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Review

The influence of asymptomatic inflammatory prostatitis on the onset and progression of lower urinary tract symptoms in men with histologic benign prostatic hyperplasia

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Abstract Benign prostatic hyperplasia (BPH) is a condition that greatly affects the quality of life of middle-aged and elderly men. Histopathologically, hyperplastic changes frequently occur in the prostate tissue of elderly men, the incidence of which has been reported to reach approximately 80% in men in their 70s. In clinical practice, approximately 25% of men with histologic BPH are assumed to experience lower urinary tract symptoms (LUTS) and receive some kind of treatment. In other words, there are some men with histologic BPH who do not exhibit LUTS. For that reason, many factors, such as the change in hormonal environment, the immune or autoimmune response, the alteration of gene expression, and so on, are thought to affect the onset and progression of LUTS in men with histologic BPH. One such factor that has long drawn attention is the presence of asymptomatic histological inflammation, which very often accompanies symptomatic BPH. Recent studies have suggested that asymptomatic histological inflammation causes repeated destruction, healing, and regeneration of the prostate tissue, leading to the enlargement of prostatic nodules, while at the same time causing stromal tissue-predominant remodeling of the prostate tissue, which can increase urination resistance and result in the condition changing from asymptomatic BPH to symptomatic BPH. In future, the biomolecular clarification of the significance of asymptomatic histological inflammation in the prostate tissue could help develop new treatment strategies for BPH accompanied by LUTS.

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1. Introduction

Benign prostatic hyperplasia (BPH) is a condition that greatly affects the quality of life (QoL) in middle-aged and elderly men. The prevalence of histologic BPH is reported to gradually increase from around 50% in men aged over 50 years to 80% in men over 70 years, indicating an increase in the incidence with age [1]. On the other hand, BPH accompanied by lower urinary tract symptoms (LUTS) poses a problem in actual clinical practice. According to one report based on 11 cross-sectional population-based studies, the incidence of at least moderate-to-severe LUTS is 29% in men in their 50s and 56% in men in their 70s [2]. These figures differ from the prevalence of histologic BPH, indicating that some patients with histologic BPH do not exhibit LUTS [3]. Furthermore, the correlation between the prostatic volume and the severity of LUTS are not so strong [4]. For that reason, many factors are thought to affect the onset and progression of LUTS in men with histologic BPH. For example, a very high incidence of inflammatory cell invasion is observed in the prostate of BPH patients with LUTS [5], we therefore believe that inflammation plays a major role in the onset of LUTS.

In recent years, several reports have revealed that inflammation contributes to the onset of LUTS in histologic BPH. To be more specific, 7.7 times more patients with BPH and LUTS have a history of prostatitis than healthy individuals [6]. In addition, approximately 20% of symptomatic BPH patients experience pain and discomfort during ejaculation; furthermore, individuals with symptoms are thought to experience more severe LUTS [7]. Like the prevalence of histologic BPH, prostatitis is also more common in elderly individuals [8]. In the present report, we discuss the mechanism underlying the onset and progression of LUTS in histologic BPH in terms of the inflammation that frequently accompanies symptomatic BPH, and review the effective mechanisms and future outlooks of symptomatic BPH treatment using drugs with an anti-inflammatory action.

2. Methods

A literature review searching PubMed was performed. The search strategy included the terms: benign prostatic hyperplasia, prostatitis, pathogenesis, progression, and LUTS. We limited out search to English-language articles published between January 2001 and December 2016. In addition, cited references from the selected articles and from review articles retrieved in our search were used to identify manuscripts that were not included in the previous search.

3. The relationship between National Institutes of Health type IV prostatitis and LUTS

Prostatitis is traditionally not viewed as a single condition but a syndrome formed from several underlying causes. In 1999, the National Institutes of Health proposed that prostatitis be classified into types I–IV [9]. In particular, type IV is classified as asymptomatic inflammatory prostatitis. This is defined by the presence of leukocytes (white blood cells) and/or bacteria in prostate-specific samples (post-prostatic massage urine, expressed prostatic secretion, semen, and prostate biopsy) as well as the absence of subjective symptoms and is therefore diagnosed solely in the laboratory. Although the presence of such asymptomatic histological inflammation has been reported before, the absence of symptoms meant that it was not subject to treatment and thus posed no clinical problem.

However, large-scale clinical trials examining the effect of drugs for symptomatic BPH, such as the Medical Therapy of Prostatic Symptoms (MTOPS) trial and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, showed the presence of asymptomatic histologic inflammation in the prostate tissue, which could be associated with the progression of BPH and LUTS. For example, in the MTOPS trial using doxazosin and finasteride [10], inflammatory findings were observed in 45% of patients who underwent prostate biopsy. Moreover, most of these patients had chronic inflammation. Meanwhile, in the REDUCE trial [11], 77.6% of patients exhibited histologic inflammation of the prostate, irrespective of the presence or absence of prostatitis. Interestingly, in the placebo group, patients with chronic inflammation of the prostate tissue exhibited a greater prostatic volume, a higher international prostate symptom score (IPSS), and a higher risk of acute urinary retention than patients without inflammation [12]. Furthermore, pathological analysis of resected tissue obtained from symptomatic BPH patients who had undergone transurethral resection of the prostate (TUR-P) for LUTS without inflammatory symptoms confirmed the presence of histological changes accompanied by inflammatory cell invasion in most patients [5,13]. Therefore, asymptomatic histologic inflammation in the prostate very frequently accompanies histologic BPH and might in fact contribute considerably to prostate enlargement as well as the onset and progression of LUTS.

4. Prostate tissue remodeling caused by asymptomatic histological inflammation

Asymptomatic histologic inflammation in the prostate tissue is likely caused by bacterial and viral infections, the mechanism underlying allergic reactions to stimuli such as seminal fluid and urine due to poor drainage and reflux into prostate tissue, as well as estrogen-producing inflammatory cells. BPH is also considered a localized autoimmune condition. Age-related weakening of the immune system and changes in the hormonal environment reportedly result in hypofunction of suppressor cells and subsequent invasion of inflammatory cells that ultimately causes asymptomatic histological inflammation [14].

We report that asymptomatic histological inflammation causes repeated destruction, healing, and regeneration of the prostate tissue, leading to the enlargement of prostatic nodules, while at the same time causing significant morphological changes to stromal tissue (remodeling), which can increase urination resistance and result in the condition changing to symptomatic BPH [5] (Fig. 1). Furthermore, reactive oxygen species produced as a result of the low-oxygen environment of the remodeled tissue reportedly induce inflammatory and proliferative cytokine expression, which can promote a vicious cycle of remodeling

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