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Reiter's Syndrome Following Intravesical Bacillus Calmette-Guérin Immunotherapy for Bladder Carcinoma *in situ*

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SUMMARY

Intravesical Bacillus Calmette-Guérin (BCG) immunotherapy after transurethral resection of non-muscle-invasive bladder cancer has been proven to reduce the recurrence and progression of the disease. Unfortunately, the treatment is associated with adverse effects that can induce other chronic health problems, such as Reiter's syndrome. In this case report, we present a 74-year-old patient from Croatia who developed Reiter's syndrome after intravesical BCG instillations. Clinical diagnosis was based on symmetric knee arthritis following bilateral conjunctivitis and urethritis. Symptoms of arthritis did not improve with nonsteroidal anti-inflammatory drugs and steroid injections to the knees. Consequently, an immunologist was consulted and Reiter's syndrome was confirmed. Oral glucocorticoids were administered, followed by full recovery of the patient's symptoms. Even though Reiter's syndrome is uncommon, it is a significant complication resulting from BCG immunotherapy. It should be immediately recognized and appropriately treated.

KEYWORDS

Reiter's syndrome; Bacillus Calmette-Guérin; Immunotherapy; Arthritis

Introduction

Carcinoma *in situ* (CIS), a type of non-muscle-invasive bladder cancer (NMIBC), is a flat, noninvasive lesion confined to the urothelium. It is regarded as a precursor to the development of invasive high-grade cancer[1]. If left untreated, 40% to 83% of CIS patients will develop muscle invasion, especially if associated with papillary tumors[2].

Intravesical instillation of Bacillus Calmette-Guérin (BCG) is commonly used to treat CIS and multiple noninvasive lesions of the bladder[3]. BCG therapy affects tumor cells directly and stimulates the patient's immune system[4]. Following transurethral

resection of the tumors (TURBT), intravesical BCG therapy reduces the recurrence and progression of the tumor in patients with CIS[3]. Intravesical BCG instillations are used weekly, over the course of 6 weeks, as induction treatment. Maintenance treatment is undertaken after a pause of 4 to 6 weeks if the patient shows good response to therapy. It consists of one instillation weekly for 3 weeks, every 3 months for at least 1 year, and then up to 3 years. This is one of the recommended schedules for intravesical BCG instillations because there is no uniform consensus for BCG instillation regimen to date[5].

A rare but severe adverse effect of BCG therapy is Reiter's syndrome. It includes the following triad of symptoms: arthritis, conjunctivitis, and urethritis. Only one-third of patients develop the standard triad of symptoms. Polyarthritis usually follows initial urinary tract symptoms, such as urethral discharge. The severity of symptoms varies widely and 15% to 20% of patients develop a chronic disease[6,7].

Case report

A 74-year-old male patient was admitted due to recurrent painless visible hematuria for the past 3 months. His medical history showed no major procedures. He took drugs for arterial hypertension and benign prostatic hyperplasia. His prostate-specific antigen level was normal. Digital rectal examination showed no suspected malignancy.

Previous workup included urine cytology which was positive for malignant cells. He had a computed tomography scan that showed thickening of the urinary bladder wall lateral to the left vesicoureteric junction in the length of 3.2 cm, with the widest part up to 8 mm. Both kidneys had a couple of Bosniak II cysts. Both ureters showed normal anatomy. There were no enlarged lymph nodes (Fig. 1).

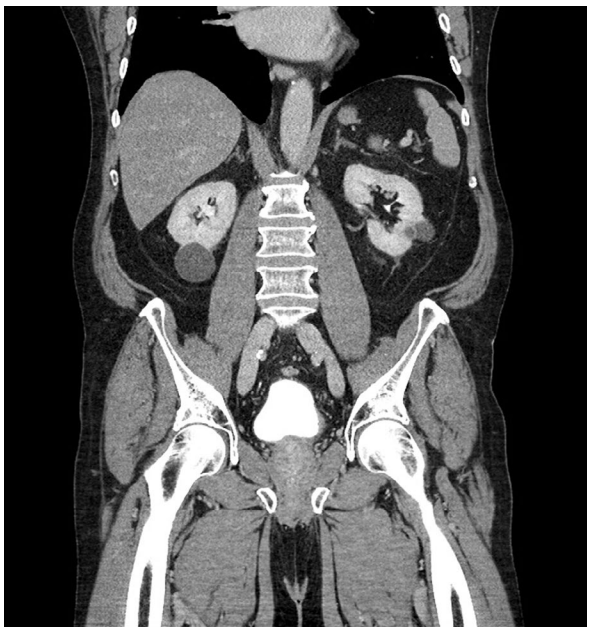

Fig. 1. Thickening of the urinary bladder wall lateral to the left vesicoureteric junction.

Cystoscopy was performed to show a velvet-like, slightly elevated area 2 cm from the left vesicoureteric junction. Consecutively, TURBT was performed. He did not receive postoperative intravesical chemotherapy. The histopathologic diagnosis was CIS with a small focus of papillary urothelial neoplasm of low malignant potential. According to histopathologic diagnosis, he was stratified in the highest-risk tumor subgroup and was therefore scheduled for intravesical BCG immunotherapy. Induction BCG instillations were administered according to a 6-weekly schedule. He had no side effects to the induction therapy.

Urine cytology at 3 months showed no malignant cells. The 3-month cystoscopy showed scarring after TURBT with small areas of suspicious mucosa around the scar. Bladder biopsy of the suspicious area was taken and a few more were taken in random fashion (urethra included). All the biopsies were negative for CIS.

Therefore, maintenance therapy was administered for three weeks. After the third instillation,

the patient reported symptoms of urinary infection. Nonsteroidal anti-inflammatory drugs (NSAIDs) were administered but there was no improvement. Therefore, urine culture was performed and the empirical antibiotic treatment with ciprofloxacin was started. Follow-up urine culture was negative. His response to treatment was good, with complete regression of urinary symptoms, and he was scheduled for cystoscopy in 3 months.

A month later, he presented with crutches and barely able to walk. Medical history revealed that both of his knees were swollen two weeks after the last instillation. He visited an orthopedic surgeon who performed physical examination and found effusion in the right knee along with a reduced range of motion and painful terminal flexion. The left knee was palpably painful in the medial joint fissure with a reduced range of motion, but without effusion. Bilateral knee radiograph showed advanced degenerative changes of both knees with medial joint space narrowing caused by osteophytes. Orthopedic surgeon diagnosed him with bilateral osteoarthritis and prescribed NSAIDs with recommendation of performing thigh muscle exercises and gait with forearm crutches. The condition worsened, so the orthopedic surgeon performed glucocorticoid injection into the joints. Since there was still no improvement, he referred the patient to our office. According to medical history data, we found that the patient also had mild bilateral conjunctivitis prior to arthritis, treated by general practitioner, to which the patient did not pay much attention due to much greater arthritic problems afterwards.

Noninfectious urethritis, bilateral conjunctivitis and oligoarthritis combined raised suspicion of Reiter's syndrome. Consequently, the patient was referred to an immunologist who performed physical examination and found mild effusion of both knees, painful on pressure, with impaired extension of both knees. Laboratory blood tests showed a high level of inflammation (leukocytes 14.03×10^9/L, C-reactive protein 106 mg/dL). Ultrasound of the knees revealed bilateral effusion, heavier in the right knee in the suprapatellar recess and parapatellarly up to 7 mm with thickened synovium, and bilaterally enhanced flows, degree II/III, during power Doppler imaging. Based on these findings, the immunologist confirmed the diagnosis of Reiter's syndrome. Since the patient did not respond adequately to NSAID and glucocorticoid injections into the joints, oral glucocorticoid was administered. On the first three days, he was prescribed 32 mg of methylprednisolone daily, followed by 16 mg for seven days, 8 mg for the next seven days, and ultimately 4 mg for the last fourteen days, then discontinued. Six weeks after discontinuation of glucocorticoid therapy, physical examination showed good clinical response confirmed with minor suprapatellar swelling in the right knee, with minimal swelling in the left knee. Follow-up laboratory tests showed low levels of inflammatory parameters (leukocytes 8.6×10^9/L, C-reactive protein 6.6 mg/dL). Therefore, a second course of oral glucocorticoid was administered. On the first seven days, he was prescribed 8 mg of methylprednisolone daily, followed by 4 mg over the next fourteen days. Complete remission of all symptoms of Reiter's syndrome was recorded six months after completion of the second course of oral glucocorticoid therapy.

The patient did not receive another BCG maintenance therapy. The 6-month, 9-month and 12-month cystoscopies showed no evidence of tumor recurrence.

This case report was approved by the Merkur University Hospital Ethics Committee. The patient signed informed consent for participation in the study and for publication of his medical data.

Discussion

Reiter's syndrome typically occurs one month after a genitourinary or gastrointestinal infection. It is a subtype of reactive arthritis characterized by triplet of symptoms consisting of seronegative arthritis, noninfectious urethritis, and conjunctivitis[8]. After excluding other common causes of reactive arthritis, diagnosis of Reiter's syndrome is based primarily on medical history and physical examination, due to the lack of specific unequivocal laboratory or radiologic findings. In the absence of specific confirmatory test, only one exclusion test should be performed, and that is synovial fluid analysis in order to rule out septic or microcrystalline arthritis.

The syndrome can also be a rare side effect after BCG instillation, i.e., a part of the well-established therapy for urinary bladder CIS tumors. It is interesting that almost all patients have conjunctivitis before the onset of arthritis, which could be an indicating sign of forthcoming Reiter's syndrome. Even though intravesical BCG instillation may cause mild arthralgia, only 0.5%-1% of patients develop severe reactive arthritis. There is no correlation of the number of instillations or interval between the procedures and onset of symptoms with symptom intensity or duration. Two main forms of arthritis associated with Reiter's syndrome are symmetric or asymmetric polyarthritis of either small or large, upper or lower joints *versus* asymmetric mono-oligoarthritis involving large joints of lower extremities. There is a lack of uniform therapeutic regimen to date, but it is reasonable to discontinue further instillations and start with NSAIDs as first-line therapy. Second-line therapy mainly consists of glucocorticoids. The usage of anti-tuberculosis drugs, including type and number of drugs, dosage regimen, and route and duration of administration is not uniformly defined[9,10]. There is one significant review of anti-tuberculosis drugs used in 43% of 101 patients, which supports the effectiveness of anti-tuberculosis drugs[11]. Despite that, recommendations related to the use of anti-tuberculosis drugs in patients with Reiter's syndrome after intravesical BCG instillation cannot be made at this point.

In our patient, Reiter's syndrome occurred progressively during maintenance BCG therapy. The primary urinary tract symptom was initially unrecognized urethritis that went into remission after antibiotic and anti-inflammatory therapy. Limited awareness of Reiter's syndrome immediately after noninfectious urethritis following BCG instillations led to the development of serious clinical condition consisting of bilateral conjunctivitis and oligoarthritis. High levels of leukocytes and C-reactive protein indicated a severe form of arthritis along with intensified, longer lasting Reiter's syndrome, similar to previous reports[9,12]. During diagnostic work-up, there was a lack of synovial fluid analysis to rule out septic or microcrystalline arthritis. In this patient, glucocorticoid therapy was administered at the discretion of immunologist. After completion of oral glucocorticoid therapy, the symptoms resolved completely, in accordance with the diagnosis of Reiter's arthritis.

Conclusion

Reiter's syndrome is a rare complication of BCG intravesical therapy, which is challenging to diagnose if all the symptoms are not present at the time of the patient's arrival in the office, but with the typical triad of symptoms, the diagnosis is straightforward, and the condition is easily treated with proper therapy. ■

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SAŽETAK

Reiterov sindrom nakon intravezikalne imunoterapije pomoću Bacillus Calmette-Guérin kod bolesnika s karcinomom *in situ* mokraćnog mjehura

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Intravezikalna imunoterapija Bacillus Calmette-Guérin (BCG) nakon transuretralne resekcije mišićno neinvazivnog karcinoma mokraćnog mjehura dokazano smanjuje povrat i progresiju bolesti. Nažalost, ovaj oblik liječenja može imati za posljedicu nuspojave koje mogu dovesti do kroničnih zdravstvenih problema poput Reiterova sindroma. U ovom prikazu slučaja predstavljamo 74-godišnjeg bolesnika iz Hrvatske u kojega se razvio Reiterov sindrom nakon intravezikalne instilacije BCG-a. Dijagnoza je uspostavljena na temelju simetričnog artritisa koljena, bilateralnog konjunktivitisa i uretritisa. Simptomi artritisa nisu se povukli usprkos liječenju nesteroidnim protuupalnim lijekovima i intraartikularnim injekcijama kortikosteroida. Slijedom navedenog konzultiran je imunolog te je potvrđena dijagnoza Reiterova sindroma. Započeto je liječenje oralnim kortikosteroidom nakon čega su se simptomi u potpunosti povukli. Usprkos tome što je Reiterov sindrom rijetka nuspojava, predstavlja značajnu komplikaciju imunoterapije BCG-om. Treba ga pravodobno prepoznati i ispravno liječiti.

KLJUČNE RIJEČI

Reiterov sindrom; BCG; Imunoterapija; Artritis