

Giant prostatic hyperplasia and its causes

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We present a case of a 59-year-old male who was admitted to the emergency department with urinary retention, with a history of lower urinary tract symptoms, with the value of serum prostate specific antigen level of 100 ng/mL and an estimated prostate size of 800 mL, according to magnetic resonance imaging. A prostate biopsy showed benign prostatic hyperplasia. Transvesical prostatectomy was performed, following additional procedure of transurethral resection of the prostate. To the best of our knowledge, this is the fourth highest prostate volume reported in medical literature. In this paper, we examine the factors that may have influenced the development of giant prostate hyperplasia.

Keywords: benign prostatic hyperplasia, giant prostatic hyperplasia, prostate, transvesical prostatectomy

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INTRODUCTION

Benign prostatic hyperplasia (BPH), also known as nodular hyperplasia, is a common non-malignant disease worldwide that affects ageing men and can be defined as an increase of the prostatic volume (due to proliferations of both stromal and glandular components) causing bladder outlet obstruction, which eventually may cause lower urinary tract symptoms. It is characterised by the occurrence of a wide spectrum of symptoms that are related to the functions of the lower urinary tract. These symptoms are caused by two components: the static one (due to the mass of the gland) and the dynamic one (due to the tone of the smooth muscle of the bladder neck, prostate and its capsule). The pivotal role in these mechanisms is played by α 1-adrenergic receptors. More than 50% of men over 50 years of age and roughly 90% of men over 80 years of age are affected by BPH (1–3). Regardless of the large number of cases and its socioeconomic impact, the pathophysiology of BPH is still not completely understood: for instance why some men have a 40-gram prostate, while others have a prostate of 150 g. The extreme cases when the prostatic volume is greater than 500 ml are defined as “giant prostatic hyperplasia” (GPH) (4). Androgens are the most important factor in the differentiation and growth of the prostate during the foetal period and puberty, but it is less significant in adulthood. The role of androgens in the development of BPH is debatable, thus it may be hypothesized that the metabolic syndrome, oestrogen, an inflammation or growth factors may be the most important ones in the aetiology of BPH. GPH is associated with more severe voiding symptoms and more complicated clinical treatment compared with smaller prostates (5). To the best of our knowledge, there are only several cases of prostate larger than 500 ml without a malignant component, and no more than ten cases of GPH reaching 700 ml that have been reported in the literature so far (6–10). We present a case of the fourth largest GPH, treated with open suprapubic prostatectomy approach. In this paper, we will look at the treatment of BPH and the factors that may have affected BPH.

CASE PRESENTATION

A 59-year-old male patient, body mass index 19.6, who presented with urinary retention and acute

kidney failure (blood tests showed high creatinine (688 μ mol/l) level), was admitted to the emergency department. Ultrasound was performed and massive retroperitoneal tumour was suspected. The patient was immediately hospitalized and suprapubic cystostomy was performed. The creatinine level dropped to normal (59 μ mol/l) three days after the procedure. The exact cause of acute urinary retention remained unclear. Because of the patient's age and elevated PSA (over 100 ng/mL), prostatic adenocarcinoma was one of the main considerations. Due to the size, another possibility was prostatic stromal sarcoma, although it is rarely associated with PSA elevation. Magnetic resonance imaging (MRI) was performed to clarify the diagnosis. Pelvic MRI showed a massive 800 ml retroperitoneal tumour with non-differentiable prostate structures and a MRI signal similar to BPH (Figs. 1–2). Prostate biopsy (twelve-core) was performed, but histology revealed a normal prostatic tissue (fibromuscular stroma and glands with double-layered epithelial lining) without evidence of neoplastic or inflammatory changes. The patient had a history of lower urinary tract symptoms for about five years. Not long before, the patient started urinating in a sedentary position, but did not take any BPH medication. There was no history of smoking, alcohol abuse, or comorbidities. According to the records in the pathology lab, this patient had been on urologic surveillance for at least eight years already (the first mentioned PSA was 77.5 ng/ml in 2012 and the prostatic volume was 371 ml in 2014), had multiple transrectal biopsies performed (each comprising 7–20 cores), but no malignant component was identified and the findings were compatible with BPH every time. Blood tests were performed to determine the cause of BPH (Table 1). During suprapubic prostatectomy with spinal anaesthesia, the hyperplastic nodules consisting of multiple pieces weighing 460 g were removed (Fig. 3). Haemostasis was attained by two stay sutures of Vicryl 0 placed at the 5 and 7 o'clock positions of the bladder neck. At the fossa of the extirpated prostate a 3-way 22F silicone catheter was placed and its balloon was inflated with 40 ml distilled water to maintain continuous bladder drainage. As a safety precaution, two suprapubic catheters were placed for extra drainage. The massively expanded bladder was closed in one layer with Vicryl 1. Also, a drainage tube was placed in the pelvis. The rectus muscle was juxtaposed with Vicryl 0 and fascia with Nylon 1,

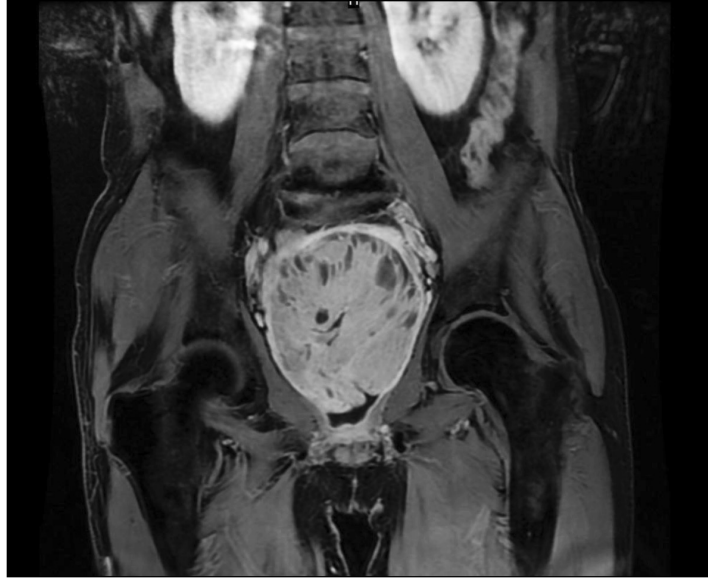


Fig. 1. Coronal MRI image showing a giant prostate occupying most of the pelvic volume

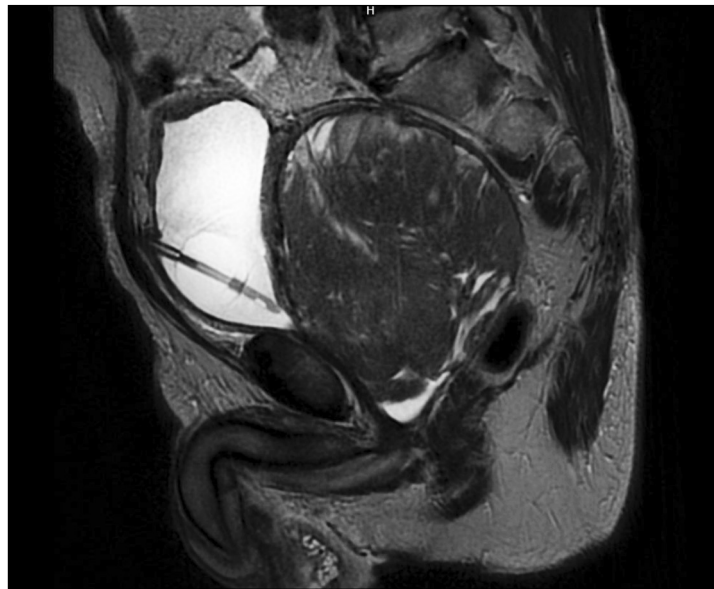


Fig. 2. Sagittal MRI image showing a giant prostate occupying most of the pelvic volume

Table 1. Hormone blood tests

Test	Norm	Result
Prolactine	45–375 IU/ml	335 IU/ml
Luteinizing hormone	0.8–7.6 mIU/ml	335 IU/ml
Luteinizing hormone	0.8–7.6 mIU/ml	5.1 mIU/ml
Testosterone	3–27.35 nmol/l	9.97 nmol/l
Oestradiol	<146.10 pmol/l	55.75 pmol/l
Glucose	4.11–5.89 mmol/l	5.3 mmol/l

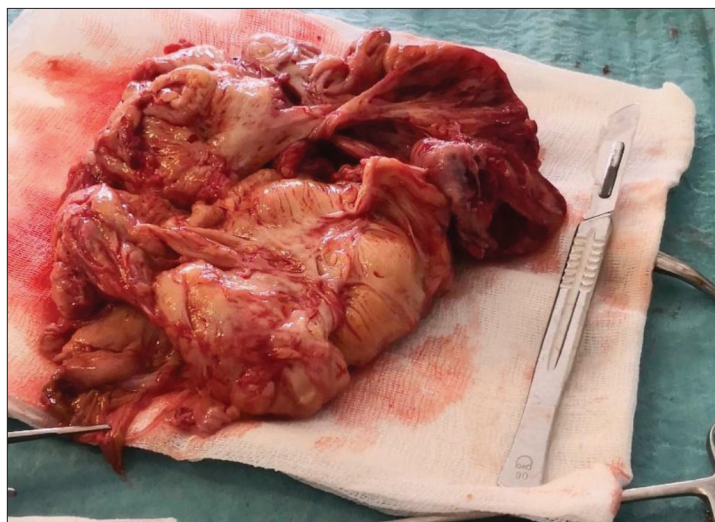


Fig. 3. Prostatic tissue extirpated in multiple pieces, weight 460 g

subcutaneous layer with Vicryl 2, and skin with Nylon 2. On the 3rd and 4th post-operative days, the suprapubic catheters were removed, and on the 10th day the urethral catheter was removed. The patient did not urinate after the removal of the Foley catheter. Eversion of the postoperative wound occurred. Epicystostomy was repeated. The suprapubic wound healed by secondary intention. One month later, the residual prostate mass was removed during transurethral prostate resection (TURP). This time there were no post-operative complications. Suprapubic catheter was removed on the 4th post-operative day. One month after transurethral resection

of prostate, the patient successfully urinated, with $Q_{max} = 22$ ml/s. Once again, a pathologic examination revealed a picture of BPH: a vaguely nodular prostatic tissue comprised of fibromuscular stroma and intermediate or large calibre glands with retained CKHMW (cytokeratin of high molecular weight), positive basal layer, papillary buds, infoldings, and cysts. Some periglandular hyalin (Congo red negative) deposition was also noted. Nuclear reactivity with an antibody for androgen receptors (AR) was heterogeneous (with predominant strong and some weak positivity zones, see Fig. 4) and on average seen in about 80% of the tissue, which is

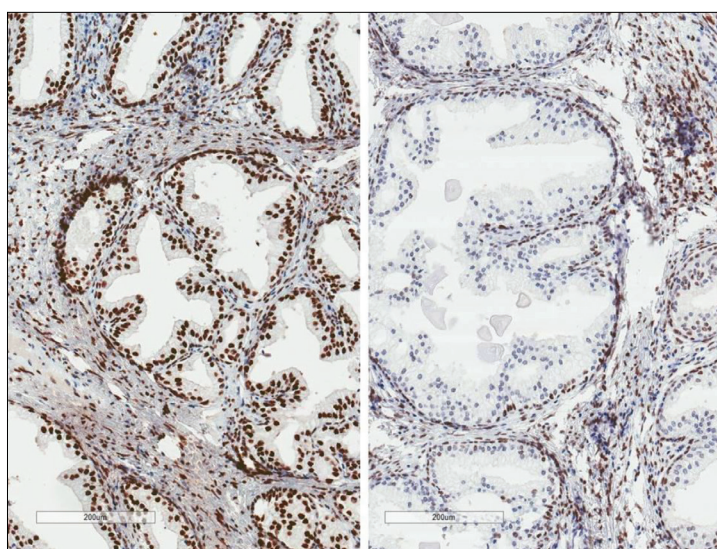


Fig. 4. Heterogenous positivity for androgen receptors in the glandular component with predominant strong zones on the left and weak zones on the right

actually even lower than reported in the literature (mean AR expression in normal prostate tissues: $85.3 \pm 9.7\%$) (11).

DISCUSSION

Benign prostatic hyperplasia is a common problem among elderly men that can lead to serious complications, such as acute urinary retention, recurrent urinary tract infections, refractory gross hematuria, stones, and diverticula formation. Transurethral resection of the prostate is the accepted management for the treatment of symptomatic small-sized BPH (less than 90 g) after failure of medical treatment. Yet the only remaining way to treat giant prostates is the traditional open prostatectomy. This procedure is the best option for patients with a large median lobe protruding into the bladder, as in our case, as well as with symptomatic bladder diverticulum or a large bladder stone the endoscopic removal of which is not feasible. If hyperplastic prostatic tissue nodes are not completely removed through the bladder, then it can be done transurethrally, as we did. During TURP, hyperplastic tissues that interfered with normal urination were removed. The largest ever removed hyperplastic tissues were considered to be a retroperitoneal tumour; it was eliminated during an exploratory laparoscopy and weighed 2410 g (12). However, the largest ever benign prostatic hyperplasia weighed 820 g and was removed by suprapubic prostatectomy, but after the surgery the patient had an uncontrolled haemorrhage and died (13). Prostatic hyperplasia that we removed falls into the top ten largest prostates removed. Unfortunately, no article in the literature addresses the causes of giant prostatic hyperplasia. It is an extremely rare condition with little knowledge about its aetiology and pathophysiology. Sex hormones, a metabolic syndrome, a chronic inflammation of the prostate, growth factors, and other causes are thought to be responsible for the development of prostatic hyperplasia. Like any other sex-accessory tissue, in its growth, sustenance and secretion the prostate is stimulated by the regular presence of certain growth factors and hormones, the main of which is testosterone. It is considered that the presence of androgens and aging are essential for the development of BPH (14). During adulthood, the levels of serum testosterone remain rather constant and start decreasing gradually after 60 years of age. There are reports

of a significant correlation of age with the volume of the prostate in aged male population (15). However, our patient was a 59-year-old man. Moreover, androgens are proven to be essential for the differentiation and for the prostate growth during the foetal period and puberty (16). On the other hand, BPH is related to and has increased incidence with aging, when the testicular testosterone production is reduced. We performed a testosterone blood test (9.97 nmol/l), which was normal. Therefore, the decrease or increase in its concentration cannot be directly linked to the development of giant prostatic hyperplasia. Although testosterone is the main plasma androgen, it functions as a prohormone, while the most active form of the androgen in the prostate is dihydrotestosterone. Hormonal regulation of BPH depends on the presence of androgen and oestrogen receptors. Androgen receptors (AR) are very common in benign epithelium and adjacent stroma. The coactivators in the prostate tissue enhance the function of AR by interacting with N-terminal, DNA-binding and/or ligand-binding domains of the receptor. Notably, alterations in AR expressions common in the cancer tissue have not been detected in benign diseases. Hence, there are no literature reports about AR gene mutations, amplifications, or an increased interaction with coactivators in BPH. In our case, nuclear activity between an antibody and AR was about 80%, which is similar to the one reported in the literature. In contrast, the levels of oestradiol remain constant during aging with the increased oestradiol/testosterone ratio. Some authors reported the relationship of this ratio and an increased incidence of BPH and LUTS (17). However, the role of oestradiol in the pathogenesis of BPH is not fully understood but the main idea is that the increased activation of oestrogen-receptor- α is associated with hyperplasia and an inflammation of the prostate (18). Unfortunately, the level of oestradiol was also normal. In the development and advancement of BPH/LUTS, there are several important age-related factors such as metabolic deviations (metabolic syndrome, dyslipidemia, obesity, and diabetes) as the results of multiple pre-clinical and clinical studies show. In our case, the patient's BMI was normal and biochemical tests showed no evidence of dyslipidemia or diabetes mellitus. The coexistence of a chronic inflammation with BPH histological changes in the pathologic specimens led to suspicion that the development of BPH/BPH and LUTS also depended on the presence

of an inflammation. Viral or bacterial infections might trigger a local inflammation, which leads to secretion of chemokines, growth factors, and cytokines involved in the inflammatory response, and, consequently, the growth of epithelial and stromal prostatic cells. However, the prostate biopsy did not show sufficient signs of a chronic inflammation of the prostate. Thus, it may be hypothesized that the development of BPH depends on other aspects, such as growth factors or an inflammation. Some authors maintain that an over-expression of prostate growth factors with diminished inhibitory elements is a possible mechanism. Theoretically, mutation of Ras and c-erbB-2 proto-oncogenes stimulating cellular proliferation signal would allow abnormal cell proliferation. Moreover, flawed expression of the p53 suppressor gene because of its mutation or deletion could be another mechanism for the hyperplasia process (6, 19). Unfortunately, since the patient had no family history of oncological prostate diseases or non-oncological rare prostate diseases, we did not continue genetic testing. Other authors agree with the theory of androgens and the influence of ageing.

CONCLUSIONS

Although there are many hypotheses about the causes of the BPH, its aetiopathology is still not fully understood. The factors responsible for the onset of the giant prostate are unknown. More research is needed to understand what factors contribute to benign prostatic hyperplasia.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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GIGANTINĖ PROSTATOS HIPERPLAZIJA IR JOS ATSIRADIMĄ LEMIANTYS VEIKSNIAI

Santrauka

Straipsnyje pateikiamas 59 metų amžiaus vyro klinikinis atvejis. Pacientas, kurį ilgą laiką vargino apatinių šlapimo takų problemos, atvyko į skubios pagalbos skyrių dėl ūminio šlapimo susilaikymo. Prostatos specifinio antigeno koncentracija buvo 100 ng/ml, o magnetiniu rezonansu išmatuotos prostatos tūris siekė 800 ml. Atlikus prostatos biopsiją gautas atsakymas – gerybinė prostatos hiperplazija. Pacientui atlikta suprapubinė prostatektomija, o vėliau transuretrinė prostatos rezekcija. Kiek yra žinoma, tai buvo ketvirta didžiausia prostata, aprašyta medicininėje literatūroje.

Straipsnyje analizuojami veiksniai, kurie galėjo lemti milžiniškos prostatos atsiradimą.

Raktažodžiai: gerybinė prostatos hiperplazija, gigantinė prostatos hiperplazija, prostata, transversinė prostatektomija