A RARE COMPLICATION OF BCG IMMUNOTHERAPY

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Abstract: Intravesical Bacillus Calmette-Guérin immunotherapy is an effective agent for superficial bladder carcinoma. The main adverse effect of this treatment is cystitis. Arthralgia and migratory arthritis occur only in 0.5% of patients. Reiter syndrome is a very rare complication that can occur after intravesical apply of Bacillus Calmette-Guérin Immunotherapy. We report the first Albanian patient who developed Reiter's syndrome, following intravesical Bacillus Calmette-Guérin. Diagnose of Reiter's Syndrome was clinically based, excluding every other reason that could have caused it. Treatment was made with non-steroid and steroid anti-inflammatory drugs, followed by a full recovery result. Even though Reiter's Syndrome is a rare, but significant complication of BCG immunotherapy, it's important to identify it in time, in order we to offer an adequate treatment.

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Introduction

Bacillus Calmette-Guérin (BCG), a live attenuated strain of *Mycobacterium bovis*, is the only agent approved for primary therapy of carcinoma in situ of the bladder. BCG therapy also reduces the risk of recurrence and the risk of progression in patients with high-grade non-muscle invasive bladder cancer (Syelvester et al., 2002).

Intravesical BCG is used as first-line therapy for carcinoma in situ of the urinary bladder. BCG therapy showed a complete response rate of 60-68% (Syelvester et al., 2002; Barmoshe et al., 2004). Persistent disease after a complete course of therapy is cause of concern (Herr et al., 1989).

However severe side effects continue to be reported in the literature. The most frequent local side effects are: cystitis in 35 % of cases, bacterial infections in 23,6 % of cases and macroscopic hematuria in 22 % of cases (Brausi et al., 2014). Fever and general malaise are the most frequent systemic side effects (Decaestecker et al., 2015).

The relationship between BCG and its side effects can be made easily, if clinical manifestations occur shortly after the administration of this therapy. Mild and short arthralgias, without consequences, occurs regularly during a BCG course. Reiter's syndrome is a very rare adverse side (Saporta et al., 1996; Pancaldi et al., 1993; Palnæs Hansen et al., 1997; Hogarth et al., 2000; Murata et al., 2004). Reiter's Syndrome is clinically presented with triad of symptoms: urethritis, arthritis and conjunctivitis. Diagnose must be done clinically; it's very difficult to confirm diagnose by a specific test. This is important for not delaying treatment.

The aim of this article is to describe the first Reiter's Syndrome Albanian case following intravesical BCG immunotherapy.

Material

We report the case of a patient who developed Reiter's syndrome following intravesical BCG installations.

Case report

A male 39-years old patient, resident in Tirana, presented at Infectious Diseases Clinic, University Hospital Center of Tirana on June 13, 2016 with a 10 days history of dysuria, urethral discharge, high fever, bilateral red and itchy eyes and arthralgia including the left knee and talocrural joints. No previous rheumatologic disease was reported by the patient.

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On December 2015 he was firstly diagnosed with bladder carcinoma (high grade papillary urothelial carcinoma. The cancer was grown in the inner lining of bladder into the lamina propria and there was no evidence of muscularis propria invasion, lymph nodes or any other organ – T1, N0, M0). He had received weekly six intravesical installations of BCG and 3 months later he started the three weekly maintenance immunotherapy of BCG.

Figure 1: Swelling of genus and talocrural joints

Source: Authors

On the day of the third installation, he did not perform immunotherapy and was hospitalized in our clinic. On examination he had swollen painful joints, especially of genus and talocrural (fig 1) with limited movements and bilateral conjunctivitis (fig 2). He had no signs of urogenital lesions.

Figure 2. Conjunctival inflammation

Source: Authors

On blood tests we noticed leucocyte count of $14900/\text{mm}^3$, *E. Coli* was grown in urine culture, urethral smear and STD tests were negative, Interferon gamma was negative also. Inflammatory tests were high erythrocyte sedimentation rate (ERS) 40mm/h, fibrinogen 736 mg/dl, C-reactive protein (CRP) 92 mg/dl. His left knee was presented with effusion on ultrasound. Diagnose was based on clinical manifestations, rheumatologist also confirmed it.

Initially we started treatment with NSAIDs and antibiotics (ciprofloxacin), but symptoms persisted, so 5 days after we started steroids (prednisolone). He was not put on therapy with anti-tubercular drugs. His conjunctivitis and urethritis were resolved 5 days after, and his arthritis after 20 days of treatment.

Discussion

Intravesical BCG is used as first-line therapy for carcinoma in situ of the urinary bladder. Cystitis, bacterial infections and macroscopic hematuria are the most common adverse effects that accompany

this treatment. More undesirable side effects are uncommon and include granulomatosis prostaticitis, which can be an asymptomatic finding in 20% to 30% (Spence et al., 2006). Reiter's Syndrome is a very rare complication that can be seen during this treatment. The syndrome developed after the third to eighth BCG intravesical administration, with conjunctivitis, aseptic urethritis and polyarthrititis (Murata et al., 2004). Our patient developed Reiter's syndrome on week third, 2 weeks after he restarted immune therapy with BCG, as a maintenance treatment, after he had performed successfully first six weeks therapy.

He interrupted therapy after the third application because he demonstrated bilateral conjunctivitis, swelling of genus and talocrural articulations. The presence of large joint oligoarthritis, urogenital tract infection and uveitis characterize Reiter's syndrome as a clinical subtype of reactive arthritis (Selmi et al., 2014). The diagnose was supported epidemiologically (a live attenuated strain of *Mycobacterium bovis* was intravesical instilled), clinically (triad of symptoms: nongonococcal urethritis, inflammatory asymmetric arthritis, conjunctivitis) and laboratorically with high inflammatory tests (ESR, CRP), which later return to normal range when the inflammation subsided.

There is no confirmatory laboratory or radiological test that can confirm diagnosis. In addition, there are also differential diagnoses of gout, gonococcal urethritis and psoriatic arthritis that must be excluded. In our case the syndrome was diagnosed based on consultations with rheumatologist.

Cessation of the intravesical BCG immunotherapy in these cases is perhaps the most important treatment together with medications aimed for symptomatic relief (Keng Lim Ng et al., 2017). Treatment of Reiter's syndrome usually revolves around providing symptomatic relief and this includes bed rest, NSAIDs, and eye ointments. Non-steroid and steroid anti-inflammatory drugs are effective in the majority of the cases with the recovery within 2 and 6 months, respectively of 70% and 93% of the patients (Bernini et al., 2013). These general symptomatic measures often will provide the remission of symptoms.

Initially our patient started treatment with non-steroidal anti-inflammatory drugs. On fifth day of the therapy, no improvement of signs and symptoms was seen. Then we continued treatment with prednisolone. Corticosteroids improved conjunctivitis and urethritis in five days, and arthritis in 3 weeks. Occasionally, steroids with or without isoniazid or rifampicin may be started if the symptoms prolong or worsen (Murata et al., 2004). There is no consensus for antibiotics use, but the urine culture of our patient was positive and *E. Coli* was grown, so we used Ciprofloxacin for 10 days. Our patient remained asymptomatic, without medication during last year of follow-up.

Conclusion

The side effects can occur at any moment from the first instillation to the last one. This makes the diagnose easier for the cause effect relationship is more evident. Even Reiter's Syndrome is a quite rare complication of BCG treatment, it must be considered in order we to be in time for early diagnose and treatment of the patient.

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