Miliary pulmonary infection after BCG intravesical instillation: a rare, misdiagnosed and mistreated complication

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SUMMARY

Intravesical Bacillus Calmette-Guérin (BCG) immunotherapy decreases the progression risk of non-muscle-invasive bladder cancer, but potentially yields a broad spectrum of side effects. We report the case of a 73-year-old man affected by miliary pulmonary BCG infection, whose microbiological diagnosis was probably hindered by empiric fluoroquinolones, focusing on imaging and clinical work-up.

Keywords: Bacillus Calmette-Guérin (BCG), bladder cancer, miliary infection, fluoroquinolones, adverse drug reactions.

INTRODUCTION

Urothelial Bladder Cancer (BC) is the 11th most diagnosed malignancy, 3 out of 4 being non-muscle-invasive (NMIBC) [1]. The bacillus Calmette–Guérin (BCG) vaccine, a live attenuated strain of *Mycobacterium bovis*, was first introduced in humans in 1921 and intravesical BCG immunotherapy is indicated in high- and intermediate-risk NMIBCs, as it decreases the risk of progression and enhances disease-specific and overall survival [2, 3].
Nonetheless, BCG administration may be associated with a broad spectrum of side effects. Overall, their incidence ranges from 69.5% to 91%, including chemical cystitis, while major adverse reactions occur in less than 5% of the cases [4]. Among severe systemic manifestations, sepsis, granulomatous hepatitis, miliary pneumonitis, bone marrow involvement, soft tissue infections, vascular aneurysms, arthritis and uveitis are described [5].
Pulmonary involvement is a rare complication occurring between 0.3 and 0.7% of treated patients, presenting as interstitial pneumonitis or miliary dissemination [4, 6]. Only a few cases of miliary BCGitis have been reported. The suggested first-line treatment is the combination of isoniazid, rifampicin, and ethambutol for 6 months, since *M. bovis* is intrinsically resistant to pyrazinamide, and low-level isoniazid resistance has been described in some strains [7, 8].
Currently, no clear and standardized recommendations are present regarding the diagnostic work-up in case of miliary pulmonary BCGitis suspicion. We report a case of miliary pulmonary BCGitis, complicated by sub-clinical pulmonary thromboembolism, focusing on the diagnostic workup and on the diagnostic delay perhaps due to initial empirical treatment with fluoroquinolones.

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CASE REPORT

A 73-year-old man presented to the accident and emergency (A&E) department of our hospital in March 2016, reporting intermittent fever with evening peak of 39°C, arisen few hours after the last BCG instillation, severe fatigue and sweating. Medical history included asthma (in treatment with montelukast *per os* and budesonide/formoterol inhalation) and a diagnosis of T1G3 NMIBC with 9 subsequent instillations of BCG immunotherapy (Connaught, ImmuCyst; CytoChemia, Ihringen, Germany), the last of which a week before the admission. Physical examination, vitals, ECG and chest X-ray were normal. Laboratory tests revealed elevated liver enzymes (AST 105 UI/l, ALT 129 UI/l) and a CRP of 19.1 mg/l.

Urine and blood cultures, serological tests for HBV, HCV, HIV, CMV and sputum Acid-Fast Bacilli (AFB) testing were negative. Urinalysis showed the presence of sterile pyuria. Prior to hospital admission, the patient had been treated empirically with ofloxacin *per os* (300 mg, twice daily) for 3 days. Clinical findings associated with anamnesis prompted to systemic BCG infection and an anti-tubercular treatment with isoniazid 300 mg/die, rifampin 600 mg/die and ethambutol 1200 mg/die intravenously was started. After 9 days, the patient was discharged in good general conditions and antitubercular therapy was continued *per os*.

However, re-admission occurred a week later because of persisting fatigue, malaise, intermittent fever and night sweats. Specific treatment was continued and, again, blood tests were normal except for a CRP of 73.5 mg/l, for liver cytolysis enzymes being still slightly above the normal range (AST 48 UI/l, ALT 65 UI/l), and for a cholestatic pattern (GGT 318 UI/l, ALP 324 UI/l, total bilirubin 1.2 mg/100ml, direct bilirubin of 0.6 mg/100 ml). Further serological investigations were performed, including EBV, Brucellosis, Salmonellosis and Parvovirus, all being negative.

To investigate pulmonary and urinary tract involvement, a contrast-enhanced chest and abdomen CT-scan was performed, demonstrating a bilateral pulmonary miliary pattern consistent with the diagnosis of miliary BCGitis (Figure 1). Furthermore, pulmonary embolism of some segmental and sub-segmental arteries was diagnosed. No deep venous thrombosis (DVT) was observed at lower limbs Doppler ultrasound, suggesting a local origin of thromboembolism. The patient was treated with low molecular weight heparin (LMWH).

Further evaluation revealed a PCR-based rapid detection test for *Mycobacterium tuberculosis* being positive in one out of two sputum specimens; conversely, the same test was negative on the bronchoalveolar lavage (BAL). FAB test and cultures were negative both on sputum and BAL samples; QuantiFERON® test was also negative, as quite expected due to the absence in BCG strain of the peptidic antigens routinely used in ISGRAs assay (RD-1 region, ESAT-6 and CFP-10).

Night sweats abruptly stopped two weeks after the second admission, whereas fever and fatigue gradually diminished. A second contrast-enhanced chest CT scan at the beginning of April 2016 showed a reduction in pulmonary micro-nodule number and the complete resolution of pulmonary segmental and sub-segmental

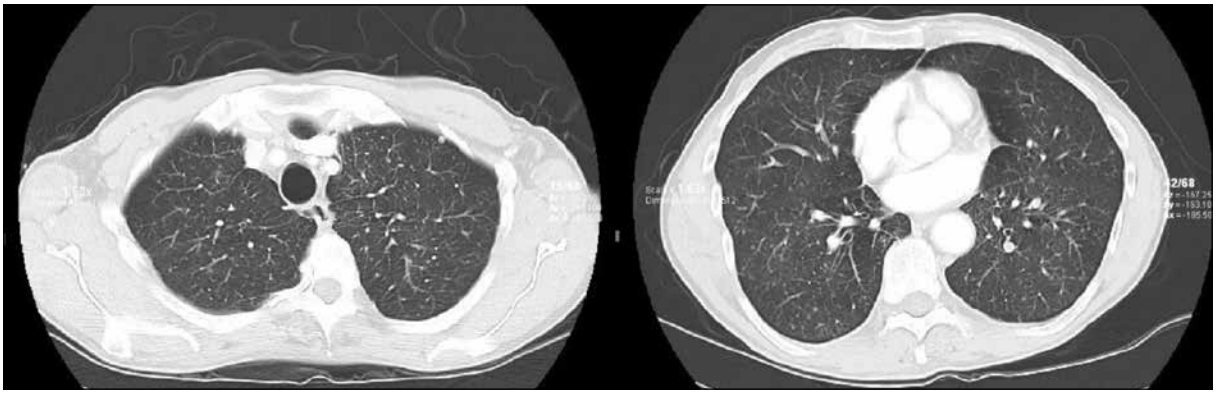

Figure 1 - Chest CT imaging at admission, showing miliary BCG infection.

embolism. The patient was discharged in good general conditions and continued anti-tubercular therapy.

DISCUSSION

Miliary pulmonary BCGitis is a very rare complication of intravesical BCG immunotherapy, but it needs to be promptly diagnosed and treated due to its non-negligible attributable mortality. Its incidence is reported up to 2.3% in retrospective series, and was recently estimated 0.4% in a large, prospective, multi-centre study [4, 5].

Normal response to intravesical BCG involves an increase of CD4 Th1 and in γδ T cells within the bladder mucosa, but the mechanism underlying the reported complication is not fully understood [9]. Both type 4 hypersensitivity reaction and haematogenous dissemination of *M. bovis* in tissues with consequent infection may be involved [10]. On the one hand, different reports have shown the presence of viable bacilli inside the lesions or have detected mycobacterial genome by PCR assays, suggesting a significant role for a disseminated BCG infection [11]. On the other hand, some Authors use the negative results of cultures and of serological and molecular tests, along with the successful use of steroids, to support their hypothesis that the granulomas in BCG disease are due to a hypersensitivity reaction and not to infection [12]. In our patient, the search for acid-fast bacilli performed on sputum, blood, and bronco-alveolar lavage returned negative, and only a single PCR-based test on a sputum sample proved positive.

This inability to identify *M. bovis* in affected tissues is not entirely unexpected: the specific role of fluoroquinolones (FQ) administration in delaying diagnosis and reducing the yield of microbiology should be also considered in this case. Similarly, in a study enrolling 33 patients with tuberculosis, 16 had received empiric levofloxacin treatment for CAP: the delay in the initiation of an appropriate treatment was 21 days in the FQ group and 5 days in the non-FQ group [13]. In a case-control study from Canada, out of 148 isolates of *M. tuberculosis*, 3 were FQ resistant and patients who had received multiple FQ prescriptions were more likely than patients who had received a single FQ prescription to be infected with FQ-resistant *M. tuberculosis* (15.0% vs. 0.0%; odds ratio, 11.4; P<.04) [14].

Our patient presented with intermittent fever, malaise and night sweats, making the anamnestic knowledge of previous BCG treatment essential for diagnosis. According to the literature, intermittent fever without any apparent origin, fatigue and malaise are frequently present at BCGitis onset. Patients often experience other non-specific symptoms including chills, dry cough, dyspnoea, weight loss and night sweats. Rarer findings are haemoptysis, arthralgia, pancytopenia and jaundice, secondary to concurrent granulomatous hepatitis [5, 10, 11, 15]. The absence of specific genitourinary or pulmonary symptoms often helps in including miliary BCG infection in the differential diagnosis.

Typically, clinical findings arise from a few days to a couple of weeks after the last BCG instillation, within the first months of therapy; however, miliary BCGitis can show up even years after the start of the BCG regimen [15]. Low grade fever arising within 24h after instillation can represent the normal immune response to BCG: in most cases, it is self-limiting and does not require anti-tuberculous therapy [16]. Nevertheless, our patient experienced fever immediately after a BCG instillation, thus showing the need for a careful evaluation of this initial sign of infection.

From our case, several crucial steps of a suspected BCGitis evaluation can be derived. First, as pointed out by a recent review, serological tests and blood cultures are negative in approximately 60% of cases, being useful especially for differential diagnosis purposes [5]. Instead, in early phases, rapid PCR-based molecular tests, either on blood, sputum or BAL samples, can often identify the agent [17].

Second, a chest CT scan should be performed in case of a negative chest X-ray and miliary BCGitis suspicion, as the latter misses up to 25% of miliary patterns [5, 11]. Therefore, early use of PCR-based tests together with CT-scan seems indicated to establish a prompt diagnosis and to start therapy without delay.

Third, when an appropriate therapy is started, the prognosis is generally favourable, although a 5.4% attributable mortality was observed by Pérez-Jacoiste Asín *et al.*, due to respiratory, liver and multi-organ failure [5]. Response to therapy can itself confirm the diagnosis on *ex juvantibus*

criterion. As in our case, it is important to bear in mind that clinical improvement often occurs after more than two weeks, sometimes boosted by the introduction of glucocorticosteroids [10, 12].
Finally, host's characteristics, including the extent of bladder mucosal damage and immunosuppression status, are considered more important than therapeutic regimen features, as the number of intravesical instillations, the total dose administered and the number of previous TURBs; in our case, miliary BCGitis presented after 9 instillations. A recent large RCT could not actually prove any difference in side-effects rates between 1yr- and 3yr-mainteinance schedule, and between full dose and reduced dose protocols [4, 5].
Regarding the use of intravesical BCG in patients treated with low dose of oral and/or inhaled steroids, retrospective studies have shown efficacy and safety profile of this treatment [18]. Moreover, also EAU guidelines does not consider inhaled steroids as an absolute or relative contraindication to BCG administration [8].
Pulmonary thromboembolism is a not uncommon complication in tuberculosis patients, in whom a hypercoagulable state could be induced by high plasma fibrinogen, reactive thrombocytosis, direct endothelial damage and use of rifampicin [19].
No routine prophylaxis protocol has demonstrated long-term efficacy for systemic BCG infections prevention [4]. Safety criteria, including delayed BCG administration (not during the first 2 weeks after resection), absence of urinary tract infection, non-traumatic catheterisation, immunocompetent patients or absence of local or systemic symptoms are well established and important to reduce BCG administration side effects [10, 16]. A better urological know-how and safer administration techniques seem associated with a decreasing incidence of adverse events. In any case, when the possibility of BCGitis is considered, considering the non-negligible mortality of this condition, a correct and prompt diagnostic work-up is needed, and fluoroquinolones should be consistently avoided.
In conclusion:

- Systemic BCGitis has to be suspected in all patients presenting with a history of BCG instillations and persistent fever, associated or not with other non-specific or respiratory symptoms (malaise, weakness, chills, cough, dyspnoea, abnormal sweating).
- Serological tests and blood cultures prove frequently negative. Rapid PCR-based molecular tests, either on blood, sputum or BAL samples, though having higher sensitivity, can miss the diagnosis in approximately 50% of cases.
- Empiric fluoroquinolones can hinder microbiologic diagnosis and should therefore be avoided when suspecting systemic BCGitis.
- A chest CT scan should be performed in case of a negative chest X-ray and suspicion of systemic dissemination of BCG.
- Clinical improvement can take several weeks, after appropriate anti-tubercular therapy is started.

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Conflict of interest
The authors report no conflict of interest. The authors alone are responsible for the content and writing of this report.

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