Reiter's syndrome following intravesical Bacillus Calmette-Guerin therapy for bladder carcinoma: a report of five cases

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Abstract

Reiter's syndrome is known to be a rare severe adverse of Bacillus Calmette-Guerin (BCG) therapy. We report five cases of patients with Reiter's syndrome following intravesical BCG therapy for bladder carcinoma, and review the clinical characteristics, treatments, and outcomes of these patients. Each patient developed polyarthritides after urinary tract symptoms, and developed conjunctivitis anywhere from the third to the eighth BCG induction cycle. One case presented a slight elevation of inflammatory responses in blood analysis, and the other four cases had a higher level of white blood cell (WBC) counts and C-reactive protein (CRP) values. WBC counts at the diagnosis of Reiter's syndrome had a positive correlation with the time from initial treatment to cure of the disease. In all cases, BCG therapy was discontinued, and non-steroidal anti-inflammatory drugs (NSAIDs), oral steroids, and anti-tuberculosis drugs were administered. Anti-rheumatic drugs were not used in these cases. Improvement of symptoms was reported from 1 to 13 months after initial treatment. No patients had recurrence of Reiter's syndrome, whereas 2 patients had alternative treatment 2 and 18 months later, respectively, because of cancer recurrence. For cases with conjunctivitis and joint pain occurring during intravesical BCG therapy, early clinical interventions such as NSAIDs, steroids, and anti-tuberculosis drugs should be introduced, especially in cases with a high level of inflammatory changes in blood analysis.

Keywords Bladder carcinoma · Bacillus Calmette-Guerin · Reiter's syndrome

Introduction

Bacillus Calmette-Guerin (BCG) is a common agent used worldwide for the primary therapy of carcinoma in situ (CIS) of the bladder and the treatment of multiple non-invasive lesions [1]. It has been widely accepted that BCG therapy can decrease the risk of recurrence of tumor, and BCG maintenance therapy contributes to a decreased risk of progression for patients with high-grade non-invasive bladder cancer [1]. However, BCG has some common adverse

effects including cystitis-like symptoms, hematuria, general malaise, and fever [2].

Reiter's syndrome is a form of arthritis affecting the conjunctivae of the eyes, the urinary tract, muscles, skin, and joints [3]. It is a rare type of reactive arthritis and is known to be a rare severe adverse effect of BCG therapy [4–8]. In particular, it is extremely rare in Japan, with a reported incidence of 0.04%, compared to that in Western countries [7]. Therefore, limited information regarding the clinical management of Reiter's syndrome has been available. We had five cases of patients with Reiter's syndrome following intravesical BCG therapy for bladder carcinoma. In the present study, the clinical characteristics, treatments, and outcomes of these patients are reported, and previous papers about this rare adverse effect are reviewed.

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Case reports

Patient 1

A 77-year-old man complained of frequent urination, mild fever, conjunctivitis after the third BCG induction cycle, and developed polyarthritis of the knees and rib joints (Table 1). BCG therapy was discontinued, and steroid eye lotion and non-steroidal anti-inflammatory drugs (NSAIDs) were initially introduced. Clinical symptoms were improved 10 days after treatment. Frequent urination remained, but it was resolved 1 month later. The patient has no recurrence of carcinoma 24 months after complete remission of Reiter's syndrome.

Patient 2

A 62-year-old man complained of high fever, then conjunctivitis and polyarthritis of the hip, knee, and ankle joints with a high white blood cell (WBC) count and C-reactive protein (CRP) value after the fifth BCG induction cycle. The patient was immediately treated with oral steroids (prednisone 25 mg/day gradually tapered, over a period of 2 months, to 10 mg/day) and steroid eye lotion, in combination with NSAIDs. Two months after the initial treatment, the patients had completely responded to the therapy. The patient remains well with no evidence of recurrence for 24 months follow-up period.

Patient 3

A 63-year-old woman complained of micturition pain and polyarthritis in the neck, wrist, hip, and knee joints after the eighth BCG induction cycle, and subsequently she was diagnosed with conjunctivitis. The WBC count and CRP value were high. Oral NSAIDs, steroids (methylprednisolone 30 mg/day for 60 days), and isoniazid (INH) (300 mg/day for 14 days) resulted in improved clinical symptoms. Complete remission of reactive arthritis was achieved 2 months later. However, cancer recurrence was observed by cystoscopic examination, and the patient received TUR 2 months after complete remission of Reiter's syndrome, and then were obliged by cancer progression to receive total cystectomy 8 months after TUR.

Patient 4

A 56-year-old woman reported conjunctivitis and polyarthritis in the hip, knee, and ankle joints after the sixth BCG induction cycle. A much higher level of inflammatory changes in blood analysis compared to the other cases was

Table 1 Clinical characteristics of patients with Reiter's syndrome following BCG therapy

Case	Age	Sex	Pathology	WBC (μ l)	CRP (mg/dl)	Period up to BCG starting from TUR (weeks)	Number of BCG instillation	Period up to disease onset from initial BCG instillation (days)	Treatment	Period up to cure of disease from initial treatment (months)	Cancer outcome (periods of follow up)
1	77	M	UC, G2	7,560	2.2	2	3	21	NSAIDs	1	No recurrence (24 months)
2	62	M	UC G2>G1	10,370	26.7	4	5	43	NSAIDs+PSL	2	No recurrence (24 months)
3	63	F	UC, CIS G3	10,400	6.4	4	8	63	NSAIDs+PSL+INH	2	TUR, cystectomy (2 months)
4	56	F	UC, CIS G3>G2	12,200	17.6	12	6	36	NSAIDs+PSL+INH	3	No recurrence (48 months)
5	73	M	UC, CIS G2>G3	15,300	3.8	4	3	22	NSAIDs+PSL	13	TUR (18 months)

WBC white blood cell, CRP C-reactive protein, BCG Bacillus Calmette-Guerin, TUR transurethral resection, U/C urothelial carcinoma, G grade, CIS carcinoma in situ, TUR transurethral resection, NSAIDs non-steroidal anti-inflammatory drugs, PSL prednisolone, INH isoniazid

noted. The patient was treated twice with an injection of steroids into the joint, oral NSAIDs, oral steroids (prednisolone 30 mg/day then gradually tapered, over a period of 5 weeks to 5 mg/day), and an anti-tuberculosis drug (INH 300 mg/day for 33 days). Clinical conditions improved after steroids for 35 days and INH for 33 days, and her disease was judged to be cured 2 months after initial treatment. The patient has no recurrence of carcinoma 48 months after cure of Reiter's syndrome.

Patient 5

A 73-year-old man had gross hematuria, conjunctivitis, and polyarthritis of the neck and knee joints after the third BCG induction cycle. The patient was treated with oral NSAIDs and steroids (methylprednisolone 500 mg/day) for three and one-half months, and clinical symptoms were improving; however, chronic pain of both knee joints continued for over a year. Complete remission of disease was determined 13 months later. However, the patients had cancer recurrence 18 months after cure of Reiter's syndrome, and TUR was performed again.

Discussion

In 1916, Hans Reiter reported a triad of non-gonococcal urethritis, conjunctivitis, and arthritis. Named Reiter's syndrome, it is now regarded as a subtype of reactive arthritis [4]. Reiter's syndrome is diagnosed based on chronic inflammatory arthritis with the following three clinical conditions: arthritis; conjunctivitis of the eye; and inflammation of the genital, urinary, or gastrointestinal systems [5]. Arthritis symptoms following intravesical BCG therapy are characterized by asymmetry, multiple occurrence, and pain mostly in lower limb joints such as the knees and ankles [3, 5]. Reiter's syndrome is caused by systemic immunochemical responses against molecular mimicry between BCG and chondrocyte or conjunctiva, and generally conjunctivitis precedes arthritis [3, 5]. Indeed, all the cases have conjunctivitis prior to polyarthritis, and conjunctivitis is likely to be a predictive sign for Reiter's syndrome following intravesical BCG therapy.

In the current cases, Reiter's syndrome occurs anywhere from the third to eighth BCG induction cycle, which is consistent with the previous findings [5, 9]. Reiter's syndrome may also occur relatively early after initiating BCG therapy. However, in our experience, the period from initial BCG induction to the onset of Reiter's syndrome is not correlated with severity and prognosis of disease. Interestingly, WBC counts at the diagnosis of Reiter's syndrome are likely to be positively correlated with the period from initial treatment to cure of the disease, suggesting that WBC counts

may be an important predictor for severity and duration of disease. Some previous reports also described severe cases of arthritis and conjunctivitis with higher WBC counts and CRP values [4, 9].

For primary management of Reiter's syndrome following BCG therapy, systemic inflammation is usually well controlled by discontinuation of induction. In addition, NSAIDs, steroids, antibiotic agents, anti-tuberculosis agents, and anti-rheumatic drugs are recommended according to symptoms and severity. Generally, patients with mild symptoms respond easily to NSAIDs. In our first case with a lower level of blood inflammatory changes, clinical symptoms are immediately improved by oral NSAIDs alone. On the other hand, in cases with severe symptoms or unsatisfactory responses to NSAIDs, steroids should be promptly administered [10]. Delayed introduction of steroids may cause a progressive and prolonged disease course [11]. Furthermore, some previous reports suggest that anti-rheumatic drugs should be considered if there is a poor response to steroids [11, 12]. In our experience, the four cases (cases 2, 3, 4, and 5) with higher WBC counts immediately received oral steroid therapy for one to three and one-half months, and all these cases achieved cure of disease without the use of anti-rheumatic drugs. Therefore, the immediate introduction of steroids may be essential to reach an earlier curative recovery, especially in cases with a high level of inflammatory changes in blood analysis.

On the other hand, there is no consensus that the use of anti-tuberculosis drugs to manage Reiter's syndrome following BCG therapy is recommended. Some previous reports support the efficacy of anti-tuberculosis drugs because Reiter's syndrome may be a systemic immune reaction caused by chronic BCG infection in the urinary tract [11, 13]. A previous review of 101 cases in Japan over 13 years noted that anti-tuberculosis drugs were used in 43% of cases [8]. We used anti-tuberculosis drugs in addition to NSAIDs and steroids for two cases with a high level of inflammatory changes, and their symptoms were improved 2–3 months after treatment. It is an interesting question whether the administration of anti-tuberculosis drugs may have contributed to more immediate improvement for case 5, which has a much higher WBC count and a longer duration of residual symptoms. However, types of drugs, dosages, and the duration of therapy have been not clarified. In addition, it has not been clarified how anti-tuberculosis drugs should be administered to patients. Further studies will be needed to reach a more definitive recommendation.

In the present study, two of five cases were obliged by cancer progression or recurrence to receive TUR or total cystectomy after complete remission of Reiter's syndrome, whereas the other patient had no recurrence of bladder carcinoma. These findings suggest that the cases with Reiter's syndrome do not always have an increased risk for cancer

progression despite not completing the full course of BCG therapy. Reiter's syndrome is considered to be caused by extreme immunochemical responses against BCG stain [5], which may result in a favorable outcome for cancer progression in some cases. Indeed, many previous studies report the cases with no evidence of cancer progression after Reiter's syndrome following BCG therapy [7, 8, 11]. However, the relationship between incidence of Reiter's syndrome and cancer progression or recurrence had been not currently investigated. In addition, information including a long-term observation has been not available, and further studies will be required to reach a more definitive conclusion.

In conclusion, we report five cases of patients with Reiter's syndrome following intravesical BCG therapy for bladder carcinoma. For cases with conjunctivitis and joint pain after intravesical BCG therapy, early clinical interventions such as NSAIDs, steroids, and anti-tuberculosis drugs should be introduced, especially in cases with a high level of inflammatory changes in blood analysis.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflicts of interest.

Ethical standards The study was approved by the Kanazawa University Hospital Institutional Review Board, and was conducted according to the Ethical Guidelines for Medical and Health Research.

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