



## Original Article

## Granulomatous prostatitis: clinical and histomorphologic survey of the disease in a tertiary care hospital



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## ABSTRACT

**Background:** Granulomatous prostatitis is an uncommon entity that is diagnosed incidentally on histopathology and is broadly classified as nonspecific, specific, postsurgical (post-transurethral resection), or secondary to other rare systemic granulomatous diseases. Only very few studies are available in the literature that describe the clinical and histomorphological spectrum of the disease.

**Methods:** A retrospective analysis of histopathological records of 1,181 prostatic specimens received in the pathology department was done over a period of 13 years (January 2003 to January 2016). All histologically proven cases of granulomatous prostatitis were retrieved, and relevant clinical data were collected from patients' records. Epstein and Hutchins classification was used to categorize these cases.

**Results:** Twenty-two cases of granulomatous prostatitis were identified, accounting for an incidence of 1.86%. Among these, nonspecific granulomatous prostatitis ( $n = 10$ ) was the most common followed by tubercular prostatitis ( $n = 5$ ), posttransurethral resection of the prostate ( $n = 3$ ), allergic ( $n = 2$ ), and xanthogranulomatous prostatitis ( $n = 2$ ). The age range of these patients was between 41 and 75 years, with the majority of patients in their 7<sup>th</sup> decade. Serum prostate-specific antigen levels ranged between 0.88 ng/mL and 19.22 ng/mL. Hard and fixed nodules were observed on digital rectal examination in 14 cases. Transrectal ultrasound revealed hypoechoic shadows in five cases.

**Conclusion:** Despite present-day advances in imaging modalities and serological investigations, it is virtually impossible to identify granulomatous prostatitis clinically. Histopathology remains the gold standard in diagnosing the disease. However, assigning an etiologic cause to the wide spectrum of granulomas in granulomatous prostatitis requires a pathologist's expertise and proper clinical correlation for appropriate patient management.

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## 1. Introduction

Granulomatous prostatitis is a group of morphologically distinct forms of chronic prostatitis that is often detected incidentally on histopathology. Although the incidence is low, it is currently diagnosed more frequently because of increased transurethral resection of the prostate (TURP), needle biopsy procedures, and extensive use of intravesical Bacillus Calmette–Guerin (BCG) instillation in non-muscle invasive bladder cancer (NMIBC).<sup>1</sup> The major concern lies in the fact that it simulates prostate malignancy on clinical as well as

radiological fronts leading to overtreatment. Thus, the diagnosis of granulomatous prostatitis is based on histological detection of epithelioid granulomas with or without other inflammatory cells. A literature search revealed only a few reports on the incidence and clinicopathological series of granulomatous prostatitis.

Considering the importance of granulomatous prostatitis in urology clinics, it is pivotal to histologically differentiate this entity from other lesions of the prostate. In the present study, the incidence of granulomatous prostatitis, its clinical and histomorphologic spectrum, was studied, emphasizing the distinction between the various types observed in a tertiary care multispecialty hospital.

## 2. Material and methods

All the resected prostatic specimens including prostatic biopsies, TURP chips, and radical prostatectomies sent to the

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**Table 1**  
Clinical details of twenty two cases of granulomatous prostatitis.

SN	Age (yr)	Clinical diagnosis	Presenting symptoms	DRE	Serum PSA (ng/mL)	Prostate weight (g)	Specimen	Urine findings	Histopathological diagnosis
1	65	Carcinoma	Dysuria	Hard, fixed nodule	8.85	52	TURP	WNL	Xanthogranulomatous
2	64	BPH	Frequency, urgency, burning micturition	Firm nodular	–	30	TURP	Pus cells >120/hpf	Nonspecific
3	63	Carcinoma	Frequency, urgency	Hard, fixed nodule	3.38	40	TURP	WNL	Nonspecific
4	73	Carcinoma	Frequency, urgency, hematuria	Firm, nodular	0.88	30	TURP	Pus cells 10–18/hpf, RBC 60–65/hpf	Nonspecific
5	57	Carcinoma	Frequency, urgency	Hard, fixed nodule	16.5	55	Prostate biopsy	WNL	Nonspecific
6	70	BPH	Frequency, urgency	Hard, fixed nodule	–	39	TURP	WNL	Tubercular
7	51	BPH	Urinary incontinence, burning micturition	Hard, fixed nodule	19.22	120	TURP	Pus cells 20–40/hpf	Tubercular
8	65	BPH	Frequency, urgency, burning micturition	Firm, nodular	–	60	TURP	Pus cells 90–95/hpf	Tubercular
9	66	Carcinoma	Frequency, urgency, hesitancy, burning micturition, hematuria	Hard, fixed nodule	–	48	TURP	Pus cells 75–80/hpf, RBC 6–10/hpf	Post-TURP
10	41	BPH	Frequency, urgency	Firm, nodular	1.82	48	TURP	WNL	Tubercular
11	69	Carcinoma	Frequency, urgency, hematuria	Hard, fixed nodule	5.20	40	TURP	Pus cells 30–35/hpf, RBC 8–10/hpf	Nonspecific
12	73	BPH	Frequency, urgency	Hard, fixed nodule	4.81	36	TURP	WNL	Tubercular
13	56	BPH	Frequency, urgency, hesitancy, dysuria	Hard, fixed nodule	2.68	49	TURP	WNL	Nonspecific
14	64	BPH	Frequency, urgency	Firm, nodular	–	117	TURP	WNL	Post-TURP
15	71	BPH	Frequency, urgency, hesitancy	Hard, fixed nodule	–	44	TURP	WNL	Allergic
16	67	BPH	Frequency, urgency	Hard, fixed nodule	3.38	60	TURP	WNL	Nonspecific
17	70	BPH	Frequency, urgency	Firm, nodular	–	35	TURP	WNL	Nonspecific
18	67	Carcinoma	Frequency, urgency, dysuria, hematuria	Hard, fixed nodule	12.80	58	Prostatic biopsy	RBC 30–40/hpf	Nonspecific, well-differentiated adenocarcinoma
19	69	BPH	Frequency, urgency dysuria	Hard, fixed nodule	–	78	TURP	WNL	Xanthogranulomatous
20	75	Carcinoma	Urinary incontinence	Hard, fixed nodule	13.6	99	TURP	WNL	Nonspecific
21	57	BPH	Frequency, urgency, hesitancy	Firm, nodular	4.80	40	TURP	WNL	Allergic
22	56	BPH	Frequency, urgency, burning micturition	Firm, nodular	6.89	29	TURP	Pus cells 80–90/hpf	Post-TURP

BPH, benign prostatic hyperplasia; DRE, digital rectal examination; PSA, prostate-specific antigen; RBC, red blood cell; SN, serial number; TURP, Transurethral resection of prostate; WNL, within normal limit.

Histopathology section of the Department of Pathology of Bhopal Memorial Hospital and Research Centre were reviewed. The prostate specimens submitted over a period of 13 years (January 2003 to January 2016) were included in the study. Inadequate biopsies were excluded. Retrospective data were collected from the patients' records and analyzed for various clinical parameters including age, presenting signs and symptoms, serum prostate-specific antigen (PSA) levels, digital rectal examination (DRE) findings, as well as radiological and other laboratory investigations. Sections from these cases were stained with hematoxylin and eosin, Gomori's silver methenamine stain, periodic acid Schiff's (PAS) stain, and Ziehl–Neelsen (ZN) stain. All cases of granulomatous prostatitis were further subdivided into specific, nonspecific, post-TURP, and allergic type according to the classification proposed by Epstein and Hutchins.<sup>2</sup>

### 3. Results

#### 3.1. Clinical findings

A total of 1,181 prostatic specimens were received in the department of pathology from January 2003 to January 2016. Among them, 22 cases of granulomatous prostatitis were observed on histopathology accounting for an incidence of 1.86%. Out of 22 cases, 20 of the prostatic specimens were TURP chips and the remaining two were needle biopsies. The age range of these patients was 41–75 years, with a mean age of 61 years. Twelve patients presented in their 7<sup>th</sup> decade. Increased frequency and urgency was noted in 19 patients, whereas five patients presented with additional symptom of burning micturition. Also, hematuria was noted in four other patients. On DRE, hard and fixed nodules were seen in 14 cases, whereas firm nodules were seen in eight cases. Most of these patients were clinically suspected as cases of benign prostatic hyperplasia, whereas in eight cases a possibility of malignancy was considered. Serum PSA levels in these patients ranged between 0.88 ng/mL and 19.22 ng/mL, and ultrasonography revealed prostatic weight ranging between 29 g and 120 g. Transrectal ultrasound showed hypoechoic shadows in five of these cases. The clinical profile of all 22 cases is described in Table 1.

#### 3.2. Histopathological findings

On histopathology, out of 22 cases of granulomatous prostatitis, five cases of tubercular prostatitis, three cases of post-TURP, two cases of allergic, two cases of xanthogranulomatous, and 10 cases of nonspecific granulomatous prostatitis were diagnosed in our study, as summarized in Table 2. The histomorphological features of the granulomas observed in our study are detailed in Table 3.

Of the 22 cases, tubercular prostatitis was diagnosed in five cases with multiple confluent granulomas in the stroma comprising the central foci of caseous necrosis surrounded by epithelioid cells, histiocytes, plasma cells, and multinucleated giant cells (both foreign body and Langhans type) (Figs. 1A, 1B). In one case, *Mycobacterium tuberculosis* polymerase chain reaction (PCR) assay was reactive, and

**Table 2**  
Classification of granulomatous prostatitis.

SN	Types	No.	Percentage (%)
1.	Nonspecific granulomatous prostatitis	10	45
2.	Tubercular granulomatous prostatitis	5	23
3.	Postsurgical granulomatous prostatitis	3	14
4.	Allergic granulomatous prostatitis	2	09
5.	Xanthogranulomatous prostatitis	2	09

SN, serial number.

**Table 3**  
Histomorphological features of granulomas.

Granulomas	Cases
1. Type of Granulomas	
(a) Diffuse	12
(b) Focal	10
(c) Well formed	14
(d) Ill formed	8
2. Necrosis	
Caseous & fibrinoid	10
3. Inflammatory cells	
(a) Lymphocytes	22
(b) Eosinophils	4
(c) Neutrophils	17
(d) Epithelioid cells	19
(e) Histiocytes	21
(f) Foamy macrophages	2
(g) Giant cells	
i. Langhans type	11
ii. Foreign body type	12
iii. Both	2

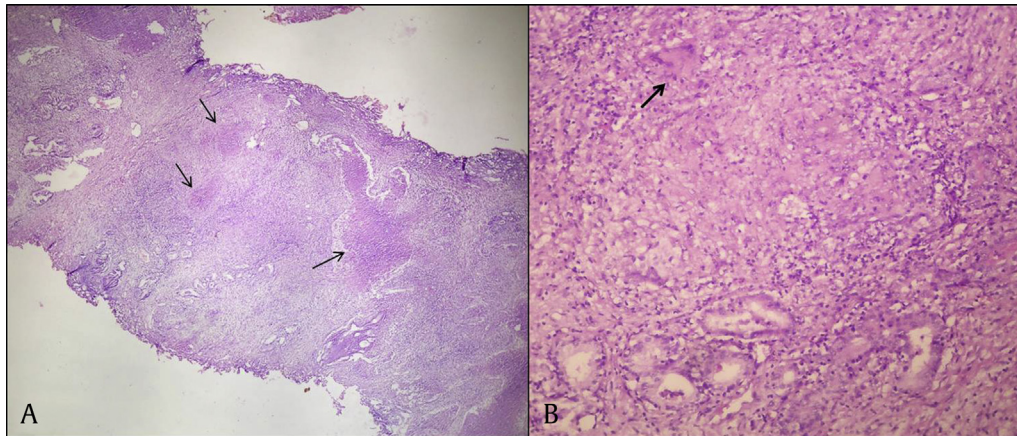
the patient on initial visit to the Out Patient Department presented with abdominal signs of gastrointestinal tuberculosis. This patient also had urinary tract infection (UTI) with plenty of pus cells and albumin (2+) in urine. In the second case, sputum culture was positive for mycobacterium tuberculi, and in two other cases, chest radiographs revealed homogenous opacities and air bronchograms in the lungs. In one other case, ZN staining showed few acid fast bacilli in areas of caseous necrosis, suggesting tubercular prostatitis. However, this case had no evidence of pulmonary or extrapulmonary tuberculosis on detailed clinical workup.

Three cases with a history of TURP showed palisading histiocytic granulomas with central region of fibrinoid necrosis and several multinucleated foreign body giant cells (Fig. 2A). Minimal surrounding inflammation by lymphocytes, plasma cells, and occasional eosinophils was observed in these cases. Hypertrophic glands with squamous metaplasia were observed in two cases. Two of these cases had associated UTI and one case presented with hematuria.

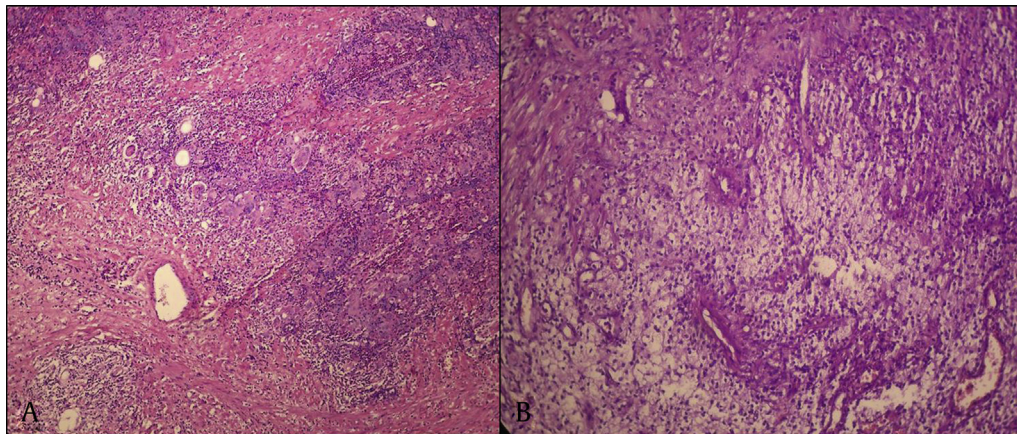
Xanthogranulomatous prostatitis was seen in two cases with sheets of foamy macrophages in the inflammatory cell infiltrate (Fig. 2B). The remaining 10 cases were classified as nonspecific granulomatous prostatitis after excluding other causes. Special stains such as Gomori methenamine silver and ZN stain did not reveal any fungal or acid fast organism. In these cases, periglandular distribution of noncaseating granulomas was seen with epithelioid histiocytes admixed with variable numbers of multinucleated giant cells, lymphocytes, plasma cells, neutrophils, and histiocytes (Fig. 3A). In some areas, the granulomas were seen effacing dilated ducts containing inspissated secretions admixed with acute inflammatory cells and desquamated epithelial cells. Additional pathological findings were adenomatous hyperplasia of the glands in all cases with squamous and transitional metaplasia in two of them (Figs. 3B, 3C). In one case, prostatic urethra showed squamous metaplasia, whereas in another case several Von Brunn nests were seen. Three out of 10 cases had UTI, and two of these cases and one other case had associated complaint of hematuria.

Two cases of allergic granulomatous prostatitis were observed in our study with multiple small, necrobiotic granulomas surrounded by numerous eosinophils with extensive infiltration of eosinophils in the surrounding stroma (Fig. 4). One patient had an associated clinical history of bronchial asthma with eosinophilia in the peripheral blood. The second patient had eosinophilic cystitis as the bladder biopsy revealed dense mixed inflammation with eosinophils as the predominant inflammatory cell. Silver methenamine staining did not reveal any fungal organism in both cases.





**Fig. 1.** Tubercular prostatitis. (A) Low-power photomicrograph of TURP specimen showing large areas of necrosis (thin arrows) bordered by epithelioid histiocytes (4 $\times$ ). (B) High-power photomicrograph demonstrating benign prostatic glands and epithelioid cell granuloma with Langhans-type giant cells (thick arrow) (20 $\times$ ). TURP, transurethral resection of the prostate.



**Fig. 2.** Types of granulomatous prostatitis. (A) Post-TURP granulomatous prostatitis. Low-power photomicrograph showing destruction of prostatic stroma by dense inflammation with presence of numerous foreign body giant cells and collection of epithelioid cells (10 $\times$ ). (B) Xanthogranulomatous prostatitis. High-power photomicrograph revealing fibromuscular stroma of prostate with presence of numerous xanthoma cells (20 $\times$ ). TURP, transurethral resection of the prostate.

Clinically, eight cases were diagnosed as carcinoma prostate based on DRE findings and/or raised PSA levels. In only one case, well-differentiated adenocarcinoma (Gleason's grade 3 + 2 = 5) was present, and the adjoining area showed nonspecific granulomatous prostatitis. The remaining seven cases revealed granulomatous prostatitis with no evidence of malignancy, and these were histologically subclassified as nonspecific granulomatous prostatitis ( $n = 5$ ), post-TURP ( $n = 1$ ), and xanthogranulomatous prostatitis ( $n = 1$ ).

#### 4. Discussion

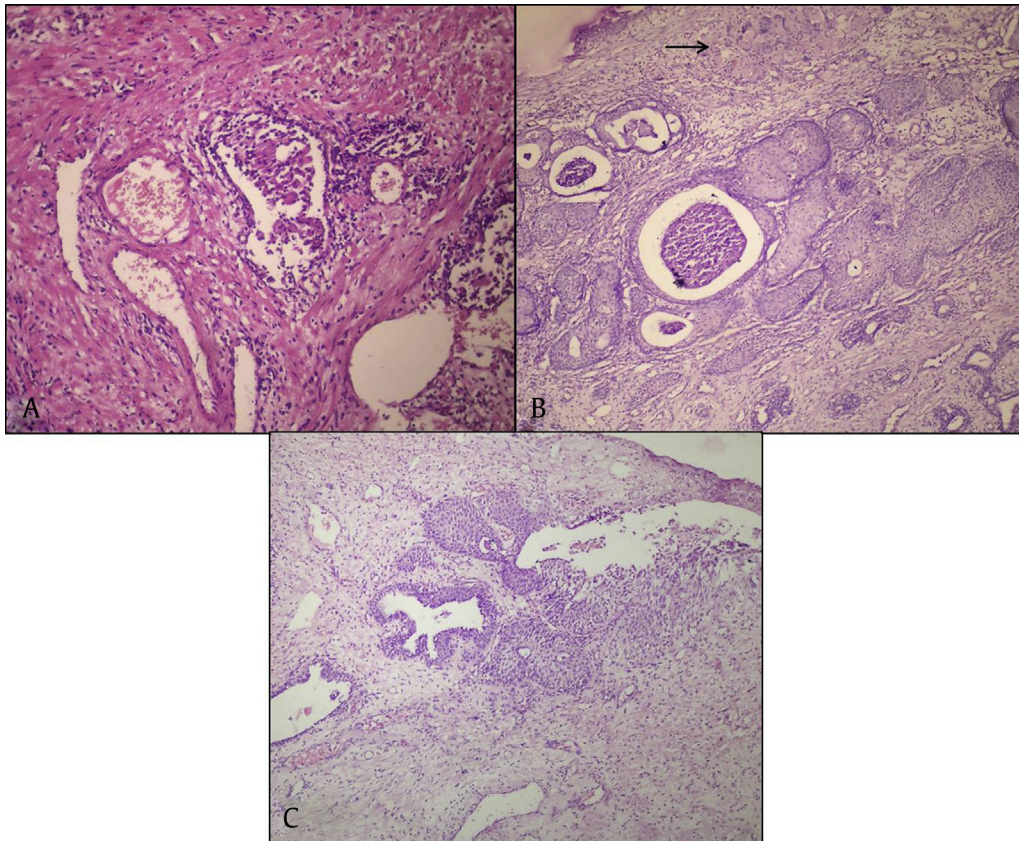
Granulomatous prostatitis was first described by Tanner and McDonald<sup>3</sup> in 1943, with an incidence of 3.3% of all benign inflammatory lesions of prostate. In most cases, the pathogenesis is uncertain, but it often results from the destruction of the epithelium and extravasation of prostatic secretions in the stroma that incites an intense localized inflammatory response. This process can occur in a normal, carcinomatous, or more commonly in nodular hyperplastic prostate glands.<sup>4</sup> In most cases, periglandular distribution of the granulomas is noted.<sup>5</sup> Various predisposing events have been associated such as UTIs (73%), surgical interventions including TURP/open prostatectomy, needle biopsy, and instillation of BCG into the bladder.<sup>1,6,7</sup>

In 1984, Epstein and Hutchins<sup>2</sup> classified granulomatous prostatitis into nonspecific, specific, postsurgical (posttransurethral resection), and secondary to other rare systemic granulomatous diseases. Uncommon forms are xanthogranulomatous prostatitis and sarcoidosis. Nonspecific granulomatous prostatitis and post-TURP type together constitute the maximum number of cases.<sup>6</sup> In the present study, nonspecific granulomatous prostatitis was also the predominant lesion, accounting for 45% of all cases. The other forms observed were tubercular (23%), post-TURP (14%), allergic (9%), and xanthogranulomatous type (9%).

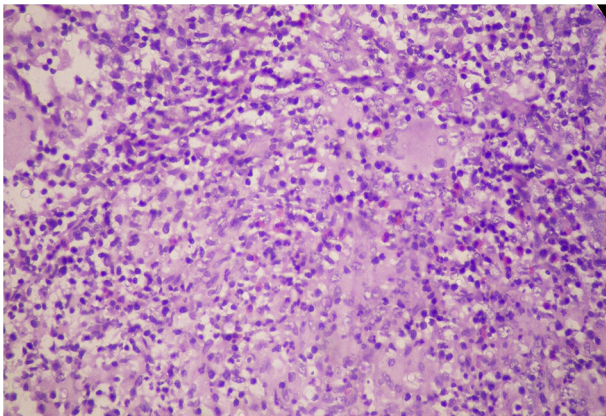
In the present study, the incidence of granulomatous prostatitis was 1.86%, which was slightly higher than those reported in other studies from the north and west regions of India, with an incidence rate of 1.5% and 1.4%, respectively.<sup>8,9</sup> Studies from other parts of the world including Islamabad (Pakistan), Malaysia, and Philadelphia (USA) reported an incidence of 1.5%, 0.65%, and 0.5%, respectively.<sup>10–12</sup> The mean age of occurrence of granulomatous prostatitis in our study was 61 years, which was comparable to that reported in other studies.<sup>11,13</sup> The most common clinical presentation was frequency, urgency, and burning micturition as seen in other studies.<sup>8,9</sup>

Clinically, granulomatous prostatitis may present as a focal or diffuse area of induration, often giving a stony hard feel on DRE with normal to raised serum PSA levels and/or hematuria. These findings pose a great clinical challenge in differentiating it from





**Fig. 3.** Nonspecific granulomatous prostatitis. (A) High-power photomicrograph showing small nodular granuloma centered on prostatic gland (20 $\times$ ). (B) Another case showing marked squamous metaplasia in the glands and a peripheral granuloma (thin arrow) with several foreign body giant cells (20 $\times$ ). (C) Photomicrograph demonstrating transitional metaplasia of prostatic glands (10 $\times$ ).



**Fig. 4.** Allergic granulomatous prostatitis. High-power photomicrograph showing granuloma with prominent eosinophilic infiltrate (40 $\times$ ).

prostate cancer.<sup>7,9</sup> In our study, eight cases were mistaken for carcinoma prostate clinically. In one case, well-differentiated adenocarcinoma of prostate was noticed with nonspecific granulomatous prostatitis. Various studies have reported the coexistence of carcinoma in 10–14% of patients with clinically diagnosed granulomatous prostatitis.<sup>14,15</sup>

Specific granulomatous prostatitis usually occurs as a result of mycobacterial tuberculosis and is referred to as tubercular prostatitis. Other uncommon causes are viruses, fungi, syphilis, and parasites. Although primary prostatic tuberculosis is rare, it can be

affected secondary to systemic or genitourinary tuberculosis or, more commonly, as a complication of BCG immunotherapy for bladder carcinoma.<sup>1</sup> The most common mode of spread is hematogenous, although descending infection and direct intracanalicular extension are also reported. Prostate is affected in 3–12% of patients with systemic tuberculosis, and more than 90% of these cases have coexisting pulmonary tuberculosis.<sup>11</sup> In patients with genitourinary tuberculosis, prostate is involved in 75–95% of cases.<sup>16,17</sup> In our study, out of five cases, secondary tubercular prostatitis was seen in four cases (80%), whereas primary involvement of the prostate was noted in one case only. In three of the cases, the primary focus of tuberculosis was in the lungs, and one case had gastrointestinal tuberculosis. Thus, 60% of the cases had coexisting pulmonary tuberculosis in the present study. None of the patients had intravesical BCG induced granulomas because such patients were referred to other center for treatment. Histologically, tubercular granulomas arise in the stroma and later spread to acini.<sup>9</sup> A hallmark of this lesion is the presence of confluent foci of caseous necrosis surrounded by epithelioid histiocytes as were seen in the present study. PCR testing for mycobacterial DNA, culture, and stains for acid-fast bacilli are effective tools in diagnosing tubercular prostatitis.

Nowadays, the incidence of post-TURP granulomatous prostatitis has increased as a reaction to cautery and thermal alterations to prostatic epithelium and stroma.<sup>2</sup> These resemble rheumatoid nodules on histopathology and reveal palisading histiocytes with foci of fibrinoid necrosis. Herein, granulomas so formed show heavy infiltration by eosinophils as was also observed in our study. In most cases, this form of prostatitis resolves spontaneously.<sup>18</sup>

Allergic granulomatous prostatitis is an exceedingly rare variety that is presumed only when a history of systemic allergic conditions such as asthma and vasculitis is present and histology reveals extensive infiltration by eosinophils in the tissue.<sup>2</sup> In our study, two cases of allergic prostatitis could be diagnosed as clinical and laboratory findings in these patients were corroborative of systemic allergy.

Xanthogranulomatous prostatitis, first described by Symmers<sup>19</sup> in 1950, is well known in the kidney and gallbladder but is rarely found in the prostate.<sup>20</sup> Histologically, it reveals several xanthoma cells in the prostate, which may cause diagnostic confusion with the hypernephroid pattern of adenocarcinoma.<sup>21</sup> Immunohistochemical markers for epithelial and prostatic cells (cytokeratin, PSA, PAP) and histiocytes (CD68) help in resolving this diagnostic dilemma.<sup>22</sup> In the present study, the incidence of xanthogranulomatous prostatitis was 0.2%, which is similar to the findings of Kumbar et al,<sup>9</sup> who reported an incidence of 0.4%.

Nonspecific granulomatous prostatitis is often diagnosed incidentally and accounts for 69–77.7% of cases.<sup>6,23</sup> In the present study, it was also the most common entity diagnosed, with an incidence of 45%. The etiology is uncertain, but it is hypothesized to result from foreign body response to colloidal substance, bacterial products, or refluxed urine. It is now believed that nonspecific granulomatous prostatitis is autoimmune based with HLA-DR15-linked T cell response against proteins in prostatic secretions, especially PSA.<sup>5,24</sup> DRE findings and PSA levels often lead to erroneous interpretation of carcinoma prostate.<sup>25</sup> Patients may present with symptoms of urinary obstruction or signs and symptoms of infection. It has been seen that increase in PSA levels is transient, which decreases with resolution of the inflammation.<sup>26</sup> In the present study, granulomas were focused around the glands and their secretions. These comprised epithelioid histiocytes, lymphocytes, plasma cells, multinucleated giant cells, fibrosis, and sometimes few eosinophils. Adjacent stroma revealed mixed inflammatory infiltrates with neutrophilic abscess and necrotic debris with ruptured ducts and acini. These findings support the hypothesis suggested by Epstein and Hutchins.<sup>2</sup> Moreover, in our study 30% of these patients presented with symptoms of UTI. It is, thus, essential to differentiate nonspecific granulomatous prostatitis from other forms of granulomatous prostatitis because of its self-limiting nature.<sup>27</sup>

Nonspecific granulomatous prostatitis and xanthogranulomatous prostatitis may occur in the transition and peripheral zones of the prostate whereas tubercular granulomas predominate within the peripheral zone of the prostate.<sup>1,28</sup> Postbiopsy granulomatous prostatitis occurs around the site of resection and along the biopsy tract. In systemic granulomatous conditions, granulomas are mostly seen centered on blood vessels, as was observed in our study.

## 5. Conclusion

Granulomatous prostatitis is a distinct clinical and pathologic entity with varied etiologies. Among the diverse causes, nonspecific granulomatous prostatitis is the most common, which is self-limiting, whereas other specific causes of granulomatous prostatitis require definite treatment. Recognition of different histomorphological patterns of granulomas in prostatic specimens aids in identifying the underlying cause. The presence of large, caseating, and confluent granulomas in prostate tissue should raise the suspicion of tubercular prostatitis. Judicious correlation of clinical, morphological, and histochemical data is, thus, necessary in directing the clinicians toward specific management.

## Conflicts of interest

None of the contributing authors have any conflicts of interest, including specific financial interests, relationships, and affiliations relevant to the subject matter or materials discussed in the manuscript.

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