



Oncology

Miliary tuberculosis following intravesical Bacillus Calmette and Guérin therapy: A rare complication of a frequent procedure

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ABSTRACT

The standard treatment for superficial vesical tumors is transurethral resection (TUR) followed by intravesical instillation of Bacillus Calmette and Guérin (BCG). Pulmonary complications of BCG-therapy are rare but could be life threatening. We report the case of a 54-year-old patient who received BCG-therapy after TUR. After the sixth session of BCG instillations, the patient was diagnosed with a miliary tuberculosis secondary to BCG-therapy. We observed a progressive clinical and radiological improvement under specific tuberculosis treatment. Early diagnosis of pulmonary side effects of BCG-therapy and prompt treatment are the keys to complete recovery and survival.

Introduction

The Bacillus Calmette-Guerin (BCG) is a live attenuated strain of *Mycobacterium bovis*. It is used as an immunological treatment of superficial bladder cancer.¹ It reduces the recurrence and progression of the tumor and increases the disease-free survival.² Thus, actual guidelines recommend the use of intravesical BCG in the treatment of non-invasive bladder cancer.³ The side effects of this procedure are usually minor, limited to irritative local reactions.³ Miliary pulmonary complication is not common, ranging between 0.3% and 0.7% in patients treated by BCG instillations.^{2,3}

Herein, we describe a case of disseminated miliary tuberculosis following intravesical BCG instillations for a superficial bladder cancer.

Case report

In June 2017, a 54 year-old patient, former smoker, underwent a transurethral resection (TUR) of a papillary superficial bladder tumor classified pT1.

One month after the TUR, the patient started a regimen of six weekly sessions of intravesical BCG immunotherapy instillations. The patient

presented one episode of cystitis after the third session treated with Doxycycline. Two days after the sixth instillation, the patient presented fever (40 °C), chills, profuse sweating, general fatigue, dyspnea and dry cough. He was treated as an outpatient with empiric antibiotic (Levofloxacin). But, the fever and dyspnea persisted. Then, he was admitted to the Pulmonology Department in October 2017.

On admission, the physical examination revealed fever at 39.5 °C. Complete blood counts and blood chemistry showed normal results, except an elevated C-reactive protein levels (63.3 mg/L). Blood culture did not show any common pathogens. Urine analysis revealed sterile pyuria (White Cells at 700 e/mm³ with no growth in the culture).

Chest X-ray performed at admission showed diffuse miliary nodular lesions and chest computed tomography (CT) revealed bi-apical emphysema and confirmed the presence of multiple diffuse micro nodules with random distribution (Fig. 1).

Flexible bronchoscopy showed normal endoscopic aspect. Trans-bronchial lung biopsy specimen revealed normal lung tissue.

Acid-fast bacilli smears were negative on urine, blood, sputum and bronchoalveolar lavage. The Tuberculin cutaneous test was negative. No other organ system was involved.

Herein, the diagnosis of a miliary tuberculosis secondary to BCG

Abbreviations: BCG, Bacillus Calmette-Guerin; TUR, Transurethral Resection; CT, Computed Tomography; PCR, polymerase chain reaction; EORTC, European Organisation for Research and Treatment of Cancer.

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instillations was retained because of the clinical signs and the radiological presentation.

We interrupted BCG-therapy and initiated specific tuberculosis treatment during nine months: two months of four-drug regimen and seven months of two-drug regimen: with three-drug regimen: Isoniazid, Rifampicin and Ethambutol during nine months.

The patient showed progressive clinical improvement with amended fever, decreased cough and weight gain.

A chest radiograph performed after two months of the beginning of the treatment revealed a significant regression of pulmonary lesions (Fig. 2). A CT scan performed six months after the end of the tuberculosis treatment indicated the regression of the pulmonary lesions with the persistence of few bilateral micro nodules (Fig. 3).

Regarding the bladder tumor, no other chemotherapy was administered and the patient did not show any signs of progression or recurrence.

Discussion

The use of intravesical BCG after TUR of superficial bladder cancer remains the gold standard for patients with high risk of disease progression.²

The exact mechanism of action of BCG remains not fully understood. However, several immunological changes appeared to contribute to its antitumor activity.¹

BCG-therapy consists of an “induction treatment” applied weekly over a course of six weeks followed by a “maintenance treatment” consisting of six-week periods of instillation every three months for one to three years, if the patient responds appropriately to the induction therapy.¹

Side effects induced by BCG therapy are frequent and vary from

minor irritative symptoms to severe systemic complications. According to the results of the largest and most recent published study by the EORTC (European Organisation for Research and Treatment of Cancer) Genito-Urinary Cancers Group, 69.5% of patients who started BCG reported local (62.8%) or systemic (30.6%) complications, 8% of them discontinued the treatment due to toxicity and only 29% completed the three-year immunotherapy.³ Different patterns could affect the lungs such as interstitial pneumonitis, empyema, diffuse alveolar damage, pneumonia and more rarely miliary tuberculosis (0.3%–0.7%).^{2,3}

Factors increasing the risk of systemic side effects include bladder biopsy, early BCG administration after TUR, and difficult or traumatic catheterizations of the bladder.² As for our patient, we did not spot any evident risk factors of disseminated side effects.

Some authors consider the miliary presentation to be a systemic infection due to the spread of BCG from the bladder to the blood circulation. While others believe it is a type IV hypersensitivity mechanism to BCG.⁴

Acid-fast bacilli staining, mycobacterial culture, and polymerase chain reaction (PCR) testing are often negative. The overall rate of positive findings is 48% on microbiological tests.² In our case, the microbiological tests did not show any common pathogen growth and mycobacteria cultures were negative. This could have been related to the prescription of empiric Fluoroquinolones. A review of the literature showed that a granulomatous inflammation on specimen is available in 86.3% of cases.² In our case, the trans-bronchial biopsy did not showed any specific lesions.

There is no standard guidelines for the management of miliary pulmonary tuberculosis secondary to BCG-therapy. Some authors recommend a triple antibiotic therapy (Isoniazid, Rifampicin and Ethambutol) for two months followed by double therapy (Isoniazid and Rifampicin) for four months.² Others recommend a three-drug regimen associating

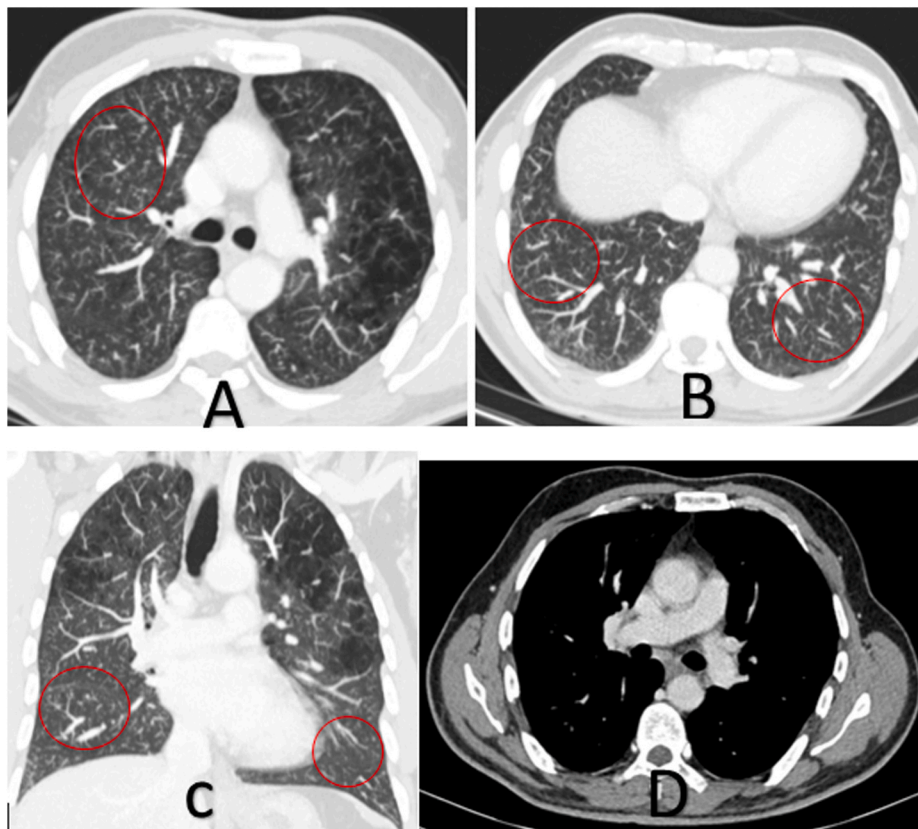


Fig. 1. Initial Thoracic CT in axial (A and B) and coronal (C) sections in parenchymal window in MIP (Maximum Intensity Projection) and axial reconstructions in mediastinal window (D) showing a diffuse bilateral micronodules (circle) with a random distribution. These micronodules have sharp contours and are not confluent consistent with a miliary pattern. In the bone window there is no mediastinal lymphadenopathy.

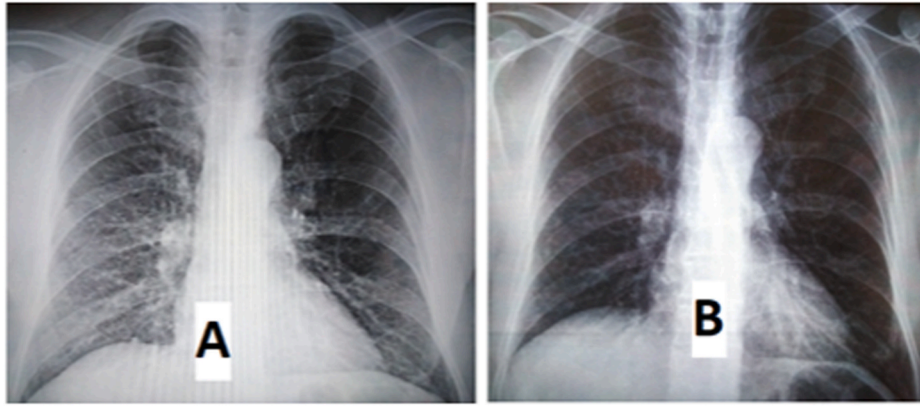


Fig. 2. Chest radiograph performed in admission (A): diffuse micronodules involving both lung fields. Chest radiograph performed two months after the treatment started (B): significant regression of the pulmonary lesions.

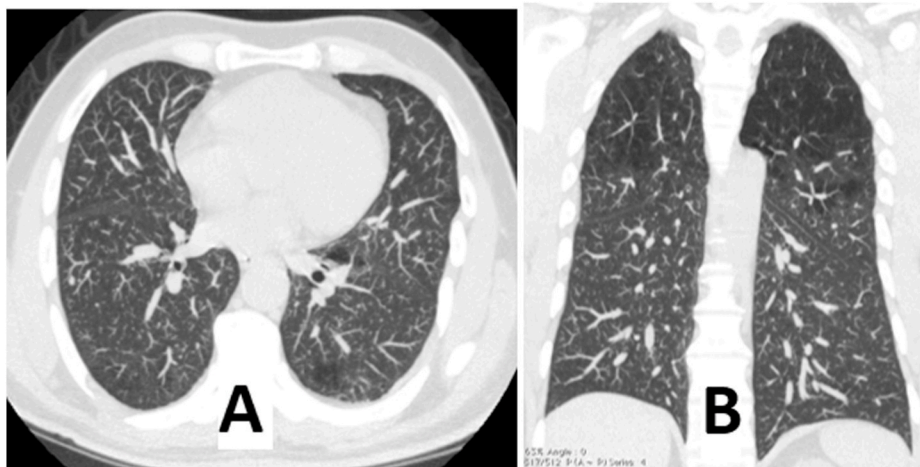


Fig. 3. Thoracic CT six months after the end of the treatment in axial (A) and coronal (B) slices in parenchymal window in MIP (Maximum Intensity Projection) reconstructions: Compared to the initial CT scan, there is a clear regression of the diffuse micronodules, testifying to the good therapeutic response. Centrilobular emphysema predominant in the upper lungs.

Isoniazid, Rifampicin and Ethambutol for a period of six to nine months.⁵ In our case, we interrupted the BCG instillations, and the patient received nine months of specific anti-tuberculosis treatment.

Our patient responded correctly to the tuberculosis treatment, however, miliary tuberculosis following BCG therapy could be fatal; a review of the literature has observed 5.4% attributable mortality, mainly due to respiratory failure.²

Conclusion

A miliary tuberculosis after BCG intravesical instillations is rare but can be life threatening. General practitioners should consider this diagnosis every time a patient undergoing BCG therapy presents with evocative symptoms. It is essential to establish a prompt diagnosis and to start specific treatment in order to avoid a fatal evolution.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Declaration of competing interest

None.

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