

# *Propionibacterium acnes* infection associated with cancerous prostate hypertrophy

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**Introduction** *Propionibacterium acnes* (*P. acnes*) is a typical opportunistic bacteria commonly occurring on the skin, especially associated with acne vulgaris. In certain circumstances, it may cause serious infections such as bacteremia, sepsis, endocarditis, infection after shoulder arthroplasty, or ophthalmia.<sup>1-4</sup> Low virulence of *P. acnes* causes benign clinical symptoms and appears only after a long-term infection. Reports on isolation of *P. acnes* from prostate cancer indicate a possible link between this microorganism and etio-pathogenesis of hypertrophic prostatitis, leading to cancerous proliferation of cells.<sup>1,5,6</sup> The occurrence of proteins in *P. acnes* that can induce cancerous hypertrophy of cells,<sup>2,7</sup> the intracellular localization of bacteria in cancer tissue, in macrophages,<sup>1,6</sup> and a stimulation of specific antibody production<sup>3,8</sup> indicate a need for routine microbiological diagnostic workup in patients with cancerous prostatic hyperplasia.

The aim of this paper was to present a diagnostic procedure and to show characteristics of isolated strains of *P. acnes* sampled from prostate cancer tissue during surgery.

**Patients and methods** The study group consisted of 20 patients who underwent radical retro-pubic prostatectomy due to organ-confined prostate cancer. The mean age of the patients was 65.6 years (range, 52–78 years). The information on past infections was obtained from interviews. None of the patients experienced urinary tract infections, kidney stones, nephrolithiasis, recurrent inflammations, or urological surgical treatment. One patient had a medical history of angina and acne, and another patient—of acne (he also complained about a need to urinate at night for the past 15 years). Three patients complained about frequent urination, the ailment lasting for 1, 1.5, or 5 years.

Preoperative cancer was diagnosed by a core needle biopsy of the prostate gland. The clinical

evaluation of the cancer stage was based on prostate-specific antigen levels, digital rectal examination, and transrectal ultrasound. Clinical cancer stages were categorized according to the following TNM criteria: 3 cases were T1c, 3 cases were T2b, and 1 case was T2c. The preoperative program involved an electrocardiogram as well as the measurement of complete blood count and the levels of clotting parameters and electrolytes. All patients received prophylactic antibiotics, that is, a single dose of the first-generation cephalosporin 1 hour before the procedure.

A surgical procedure was performed according to the Walsh–Donker technique. After removal of the prostate gland, 2 fragments of 1 ml each from both lobes were taken in sterile conditions and directly put into culture medium. The fragments of tissues sampled during surgery were placed in 2 independent liquid substrates (thioglycollate broth with resazurin and Trypcase-soy broth) and incubated for up to 4 days at 37°C. In addition, a microscopic preparation stained with the Gram's method was performed on collected cancer tissue samples and liquid culture. Next, the fluid culture was inoculated on the Casman's medium base (Becton Dickinson and Company, Sparks, Maryland, United States) and Columbia agar base with 5% sheep blood (bioMérieux, Marcy-l'Etoile, France). The incubation was cultivated at 35°C for 7 days in GENbag (bioMérieux) under anaerobic conditions.

The identification of the cultivated bacteria was made based on morphological and biochemical characteristics, using an API 20A (bioMérieux) according to the manufacturer's instructions. *Staphylococci* was identified using a set of ID32Staph (bioMérieux). The results were read using the API-WEB program ver. Poland (bioMérieux). The antibiotic sensitivity was determined using the ATB ANA set (bioMérieux) to define sensitivity to penicillin G, amoxicillin, amoxicillin/acid clavulanic, ticarcillin, ticarcillin/acid clavulanic, piperacillin,

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piperacillin/tazobactam, cefoxitin, cefotetan, imipenem, moxifloxacin, vancomycin, rifampicin, chloramphenicol, and methronidazole. Erythromycin, clindamycin, and tetracycline were identified using the Etest as recommended by the manufacturer (bioMérieux).

**Results** In the group of 20 patients, *P. acnes* was isolated in the form of abundant growth of culture from the material sampled from 7 patients (35%). The results were consistent with the microscopic preparations made from the tested material in which Gram-positive pleomorphic rods were observed, placed outside and intracellularly. The strains showed biochemical characteristics typical of *P. acnes*; their identification did not cause any problems. The numerical profiles 50025442 in 5 strains and 40025442 in 2 strains (not producing urease) obtained in API 20A showed an “excellent identification” (ID, 99.9%) according to the APILAB program (bioMérieux). In 3 samples (15%), the presence of single other bacterial species of *Staphylococcus capitis*, *Staphylococcus epidermidis*, and *Bacillus spp.* were found. Due to their single colonies in the culture, these isolates were considered a contamination. No bacteria were cultured in samples collected from 10 patients (50%).

The isolated strains of *P. acnes* showed a wide range of susceptibility to antibiotics. Each of the strains was sensitive to penicillin G, amoxicillin, amoxicillin/acid clavulanic, piperacillin, piperacillin/tazobactam, ticarcillin, ticarcillin/acid clavulanic, cefoxitin, clindamycin, imipenem, moxifloxacin, vancomycin, rifampicin, chloramphenicol, and tetracycline. Two strains (10%) were resistant to erythromycin, whereas one strain (5%) had the constitutive mechanism of antibiotic resistance MLSB (cross-resistance to macrolides, lincosamides and streptogramin). All strains were resistant to metronidazole, which confirmed their natural resistance to this antibiotic.

**Discussion** The presence of *P. acnes* in proliferative tissue of the prostate gland was highlighted by numerous authors.<sup>1,5,6,8</sup> The development of bacteria with this type of location in the human body is affected by their adaptation to the anaerobic conditions. *P. acnes* do not produce toxins or strong virulence factors; therefore, the course of infection is chronic, subacute, and with a low level of inflammatory markers. The production of hyaluronidase<sup>2</sup> (more than 20 proteins produced during biofilm formation and planktonic growth, of which the ABC transporter protein has a highly immunogenic nature)<sup>3</sup> may drive cancer growth of the prostate gland cells, whereas the expression levels of certain proteins (eg, the methylmalonyl-CoA epimerase and Christie-Atkins-Munch-Petersen factor) may be related to the effect of the microenvironment on the development of *P. acnes*.<sup>9</sup>

Studies conducted on animal models and in vitro experiments confirmed the inductive effect

of chronic infection of *P. acnes*.<sup>1</sup> A chronic infection and metabolic activity of *P. acnes* promotes cell proliferation and their malignant transformation.<sup>5</sup> Furthermore, our results indicate that *P. acnes* infection may be a contributing factor to the formation of prostate carcinoma, as suggested by other authors.<sup>1,6,7</sup> In our study, 35% of the samples contained numerous *P. acnes* strains. The information about the presence of pleomorphic Gram-positive bacteria in the microscopic slide of tissue sampled during surgery is a valuable diagnostic tool and can be used for an early diagnosis of infection, which may indicate a need to initiate an antibiotic therapy to target these microorganisms.

It appears that an early eradication of *P. acnes* can prevent the consequences of a chronic infection and the potential proliferation of prostate cells. It is important to perform a quick and reliable microbiological diagnostic workup. Obtaining a positive culture in our tests with abundant growth of bacteria within 4 days confirmed the participation of *P. acnes*, in comparison with the cases with contamination of cultures by these bacteria, whose growth was visible only after 10 days of incubation. The application of a liquid substrate with thioglycollate provides optimal conditions for isolation of *P. acnes*, which was confirmed by other authors.<sup>10</sup>

In our study, we observed the sensitivity of isolated strains of *P. acnes* to numerous antibiotics of the  $\beta$ -lactam group, fluoroquinolones, glycopeptides, rifamycin, chloramphenicol, and tetracycline, which was also reported by Khassebaf et al.<sup>4</sup> High effectiveness of penicillin and cephalosporin, as well as of clindamycin and vancomycin, in the treatment of *P. acnes* has been highlighted.<sup>10,11</sup> The presence of the *ermX* gene responsible for the mechanism of constitutive resistance MLSB was found in one strain in our research. This confirms the reports of other authors about the occurrence of this mechanism in *P. acnes*.<sup>12</sup> Furthermore, we observed resistance of *P. acnes* to clindamycin and erythromycin, which is in line with the study by Saper et al.<sup>10</sup> In addition, we confirmed the natural resistance of all strains to metronidazole.

Microbiological tests combined with microscopic evaluation of the collected tissue samples for the presence of microorganisms should be an important component of the diagnostic workup for cancer prostatitis. An early diagnosis of the infection caused by *P. acnes* in people with hyper trophy prostatitis is important and constitutes an indication for an antibiotic treatment. Eradication of *P. acnes* may reduce the risk of cancerous transformation of prostate cells during a chronic infection.

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