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BCGitis after Bacille Calmette-Guerin intravesical administration from two referral centers: clinical characteristics and risk factors

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SUMMARY

Bacillus Calmette-Guerin (BCG) is commonly and safely used as intravesical instillation to treat bladder cancer. Adverse effects are widely described in case report and series with a broad range of clinical presentations known as "BCGitis". Moreover, microbiological identification is often inconclusive leading to diagnostic uncertainty and no standardisation of definitions is available. We retrospectively collected all cases of BCGitis (n=19) after BCG intravesical administration occurred in 2 major Italian hospitals in the last 10 years. Median age was 71.8 years and among comorbidities hypertension affected 60% of patients. The delay in the onset of symptoms was < one week and an inverse correlation was observed between the number of instillations and the time to the onset of symptoms. Moreover, a febrile presentation was the commonest clinical symptom (85%) and an interstitial or micronodular pattern at chest X-ray or CT scan was found positive in about 70% and 90% of cases, respectively. Larger cohorts are needed in order to inform clinically relevant algorythms for this uncommon disease.

Keywords: BCG, BCGitis, bladder, instillation, epidemiology.

INTRODUCTION

Bacillus Calmette-Guerin (BCG) is commonly used as an intravesical immunotherapy to treat superficial bladder cancer, accounting for approximately 550000 new cases/year [1]. BCG is a live, attenuated strain of *Mycobacterium bovis* originally used for vaccination against tuberculosis, but it has been used in the treatment of bladder cancer since 1976 after the positive results published by Morales and colleagues [2]. This therapy exploits the local interaction with the immune system after the instillation of BCG in order to elicit the anti-tumor immune response and it represents the first *ante litteram* "cancer immune therapy". Several reports have described its efficacy as an alternative to chemotherapy, making it currently the gold standard in the treatment of non-muscle-invasive bladder cancer (NMIBC) with a high risk of progression and a potential treatment of intermediate-risk NMIBC [3]. It is considered safe, but adverse effects are widely reported [4]. Most commonly patients experience local bladder symptoms including dysuria and haematuria, but also systemic adverse reactions are reported. [5] Among the systemic complications described in the Literature, we may list active tuberculosis (typically associated with a

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miliary pattern), BCG sepsis, hepatitis, nephritis, meningitis, arthritis, osteomyelitis and also the hypothesis that BCGitis might be due to a systemic immune reaction in place of a direct mycobacterial pathogenic effect has been proposed.
There are several case reports describing complications after BCG instillation and a few case series, the last one published in 2021 in Italy [3, 6-12]. In addition to the broad range of clinical presentations, the difficulty in obtaining direct microbiological demonstration of the mycobacterium and the lack of indirect diagnostic tests lead to diagnostic uncertainty and under reporting. Moreover, to date no standardisation of definitions is available averting the possibility to confront different retrospective series and to design future prospective studies. For these reasons, we decided to propose a new operational diagnostic criteria classification and to collect all confirmed or suspected cases of BCGitis after BCG intravesical administration occurred in 2 major Italian hospitals in the last 10 years.

PATIENTS AND METHODS

We retrospectively collected all confirmed or suspected cases of mycobacterial infection observed after BCG intravesical administration from 1st January 2008 to 31st December 2017 in two Infectious Diseases Centers in Northern Italy ("Amedeo di Savoia Hospital", University of Torino, Torino and "San Gerardo Hospital", ASST Monza, Monza). The study was approved by both Institutions Ethical Committees.
Inclusion criteria were: age >18 years, at least one BCG intravesical administration received and at least one diagnostic criterion for BCGitis, defined as follow:

1) persisting fever, dyspnea or cough after other causes exclusion OR persisting fever, dyspnea or cough with positive response to antimicobacterial treatment (possible BCGitis);
2) suggestive chest X ray or CT scan AND positive smear for alcohol-acid fast bacilli on sputum or bronco-alveolar lavage (likely BCGitis);
3) positive blood or bronco-alveolar lavage cultures for *Mycobacterium bovis* (confirmed BCGitis).

Data collection from clinical records included: demographic information (age, gender, ethnicity), co-morbidities, bladder carcinoma stage according to both WHO (high or low grade) and TNM scoring system (T1: non-invasive, T2-T3-T4: invasive), use of urinary catheter for BCG administration, previous chemotherapies, number of BCG instillations, delay in symptoms onset from last BCG instillation, clinical symptoms of BCGitis (fever, cough, dyspnea, other), chest X ray and CT scan pattern, laboratory findings including full blood count and liver (total and direct bilirubin, aspartate and alanine transaminase, gamma-glutamyl transferase, alkaline phosphatase) and kidney function (EGFR, creatinine), microbiological data (polymerase chain reaction on sputum and bronchoalveolar lavage; sputum and bronchoalveolar lavage smear for acid-alcohol-fast bacilli; blood and bronchoalveolar lavage cultures for *M. bovis*), treatment of BCGitis and outcome.
For descriptive analysis, continuous variables were summarized as median and inter-quartile range (IQR) while categorical variables were described as frequencies and percentages; non-parametric tests were used for correlations. Statistical analyses were conducted by IBM, SPSS software package ver. 26.0 (Chicago, IL, USA).

RESULTS

We identified 19 male patients between 2010 and 2019: median age was 71.8 years (67.5-80.0) and seventeen (89.5%) were of European ancestry. Several co-morbidities were recorded with the most prevalent being hypertension (10/17), diabetes/glucose intolerance (6/17), COPD (4/17), ischemic heart disease (4/17) and occlusive peripheral arterial disease (4/17). Urinary catheters were used by 2 participants (10.5%). Bladder carcinoma stage was high-grade in 14/17 (82.3%) with 12/15 (80%) having a T (of TNM scoring system) above 1.
Patients had received a median of 7 (4-10) intravesical BCG instillations. Symptoms appeared within one day after the last BCG instillation in the majority of individuals with two having a delayed onset (one at 5 and one at 7 days). An inverse correlation was observed between the number of instillation and the time to the onset of symptoms: the more the quicker (rho=-0.785, p=0.01) (Figure 1 and Table 1).
At clinical presentation patients presented with fever (84.2%), urinary symptoms (26.3%), dyspnea (21.1%) and cough (10.5%) plus individual non-specific symptoms (chills, arthralgia, confusion). Chest X-ray and CT-scan revealed an inter-

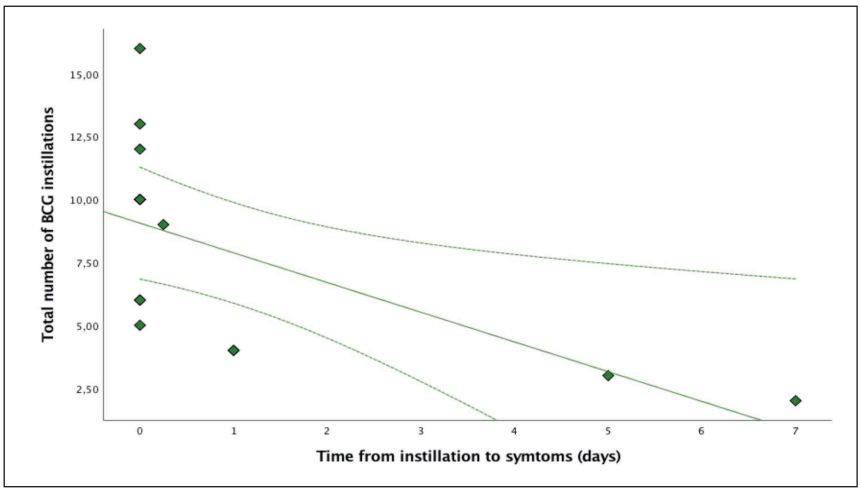

Figure 1 - Inverse correlation between the number of instillation and the time to the onset of symptoms (rho=-0.785, p=0.01).

Table 1 - Characteristics of the study population (N=19).

	N (%) or median (IQR)
Age	71.8 (67.5- 80.0)
European ancestry	17/19 (89.5)
Comorbidities	
Hypertension	10/17 (58.8)
Diabetes/glucose intolerance	6/17 (35.2)
COPD	4/17 (23.5)
Ischemic heart disease	4/17 (23.5)
Occlusive peripheral arterial disease	4/17 (23.5)
Urinary catheter use	2 (10.5)
Bladder carcinoma stage	
High-grade (WHO stage)	14/17 (82.3)
T >1 (TNM scoring system)	12/15 (80.0)
Intravesical BCG instillations	7 (4-10)
Clinical symptoms at onset	
Fever	16/19 (84.2)
Urinary symptoms	5/19 (26.3)
Dyspnea	4/19 (21.1)
Cough	2/19 (10.5)
Interstitial or micronodular pattern	
Chest X-ray	12/17 (70.6)
Chest CT-scan	16/18 (88.9)
Organ involvement	
Pulmonary	13/19 (68.4)
Disseminated (including lungs)	5/19 (26.3)
Treatment including	
Rifampicin	18/18 (100)
Isoniazid	17/18 (94.4)
Ethambutol	16/18 (88.9)
Moxifloxacin	7/18 (38.9)
Clinical response after 6 months follow-up	8/9 (88.9)

stitial or micronodular pattern in 12/17 (70.6%) and 16/18 (88.9%) patients. One patient had a negative chest CT-scan the day symptoms started but a nodular pattern was observed 14 days afterwards (Figure 2).

The majority of participants had either pulmonary (13, 68.4%) or disseminated (including lungs involvement, 5, 26.3%); one patient had uniquely a urinary involvement (with a pelvic abscess). Laboratory investigations were within the range of normality with the exception of moderately elevated liver function tests: aspartate and alanine transaminase were 46 (25-100) IU/L and 53 (40-80) IU/L.

A diagnosis of likely BCGitis was made without identification of BCG either on respiratory or blood samples. Antimycobacterial treatment was started in all but one participant and included rifampicin (18, 100%), isoniazid (17, 94.4%), ethambutol (16, 88.9%) and moxifloxacin (7, 38.9%). An initial clinical response was observed in all patients with 6 months outcome available in 9 (8 cured, 1 relapse). The patient who relapsed was immunocompetent and received a dose of 600 mg of rifampicin (body weight 75 kg; 8 mg/kg), isoniazid 300 mg and ethambutol 1200 mg. Self-reported treatment adherence were adequate and no malabsorption was recorded. Even though major and moderate drug-drug interactions are described among rifampicin and concomitant medications such as amiodaron, simvastatin and omeprazole, these are not known to decrease rifampicin plasmatic levels. Moreover, no further instillation was administered after BCGitis onset.

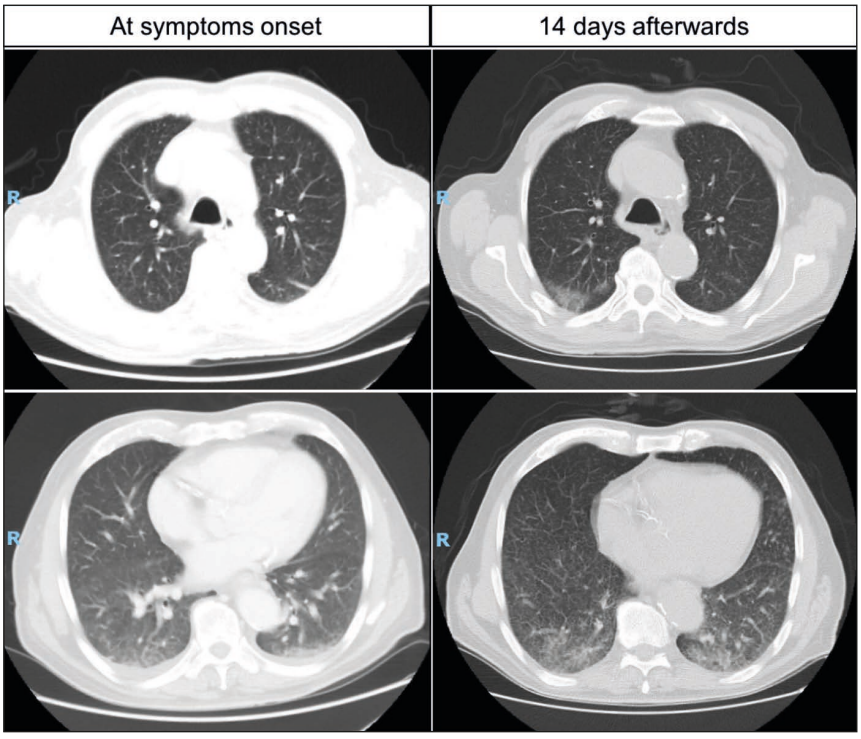

Figure 2 - Negative chest CT scan at symptoms onset and nodular pattern 14 days afterwards.

DISCUSSION

We presented 19 cases of likely BCGitis describing one of the largest case series to date. Nevertheless, a significant limitation of our and other studies on this subject is represented by the relatively rareness of the event "BCGitis" thus preventing a robust assessment of risk factors and prognosis. In our study, the majority of patients with BCGitis were elderly with a median age over 70 years old. Among comorbidities, none of them was particularly prevalent a part of hypertension that affected almost the 60% of patients. Even though previous case reports had identified the traumatic use of urinary catheter as a possible risk factor to develop BCGitis after intravesical instillations, we did not confirm this finding since only 10% of our participants were using this device [6-12]. On the other hand, since our small cohort is retrospective, we are not able to recall if any traumatic catheterization occurred in the rest of the population who did not permanently wear a urinary catheter. Nonetheless, the role of intravesical traumatism and consequent mucosal disruption might still represent a potential risk factor in the development of BCG dissemination. In fact, we found that the vast majority showed a high-grade tumor according to WHO classification and at the same time higher T than 1 according to TNM classification. This high local invasiveness might cause a damage in the bladder mucosa accounting for a higher risk of BCG systemic spread through the blood stream.

Interestingly, in our case series the delay in the onset of symptoms was very short, less than one week, and an inverse correlation was observed between the number of instillations and the time to the onset of symptoms. This finding, taken together with the absence of microbiological isolates in our population, might support the hypothesis of a hypersensitivity reaction at the base of the pathogenesis and clinical presentation of BCGitis, over the hypothesis of a reactivation of the inactivated strain of BCG. Nevertheless, the latency from the onset of symptoms to a clinically relevant syndrome including a radiological correlate might last up to 14 days, as our case might suggest with a negative chest CT-scan the day symptoms started but a nodular pattern observed 14 days afterwards (Figure 1). Even though no case

met our diagnostic criteria of confirmed BCGitis and we collected only likely BCGitis with probably missing cases due to the retrospective design of the study, we observed that the majority of cases presented with a pulmonary involvement. Furthermore, an interstitial or micronodular pattern at chest X-ray or CT scan was found positive in about 70% and 90% of cases, respectively. In addition, a febrile presentation at the onset was the commonest clinical symptom being positive in almost 85% of cases. The positive and negative predictive values of these criteria in the diagnosis of BCGitis need to be investigated in larger cohorts in order to inform clinically relevant algorithms for this uncommon disease. Moreover, optimal dose and number of drugs and treatment duration is currently unknown.

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Ethical statement
The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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