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Original Article

The natural course of bacillus Calmette-Guérin induced bladder lesions: A long-term follow-up study and systematic review

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KEYWORDS
Bacillus Calmette-Guérin;
Bladder cancer;
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Follow-up

Abstract *Objective:* Bacillus Calmette-Guérin (BCG) instillation is the standard adjuvant treatment for intermediate- and high-risk non-muscle-invasive bladder cancer after transurethral resection. Nevertheless, its toxicity often causes bladder complications. On follow-up cystoscopy, post-BCG bladder lesions can be pathologically benign, urothelial carcinoma recurrence, or other types of bladder malignancy. Only a small number of case reports have been published on post-BCG bladder lesions. Their clinical features, natural course, and management remain unknown.
Methods: We retrospectively studied cystoscopic videos and medical records of BCG-treated bladder cancer patients at our center. During a long-term follow-up, we took biopsies on tumor-like lesions and described their changes. In addition, we summarized previous studies on post-BCG bladder lesions by systematic literature searching and review.
Results: We described a series of three cases with post-BCG bladder lesions mimicking tumor recurrence from a total of 38 cases with follow-up data for more than 5 years. Those lesions

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could last, grow, or disappear spontaneously, and remain pathological benign for years. In systematic review, we identified and analyzed a total of 15 cases with post-BCG bladder lesions with detailed clinical information. Eleven of the 15 were benign and have a good prognosis with nephrogenic adenoma being the most common pathological type.
Conclusion: Based on previous studies and our experience, benign lesions after BCG instillation cannot distinguish with cancer recurrence by cystoscopy alone, even under narrow band imaging mode. Nonetheless, given most of them have a good prognosis, random biopsy or transurethral resection might be spared in the patients with long-term negative biopsy and urine cytology.

1. Introduction

Non-muscle-invasive bladder cancer (NMIBC) accounts for approximately 70% of bladder cancer cases and can be stratified into low-, intermediate-, and high-risk categories, according to the European Association of Urology guidelines [1,2]. After transurethral resection (TUR), the standard adjuvant treatment for intermediate- and high-risk NMIBC is intravesical bacillus Calmette-Guérin (BCG) instillation [3]. Nevertheless, BCG's immune reaction can generate local side effects like cystitis, with an incidence up to 85% [4]. On follow-up cystoscopy, local toxicity of BCG can significantly alter morphology and histology of urothelium, making it difficult to distinguish tumor recurrence from other bladder diseases [5].

However, many previous studies on BCG local side effects only focused on symptoms and treatments without providing detailed descriptions of cystoscopic morphology and pathological changes [6,7]. Although a small number of case reports have published clinical features of the post-BCG lesion, long-term follow-up data are insufficient [8–10]. The lack of the knowledge on the natural course of these lesions has led to controversy over whether all masses detected after BCG should be removed. Additionally, high-quality guidelines and textbooks provide no clear recommendations for managing post-BCG lesions, leaving many urologists to rely on random bladder biopsy or diagnostic TUR when suspicious lesions are identified [11,12]. These progressive procedures are usually carried out under general anesthesia, which increases perioperative risks and economic cost. Understanding the natural course of BCG-induced lesions based on evidence from long-term follow-up studies can provide valuable guidance for clinical decision-making.

In this study, we aimed to describe a series of BCG-treated cases with lesions mimicking bladder cancer recurrence on cystoscopy, providing detailed morphological and pathological reports over years. In addition, through a systematic review of previous studies, we aimed to identify and analyze BCG-associated bladder lesions to provide original references for managing these lesions based on a combination of our own experience and previous reports. To the best of our knowledge, this study is the first to focus on this clinical issue in such detail, providing insights into the management of post-BCG bladder lesions.

2. Methods

2.1. Patients

We selected patients treated with BCG for NMIBC or carcinoma *in situ* with follow-up data of more than 5 years at Changhai Hospital, shanghai, China. To clarify their long-term natural course, we only focused on the post-BCG lesions that last for more than 1 year without another TUR or cauterization. Prior to the initiation of BCG instillation, all patients had undergone at least one TUR and were pathologically confirmed as intermediate- or high-risk urothelial carcinoma (UC). Our BCG protocol followed the Southwest Oncology Group schedule [13]. The maintenance period lasted from 1 year to 3 years depending on the tolerance of each patient. In addition, each patient was told to have regular cystoscopy follow-up according to the European Association of Urology guidelines [2]. Written informed consent was obtained from each patient for treatment and publication, including the use of medical images. Ethics review was approved by the ethical boards of Changhai Hospital (No. 81172425).

2.2. Cystoscopy and biopsy

Intraurethral 2% lidocaine (Kelun, Yueyang, Hunan, China) was given 5 min before the examination. All cystoscopies were carried out by experienced urologists (Ma C and Zeng S). All procedures were performed with flexible cystoscope (Olympus CYF-VH and color video system, Olympus Medical Systems Corp., Hachioji-shi, Tokyo, Japan) with white light and narrow band imaging (NBI) (Olympus CV-180 Evis Exera II Video System, Olympus Medical Systems Corp., Hachioji-shi, Tokyo, Japan). The location, size, number, appearance, and the time of discovery of all suspicious findings were documented. Any lesion that arose from the surface of urothelium was defined as "tumor-like" and biopsied by cold-cup [14]. In contrast, red or purple patches within urothelium were documented in detail without biopsy. If the flat anomaly grew or arose, biopsy would be taken. Videos and medical records were double-checked to make sure the lesions observed were the same. Once cancer cells were verified by biopsy or urine cytology, the lesions would be considered

cancer recurrence instead of "tumor-like", and TUR was taken for comprehensive pathological analysis. Two pathologists confirmed the histological result of each sample.

2.3. Systematic review

Preferred Reporting Items for Systematic review and Meta-Analysis protocols for patient-focused research were used to facilitate the systematic review [15]. The size, location, appearance, pathology, treatment, and outcome of the lesions were collected, as well as their BCG schedule. Since there is no well-accepted term to describe "post-BCG bladder lesion", and many relevant studies only describe this phenomenon as one type of BCG cystitis or side effects, we used a wide-ranging search strategy to avoid missing. PubMed and Embase databases were searched using the following query: "(((BCG [Title/Abstract]) OR (Bacillus Calmette Guérin [Title/Abstract]) OR (Bacillus Calmette-Guérin)) AND ((bladder cancer [Title/Abstract]) OR (urothelial carcinoma [Title/Abstract]) OR (transitional cell carcinoma [Title/Abstract])) AND ((cystitis [Title/Abstract]) OR (side effects [Title/Abstract]) OR (side effect [Title/Abstract]) OR (case report [Title/Abstract]) OR (case series [Title/Abstract]))) AND (English [Language])". In Embase, query "[Title/Abstract]" is coded as ":ab, ti". After removing duplicates, reviewing was assessed by two reviewers (Ma C and Dai L) independently. Full texts and references of the screened studies were evaluated. Studies on BCG-induced diseases on organs other than the bladder were not considered; studies without descriptions of cystoscopic appearance or pathological results were excluded. Meta-analysis or other statistics were not suitable for the screened studies.

3. Results

3.1. Retrospective study

A total of 38 BCG-treated patients had follow-up data for more than 5 years at our center. Among them, three (3/38, 7.9%) had post-BCG bladder lesions mimicking cancer and lasted for more than 1 year. The pathology before the initiation of BCG confirmed the three cases as high-grade bladder cancer without signs of invasion (detrusor muscle in the specimen). Therefore, no second TUR was carried out before BCG. None of them had chronic immune diseases, which may influence BCG response and side effects. We followed up with them for 10 years, 7 years, and 6 years, respectively. Neither regular white light cystoscopy nor NBI mode could distinguish those suspicious lesions from UC. The urine cytology of the series was negative during the follow-up. As for the natural course, those tumor-like lesions could remain for years or disappear spontaneously. For pathological changes, our cases shared a pathway: from granulomatous cystitis to chronic cystitis featuring lymph cells, and to metaplasia or disappear. Their clinical information is summarized in Table 1.

Case 1 was a 53-year-old male with high-risk NMIBC on the left and posterior walls. He initiated intravesical BCG since December 2011 after TUR. He often suffered from cystitis symptoms after BCG instillation. These symptoms could be

Table 1 Clinical information of three cases with post-BCG tumor-like lesions.

Case	Age, year	Sex	BCa before BCG		BCG				Time from BCG to lesion, month	Cystoscopy	Treatment	Follow-up time, year	Outcome
			Recurrence, *n*	Pathology	Strain	Dosage, mg	Schedule	Symptom					
1	53	Male	3	Ta HG	Danish	80	6 weekly maintenance 3 years	Frequency dysuria	14	Papillary neoplasms	Follow-up and biopsy	10	No UC recurrence
2	47	Male	0	Ta HG	Danish	80	6 weekly maintenance 1 year	Frequency urgency	4	Papillary neoplasms arising from velvet-like mucosal erythema	Follow-up and biopsy	7	No UC recurrence
3	67	Male	1	Ta HG	Danish	80	6 weekly maintenance 1 year	Frequency urgency pain fever	12	Velvet-like neoplasms	Follow-up and biopsy	6	No UC recurrence

BCG, bacillus Calmette-Guérin; BCa, bladder cancer; HG, high-grade urothelial carcinoma; UC, urothelial carcinoma.

spontaneously relieved within 2–3 days. Tumor-like lesions were identified on the left and posterior walls of his bladder by follow-up cystoscopy. On cystoscopy, those lesions were several papillary neoplasms and were near previous resection scar (Fig. 1A). Samples obtained in April 2013 and January 2014 were diagnosed as granulomatous cystitis In March 2015, the pathology and immunohistochemistry turned out to be mucosal chronic inflammation with lymphatic nodules (Fig. 1B). The patient completed 3-year BCG schedule and had three more cystoscopies in May 2016, January 2019, and September 2020, respectively. The suspicious lesions on the left and posterior walls of his bladder remained stable in appearance (Fig. 1C). Interestingly, in May 2016, 4 years after the initiation and 1 year after the completion of intravesical BCG therapy, the pathology of BCG-induced lesions changed into nephrogenic adenoma (NA), which remained unchanged in January 2019 and September 2020 (Fig. 1D). The patient had no urological symptoms and no evidence of bladder cancer recurrence or metastasis.

Case 2, a 47-year-old male with eight papillary lesions on the dome and right wall underwent TUR in October 2012. He started intravesical BCG 1 month after TUR. This patient often complained of urgency and frequency 2–3 days after BCG instillation. Levofloxacin was given to relieve the symptoms. Four months after BCG initiation, tumor-like lesions were observed on the dome and right wall of his bladder. On white light cystoscopy, these lesions were several papillary neoplasms arising from velvet-like mucosal erythema covering an area of approximately 1.5 cm × 1.0 cm (Supplementary Fig. 1A). On NBI mode, these lesions had signs of vascular proliferation, which mimicked tumor recurrence (Supplementary Fig. 1B). The pathology of the tumor-like lesion was vascular hyperplasia and lymphocytes invasion with lymphoid follicles (Supplementary Fig. 1C). The patient completed the one-year BCG immunotherapy schedule and underwent follow-up cystoscopy until December 2019. The tumor-like lesion lasted until November 2018 and disappeared spontaneously in December 2019.

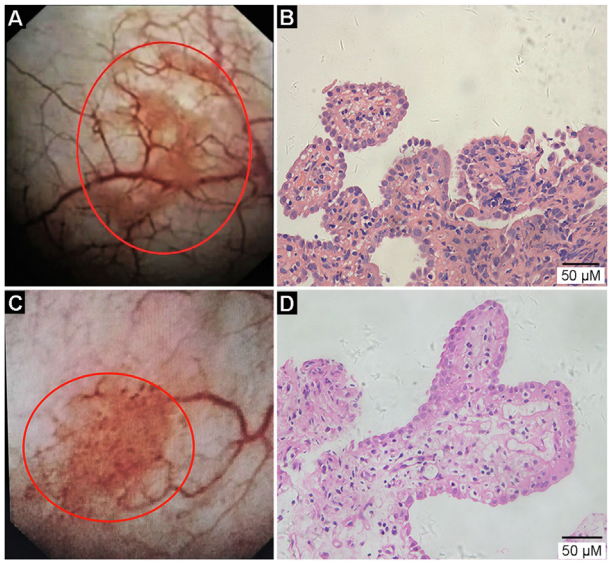

Figure 1 The post-BCG tumor-like lesion changes on cystoscope and microscope of Case 1. (A) The tumor-like inflammatory lesion; (B) Hematoxylin-eosin staining image of chronic inflammation; (C) The tumor-like nephrogenic adenoma; (D) Hematoxylin-eosin staining image of nephrogenic adenoma. The red circle highlights the post-BCG lesion. BCG, bacillus Calmette-Guérin.

Case 3, a 67-year-old male was diagnosed as high-grade UC on the left and posterior walls of his bladder in June 2015 after TUR. One month later, he initiated intravesical BCG. The patient often had a fever the night after BCG and suffered from urgency, frequency, and lower abdominal pain for several days. The symptoms could be relieved by oral levofloxacin. In the cystoscopy of March 2016, papillary neoplasm measuring 1.0 cm × 1.0 cm was observed on the left wall (Supplementary Fig. 2A). NBI demonstrated this lesion was hypervascular (Supplementary Fig. 2B). Biopsy showed that it was atypical reactive proliferation of the urothelium (Supplementary Fig. 2C). No further treatment was given according to the patient's willing. The papillary neoplasm lasted without significant changes on morphology until the cystoscopic examination in November 2018. In May and September 2019, he had two more cystoscopies. No suspicious lesion was found, and the patient remained well.

3.2. Systematic review

A total of 1181 records were available from PubMed and Embase databases according to the above query on March 26, 2022. A remarkable increase of the publications of BCG side effects can be observed in the recent decade (Supplementary Fig. 3). After removing duplicates, we went through titles and abstracts of 751 records from which 37 studies with descriptions of post-BCG bladder lesions were screened for full text reviewing as well as their references. Ströck et al. [16] reported a series of eight cases of BCG induced bladder necrosis, and data of each individual case were unavailable. We included this study by using median values of the eight cases. Studies without detailed clinical information were excluded [13,14]. Studies reported bladder contracture as a side effect of BCG were not included, since bladder contracture often features diverticulum rather than mucosal lesions [17]. The literature flow diagram represents steps of the reviewing and selection of articles (Fig. 2). As a result, a total of 15 cases with detailed cystoscopic and pathologic descriptions from 14 studies were identified [8–10,16,18–27]. The clinical characteristics of the selected cases were summarized in Supplementary Table 1.

Stilmant and Siroky [8] first associated NA with intravesical BCG treatment in 1986. Thereafter, several cases of BCG-induced bladder NA have been reported [18,20,23,28]. Other than NA, BCG instillation was reported to cause unusual acute cystitis cases like eosinophilic cystitis and *Mycobacterium abscesses* granulomatous cystitis [9,10]. Langerhans cell histiocytosis has also been described after BCG [21]. In addition to benign bladder diseases, BCG instillation was considered by some researchers a risk factor for some rare types of bladder malignancies. Brenner et al. [24] described a case of squamous cell carcinoma and first linked non-urothelial bladder cancer development with BCG instillation. Another case of bladder squamous cell

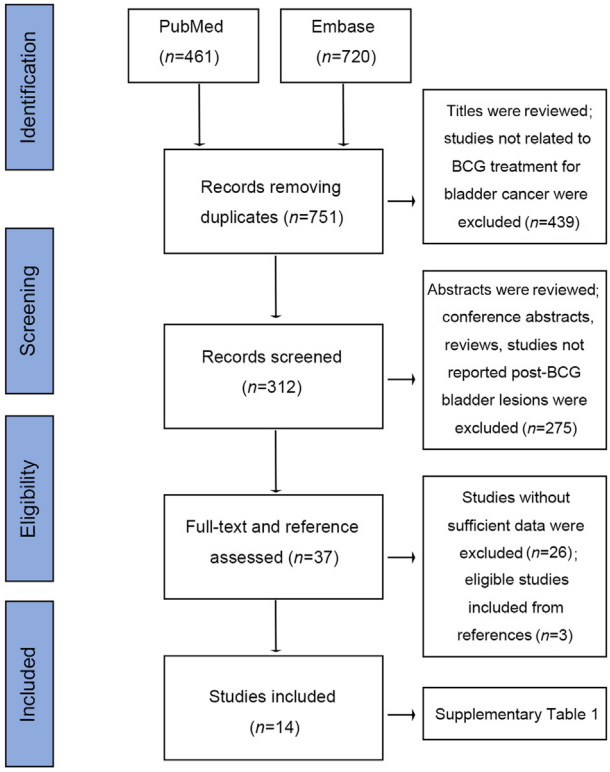

Figure 2 Flow diagram of study reviewing and selection. BCG, bacillus Calmette-Guérin.

carcinoma had been diagnosed 3 years after BCG instillation [25]. Other rare bladder cancer types such as sarcomatoid carcinoma and small cell carcinoma had also been associated with intravesical BCG [26,27]. Their clinical features were included on Supplementary Table 1.

Though all three of our cases are male, gender ratio of the selected cases was approximately 3:1 (male:female), consistent with bladder cancer prevalence. Most BCG-induced bladder diseases, whether benign or malignant, had a history of UC recurrence and hadmultiple TURs. Combined the included studies with our series, we could not find a correlation between different BCG schedules, dosages, or strains with BCG-induced urothelial anomalies. Various BCG strains like Pasteur, Tokyo, and Tice had been associated with post-BCG lesions, though their immunogenicity and toxicity could be different. For BCG schedule, NA reported by Stilmant and Siroky [8] had a two-year course with both induction and maintenance periods. In our series, Case 1 had BCG maintenance for 3 years, and developed NA. However, some cases above with post-BCG malignancy only had six- or eight-week BCG induction. Therefore, long duration of BCG therapy does not seem necessary to induce histological changes in urothelium. BCG dosage in the included studies ranged from 40 mg to 120 mg per instillation, no larger than the common practice. The interval between the initiation of BCG instillation and the identification of suspicious lesions on follow-up cystoscopy ranged from 6 weeks to 4 years. Eosinophilic cystitis was documented 6 weeks after BCG initiation. NA and some rare types of bladder cancer often appear more than 6 months after the start of BCG treatment.

Only half of the previously reported cases had information of symptoms after BCG instillation, from which we could not find local or systematic symptoms that have prediction value for pathology of post-BCG lesions. Although not all of the studies above detailed their exact locations, BCG-induced lesions tend to appear just on or close to the primary UC sites [8,16]. We noticed this phenomenon in all three cases as well.

TUR was usually employed to treat suspicious lesions after BCG. Eight of the eleven (72.7%) BCG-related benign bladder lesions selected by systematic review were removed by TUR. Two NA cases reported by Stilmant and Siroky [8] and all of our cases were given biopsy just on suspicious sites and did not have tumor recur during follow-up. In contrast, rare types of bladder cancer such as squamous cell carcinoma after BCG instillation easily developed lymph node metastasis and could be fatal even after radical cystectomy [26,27].

4. Discussion

This article presents a comprehensive analysis of a case series involving suspicious lesions that mimic cancer recurrence after intravesical BCG immunotherapy. We described their natural course of morphology and pathology over an extended period of time and conducted a systematic review of previous studies on benign and malignant BCG-related bladder lesions. Together with our experience, we find benign post-BCG bladder lesions often appear in close proximity to the primary tumor and cannot distinguish from cancer recurrence on cystoscopy, even with the use of NBI mode. They may persist for several years after BCG instillation. Neither symptoms after BCG instillation nor different BCG strains or schedules could predict their pathology. Nevertheless, once verified negative by biopsy and urine cytology, some of those lesions have a favorable long-term prognosis. Given our findings, we suggest that regular follow-up by cystoscopic biopsy and urine cytology could be an alternative to TUR or random biopsy in selected post-BCG lesions. We acknowledge that the small sample size of our study warrants caution in interpreting these results and drawing conclusions. Nonetheless, we believe our study provides valuable insights into the natural course of BCG-induced lesions and will aid urologists in making informed decisions.

This study distinguishes itself by providing detailed clinical information over a long-term follow-up period, a feature that is rarely seen in the existing literature on BCG-related bladder lesions. Only a few studies described the detailed information of appearance, size, and location of BCG-related bladder lesions. Lack of these information adds difficulties to analyze relations among primary bladder tumor, newly identified lesions, and BCG instillation. Aggressive preventions like TUR or cauterization will interrupt the natural course of the post-BCG lesions and limit our knowledge of their prognosis. The other feature of our study is the systematic search and review of post-BCG bladder lesions. Since previous studies focusing on the post-BCG lesion are scarce and have typically reported only one or two cases, the combination of our experience and the systematic review provides a more comprehensive and informative analysis. In the systematic review, the post-

BCG lesion, once confirmed benign by biopsy or TUR, had a good prognosis. These results are consistent and supplements to our experience. Though many urologists have encountered suspicious bladder lesions after BCG instillation, there are limited publications available to guide clinical decision-making. As far as we know, no similar study has been published before.

4.1. Pathological change after BCG instillation

Granuloma or granulomatous cystitis is believed a specific response of BCG treatment [29]. We find this pathology change in all of our cases, and we think that chronic inflammation featuring lymphocytes invasion and repairing process with vascular proliferation can last throughout BCG treatment or even longer. Bilen et al. [30] described pathological changes after intravesical BCG: all BCG-treated cases will develop chronic bladder inflammation and 17% will have granuloma formation. They did not find granuloma formation correlated with symptoms or cancer recurrence. However, this study did not have follow-up data for more than 2 years, nor did mention that NA can be a further pathological change. Stilmant and Siroky [8] believed NA was overlooked or misdiagnosed as cystitis cystica or glandularis in BCG-treated patients. In one of our cases, tumor-like lesion was confirmed NA, and remained so for several years. NA is perhaps the most common tumor-like lesions after intravesical BCG, and often identified 6 months or later after BCG initiation, indicating a late and chronic process. A review by Kunju [31] described NA appearances as papillary (56%), polypoid (10%), and fungating or sessile (10%) lesions. Kunju [31] also thought that the appearance of NA could mimic UC *in situ*. Hidoussi et al. [9] reported a rare case of eosinophilic cystitis after BCG instillation and reminded its tumor-like appearance.

An early study suggested that cystoscopic evidence of cystitis lasting more than 6 months after BCG completion was usually associated with cancer recurrence [32]. However, in our series, we observed chronic cystitis and tumor-like benign lesions could last for several years without tumor recurrence after BCG treatment, and longer maintenance of BCG does not necessarily provoke bladder lesions. A meta-analysis of our team found low-dose BCG can reduce the incidence of systemic side effects, especially fever and malaise; while local side effects (*e.g.*, cystitis) were comparable in the low and standard dose arms [33].

4.2. Second TUR and random bladder biopsy

Given the high recurrence rate of bladder cancer, second TUR is recommended in the following situations: incomplete initial TUR; no detrusor muscle in the specimen after initial resection, with the exception of Ta low-grade tumors and primary carcinoma *in situ* in T1 tumors [2]. For patients without definite indications for second TUR, the method for pathological analysis of post-BCG lesions is debatable. Active surveillance in cancer follow-up attracts increasing interest in recent years. In bladder cancer, the main purpose of active surveillance is to reduce the number of TUR and cost throughout the patients' life [34]. Many studies have showed the safety of active surveillance in the follow-up of low-risk bladder cancer [2]. On the contrary, a large survey of urologists suggested that routine biopsy is common after BCG instillation even without positive findings on cystoscopy and urine cytology [35]. Emerging evidence questions this routine practice. A meta-analysis including seven studies showed the cumulative negative predict value of normal cystoscopy and negative cytology was 95%, and the authors concluded that random biopsy can be spared in these patients [6]. Takamatsu et al. [12] has similar argument that random bladder biopsy is unnecessary for carcinoma *in situ* patients with normal cystoscopy and negative cytology after BCG instillation.

Our management of post-BCG bladder lesions is virtually an active surveillance strategy. For one thing, take biopsy only on suspicious lesions instead of random biopsy. For the other, take TUR of the post-BCG lesions once the biopsy or urine cytology confirmed cancer recurrence. Random bladder biopsy or more aggressive procedure TUR not only causes more traumas on bladder urothelium, but often requires general anesthesia, more cost, and anticoagulation cessation in elderly patients. Those inconveniences are more prominent in developing regions like China, where cystoscopy is usually taken under local anesthesia and with rigid cystoscope.

4.3. Mechanisms of BCG associated lesions

Primary carcinogens, surgical trauma together with BCG induced immune and inflammatory reactions have been considered risks for post-BCG bladder lesions. After instillation, BCG can attach to extracellular protein fibronectin and be internalized by urothelium, recruiting immune cells [36]. Tumor can be repressed by T cells from immunity with various cytokines such as IL-2, TNF-α, and BCG itself [37]. On the other hand, BCG is believed to have an additional effect on the pathogenesis of urothelial abnormality. BCG antigens can generate hypersensitivity reaction in acute eosinophilic cystitis [9]. Metaplastic reaction secondary to trauma, infection, or intravesical treatment has a role in chronic pathological change [18]. Therefore, post-BCG lesions in our cases and previous similar cases usually appear near or even on the site of primary UC. We suggest more attention be paid to the location of primary tumors when follow-up cystoscopy is taken. The relation between BCG side effects and anti-tumor effectiveness has not been concluded. Nonetheless, some researchers suggested symptoms of cystitis and bladder granuloma formation may indicate better BCG response [32]. Besides BCG instillation, anti-programmed cell death protein 1 or PD ligand 1 (PD-L1) treatment as another immunotherapy is on the rise. There is a study that attempts to predict the efficacy of PD-1 or PD-L1 inhibitors based on the principles of BCG treatment [38]. We agree that researches on BCG induced response can provide a unique reference for anti-programmed cell death protein 1 or PD-L1 treatment.

4.4. Limitations

This article details a series having post-BCG lesions with probably the longest follow-up and has a systematic review of previous cases. Still, we are aware of certain limitations

within. First, our own series had a relatively small sample size. Our major purpose was to observe the natural course of the post-BCG lesion. Therefore, we only included post-BCG lesions that lasted more than a year without another TUR or cauterization and had cystoscopic videos across the years. Cases met these criteria were rare. The sample size reminds us to take our conclusion with much caution. Further study with larger volume surely demands to verify the findings of this article. Second, like previously reported cases, we observed these tumor-like lesions after BCG but cannot attribute BCG as the only pathological cause. We believe more robust investigations, especially on molecular and cellular levels should be carried out to confirm the causal relationship. Third, cohort studies, especially prospective ones, are better designs to clarify the proper management of post-BCG lesions.

5. Conclusion

Combining our experience with the systematic review, though mimicking cancer recurrence, some post-BCG benign lesions like NA have a good prognosis in the long term. Biopsy on the suspicious sites with urine cytology during follow-up could be considered as a promising alternative to random biopsy. Studies with larger volume and random controlled design are surely needed to verify these results.

Author contributions

Study concept and design: Xing Ai, Chuanliang Xu.
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Data analysis: Huan Han, Ruixiang Song, Jinshan Xu.
Drafting of manuscript: Chong Ma, Shuxiong Zeng.
Critical revision of the manuscript: Chong Ma, Shuxiong Zeng.

Conflicts of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajur.2022.12.006.

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