INTRODUCTION

Granulomatous prostatitis (GP) is a self-limited inflammatory process, which most frequently presents with low-grade fever, dysuria, and frequency.[1,2]
the prostate.\textsuperscript{[3,5]} Morphologically, NSGP is a diffuse, chronic inflammation associated with focal necrosis and multinucleated giant cells in the absence of acid-fast bacteria or other special microorganisms, and without relationship to previous transurethral resection of the prostate (TURP) or systemic granulomatous disease.\textsuperscript{[6]}

Although the exact pathogenesis of NSGP still remains unknown, it is suggested that duct/acinar obstruction and rupture followed by an inflammatory/autoimmune response to altered extravasated prostatic secretions might be a leading pathogenic mechanism.\textsuperscript{[7,9]}

The histological diagnosis is important in differentiating from high Gleason grade prostatic adenocarcinoma (PCa).\textsuperscript{[4]} An immunohistochemical panel has been proposed to distinguish reliably both conditions.\textsuperscript{[10,13]}

Current literature is insufficient with regard to benign epithelial changes in the areas of NSGP and around it, except for cribiform glandular structures.\textsuperscript{[4]}

The presence of bright eosinophilic cytoplasmic granules in prostatic epithelium on routine hematoxylin and eosin (HE)-stained sections is a vaguely recognized morphological phenomenon, which in the early descriptions is known as Paneth cell-like changes (PCLC) or Paneth cell-like metaplasia (PCLM).\textsuperscript{[12,13]} According to the modern concepts of this prostatic epithelial metaplasia, the terms PCLC or PCLM remain reserved only for PCa, containing neuroendocrine cells with large eosinophilic granules.\textsuperscript{[14,15]} The presence of eosinophilic granules in benign prostatic epithelium is called so far « eosinophilic metaplasia » (EM).\textsuperscript{[16]} The nature of EM is quite unclear. The only sure fact is that the limited data available do not support “true” Paneth cell or endocrine cell differentiation.\textsuperscript{[12-15]}

In all zones of the normal prostate, the epithelium contains isolated, randomly scattered endocrine–paracrine cells are known to occur with cell processes extending to lumen, but as Weaver et al. notes [Table 3 in their article], there is no morphologic difference from normal prostatic epithelium in routinely stained sections.\textsuperscript{[12]}

Recently, we reported two cases about association of NSGP with extensive EM in benign prostatic epithelium.\textsuperscript{[16,17]}

The aim of the current study is to investigate the frequency of association and correlation between NSGP and EM in a large series of cases and their relationship with the basic prostate pathology processes: benign prostatic hyperplasia (BPH), National Institutes of Health (NIH)-category IV prostatitis (so-called histologic prostatitis (HP)), and PCa. We try to clarify the pathogenesis of both histological findings, the diagnosis of NSGP, and its differential diagnosis with other types of GP, PCa, and PCa containing PCLC-areas in particular.

**MATERIALS AND METHODS**

A retrospective record review was performed on all types of prostatic material (TURP, adenoectomies, needle biopsies, autopsies) at the Departments of Pathology of Grand Hospital de l’Est Francilien, France from 01.01.1998 to 31.12.2015 and at the St. George University Hospital of Plovdiv, Bulgaria for the period of 2 years (2014–2015). A total of 2366 (1484 + 882) prostatic specimens were examined. The study was approved by the local Ethics Committees of both hospitals. Nine cases with NSGP were detected and all of them were re-examined independently by three pathologists (DD, JFB, and MK). Clinical data and follow-up data were obtained from medical records and surgical pathology files. None of the patients had histories of asthma, allergies, systemic granulomatous disease, and previous prostate surgery. Blood eosinophil counts were within normal limits. A total of six cases were selected for comparison from surgical pathology and biopsy files. Two of them were cases of iatrogenic GP, bacillus Calmette–Guerin (BCG)-associated GP and were used as a control group for granulomatous prostate inflammation. The rest four cases of intermediary and high Gleason grade PCa (grade groups 3 and 4, WHO 2016) with focal areas with endocrine differentiation (PCLC-zones) were examined as a control group for PCa, containing neuroendocrine cells with large eosinophilic granules (PCLC). All specimens were routinely fixed in 10% buffered formalin or Bouin fluid and embedded in paraffin for histological evaluation. A total of 4 µm thick consecutive tissue sections were cut from 1 to 10 paraffin blocks for each case. Sections were stained with HE, hematoxylin-eosin-safran, peridate-Schiff’s procedure with diastase digestion (PAS.D), Grocott, Ziehl–Neelsen stains (ZN), and modified (long) ZN-stain. Fluorescence microscopy was applied to visualize the lipofuscin pigment.\textsuperscript{[18]} All cases of NSGP with EM and the control cases were evaluated immunohistochemically by avidin–biotin complex or peroxidase–antiperoxidase techniques. The following primary antibodies (Dako, Caripenteria, California, USA and Diagomics, France) were used: antihuman chromogranin (working dilution 1:75), antihuman synaptophysin (working dilution 1:75), antihuman α-1-antichymotrypsin (α-1-ACT) (dilution 1:1000), and a combined P5045/p63 stain (PIN-cocktail, dilution 1:50).

**DEFINITIONS**

To define a prostatic lesion as NSGP, we referred to the original description of Tanner and McDonald,\textsuperscript{[19]} presence of noncaseating granulomas, composed of epitheloid histiocytes, giant cells, lymphocytes, plasma cells, and polynuclear cells and no clinical data for previous diagnostic and surgical interventions of prostate or systemic granulomatous disease. Figure 1] EM is characterized by the presence of eosinophilic cytoplasmic granules with different size filling the apical cytoplasm in benign prostatic epithelium [Figures 1 and 2].\textsuperscript{[15]} PCLC is presented by large eosinophilic, intracytoplasmic granules [Figure 3a] with endocrine differentiation (chromogranin+, synaptophysin+) within tumor cells of 10% of PCa [Figure 3b and c].\textsuperscript{[12,14,15]}
The so-called acute prostatitis (AP) is an inflammatory process characterized by the presence of polymorphonuclear neutrophils in the lumen of the acini and ducts [Figure 2a].

NIH-category IV prostatitis or HP is an incidental pathological finding, which appears to be the most common type of prostatic inflammation in peripheral and transition zones of the prostate in men with no clinical symptoms related to urinary tract infection or pelvic pain. HP was evaluated using NIH consensus system [Figures 2b and 4a].

**RESULTS**

**Clinical findings**

Most of the examined prostate materials were obtained by TURP.

The mean incidence of NSGP in prostatic specimens was 0.38%: 0.47% in those from France and 0.20% in Bulgarian prostatic materials.

The age of the nine patients with NSGP ranged from 53 to 83 years (mean age 72). The leading clinical symptoms covered the so-called prostatic syndrome typical for BPH, presented by irritative and/or obstructive voiding with frequency and dysuria, with or without hematuria and fever.

The average value of prostate-specific antigen was 6.72 ng/mL (range from 4.3 to 10 ng/mL).

Results are summarized in Table 1.

**Histopathological findings**

NSGP was localized in the periphery of TZ of the prostate in all of the cases [Figure 1].

The stains for acid-fast bacilli and fungi were negative in noncaseating granulomas (data not shown). Foci of EM with frequency ranging from 5% to 60% in benign prostatic glands were detected in all of the investigated cases of NSGP (100%) [Figures 1, 2 and 4a]. They were found in well-outlined structures with ducal or acinar architecture adjacent to granulomatous lesions [Figures 1 and 4a]. Apical portions of secretory epithelial cells were filled with eosinophilic cytoplasmic granules. Their nuclei had basal location and nucleoli were sometimes seen [Figure 2b]. No EM was observed in some of so-called mimics of PCa (areas of atrophy and cribriform hyperplasia). In the control cases, no EM was observed in peritumoral glands within the vicinity of PCa containing PCLC-areas.

BPH is seen in 6/9 (66.7%) of cases with NSGP, in 1 (10.1%) of them is combined with low Gleason grade PCa (3 + 3) but

| Case n°/ source | Age (years) | PSA ng/mL | Clinical features | Specimen type | Principal pathologic findings | EM; distribution | Associated pathologic findings |
|-----------------|-------------|-----------|-------------------|---------------|------------------------------|-----------------|-----------------------------|
| 1 France        | 53          | 5.2       | P.S.              | TURP          | NSGP, BPH                    | Focal; large groups of cells | AP, HP |
| 2 France        | 83          | 8         | P.S.              | TURP          | NSGP, BPH                    | Focal; single cells and small groups of cells | AP, HP |
| 3 France        | 72          | 7.2       | P.S.              | TURP          | NSGP, BPH, PCa               | Focal; large groups of cells | AP, HP |
| 4 France        | 70          | 6         | P.S.              | TURP          | NSGP, BPH                    | Diffuse; single cells       | AP, HP |
| 5 France        | 74          | 7.5       | P.S.              | TURP          | NSGP, BPH                    | Focal; single cells and small groups of cells | AP, HP |
| 6 France*       | 71          | 10        | P.S.              | TURP          | NSGP, BPH                    | Focal; small groups of cells | AP, HP |
| 7 France        | 70          | 4.3       | P.S.              | TURP          | NSGP, BPH                    | Focal; large groups of cells | AP, HP |
| 8 Bulgaria      | 75          | 7.2       | P.S.              | TURP          | NSGP                        | Focal; single cells and small groups of cells | AP, HP |
| 9 Bulgaria      | 82          | 5         | P.S.              | TURP          | NSGP                        | Focal; large groups of cells | AP, HP |

*The case has been already published [16]; NSGP, nonspecific granulomatous prostatitis; BPH, benign prostatic hypertrophy; P.S., prostatic syndrome (irritative and/or obstructive voiding with or without hematuria and fever); PCa, prostatic adenocarcinoma (Gleason 6: 3+3); AP, acute glandular and stromal prostatitis; HP, histologic prostatitis (category IV prostatitis); EM, eosinophilic metaplasia.
not in association with endocrine differentiation. AP and HP of moderate to severe grade with glandular, periglandular and stromal localization [Figures 2 and 4a] were identified in all cases of NSGP with EM (100%). No areas with EM and AP were detected in both control cases with BCG-GP, while HP was of focal and mild grade.

Results are summarized in Table 1.

Histochemical and immunohistochemical findings
In cells with EM, the granules were PAS.D and α-1-ACT positive and were stained negatively for chromogranin [Figure 4b-d] and synaptophysin (data not shown). No autofluorescence was noticed on fluorescent microscopy and no staining by modified ZN-stain for lipofuscin pigment was detected (data not shown).

In 4/9 cases of NSGP with EM, p504s stains were negative. In 5/9 cases (55.5%) in about half of the secretory cells with EM, there was weak focal apical intracytoplasmic immunostaining for p504s. In all cases the surrounding basal cells were intensively expressing p63 [Figure 4e]. In the control cases with PCa [Figure 3a], the whole cell cytoplasm was intensively and diffusely stained for p504s, while basal cells were negative for p63 [Figure 3d]. In these cases PAS.D [Figure 3e], α-1-ACT (data not shown) stainings were negative, while the positive expression of chromogranin and synaptophysin were evident [Figure 3b and c].

Results are summarized in Table 2.

DISCUSSION
Since the original description of Tanner and McDonald in 1943 there is a serious number of articles on NSGP. The frequency

![Figure 3: Prostatic adenocarcinoma with focal endocrine cell differentiation (Paneth cell-like changes) (arrows): (a) (hematoxylin-phloxine-saffron, x400); (b) (chromogranin immunostain, x400); (c) (synaptophysin immunostain, x400); (d) (combined P504S/P63 immunostain; x400); (e) (periodate Schiff's procedure with diastase digestion, x400)]

![Figure 4: EM in benign prostatic epithelium adjacent to lesions of nonspecific granulomatous prostatitis: (a) EM is focal, in large groups of cells (arrows) combined with acute and chronic histologic prostatitis (hematoxylin-phloxine-saffron, x100); EM is stained positively with PAS.D (b: PAS.D, x100); α-1-antichymotrypsin (c: α-1-antichymotrypsin immunostain, x 00); EM cells are negative for chromogranin (d: chromogranin immunostain, x100) and p504s with focal, weakly false-positive reactivity (arrow) surrounded by P63 positive basal cells (e: combined p504S/p63, x400)]

Table 2: Histochemical and immunohistochemical reactivity of eosinophilic metaplasia in nonspecific granulomatous prostatitis compared with Paneth cell-like changes in prostatic adenocarcinoma

| Pathologic findings/disease | Total cases | PAS.D positivity (%) | P504s positivity (%) | P63 positivity (%) | Chromogranin positivity (%) | Synaptophysin positivity (%) | α-1-ACT positivity (%) |
|----------------------------|-------------|----------------------|----------------------|---------------------|----------------------------|---------------------------|-------------------------|
| EM in NSGP                | 9           | 9/9 (100%)           | 5/9 (55.5%)          | 9/9 (100%)          | 0/9 (0%)                  | 0/9 (0%)                  | 9/9 (100%)              |
| PCLC in PCa                | 4           | 0/4 (0%)             | 4/4 (100%)           | 0/4 (0%)            | 4/4 (100%)                | 4/4 (100%)                | 0/4 (0%)                |

NSGP: nonspecific granulomatous prostatitis; EM, eosinophilic metaplasia; PCLC, Paneth cell-like changes in prostatic adenocarcinoma (control cases); PCa, prostatic adenocarcinoma (Gleason B: 4+4); PAS.D, periodate-Schiff's procedure with diastase digestion; α-1-ACT, α-1-antichymotrypsin
of NSGP is very low and varies from 0.36% to 3.4% of all histologically investigated materials of the prostate gland.\cite{2,21} Our results show that the frequency of NSGP among all examined prostatic specimens is 0.38%. NSGP usually occurs in patients between 18 and 70 years of age (mean age between 62 and 65).\cite{12,21} The mean age of our patients is 72 years (ranging from 53 to 83).

The frequency of EM varies from 12% to 23% of prostatic needle biopsies and presents 20% of total prostatic biopsies.\cite{15} Only single cases of EM in TURP-material have been described so far.\cite{12,13} The granules are PAS.D positive and immunohistochemically positive for PSA, and \(\alpha-1\)-ACT while neuroendocrine markers (chromogranin, serotonin, ACTH, and neuron-specific enolase), lysozyme, PS-100, immunoglobulin A remain negative.\cite{12,13,15} Our results confirm the histological and immunohistochemical profile of EM.

There are only four published observations for the presence of EM in intra- or perilesional benign epithelial cells in GP and NSGP, in particular. The first one is a cytological study and the others are case reports. In a series of eight cases of cytologically verified GP, García Solano et al. discovered « cytoplasmic red granules » and « cytoplasmic intravacuolar granules » in 25 and 50% of the cases, respectively. The granules were colored with the eosin containing cytologic coloration Diff-Quik.\cite{22} The authors assumed that the presence of epithelial cytoplasmic granules served as morphological adjuncts for cytologic diagnosis of NSGP. Bostwick et al. present a coexistence of GP and EM on a microphotograph, published in Urologic Surgical Pathology (Figures 8–31, page 372) but there is no comment in the text.\cite{22} Recently, we published two case reports about the association of NSGP and EM without and with PCA in TURP material.\cite{16,17}

We hereby report the same association in 100% of the cases in the actual large series of patients. Our results provide extra data about the patho- and morphogenesis of both NSGP and EM. NSGP has been hypothesized to result from a foreign body response to a colloidal substance, bacterial products, or refluxed urine arising from ducts, obstructed by BPH or/and inflammation.\cite{4,7,9,24} EM is more frequently observed in prostate specimens from adenomectomies and TURP with BPH rather than in thin needle biopsies and radical prostatectomies.\cite{12,13,15} BPH is found in 71.5% of the cases with NSGP.\cite{21} In 6/9 cases (66.7%), we detected a coexistence of BPH and NSGP with EM.

In a histopathological study of the epididymis, EM (PCLC) is interpreted as intracytoplasmic lysosomal accumulation which serves as a microscopic indicator of ductal obstruction.\cite{25} The coexistence of NSGP and EM in 100% of our cases shows that NSGP and its accompanying EM are processes that reflect the morphological status of urinary obstruction due to BPH and the supplementary low- or high-grade HP.

In all of our cases, NSGP was localized in the periphery of TZ of the prostate and thus supports the obstructive theory and the role of mechanic (BPH) and inflammatory (HP) insults in NSGP development. The association between NSGP and EM supports the fact that it is a morphological phenomenon, which appears in sites of repeated chronic cell injury. This hypothesis is supported by the limited literature data on EM combined with chronic inflammatory conditions and atrophy.\cite{15} We assume that the presence of a less expressed or a more extensive EM around the chronically inflamed and dilated prostate glands and ducts in NSGP represents a mechanism of phenotypic cellular adaptation to the changes in the prostate due to persistent active inflammation.\cite{16} The so-called AP is an inflammation with intraluminal location.\cite{16} AP is a frequent phenomenon in NSGP\cite{25} and in EM,\cite{15} or as a combination of both as it is in 100% of our samples. It probably reflects the multiple consequential insults from the causal agent(s) and represents part of the so called mixed (active and chronic) inflammation, which might be an autoimmune phenomenon.\cite{26}

The ductal obstruction in NSGP, resulting from BPH or/and prostatitis is followed by stagnation with local alterations in the character of prostatic secretions with deposition into the fibromuscular stroma.\cite{27} A T-cell mediated damage and destruction of ductal and acinar epithelium is developed.\cite{15} An autoimmune reaction with epitheliolymphoid inflammatory response is detected.\cite{11,24} Some authors speculate that individuals with particular HLA haplotypes may be at increased risk of developing this disease.\cite{29}

Having in mind the autoimmune character of the inflammatory process in NSGP\cite{28} and considering the similar changes in the thyroid gland in De Quervain’s thyroiditis,\cite{29} we could speculate that EM might serve as a morphological precursor of the immunologic phase of the disease.

Mixed aggregates of B- and T-cells are found to surround dilated prostatic ducts with distinctive local loss of both prostatic epithelial markers (PSA and PAP) in areas of granulomatous inflammation.\cite{24} This is followed by their passive tissue diffusion, manifested with increased serum level of PSA in 79% of cases.\cite{4} Our results confirm the presence of moderate to marked change in the levels of serum PSA (mean 6.72ng/mL). The early loss of PSA in areas of NSGP is the result of T-cell or macrophage-mediated alteration of epithelial cells through cytokine secretion.\cite{30} In NSGP foci, expression of free \(\alpha-1\)-AT is detected.\cite{28} It is typical of macrophages and multinucleated giant cells, but also represents a nonspecific marker of EM.\cite{12} In zones of EM in 100% of the cases of NSGP, we observed the expression of another lysosomal marker, \(\alpha-1\)-ACT. The inflammation increased PSA concentrations due to disruption of the glandular prostatic epithelium. As it is known, PSA is exclusively produced by prostate epithelium and at its own passage in the serum, PSA is bond to \(\alpha-1\)-ACT.\cite{31}

The observed by us expression of a-1-ACT in the EM - epithelium can be explained by the compensatory mobilization of protective lysosomal activity in the conditions of chronic cellular injury.

The histopathological differential diagnosis of NSGP includes other types of GP and high Gleason grade PCA.\cite{4} Apart from the
lack of clinical signs of previous TURP, BCG-therapy, and systemic diseases and the negative ZN and Grocott stains, the presence of foci of EM in inflammatory granulomatous prostatic inflammation might serve as additional diagnostic marker supporting NSGP. EM is not detected in other types of GP. We confirm this finding with the lack of EM in two cases of BCG-associated GP, used as a control group for granulomatous prostate inflammation. Clinically, in 59% NSGP may mimic PCa\(^{[4,10]}\). Histologically, effacement of ductal and acinar prostatic architecture is usually presented in both processes.\(^{[4]}\) Immunohistochemistry is useful for addressing this differential diagnosis, since the epithelioid histiocytes of NSGP are cytokeratin negative and show expression of CD68, while PCa generally express cytokeratins, PSA, prostatic acid phosphatase, and pan-cytokeratins.\(^{[4,10]}\)

Our results show that NSGP and PCa can be reliably distinguished by the presence of EM. The coexistence of EM with NSGP is present in 100% of our cases and can be used as a marker for diagnostics of NSGP and for differential diagnosis between NSGP and undifferentiated PCa.

On the contrary, the frequent coexistence of NSGP with EM imposes another differential diagnosis – between NSGP with EM and PCa with PCLC-areas, and it is due to the morphological similarity of eosinophilic granules in EM and PCLC in routinely stained sections [Figures 2a and 3a]. As far as morphological and immunohistochemical differences between EM and PCLC – granules are concerned, the differential diagnosis is successfully performed by Cheng et al.\(^{[31]}\)

Our results answer the question about the false-positive p504s reactivity in EM observed in the lately published two cases with EM-foci expressing p504s.\(^{[13]}\) The authors describe the presence of intense false-positive p504s signal in benign prostatic epithelium with EM in core biopsies of two patients with PCa.\(^{[13]}\)

We are the first to report recently a case of coexistence of NSGP with EM and PCa.\(^{[17]}\) In the current study of nine patients with NSGP in association with EM, we find one case with low-grade PCa without areas of endocrine differentiation. We suggest EM to be included in the differential diagnosis of NSGP and PCa, especially as there are data for false-positive p504s reactivity in EM. In the present study of a large series of patients and control groups in 50% of the secretory cells with EM, positive apical cytoplasmic staining for P504s in benign epithelium of TURP and adenomectomies was recorded. The reactivity was less intensive and acini were surrounded by strongly stained p63 positive basal cells. We assume that the differences in the intensity of false-positive p504s staining in EM, is caused either by the difference in the prostatic material or by difference in immunostaining procedures.

In the contrary, the presence of weak, focal p504s-staining in isolation without relevant basal cell immunostaining has no relevance in reporting of doubtful cases. This is well-known phenomenon in the routine diagnostic practice of urologist, who knows well the list of causes of false-positive p504s reactivity.\(^{[31]}\)

In conclusion, the basic finding of the present study is the intimate coexistence of NSGP and EM in the prostate gland and their pathophysiologic and morphogenetic relationships. In a large series of cases, our results provide extra data about the patho- and morphogenesis of both NSGP and EM and their close association with BPH and NIH-category IV prostatitis (HP). This constant morphologic association could facilitate the histopathological differential diagnosis of NSGP with other types of granulomatous prostatitis and high Gleason grade PCa with or without PCLC-endocrine differentiation.

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Conflicts of interest
There are no conflicts of interest.

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