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Severe Hematuria in the Recurrent Benign Hyperplastic Prostate: Underlying Pathology

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Abstract

Objective: To investigate the underlying morphology and pathology of severe hematuria in recurrent prostatic hyperplasia.

Methods: We reviewed records for 801 primary BPH patients and 57 recurrent BPH patients. We collected prostate tissues from 29 patients who accepted TURP twice for BPH and collected intraoperative images to compare the proportion of the prostatic epithelium, glandular lumen, smooth muscle and micro-vessel density between primary and recurrent BPH tissues.

Results: Severe hematuria is the main reason for hospitalization in patients with recurrent BPH, accounting for approximately 45.61%. In the primary BPH group, the average proportions of the prostatic epithelium, glandular lumen, and smooth muscle were 18.4% ± 13.2%, 9.3% ± 3.5%, and 35.7% ± 15.2%, respectively, and the average proportions of those in the recurrent BPH group were 16.4% ± 8.5%, 8.6% ± 3.3%, and 29.7% ± 12.2%. The proportion of smooth muscle was lower than that of the primary BPH group ($P<0.05$). The MVD value was higher in the recurrent BPH group than in the primary BPH group (27.5 ± 9.3) ($P<0.05$).

Conclusion: The general appearance of the recurrent hyperplastic prostate was irregular nodular hyperplasia, and the surface bled easily. Recurrent hyperplastic adenomas with a higher MVD and thinner blood vessel walls may also be more likely to bleed.

Keywords: Prostatic hyperplasia; Recurrence; Hematuria; Pathology; Immunohistochemistry

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Introduction

Benign Prostatic Hyperplasia (BPH) is the most common etiology of lower urinary tract symptoms in older men. Age and functional testicles are recognized as the main causes of prostatic hyperplasia. In addition, growth factors, interstitial-epithelial interactions, cell proliferation and apoptosis are also associated with prostatic hyperplasia [1]. The histology of prostatic hyperplasia shows glandular and interstitial tissue in the transitional area and the glandular area around the urethra. The major clinical manifestations of Lower Urinary Tract Symptoms (LUTS) with frequent urination, dysuria, recurrent urinary tract infection, bladder stones, filling urinary incontinence, hydronephrosis, renal dysfunction and other complications. For treatment, watchful waiting and conservative treatment, including α-blockers and 5α-reductase, can be used for patients with mild symptoms. However, in some patients, symptoms are gradually aggravated, and various complications may appear. Eventually, surgical treatment is necessary for patients with severe LUTS and complications. Transurethral Resection of the Prostate (TURP) is a standard technique for the treatment of BPH, providing less trauma, shorter operation time, and quicker postoperative recovery compared with traditional open prostatectomy. Nevertheless, regardless of the kind of operation performed, the residual prostate glands can grow gradually under the action of androgens and related hormones, and then recurrent prostate hyperplasia will present [2].

The clinical presentation of recurrent BPH is similar to that of primary BPH. All patients can have LUTS and various urinary system complications. In addition, there are great differences between the two groups regarding admission reasons. We reviewed archives of inpatient medical records and found that patients with primary BPH were mainly admitted for LUTS, including dysuria, frequency, and nocturia, while severe hematuria was the primary reason for admission in patients with recurrent BPH. Compared with LUTS, slight gross hematuria may cause psychological fear in patients. Severe hematuria can cause blood clots and urinary retention, resulting in massive bleeding and severe complications, such as severe anemia and even hemorrhagic shock.

Hematuria is a common symptom of many diseases of the urinary system, although only a few studies concerning hematuria due to BPH, especially recurrent BPH, have been conducted. In this study, we found that severe hematuria is the first-ranked reason for recurrent BPH, but the underlying mechanism is yet to be investigated. We hypothesized that the components of prostatic tissue after TURP were significantly different from those of primary hyperplasia, which may be the main cause of recurrent hematuria in patients with recurrent BPH. The clinical data of 29 patients with recurrent cases of BPH in our hospital were reviewed retrospectively, and these 29 patients treated with TURP twice for BPH were enrolled in this study. Intraoperative images were collected, and the expression of Prostate-Specific Antigen (PSA), CD34 and Smooth Muscle Antigen (SMA) was detected in two groups of prostate tissues using immunohistochemistry. The proportion of the prostatic epithelium, glandular lumen, and smooth muscle was calculated, and Micro-Vessel Density (MVD) was analyzed.

Materials and Methods

Patient population

We reviewed the medical records of 801 primary BPH patients and 57 recurrent BPH patients from January 2008 to January 2017 in the Department of Urology, Zhongshan Hospital Xiamen University (Xiamen, China). No prostate cancer, urothelial cancer, acute urinary tract infection, urinary calculus or coagulation disorders were diagnosed prior to or six months after the operation in these patients. All patients underwent TURP, and postoperative histological examination confirmed the diagnosis of BPH. Of these recurrent BPH patients, 29 cases accepted the initial and repeat TURP procedure at our hospital. From these patients, we collected 29 pairs of prostate tissues, which were then fixed in formalin and embedded in paraffin for further research.

Immunohistochemical assay

We prepared 5 μm sections from the paraffin-embedded prostate tissues. Hematoxylin and Eosin (HE) staining was performed to confirm the diagnosis of BPH. Immunocytochemistry was performed on these sections after they were deparaffinized in xylene and rehydrated in a sequential graded alcohol series. Antigen retrieval was performed by boiling the sections in citrate buffer (pH 6.0) for 30 min. After preincubation with blocking buffer (10% normal goat serum in PBS) for 1 h at room temperature, the sections were incubated with anti-CD34 (diluted 1:200), anti-SMA and anti-PSA overnight at 4°C, followed by incubation with a secondary antibody (KIT-5010, MaxVision™) for 1 h. The signals were visualized by DAB staining.

The relative component of the prostate

The relative content of epithelial and glandular lumen was calculated with anti-PSA immunohistochemically stained sections using a computer-aided image analysis system. The anti-SMA stained sections were used to calculate the relative content of smooth muscle. Each section was measured in 5 random hyperfields.

Determination of MVD

MVD values were determined using anti-CD34 immunohistochemically stained sections using a computer-aided image analysis system described previously [3]. The microvascular dense area was found at a low magnification field. Then, the number of micro vessels in five consecutive non-overlapping fields was counted under a high-power field, and the average value was taken as the MVD value.

Table 1: The primary reason for admission in patients with primary BPH and recurrent BPH.

	Primary BPH	Recurrent BPH
Total	801	57
Dysuria	460 (57.4%)	20 (36.1%)
Frequency	277 (34.6%)	8 (13.9%)
Noctura	46 (5.7%)	3 (5.6%)
Severe hematuria	18 (2.5%)	26 (44.4%)

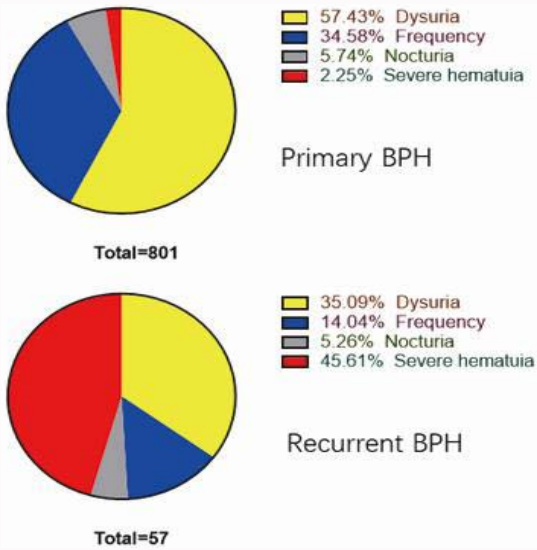

Figure 1: The main complaints in patients with primary BPH and recurrent BPH.
After analyzing the proportion of the main complaints of patients with primary and recurrent BPH, we found that patients with primary BPH were mainly admitted due to dysuria, accounting for 57.43% of admissions, and only 2.25% of them were admitted to the hospital due to severe hematuria. However, patients with recurrent BPH were mainly admitted to the hospital for severe hematuria, accounting for 45.61% of admissions, and the difference was statistically significant.

Statistical analysis

All statistical analyses were performed with SPSS 20.0. Data are expressed as the mean ± standard deviation. The difference between groups was analyzed using the χ^2 test. The difference between the relative content of each tissue component in two groups of paired samples was analyzed by a paired t-test. Statistical significance was achieved when the p-value was <0.05.

Results

We found that patients with primary BPH were mainly admitted due to dysuria, accounting for 57.43% of admissions in this group, and only 2.25% of patients were admitted to the hospital due to severe hematuria. However, patients with recurrent BPH were mainly admitted to the hospital for severe hematuria, accounting for 45.61% of admissions in this group, and the difference was statistically significant (summarized in Table 1 and Figure 1).

As shown in Figure 2, in primary BPH patients, the prostate gland generally appeared as smooth mucosa without obvious nodules or bleeding under transurethral resectoscope, while in recurrent BPH patients; irregular nodular hyperplasia protruding into the posterior urethra, mucosal hyperemia, and obvious bleeding may be present.

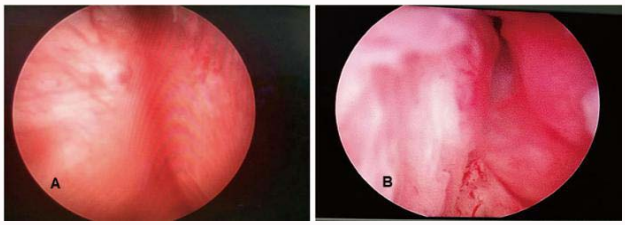

Figure 2: The appearance of prostate tissue under transurethral resectoscope.
The prostate gland generally appears as smooth mucosa without obvious nodules or bleeding in primary BPH patients (A). The prostate appears as irregular nodular hyperplasia protruding into the posterior urethra, with mucosal hyperemia and obvious bleeding (B).

Table 2: The relative component of the prostate in patients with primary BPH and recurrent BPH.

	Primary BPH	Recurrent BPH	t-test	*P*
Epithelial (%)	18.4 ± 13.2	16.4 ± 8.5	-1.433	0.162
Glandular Lumen (%)	9.3 ± 3.5	8.6 ± 3.3	0.312	0.124
Smooth Muscle (%)	35.7 ± 15.2	29.7 ± 12.2	2.135	0.045
MVD	22.9 ± 9.1	27.5 ± 9.3	1.425	0.033

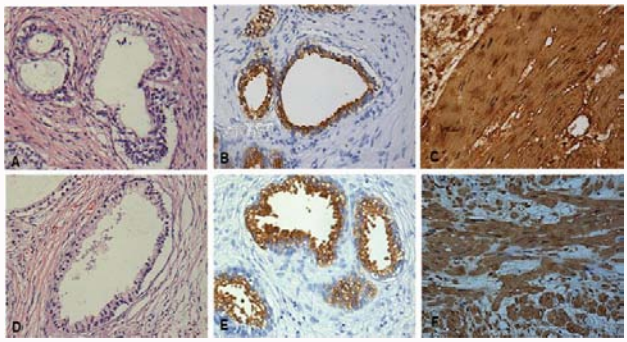

Figure 3: The relative component of the prostate.
HE staining (A) and immunohistochemical staining for PSA (B) and SMA (C) in the primary BPH group. HE staining (D) Immunohistochemical staining for PSA (E) and SMA (F) in the recurrent BPH group. (Original magnification x400).
The relative content of the epithelial and glandular lumen was calculated with anti-PSA immunohistochemically stained sections using a computer-aided image analysis system. The anti-SMA stained sections were used to calculate the relative content of smooth muscle. The glandular lumen was defined as neither immunohistochemically stained nor HE stained.
In the primary BPH group, the average proportions of the prostatic epithelium, glandular lumen, and smooth muscle were 18.4 ± 13.2%, 9.3 ± 3.5%, and 35.7 ± 15.2%, respectively, and the average proportions in the recurrent BPH group were 16.4 ± 8.5%, 8.6 ± 3.3%, and 29.7 ± 12.2%, respectively. The relative content of smooth muscle in the recurrent BPH group was lower than that of the primary BPH group (P<0.05). There was no significant difference in the proportion of the epithelial and glandular lumen between the two groups.

As shown in Table 2 and Figure 3, in the primary BPH group, the average proportions of the prostatic epithelium, glandular lumen, and smooth muscle were 18.4 ± 13.2%, 9.3 ± 3.5%, and 35.7 ± 15.2%, respectively, and the average proportions of those in the recurrent BPH group were 16.4 ± 8.5%, 8.6 ± 3.3%, and 29.7 ± 12.2%, respectively. The relative content of smooth muscle was lower in the recurrent BPH group than in the primary BPH group (P<0.05). There was no significant difference in the proportion of epithelial and glandular lumen between the two groups. The glandular lumen is a cavity structure enclosed by the gland lumen epithelium, and the glandular lumen is defined as neither immunohistochemically stained nor HE stained.

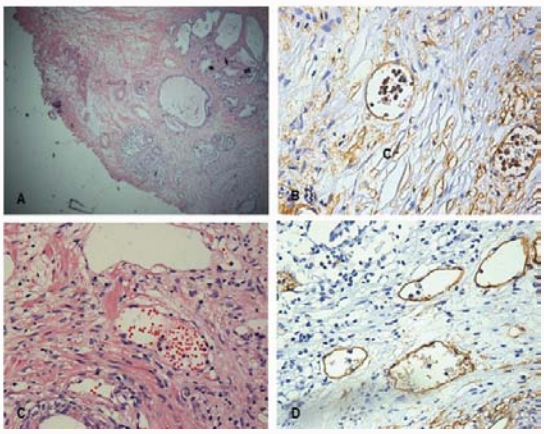

Figure 4: HE staining (A) and immunohistochemical staining for CD34 protein (B) in the primary BPH group. HE staining (C) and immunohistochemical staining for CD34 protein (D) in the recurrent BPH group. CD34 is a vascular endothelial cell marker (Original magnification x400). The mean MVD of the primary BPH group was 8.6 ± 3.3%, while that in the recurrent BPH group was 27.5 ± 9.3%. The difference was statistically significant (P<0.05).

Smooth muscle is stained in anti-SMA-labeled immunohistochemical sections (Figure 3C, Figure 3F). The prostate tissues in the recurrent BPH group had less smooth muscle composition and a disordered structure compared with those in the primary BPH group. The relative content of smooth muscle in the primary group was 35.7 ± 15.2%, while the relative content of smooth muscle in the regenerative group was 29.7 ± 12.2%. The difference was statistically significant (P=0.045 <0.05).

CD34 is mainly expressed in the membrane and cytoplasm of vascular endothelial cells (Figure 4). The mean MVD of the primary BPH group was 8.6 ± 3.3%, while that in the recurrent BPH group was 27.5 ± 9.3%. The difference was statistically significant (P<0.05).

Discussion

Recurrent BPH is one important reason for long-term hospitalization after TURP. Recurrent BPH may result in the natural growth of the prostate gland and possible residual gland [4]. Patients with recurrent BPH and those with primary hyperplasia may have similar clinical manifestations [5]: (1) LUTS, such as urinary frequency, urgency and dysuria; (2) hematuria, usually painless gross hematuria or even severe hematuria, although in some cases, sustained hematuria or clot urethra congestion may cause urinary retention; and (3) related complications, such as secondary renal insufficiency, recurrent urinary tract infection, bladder calculus and filling incontinence. Although both groups may share similar clinical manifestations, the clinical incidence is not the same. Our study found that patients with primary BPH were mainly admitted for dysuria, accounting for approximately 57.43% of admissions in this group, and that only 2.25% were admitted for severe hematuria. However, the recurrent BPH patients were mainly admitted to the hospital because of severe hematuria, accounting for approximately 45.61% of admissions. A retrospective study compared the data for 1225 patients who received TURP for BPH from 1981 to 2001 and found that fifty-seven patients experienced repeat TURP with an incidence rate of 4.65% and that 69.8% manifested gross hematuria [6].

Reoperation incidence after TURP in the first, fifth, and eighth years is 1.25%, 4.16% and 6.63%, respectively [7]. Twenty-nine patients in this study underwent reoperation after ineffective conservative treatment. BPH is a common benign cause of hematuria in older men, mainly due to turbulent flow and friable blood vessels, and the hematuria related to BPH means the exclusion of malignancy and other benign diseases and nephropathy. Of 801 cases of primary BPH patients, only 2.25% presented with severe hematuria, while 45.61% of patients with recurrent BPH suffered severe hematuria. A previous study and our observation confirmed the significant differences.

We inspected the appearance of prostate tissue under a resectoscope and found that the prostate showed irregular nodular hyperplasia protruding into the posterior urethra with abundant blood vessels in recurrent BPH patients. However, the prostate gland generally appeared as smooth mucosa without obvious nodules or bleeding in primary BPH patients. Urinary flow in the urethra through the irregular hyperplasia of the urethra can easily form a vortex, making the urinary tract dilate after urinary tract pressure increases and thus affect the blood vessels, resulting in bleeding.

There may also be some differences between the underlying histological components in these different hyperplastic forms. Histologically, the prostate tissue includes glandular and interstitial components. The gland is mainly composed of epithelial and interstitial cells, including fibrous tissue, fibrous muscle tissue or muscle tissue. As a result, BPH can be divided into gland hyperplasia and interstitial hyperplasia. Gland hyperplasia refers to the cell proliferation of glandular epithelial cells that are secretory and can cause increased acinar cell proliferation; interstitial hyperplasia mainly refers to the proliferation of smooth muscle cells and blood vessels within the prostate tissue. Pathological studies have shown that the clinical manifestations of BPH and the histopathological changes in the prostate are closely related [8]. In this study, we histologically analyzed prostate specimens from patients with BPH who accepted TURP twice to investigate the histopathological basis of recurrent BPH and hematuria. The results showed that the relative content of smooth muscle in the newly proliferated prostate tissue, which is undeveloped and disorderly in morphology, was lower than that in tissue of the primary prostatic hyperplasia. The MVD of recurrent BPH was higher than that of primary BPH, and more thin-walled vessels were observed in the recurrent BPH samples. This finding shows that recurrent BPH hematuria may be related to reduced smooth muscle content, structural disorders, and vascular hyperplasia. In recent years, studies have found that vascular hyperplasia is also associated with benign prostatic hyperplasia [9]. Foley [10] reported that prostatic tissue hyperplasia of prostate tissue blood flow is more abundant, and rich blood supply may lead to hematuria and other related symptoms.

Based on the above clinical and pathological analysis, we speculate that the mechanism of severe hematuria in recurrent BPH involved the following: The general appearance of the recurrent hyperplastic prostate showed irregular nodular hyperplasia, and the surface bled easily. The presence of severe hematuria in recurrent BPH may be associated with higher MVD, thinner blood vessel walls and reduced smooth muscle with impaired structures.

Hematuria can be managed with finasteride and other treatment options, including androgen deprivation and surgery (TURP). Recurrent BPH patients mainly have increased age, poor health status, and poor tolerance to surgery. Therefore, mild symptoms can be treated with α-blockers, 5α-reductase inhibitors, or a combination. Studies have shown that finasteride, a 5α-reductase inhibitor, can reduce the volume of BPH [3,11]. Moreover, it is advisable to take finasteride for a period after surgery to prevent hematuria.

Increased prostate MVD, decreased smooth muscle and structural disorders may contribute to severe hematuria in recurrent BPH patients. This finding provides an important clue for the prevention and treatment of hematuria caused by BPH. Finasteride can reduce MVD [11] in patients with prostatic hyperplasia, and prophylactic use of finasteride may reduce bleeding after TURP [12]. For the prevention and treatment of hematuria, patients with high MVD may benefit from finasteride.

The present study indeed had limitations. This study is a single-center retrospective study with a relatively small size. More studies are needed to elucidate the mechanism of severe hematuria in recurrent BPH patients.

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