study it was 0.2 – 77.1 ng/ml which is relatively a wide range compared to above studies. Increased PSA in GP is a transient phenomenon and may decrease with resolution of inflammation (7, 9).

There is no specific pattern on transrectal ultrasound scan (TRUS) or multiparametric MRI (mpMRI) that allows specific diagnosis of GP or differentiation from prostate cancer (7). In TRUS, GP lesions

appear as hypoechoic shadows which is typical for prostate cancer as well (2). Among the seven individuals who had TRUS in the current study, five showed hypoechoic areas in the peripheral zone that resembled prostate cancer. In mpMRI, GP lesions typically show low intensity signal in T2 weighted images and diffusion restriction with high intensity signal in diffusion weighted images (DWI). Their apparent diffusion coefficient (ADC) value is also low and there is moderate to marked enhancement of the periphery of the lesion in dynamic contrast enhanced (DCE) images. These mpMRI findings are compatible with PIRADS-4 or PIRADS-5 score lesions which are moderately or highly suspicious for harboring prostate cancer. Two of the three individuals who had mpMRIs in this study revealed PIRADS 3 and 4 lesions which are concerning for prostate cancer. However, a TRUS biopsy did not identify prostate cancer in any of the aforementioned patients whose imaging results indicated prostate cancer. Therefore, there is an overlap between GP and prostate cancer in TRUS and mpMRI findings and it is most often mistaken radiologically for prostate cancer (3, 10, 11).

Widely accepted and generally used classification for GP was proposed by Epstein and Hutchins in 1984. This includes Non-specific (Idiopathic), Specific (Infectious), Iatrogenic, Malakoplakic and Systemic granulomatous disease associated (Allergic) GP subtypes based on aetiology and histopathology. Out of these, majority of cases belongs to Non-specific and Iatrogenic GP subtypes (2, 4, 9). In our study also, NSGP predominated in most of the patients, with infectious GP being the second most prevalent subtype.

NSGP is the most common subtype, accounting for 62.5% of all GP cases. Usually, it is incidentally detected and the reported incidence is less than 3.4%. NSGP commonly occurs in patients aged more than 50 years. But, according to Uzoh C. et al. from the UK, it can have a median age distribution of 18-86 years (7). The exact pathogenesis of the condition is uncertain and autoimmunity is considered the key underlying pathophysiological basis (2, 4). This is an HLA-DR 15-linked T-cell response principally against the PSA in extravasated prostatic secretions in the stroma (4, 7, 12, 13). Bacterial products, spermatozoa, refluxed urine, and colloidal substances in the stroma can also trigger the same immunological response (3,4,9,14). This leads to an intense, localized foreign body inflammatory reaction, leading to the formation of granulomas with periglandular and periductal distribution in most cases (2, 4, 7).

Xanthogranulomatous prostatitis (XGP) is a rare form of NSGP first described by Symmers in 1950. Extravasation of altered prostatic secretions, recurrent UTI, especially with Escherichia coli, autoimmune diseases, and hyperlipidemia are considered as possible aetiological factors. Histopathology is mandatory for the diagnosis of XGP. The presence of granulomas mainly in the central and peripheral zones of the prostate containing a large number of foamy macrophages (Histiocytes/Xanthoma cells) with dark, eccentric nuclei with little or no other inflammatory cell infiltrate is a characteristic feature. This can cause diagnostic confusion with clear cell prostate cancer, and immune-histochemical markers can be used to differentiate clear cell prostate cancerfrom XGP. These markers include cytokeratin, PSA, and prostatic acid phosphatase (PAP) for prostatic epithelial and acinar cells, and CD-68 for histiocytes (1,2,4,9)

Specific (Infectious) GP is caused by bacteria, fungi, parasites, and viruses. Mycobacterium tuberculosis is the commonest organism causing bacterial GP and is referred to as Tuberculous GP (2,4,5,7,9). Primary prostatic tuberculosis is rare. More common secondary forms can occur with systemic tuberculosis (3-12%), GU-TB (75-95%) and very rarely following BCG immunotherapy for bladder cancer. Macroscopically, in a cut section of the prostate, there are bilateral lesions with caseous liquefaction, cavitation, and sinus tract formation. In late stages, the prostate is shrunken, fibrotic, and hard, simulating prostate cancer on palpation. The hallmark of tubercular granulomas is the presence of confluent foci of caseous necrosis surrounded by epithelioid histiocytes and incomplete fibrous encapsulation. Unlike NSGP, these granulomas arise in the stroma and later spread to the periglandular and periductal regions (2,4,15). But, absence of caseation on biopsy does not necessarily exclude tuberculous prostatitis as there is a chance of sampling a non-caseating granuloma during needle prostate biopsy. Furthermore, special stains for AFB might be negative if the tissue sample is inadequate. Therefore, if clinical suspicion is high, a second biopsy specimen should be taken for tuberculosisculture (TB-Culture) (7). Other effective tools for diagnosing tuberculous prostatitis (TB prostatitis) include polymerase chain reaction for tuberculosis (TB-PCR), TB-Culture, and histochemical stains like Periodic Acid-Schiff (PAS) stain, Gomori's stain, and Ziehl Neelsen stain (16). One of the patients in our study tested positive for acid-fast bacilli (AFB) in the urine twice and his TRUS biopsy revealed granulomas with epithelioid histiocytes and Langerhansmultinucleated giant cells, but the Ziehl Neelsen staining was negative for mycobacteria.

GP due to atypical mycobacteria is extremely rare. According to Chuang AY. Et al. from Taiwan, Mycobacterium abscessus is one such organism that can induce more pronounced granulomatous inflammation with large neutrophilic abscess formation along with caseous necrosis. Correct pathologic identification of this is important as antimicrobial therapy for Mycobacterium abscessus differs from usual TB prostatitis (17).

Other less frequent species causing bacterial GP include Brucella, Treponema pallidum, and Escherichia coli (2,4,5,9). Immunocompromised patients are more likely to develop fungal (mycotic) GP, which is caused by coccidioidomycosis, paracoccidioidomycosis, blastomycosis, actinomycosis, histoplasmosis, and candidiasis (14,18). The histology of two of our patients revealed features of suppurative GP. However, neither fungi nor bacteria were detected by their histochemical staining. Parasitic GP can be brought on by schistosomiasis, echinococcosis, and enterobiasis. Herpes simplex virus (HSV) is the cause of viral GP (2,4,5,9).

Iatrogenic GP can occur following TURP and transurethral resection of bladder tumour (TURBT), open prostate surgery, prostate biopsy, pelvic radiotherapy and BCG instillation for NMIBC (2,4,5,9). Post-surgical GP is the second most common GP subtype and, together with NSGP, constitutes 95% of the cases of diagnosed GP. This occurs as a result of surgery-induced changes to the epithelium and stroma. Granulomas in post-surgical GP mimic rheumatoid nodules histologically, although they are unrelated to any connective tissue disease. It is important to note that these granulomas tend to disappear with time (7,9) Clinical or histological evidence of iatrogenic GP was

not present in any of the patients included in our study.

BCG induced GP occurs in 1.3% of patients following intravesical BCG treatment for NMIBC (2,5,7). It generally occurs 3–25 months (averagely one year) after the start of BCG treatment. The presence or pattern of BCG-induced GP is not related to the number of BCG instillations or the time interval between the bladder tumour resection and the last dose of BCG therapy. Intraductal reflux of BCG-contaminated urine is considered the likely pathogenesis. This reflux specifically occurs in the ducts draining the peripheral zone of the prostate due to their microanatomical arrangement, and therefore the peripheral zone of the prostate is predominantly affected by the BCG induced GP (3,19). Clinical history, physical examination, laboratory evaluation, and imaging are unreliable and, therefore, require histopathology for definitive diagnosis (5). Because of this, some authors recommend doing DRE and serum PSA assessment before starting BCG instillations to avoid unnecessary TRUS biopsy (6,20). In our study we did not encounter any patients with BCG induced GP.

In BCG-induced GP, epithelioid granulomas are predominantly (95.5%) located in the peripheral zone of the prostate, and this is consistent with the underlying pathogenesis. In 18.2% of cases, they are present in the transitional zone either solely (4.5%) or in association with the peripheralzone (13.6%). They may occasionally affect the prostate in a generalized manner. In BCG-induced GP, caseating or non-caseating granulomas are both possible, and non-caseating granulomas are often present in the duct lumen, wall, or peri-ductal areas (2,19).

Malakoplakia of the prostate is a rare granulomatous disease first described by Carruthers in 1959. Presence of intracellular Michaelis-Gutmann bodies is pathognomonic for the condition. They are a composite of calcium salts, iron, intact and degenerating bacteria within the phagolysosomal bodies. A defect in the intracellular lysosomal digestion of bacteria is considered as the underlying aetiology. There is a link with immunosuppression also. Commonly caused by gram negative bacteria like Escherichia coli and Klebsiella pneumoniae. Other organisms include Rhodococcus equi, Pseudomonas aeruginosa, Staphylococcus aureus and Mycobacterium bovis. In H and E staining, they appear as basophilic, concentrically laminated, target shape structures measuring 2-10μm in diameter. Electron-microscopically, Michaelis-Gutmann bodies contain intact and digested bacilli within phagolysosomes in the cytoplasm of the histiocytes (9,21,22).Present study and none of the other South Asian studies found GP due to Malakopakia in histopathological evaluation.

GP can also occur secondary to rare systemic granulomatous diseases. This is an exceedingly rare subtype associated with systemic allergic conditions like sarcoidosis, rheumatoid arthritis, Wegener's granulomatosis, polyarteritis nodosa and Churg Strauss syndrome (2,4,9). Granulomas with extensive tissue infiltration of eosinophils in histology is characteristic for the condition and therefore also known as allergic GP (7). Shukla P. et al from India has found two cases of allergic GP associated with bronchial asthma and eosinophilic cystitis in their study (4). Within this current study, we discovered granulomas in one patient with a high eosinophil infiltration rate, indicating the possibility for an allergic form of GP. However, it is interesting to

note that he didn't exhibit any of the systemic allergic conditions listed above.

Treatment for GP is difficult (9). The majority of individuals (60–90%) with NSGP experience spontaneous resolution and simply need supportive therapy and reassurance (3, 7). Initially, it is preferable to avoid surgical therapy due to its higher risk of complications (2, 9). But, 10-40% of patients eventually require TURP or prostatectomy for symptomatic relief as they are refractory to conservative therapy. Depending on the underlying cause, specific (infectious) GP requires treatment with antibiotics including antitubercular therapy, antifungals, or antiparasitic drugs.Iatrogenic GP is a self-limiting condition that eventually resolves on its own (7,9).

The isolated organism and the patient's underlying immune status are taken into account when treating Malakoplakic GP. Ciprofloxacin and Trimethoprim-Sulfamethoxazole can enter histiocytes and kill the partially digested bacteria. By elevating phagocytes' cGMP levels, bethanechol enhances their bactericidal action. The condition can also be reversed with an improvement in the patient's immunosuppressive state. Only in cases when medical treatment is found to be ineffective is surgical treatment, such as a TURP or prostatectomy, indicated (22). In systemic granulomatous disease associated (allergic) GP, any related or underlying disease should be identified and accordingly treated (7).

With proper treatment, the serum PSA level should return to the normal range for the patient. The DRE is not appropriate for follow-up decision making since the prostate gland may continue to be abnormal for years. Therefore, a repeat prostate biopsy is recommended during follow-up if serum PSA is persistently elevated (7).

Conclusion

GP is rarely encountered during the histopathological evaluation of prostate specimens. In terms of clinical presentation, it can resemble prostate cancer and is difficult to diagnose using the history, DRE, PSA assessment, TRUS and mpMRI. Even with histology, diagnosis can be challenging in certain instances. Most patients recover on their own with supportive therapy; a smaller percentage require antibiotics, antitubercular therapy, antifungals or antiparasitic medications, depending on the underlying cause. Surgical therapy should only be used in situations that do not respond to standard medical treatment. Repeat prostate biopsy during follow-up is indicated if there is a persistently increased PSA in the context of a long-standing abnormal DRE.

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