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Case Report
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First Report of *Propionibacterium acnes* in Prostate from Chilean Patients

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Abstract

Introduction: In prostate, inflammatory foci are usual and could be associated with chronic infections, and later with cancer development. *Propionibacterium acnes* were described as the most abundant bacteria in prostatic tissue and our goal was to detect it for the first time in prostate tissue samples of Chilean patients.

Material and Methods: Sixteen samples of prostate tissue from patients with cancer and benign prostatic hyperplasia were obtained from tissue bank from two clinical centers with authorization of the institutional ethics committee. Immunohistochemistry was performed to detect *Propionibacterium acnes* positive glands.

Results: *Propionibacterium acnes* was detected in 7 cancer samples (100%, n=7) and 4 non cancer samples (44%, n=9). In all cancer samples, the bacteria were mainly located in non-cancerous glands (100% of patients), with low presence in cancerous glands (only 4 patients, 57.1%). Inflammatory infiltrate associated with the presence of bacteria was not significant.

Conclusion: This is the first report of the presence of *Propionibacterium acnes* in prostate from Chilean patients. Consistent with other populations, its prevalence is high in prostate, moreover in patients with cancer, where the bacteria are located in non-tumor glands. Its presence, causing chronic infection, could have a role in prostate carcinogenesis.

Keywords: Propionibacterium acnes; Prostate cancer; Prostate

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Introduction

Prostate cancer (PCa) is the second leading cause of cancer death among males in developed countries. At least one in six men will be diagnosed with CaP at some point in their lives [1]. In 2012, 2,045 men died from PCa in Chile, and its mortality, unlike other tumors, keeps rising [2].

Early diagnosis of the disease allows performing surgery or radiotherapy with curative intention, but in advanced stages there are no therapies that achieve significant survival improvement. The study of prostate carcinogenesis would help to develop new strategies to prevent progression, improve treatment and reduce the mortality associated with PCa in our country [3].

Prostate carcinogenesis is mainly related with somatic mutations and environmental factors. Among these last is chronic inflammation, which has been linked to the development of various types of cancer. Persistent Helicobacter pylori, Hepatitis B Virus, Schistosoma species and Bacteroides infection are risk factor for the development of gastric cancer, hepatocellular carcinoma, bladder cancer and colon respectively [4].

In prostate, proliferative inflammatory atrophy is a common finding abundant in inflammatory cells that was first described by De Marzo et al. [5] in 1999, who identified it as a precursor lesion of prostatic intraepithelial neoplasia. The inflammatory foci could be associated with bacteria that inhabit chronically prostate and could be responsible for the development of prostatic diseases. Within these, *Propionibacterium acnes* (P. acnes) are the most abundant bacteria in hyperplastic prostate tissue and its presence is more common in patients who were diagnosed with cancer later [6]. *P. acnes* are usually located on the skin and are the primarily responsible for acne. However, a number of reports have described its presence in other organs. Cohen et al. [7] reported that *P. acnes* are detected by culture in 35% of PCa samples. Fassi Fehri et al. [8] detected *P. acnes* by in situ

Table 1: Clinical information of the patients included in the study.

Patients	Benign Prostatic Hyperplasia	Prostate Cancer
Age *years* Average	68	59
Range	(56-81)	(46-71)
No of samples	9	7
Score Gleason	6	1
	7	3
	8	2
	9	1

immunofluorescence in 81.7% of samples from patients with PCa, while non-cancer patients tested negative for the bacteria.

The presence of *P. acnes* in prostate would activate an inflammatory response, which could trigger tumor development [5]. Cohen et al. [7] described in *P. acnes* positive prostatectomies samples a greater number of foci of acute or chronic inflammation compared to foci negative to the bacteria. Besides, Fassi Fehri et al. [8] described that *P. acnes* infection in prostate cells promotes a strong inflammatory response, while the chronic infection changes cell proliferation and growth. All these findings suggest a possible role of *P. acnes* in prostate carcinogenesis.

Despite the high prevalence of acne caused by *P. acnes* worldwide, and high presence of this bacteria in the prostate, acne have not relation with increased risk of developing PCa [9]. So far, little is known about the role of chronic infection by *P. acnes* in organs other than the skin and the prevalence of this infection in prostate patients of Latin-American population. That is why we decided, first, to detect *P. acnes* in prostates Chilean patients and the future to establish a relationship with tumor development.

Materials and Methods

Samples

Prostates samples formalin-fixed paraffin-embedded (FFPE), surgically obtained from patients with benign prostatic hyperplasia (BPH) and PCa were included. Samples were obtained from the Pathology Departments of two Chilean clinical centers. PCa samples included tumors with different Gleason Score.

The use of these samples was done under the consent of the institutional ethics committee.

Immunohistochemistry (IHC)

P. acnes were detected by IHC performed with previously characterized antibodies developed by the Department of Pathology from the Tokyo Medical and Dental University (Japan). The technique was performed according to protocols previously described, using FFPE liver samples from rats inoculated with the bacteria as positive control [10]. Prostate glands were considered as positive if at least one epithelial cell was positive to P. acnes. An institutional pathologist analyzed the presence of bacteria in normal and cancer glands.

Results

Samples of 9 patients without cancer (BPH) and 7 samples from patients with PCa with different Gleason Score (Table 1) were analyzed. Tissue sections were stained with hematoxylin and eosin for delimiting areas with cancerous tissue. Subsequently, in a serial cut, *P. acnes* presence was evaluated by IHC, using as positive control rat livers inoculated with the bacteria where it is detected primarily inside Kupffer cells (Figure 1a).

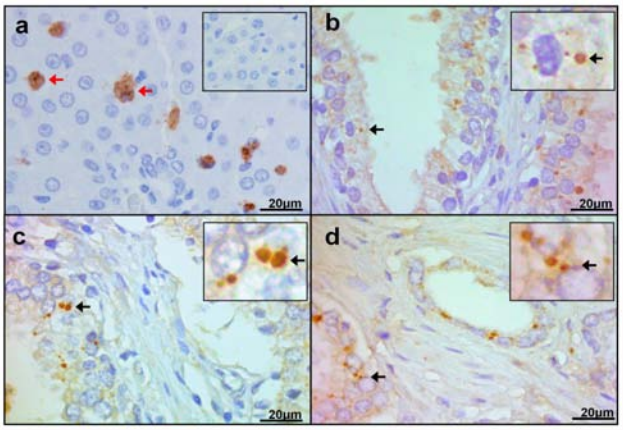

Figure 1: Immunohistochemistry for *P. acnes*. a) Liver from rat inoculated with *P. acnes*. The insert shows negative control. b) *P. acnes* in hyperplastic prostatic glands from a non-cancer patient; c) *P. acnes* in hyperplastic prostatic glands from a cancer patient; d) *P. acnes* in cancer prostatic glands. 100X magnification, Bar: 20 µm. Arrows: red, Kupffer cells; black, *P. acnes*. Staining IHC, DAB; counterstaining: hematoxylin. The inserts in b, c and d show a zoom in the area indicated by the arrow.

P. acnes were detected in prostate tissue from Chileans patients (Figure 1). The bacteria were localized exclusively in the cytoplasm of epithelial cells, in some cases forming clusters.

The presence of *P. acnes* was not specific for cancerous tissue. In patients without cancer (BPH) was able to find the bacteria in 44% of the cases analyzed (Table 2, Figure 1b).

Table 2: *P.* acnes positivity in prostate according to pathology.

Samples	Total	Positive	
		N	(%)
Benign prostatic hyperplasia	9	4	44,4
Prostate cancer	7		
Cancer glands		4	57,1
Non-cancer glands		7	100
Total	16		

The presence of the bacteria was higher in cancer patients (Figure 1b), since the bacteria were detected in all PCa patients (100% positive) (Table 2). In these samples the bacteria were mainly located in non-cancerous glands (100% of the samples, Table 2, Figure 1c), while in cancerous glands its presence was very low, and was only found in 4 patients (57.1%, Figure 1d). The amount of positive cancer glands in the patients was significantly lower than in non-cancerous glands.

The inflammatory response associated with the presence of the bacteria was low. Foci of inflammatory infiltrate around cancerous and noncancerous glands were observed in cancer samples, with no relation with the presence of the bacteria.

Discussion

The results of this study allow us to demonstrate for the first time in Latin America, and particularly in Chilean patients, the presence of *P. acnes* in the prostate tissue.

There is small evidence about the prevalence of *P. acnes* in prostate worldwide, and our results confirm the few existing reports that were made in Asian population. Consistent with them, we found

a high prevalence of the bacteria in samples of prostate tissue from patients Chileans, being greater in samples from PCa patients [6,7]. In these samples, the bacteria is present in cancerous glands, however, the amount of bacteria is higher in normal glands adjacent to tumor glands, according to what was reported in Asian populations [11,12]. In the samples analyzed, the bacteria were also found in patients without cancer. The presence of bacteria in normal glands, mainly those adjacent to the tumor, could be related to the development of cancer in the future, a phenomenon that has been reported previously [6].

To characterize the geographical distribution of the prostatic *P. acnes* infection is important because the strains isolated from prostate do not correspond to the same strains that cause acne (that have high prevalence and are distributed worldwide), but are similar strains of opportunistic infections and those located in urethral microflora [13]. These strains are able to induce chronic persistent inflammatory response with increased cell proliferation and decreased expression of the androgen receptor [14]. It is likely that the bacterial infection may not produce cancer, but as bacteria is located mainly in non-cancer cells, the state of chronic inflammation could influence cancer development.

Inflammatory foci associated with infection were observed in some samples, especially in patients with PCa, although no difference between cancerous or infected hyperplastic glands was found. The foci of acute and chronic inflammation produce molecules with carcinogenic action. In particular, in infected glands the expression of NF-kB nuclear increases promoting prostate carcinogenesis [12].

Our results will allow us to continue large-scale studies that establish the relationship between the presence of *P. acnes* and PCa in order to establish possible molecular mechanisms to associate P. acnes, chronic inflammation and development PCa.

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