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Inflammation: predictive factor for negative evolution of prostate diseases

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Abstract

The most frequent prostate diseases depending on age are prostatitis in young men, benign prostate hypertrophy in men over 50 years old, and prostate cancer (PCa) in elderly patients. The purpose of our study is to evaluate the role of inflammation in the progression of prostate diseases. We used clinical and paraclinical techniques for the positive diagnosis [serum prostate-specific antigen (PSA) determination, we performed transrectal ultrasound to asses the prostate volume and prostate biopsy or transurethral resection of the prostate, where it was imposed]. The prostate tissue specimens were analyzed histopathologically and immunohistochemically. Our results show that PCa patients with higher inflammation rates had a higher Gleason score in both the castration-resistant prostate cancer (CRPC) group and the castration-sensitive group. We have noticed that patients with high inflammation grade also had a much higher *International Prostate Symptom Score* (IPSS). In conclusion, we can say that in our study, inflammation played an important role in the evolution of benign and malignant prostate diseases; its presence has influenced directly the severity of symptoms, and the aggressiveness of the diseases.

Keywords: prostate hypertrophy, inflammation, acinar proliferation, intraepithelial neoplasia, immunohistochemistry.

Introduction

The most frequent prostate diseases depending on age are: prostatitis in young men, benign prostate hypertrophy (BPH) in men over 50 years old, and prostate cancer (PCa) in elderly patients but we noticed decrease in the diagnostic age of this pathology being more and more commonly diagnosed in patients less than 60 years old. We can also diagnose some premalignant lesions of the prostate, associated mostly with BPH or prostatitis.

Prostate carcinoma is the second most common type of cancer among men from North America and Europe [1, 2]. As well as the second most common cause of cancer-related death in this category of patients [1]. This disease is a serious health concern, especially in developed countries, where the elderly population is proportionally higher [3]. Although studies have shown that BPH never turns into PCa, it is known that the two diseases can co-exist. In latent forms of PCa, the differential diagnosis between the two diseases can be very difficult [4].

The blood test used to detect PCa is prostate-specific antigen (PSA), though PSA alone does not enable PCa to be distinguished from benign diseases. An elevated PSA level is not specific only for PCa; it can also be associated with other prostate pathologies, such as BPH or prostatitis [3]. Despite of disadvantages, PSA measurement remains the gold standard in PCa screening, given that no new biomarkers are currently accepted for the diagnosis of PCa. Castration-resistant prostate cancer (CRPC) presents various clinical forms: from high PSA levels without metastases or the worsening of the symptoms despite the androgen deprivation therapy (ADT), the occurrence of metastases and significant aggravation of the patient's quality of life (QoL). CRPC is suspected in patients in case of the appearance of new symptoms on ADT, increasing PSA levels or in case of evidence of new bone lesions on bone scans or computed tomography scans [5].

Pathogenesis of PCa involves hereditary factors and environmental factors, and an important role in carcinogenesis and tumor progression appears to have chronic inflammation. The role of chronic prostate inflammation appears to be highlighted in the progression of a BPH.

The purpose of our study is to evaluate the role of inflammation in the progression of prostate diseases.

Patients, Materials and Methods

This study is a combination between a retrospective and a prospective research that aims to analyze the prognostic factors in benign (BPH) and malignant prostate diseases [castration-sensitive prostate cancer (CSPC) and CRPC]. The study population consists of male adults over 50 years old, who provided written consent to participate and fulfill the inclusion criteria.

Our study was performed at the Clinic of Urology,

Emergency County Hospital, Arad, Romania, during a four years period, between 2013–2016, follow-up every six months. We selected 342 patients, as follow: 181 patients with BPH, 19 healthy subjects as a control group, 12 patients with premalignant lesions, like atypical small acinar proliferation (ASAP) and high-grade prostate intraepithelial neoplasia (HGPIN), 59 CSPC patients and 71 CRPC patients.

All patients were interviewed for personal medical history, family history, consumption of toxic substances (alcohol, smoking, etc.) We evaluated the prostate volume using transabdominal prostate ultrasonography in conjunction with digital rectal examination (DRE) and determinate the PSA from peripheral venous blood for PSA determination. Histopathological (HP) diagnosis of PCa has been established by transrectal ultrasound-guided (TRUS) biopsy, after an abnormal finding in DRE or increased value of serum PSA [3] or incidentally at microscopic examination of the resected tissue after transurethral resection of the prostate (TURP) for symptomatic BPH. We did not have prostatectomized patients in the study.

The prostate tissues were fixed in 10% neutral formalin solution and processed by the histological technique of paraffin inclusion. First step was the evaluation of all the slides in usual Hematoxylin–Eosin (HE) staining. We selected the representative slides with different degrees of inflammation within the tumor and in the front of tumor. New slides were immunohistochemically-stained with anti-cluster of differentiation (CD) 3 antibody (polyclonal, Cell Marque, ready-to-use, code REF201M98) and anti-CD20 antibody (clone L26, Cell Marque, ready-to-use, code REF120M88). For immunostaining, we used a polymer detection system (Novolink, Novocastra, code RE7280-K), visualized with 3,3'-Diaminobenzidine (DAB) and counterstained with Hematoxylin. The immunohistochemistry (IHC) slides were performed on a Leica Bond Max autostainer, following the manufacturer's protocol, with heat-induced epitope retrieval, at pH 6.

For differential diagnosis of poorly differentiated or undifferentiated prostatic adenocarcinomas by urothelial tumors, we used also IHC stainings. The slides were labeled with anti-PSA antibodies (polyclonal, Dako, pH 9) (Figure 1) and anti-prostate specific membrane antigen (PSMA) antibodies (clone D6, Novocastra, pH 6). In PCa with neuroendocrine differentiation (NED), we used anti-chromogranin A (CgA) antibodies (clone LK2H10, Immunologic Systems, pH 6) (Figure 2). For immunostainings, we used also a polymer detection system visualized with DAB and counterstained with Hematoxylin.

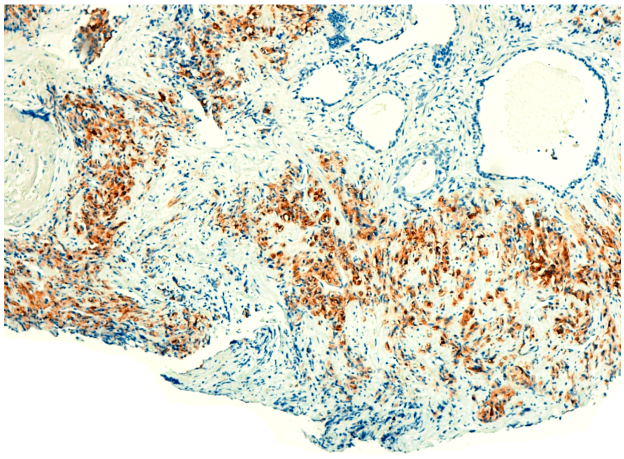

Figure 1 – ***Poorly differentiated prostate adenocarcinoma (Gleason pattern 5+4). Positive reaction for PSA in infiltrative tumor cells (intense, diffuse staining) (Anti-PSA antibody immunostaining, ×100. PSA: Prostate-specific antigen.***

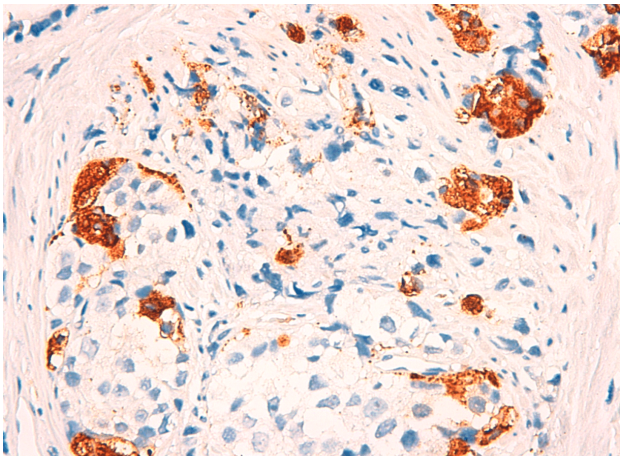

Figure 2 – ***Dispersed and clustered neuroendocrine cells express CgA in a solid growth prostate adenocarcinoma (Anti-CgA antibody immunostaining, ×400). CgA: Chromogranin A.***

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, respects ethical demands that require research with human subjects. Before starting the study, we obtained the agreement of the Ethics Committee of the Emergency County Hospital, Arad and "Vasile Goldiş" Western University of Arad.

Statistical analysis

The statistical analyses were conducted using Microsoft Office Excel 2016 and Statistica 10. The Kruskal–Wallis test was used to study differences in the inflammation grades and the severity of the diseases in age-matched patients, with the Dunn's test being applied as a *post-hoc* analysis to compare two groups in the case of some significant values of p for the Kruskal–Wallis test.

Results

For the right selection of patients for the study groups, we consulted up to 600 men over 50 years old. During the study period in the Clinic of Urology, Emergency County Hospital, Arad, we selected a number of 59 CSPC patients, 71 CRPC patients, 181 patients with BPH irrespective of age, social status or ethnicity, 12 patients with premalignant lesions and 19 healthy patients as a control group.

The most frequent prostate disease in men over 50 years old was BPH. We noticed that the patients included in the study showed significant variations in the follow-up factors (Table 1). Patients in the control group presented the lowest PSA values, age and prostate volumes. The highest values of these factors were recorded in the CRPC group. We also noticed that patients in the control and BPH groups mostly have rural origin, and neoplastic

patients predominantly are of urban origin. This aspect is probably due to easier access to medical services for urban patients and better health education, rural patients presenting to the specialist most often in advanced stages of the disease by neglecting the initial symptoms.

Table 1 – *Clinical and paraclinical characteristics of the study patients*

Study groups	Clinical and paraclinical characteristics			Environmental origin	
	PSA [ng/mL]	*Age [years]*	*Prostate volume [g]*	*Rural (n)*	*Urban (n)*
Control	0.93± 0.83	62.21± 3.1	17.36± 3.86	17	2
BPH	2.38± 3.29	68.31± 5.54	37.64± 16.12	122	59
ASAP/HGPIN	5.23± 2.67	70.98± 4.78	28.76± 17.53	6	6
CSPC	34.01± 54.51	68.34± 7.05	39.01± 13.47	26	33
CRPC	132.34± 118.51	76.85± 7.57	51.06± 23.47	30	41

Values are presented as medians with standard deviations and absolute numbers. PSA: Prostate-specific antigen; *n*: No. of cases; BPH: Benign prostate hypertrophy; ASAP/HGPIN: Atypical small acinar proliferation/high-grade prostate intraepithelial neoplasia; CSPC: Castration-sensitive prostate cancer; CRPC: Castration-resistant prostate cancer.

Our study focused on defining the relationship between inflammation grades and Gleason score in PCa patients (Figures 3, 5 and 6) and the role of the inflammation grades found on HP specimens in the symptoms severity experienced by BPH patients (Figures 4 and 7). Based on the HP and IHC examinations, we classified the inflammation grades into four categories: 0 – without inflammation, 1 – mild inflammation, 2 – moderate inflammation, 3 – severe inflammation. The evaluation of the inflammation grades was performed by standard HP methods of optical microscopy in HE staining and IHC methods with specific markers (anti-CD3 antibody to identify T-lymphocytes and anti-CD20 antibody to identify B-lymphocytes on the bioptic tissues).

We noticed that PCa patients presents positive reactions in all of the cases for the anti-CD3 antibody and those patients with higher inflammation rates had a higher Gleason score in both CRPC and CSPC groups (Figure 3). In BPH and ASAP/HGPIN patients, we reported the degree of inflammation to the severity of the symptoms, as measured by the *International Prostate Symptom Score* (IPSS). We noticed that patients with higher inflammation grade also had a much higher IPSS value (Figure 4). In the BPH and ASAP/HGPIN study groups, the *post-hoc* analysis demonstrated the increase of IPSS value with the degree of inflammation, the differences from patients in the control group (group 0) being highly significant in patients with moderate inflammation in the BPH group (Dunn's test, p=0.003), and very high in patients with severe inflammation in both study groups (Dunn's test, p<0.001, Figure 4).

Of the total number of patients with BPH included in the study (n=181), only from 10 subjects we obtained HP samples, being undergoing surgery due to the complications of the disease. Patients who were not operated, respectively 171 subjects (representing 94.48% of the total BPH cases), were classified as undefined (grade 0). The operated patients were classified as follows: four subjects (representing 2.2% of the total BPH cases) experienced moderate inflammation (grade 2), while six subjects (representing 3.32% of the total BPH cases) severe inflammation (grade 3). We did not noticed mild inflammation (grade 1) in patients with BPH. In the CSPC group (n=59), the highest percentage of patients had grade 1 inflammation (44%). The remaining patients showed lower but similar percentages, respectively 29% of cases had grade 2 inflammation and 27% grade 3 inflammation. In the CRPC group (n=71) the highest percentage of patients (40.85%) experienced severe inflammation, 35.21% of patients had mild inflammation, 15.49% moderate inflammation, and 8.45% no inflammation (Table 2). We noticed on the HP specimens the gradual decrease of inflammation in cancer foci consistent with disease aggressiveness. The inflammation remained detectable in the tissue halos surrounding the cancerous foci.

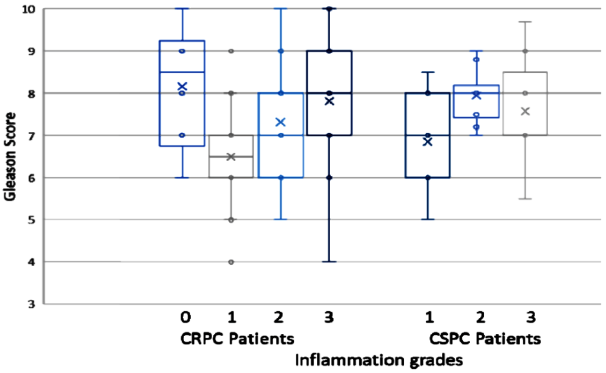

Figure 3 – *Inflammation grades in prostate cancer patients. CRPC: Castration-resistant prostate cancer; CSPC: Castration-sensitive prostate cancer.*

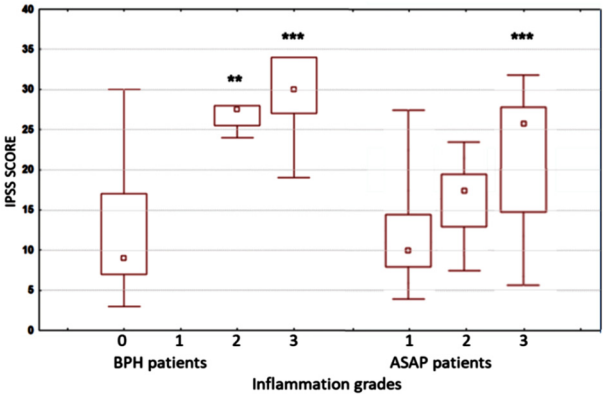

Figure 4 – *Inflammation grades in BPH and ASAP patients. BPH: Benign prostate hypertrophy; ASAP: Atypical small acinar proliferation; IPSS: International Prostate Symptom Score.*

Table 2 – *Distribution of patients with prostate diseases depending on the degree of inflammation*

Prostate pathology \ Inflammation degree	*Undefined/No inflammation*	*Grade 1*	*Grade 2*	*Grade 3*
BPH	171	–	4	6
ASAP/HGPIN	–	3	5	4
CSPC	–	26	17	16
CRPC	6	25	11	29

Values are presented as absolute numbers. BPH: Benign prostate hypertrophy; ASAP/HGPIN: Atypical small acinar proliferation/high-grade prostate intraepithelial neoplasia; CSPC: Castration-sensitive prostate cancer; CRPC: Castration-resistant prostate cancer.

In most cases, HP examination under optical microscopy in HE staining was sufficient for the positive diagnosis of PCa. Our study shows that patients who required IHC for positive diagnosis had lower age compared to the group where testing was not necessary and the Gleason pattern was significantly higher, but we also had two cases with a Gleason score <7, where IHC examination was necessary. IHC examination helped us to differentiate between poorly differentiated prostate adenocarcinoma and poorly differentiated urothelial carcinomas of the prostate.

We explored also the effect of the amount of T- and B-lymphocytes on disease evolution in PCa tissue samples. The amount of PCa-infiltrating CD3+ T-cells and CD20+ B-cells on a tissue sample was determined by IHC and we sought correlations between clinical symptomatology and paraclinical data in patients from the same study group. The patients who presented decreased or increased levels of CD3+ T-cells (Figure 8) experienced more severe evolution, with the occurrence of complications determined both by local development and the occurrence of metastases compared to patients with intermediate numbers of T-cells (Figure 9). The amount of CD20+ B-cells in the tissue assay was not correlated with clinical and HP parameters (Figure 10).

Discussions

The Population and Housing Census in Romania in 2011 and *National Institute of Statistics* data of Romania in 2013 show that Arad County had a population of 451 434 inhabitants, of which 218 148 (48.3%) males, and of these 37 952 were over 50 years old. Corroborating national data with international statistics on the prevalence of BPH, we estimate that 2531 men would present low urinary tract symptoms (LUTS) in Arad County. The real number of patients undergoing treatment is unknown.

PCa is ranked second most frequent neoplasia in men around the world, and the fifth cause of death by neoplasia in men. In Arad County, the fight against cancer has a special significance because this county has one of the highest rates of illness. Thus, according to Arad's Public Health Department statistics, in 2016 there were detected 1767 new cases of malignant tumors, from which a number of 101 PCa cases were added to the approximately 13 500 cancer cases already found in doctors' medical records in the past years.

For these reasons, we considered very important this study, which provides an overview on the clinical and paraclinical characteristics of patients diagnosed with benign and malignant prostate diseases.

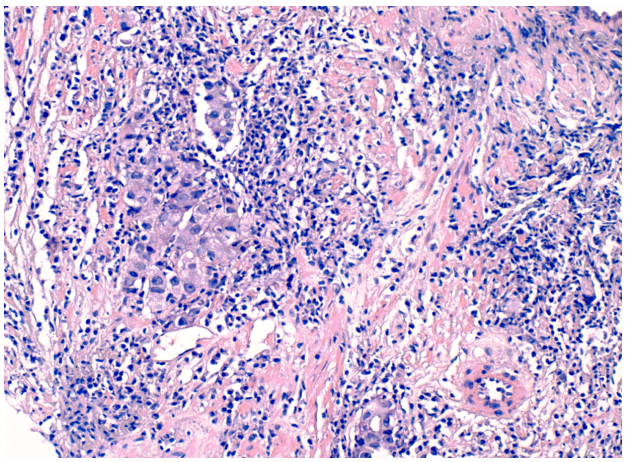

Figure 5 – ***Poorly differentiated prostate adenocarcinoma (Gleason pattern 4+3) in a TURP specimen with severe inflammation (grade 3) (HE staining, ×200). TURP: Transurethral resection of the prostate.***

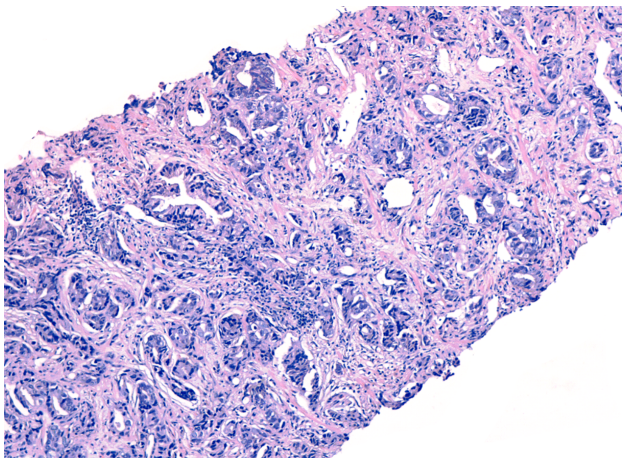

Figure 6 – ***Poorly differentiated prostate adenocarcinoma (Gleason pattern 3+4) with moderate inflammation (grade 2) (HE staining, ×100).***

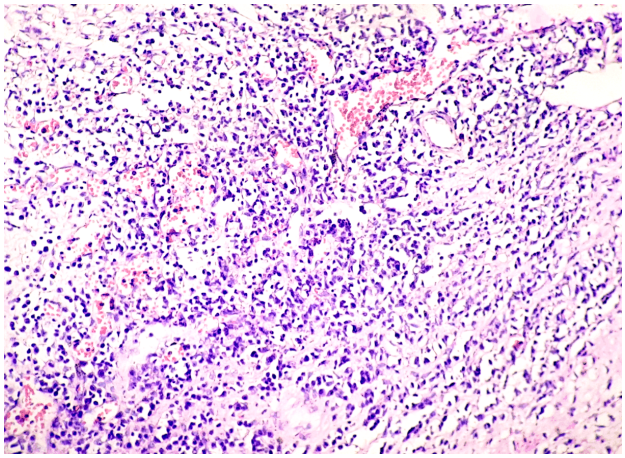

Figure 7 – ***Benign prostate hypertrophy with severe inflammatory infiltrate (HE staining, ×200).***

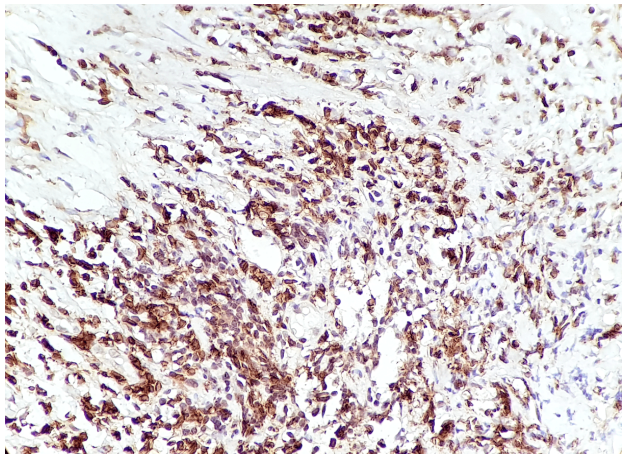

Figure 8 – ***Prostate adenocarcinoma (Gleason pattern 4+3) with severe inflammation (grade 3); CD3+ T-lymphocytes (Anti-CD3 antibody immunostaining, ×200). CD3: Cluster of differentiation 3.***

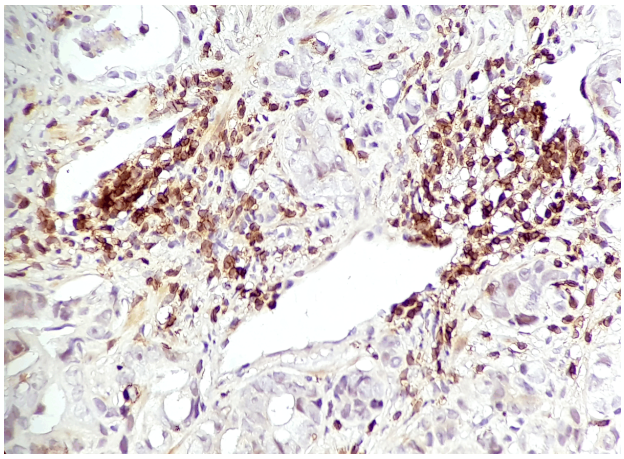

Figure 9 – ***Small acinar prostate adenocarcinoma, (Gleason pattern 3+4) with moderate inflammation (grade 2), CD3+ T-lymphocytes (Anti-CD3 antibody immunostaining, ×200). CD3: Cluster of differentiation 3.***

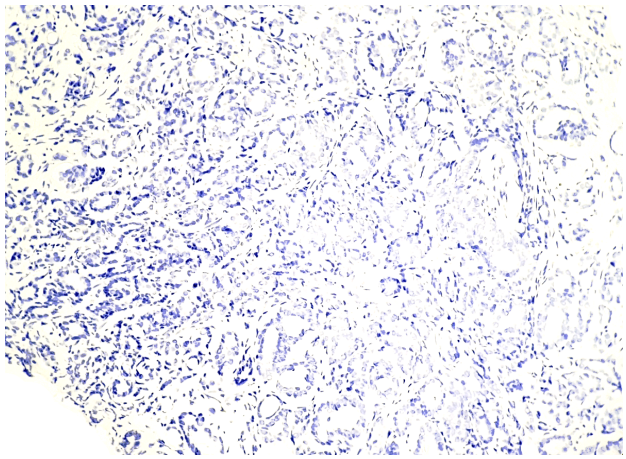

Figure 10 – ***Small acinar prostate adenocarcinoma, (Gleason pattern 3+4) with inflammation grade 2, the inflammatory cells negative for CD20 (Anti-CD20 antibody immunostaining, ×100). CD20: Cluster of differentiation 20.***

According to the *European Urology Guidelines*, we put the CRPC diagnosis on the following criteria: three consecutive PSA increases in determinations performed one week apart, including two mandatory results with 50% above the lowest PSA value, with PSA >2 ng/mL or radiological progression – the discovery of two or more new bone lesions. The heterogeneous values of PSA in our study at the moment of CRPC diagnosis are due largely to the noncompliance of patients to oncological treatment and to periodic urological follow-up.

An important and much debated factor in the evolution of different diseases is the presence of chronic inflammation. Studies have shown that inflammation is always present in BPH, being a marker for negative evolution of the disease.

In our study, the inflammation grade was determined by HP examination of the prostatic tissues at optical microscopy, in standard HE staining and by IHC methods – labeling with anti-CD3 and anti-CD20 antibodies. We noticed in BPH and ASAP/HGPIN patients the higher the IPSS value the higher inflammation grade. In accordance with our study, Nickel *et al.* [6] found that there is a correlation between the inflammation degree and LUTS severity. It was observed that there is a relationship between the storage symptoms (nocturia, urgency, frequency, precipitancy, urge incontinence) and the inflammation degree [6]. Robert *et al.* [7] showed a statistically significant correlation between IPSS and histological inflammation. Furthermore, patients diagnosed with BPH who do not respond to drug therapy have a higher degree of intraprostatic inflammation [8].

Nickel *et al.* [9] examined histological samples from 80 BPH patients who have undergone TURP treatment. They identified inflammation in all cases, but they analyzed only 1.1% of the total TURP specimens, and observed higher inflammation grade in the periglandular areas (0.5%).

Atan *et al.* [10] found no significant relationships between the histopathologically demonstrated inflammation and the irritative symptom score in surgically treated BPH patients. Anjum *et al.* [11] observed that BPH patients who were operated after an acute urinary retention event presented higher periglandular inflammation in comparison with the BPH patients from the control group, where inflammation was predominantly observed in the prostate stroma.

Our study shows positive B-lymphocytes activity predominantly in CRPC patients and those with complicated, long-term BPH that have been operated by TURP. Our study suggests, that T-lymphocytes activity is the major inflammatory factor, and B-lymphocyte activity appears late in disease progression.

A study conducted by Anim *et al.* [12] tried to identify the different types of inflammatory cells in the prostate stroma in BPH patients. This study showed that macrophages appear first, followed by the T-lymphocytes, which participate in the inflammatory response. B-cell activity appears as a late event in the pathogenesis of inflammation.

Another study conducted in our Clinic to another group of patients found no relationship between the inflammation grade and Gleason score. This aspect may be due to the fact that the specimens were obtained by prostatic biopsy puncture and the inflammation is no longer present in the tumor stroma, only in the adjacent tissue of the peritumoral hypermethylation halo.

Chronic inflammation is discussed in PCa patients as an important part of tumor development by determining a microenvironment that may favor the appearance and progression of cancer [13]. Inflammation is considered a risk factor for the development of many types of cancer including the prostate neoplasia. Chronic inflammation favors cellular and deoxyribonucleic acid (DNA) damage and promotes cellular turnover. Chronic inflammation leads to the appearance of reactive nitrogen and oxygen species, reactive aldehydes, cytokines, chemokines, and growth factors. These substances can affect the normal processes responsible for maintaining the cellular homeostasis, which lead to uncontrolled proliferative reactions, genomic variability and risk of PCa development [14–16].

Also, the high amount of inflammatory cells found in fragments of the prostate obtained by radical prostatectomy, prostate core biopsy and TURP specimens has highlighted a possible correlation between inflammation and PCa [17, 18].

Multiple studies suggest the link between inflammatory processes and prostate tumorigenesis. In PCa 'risk factor' lesions represented by regenerative epithelium may precede the occurrence of prostatic intraepithelial neoplasia (PIN) and early carcinoma. Proliferative inflammatory atrophy (PIA) appears in association with inflammation, and it may be a possible precursor to PCa [16]. PIA lesions are the consequences of the regenerative proliferation of prostate epithelial cells due to the inflammation; this may cause somatic mutations, gene deletions, gene amplifications, chromosomal arrangements and changes in DNA methylation, along with molecular signs of stress – a convenient environment for tumor growth [16].

IHC investigations are useful in the differential diagnosis of poorly differentiated or undifferentiated prostatic adenocarcinomas by urothelial tumors, due to the sensitivity of these tumors to specific IHC markers, such as anti-PSA, anti-PSMA, anti-CgA (in PCa with NED).

PSA is a serine protease used to confirm the prostatic origin of metastatic carcinoma [19], however PSA is not entirely prostate-specific and it can be detected in breast and ovary carcinomas [20].

PSMA is a folate hydrolase expressed by most prostate carcinomas and their metastases [21]. PSMA shows increased levels in high-grade prostate tumors and metastases, however, it is well known that it is widely expressed in renal cancer, gastrointestinal neoplasms and urothelial carcinomas [22–24].

NED secondary to ADT may be frequent in various stages of PCa, particularly in CRPC. NED generally involves more aggressive PCa clinical outcome and negative prognosis [25].

Conclusions

Our study shows that inflammation plays an important role in progression of prostate diseases (both in BPH and in PCa). We find slight correlation between Gleason score and inflammation grade. The patients with higher inflammation grade also had higher median values of Gleason score. We consider inflammation also a risk factor for the severity of LUTS. The patients diagnosed with BPH with higher inflammation grade also exhibited more severe symptoms than BPH patients with minor symptoms and low-grade inflammation did. Our study indicates that the density of T-cells plays an important, functional role in the development of PCa and may have an impact on clinical outcome in this neoplasia.

Conflict of interests

The authors declare that they have no conflict of interests.

Authors' contribution

Authors with equal rights (as first authors) are Adrian Silviu Crişan and Imola Miklos.

References

[1] Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin, 2014, 64(1):9–29.
[2] Arnold M, Karim-Kos HE, Coebergh JW, Byrnes G, Antilla A, Ferlay J, Renehan AG, Forman D, Soerjomataram I. Recent trends in incidence of five common cancers in 26 European countries since 1988: analysis of the European Cancer Observatory. Eur J Cancer, 2015, 51(9):1164–1187.
[3] Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, Mason M, Matveev V, Wiegel T, Zattoni F, Mottet N; European Association of Urology. EAU guidelines on prostate cancer. Part 1: Screening, diagnosis, and local treatment with curative intent – update 2013. Eur Urol, 2014, 65(1):124–137.
[4] Gao P, Shi C, Zhao L, Zhou Q, Luo L. Differential diagnosis of prostate cancer and noncancerous tissue in the peripheral zone and central gland using the quantitative parameters of DCE-MRI: a meta-analysis. Medicine (Baltimore), 2016, 95(52):e5715.
[5] Hotte SJ, Saad F. Current management of castrate-resistant prostate cancer Curr Oncol, 2010, 17(Suppl 2):S72–S79.
[6] Nickel JC, Roehrborn CG, O'Leary MP, Bostwick DG, Somerville MC, Rittmaster RS. The relationship between prostate inflammation and lower urinary tract symptoms: examination of baseline data from the REDUCE trial. Eur Urol, 2008, 54(6):1379–1384.
[7] Robert G, Descazeaud A, Nicolaïew N, Terry S, Sirab N, Vacherot F, Maillé P, Allory Y, de la Taille A. Inflammation in benign prostatic hyperplasia: a 282 patients' immunohistochemical analysis. Prostate, 2009, 69(16):1774–1780.
[8] Kwon YK, Choe MS, Seo KW, Park CH, Chang HS, Kim BH, Kim CI. The effect of intraprostatic chronic inflammation on benign prostatic hyperplasia treatment. Korean J Urol, 2010, 51(4):266–270.
[9] Nickel JC, Downey J, Young I, Boag A. Asymptomatic inflammation and/or infection in benign prostatic hyperplasia. BJU Int, 1999, 84(9):976–981.
[10] Atan A, Horn T, Hansen F, Jakobsen H, Hald T. Benign prostatic hyperplasia. Does a correlation exist between prostatic morphology and irritative symptoms? Scand J Urol Nephrol, 1996, 30(4):303–306.
[11] Anjum I, Ahmed M, Azzopardi A, Mufti GR. Prostatic infarction/ infection in acute urinary retention secondary to benign prostatic hyperplasia. J Urol, 1998, 160(3 Pt 1):792–793.
[12] Anim JT, Udo C, John B. Characterization of inflammatory cells in benign prostatic hyperplasia. Acta Histochem, 1998, 100(4):439–449.
[13] De Marzo AM, Platz EA, Sutcliffe S, Xu J, Grönberg H, Drake CG, Nakai Y, Isaacs WB, Nelson WG. Inflammation in prostate carcinogenesis. Nat Rev Cancer, 2007, 7(4):256–269.
[14] Nelson WG, De Marzo AM, DeWeese TL, Isaacs WB. The role of inflammation in the pathogenesis of prostate cancer. J Urol, 2004, 172(5 Pt 2):S6–S11; discussion S11–S12.
[15] Palapattu GS, Sutcliffe S, Bastian PJ, Platz EA, De Marzo AM, Isaacs WB, Nelson WG. Prostate carcinogenesis and inflammation: emerging insights. Carcinogenesis, 2005, 26(7):1170–1181.
[16] De Marzo AM, Meeker AK, Zha S, Luo J, Nakayama M, Platz EA, Isaacs WB, Nelson WG. Human prostate cancer precursors and pathobiology. Urology, 2003, 62(5 Suppl 1): 55–62.
[17] Nelson WG, De Marzo AM, Isaacs WB. Prostate cancer. N Engl J Med, 2003, 349(4):366–381.
[18] DeMarzo AM, Nelson WG, Isaacs WB, Epstein JI. Pathological and molecular aspects of prostate cancer. Lancet, 2003, 361(9361):955–964.
[19] Bostwick DG. Prostate-specific antigen. Current role in diagnostic pathology of prostate cancer. Am J Clin Pathol, 1994, 102(4 Suppl 1):S31–S37.
[20] Kraus TS, Cohen C, Siddiqui MT. Prostate-specific antigen and hormone receptor expression in male and female breast carcinoma. Diagn Pathol, 2010, 5:63.
[21] Wright GL Jr, Haley C, Beckett ML, Schellhammer PF. Expression of prostate-specific membrane antigen in normal, benign, and malignant prostate tissues. Urol Oncol, 1995, 1(1):18–28.

[22] Troyer JK, Beckett ML, Wright GL Jr. Detection and characterization of the prostate-specific membrane antigen (PSMA) in tissue extracts and body fluids. Int J Cancer, 1995, 62(5): 552–558.
[23] Kinoshita Y, Kuratsukuri K, Landas S, Imaida K, Rovito PM Jr, Wang CY, Haas GP. Expression of prostate-specific membrane antigen in normal and malignant human tissues. World J Surg, 2006, 30(4):628–636.
[24] Samplaski MK, Heston W, Elson P, Magi-Galluzzi C, Hansel DE. Folate hydrolase (prostate-specific membrane antigen) 1 expression in bladder cancer subtypes and associated tumor neovasculature. Mod Pathol, 2011, 24(11):1521–1529.
[25] Conteduca V, Aieta M, Amadori D, De Giorgi U. Neuroendocrine differentiation in prostate cancer: current and emerging therapy strategies. Crit Rev Oncol Hematol, 2014, 92(1):11–24.

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