Inmunological pulmonary reaction after intravesical bacillus Calmette-Guérin instillation as therapy for bladder cancer

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Learning objectives

We propose to attend these objectives:

• Describe the immunological reaction, secondary to the use of intravesical BCG instillation, as a treatment in bladder cancer.

• Describe the clinical manifestations of this entity and specify that it can also occur in asymptomatic patients as in our cases, although this is unusual.

• Detail and illustrate the radiological findings visualized in this entity.

• Explain briefly the treatment.

Background

Intravesical bacillus Calmette-Guérin (BCG) is an important treatment of non-muscle invasive bladder cancer, used since the decade of the 70s. It is used for more than 68% of all bladder carcinoma.

The bacillus Calmette-Guerin is a live attenuated strain of *Mycobacterium bovis*, a species of the *Mycobacterium tuberculosis* complex group.

The intravesical BCG administration is generally well tolerated by most patients, but a side effects are common and generally self-limiting, mainly like a local inflammatory reactions.

The most common local presentation is cystitis, which manifest with dysuria and hematuria. Another local reactions have been reported like a prostatitis, urethral obstruction, orchitis and balanitis.

This therapy can also be associated with systemic reactions. These can be potentially deadly, developed in 1 to 5% of the treated patients. The most common systemic side effects is fever. However, there are many possible entities such as granulomatous hepatitis, arthritis, pneumonitis, sepsis, disseminated intravascular coagulation, miliary tuberculosis, multi-organ failure, and various forms of respiratory impairment.
Pulmonary involvement is rare and the miliary tuberculosis represents the most frequent pulmonary complication. Also exist an interstitial pneumonitis or diffuse alveolar damage.

Another type of manifestations is a immunological pulmonary reaction, it was postulated as a immunoallergic phenomenon by hypersensitivity reaction.

The pathogenesis of systemic involvement is not clear. It was postulated as a systemic infection due to hematogenous spread from the bladder, other theory is a type IV hypersensitivity mechanism to the BCG.

There are some situations that increase the passage of BCG into the bloodstream, like traumatic catheterizations, instillation in a damaged bladder or biopsy. Also exist another risk factors as use of immunosuppressive therapy, diseases like diabetes and cancer in another locations.

Also it has been described that the dose of intravesical BCG instillation is an important risk factor. Most of studies showed that low dose reduced the side effects.

Severe and systemic side effects are uncommon, but must be known and recognized.

The immunological pulmonary reaction like a system side effect after intravesical BCG administration is uncommon. The clinical manifestations are fever, malaise and cough, but unusually can occur in asymptomatic patients. The diagnosis is made by a chest radiography and high resolution computed tomography (HRTC) of the lung, both studies shows a uncountable uniforms pulmonary micronodules randomly distributed throughout both lungs, compatible with micronodular pattern. The finding generally are confirmed by pathological study.

The treatment depends on the patient’s symptomatology, corticosteroid and/or antituberculosis therapy can be used.

Findings and procedure details

Patients received intravesical BCG theraphy for bladder tumors. After therapy a micronodular pattern was identified in their chest radiographs and thorax CT.
First patient was a 60-year-old man, with personal history of migraine and squamous cell carcinoma of glottis treated with surgery and radiation therapy in 2011.

In December 2014, he was operated for a papillary urothelial bladder carcinoma, grade III (WHO) and stage pT1 G3 in TNM system (the tumor has spread to the subepithelial connective tissue but does not involve the bladder wall muscle). Intravesical BCG instillation protocol was indicated after the intervention: induction and maintenance. He had normal chest x-ray and thorax CT before beginning intravesical therapy.

Eight months later, a thorax CT (figure 1 and 2) was performed with intravenous contrast as a control and follow-up study for the history of squamous cell carcinoma of the glottis. This study showed a uncountable uniform sized pulmonary micronodules, well-defined, randomly and diffuse distributed in both lungs, compatible with micronodular pattern, which was not visualized in previous thorax CT. Without finding other parenchymal or mediastinic lesions.

The patient denied having any respiratory symptomatology and the blood tests were completely normal. A bronchoscopy with transbronchial biopsies and broncoalveolar lavage was performed.

A periseptal lymphohistiocytic aggregates was identified in the transbronchial biopsy, ill defined, in which the lymphocyte component predominated. The conclusion of this study was that the presence of lymphoepithelial micro-aggregates could be related to BCG instillations as an associated immunological reaction.

The patient was not treated with drugs, because he did not has any respiratory or general symptoms, what is unusual. Control and follow-up was indicated. A thorax CT was performed 4 months later without changes from previous study.

The patient was remained asymptomatic and thorax CT (figure 3) control again was made 12 months later, showing almost complete resolution of the micronodular pattern in both lungs.

Second patient was a 59-year-old man, with personal history of dyslipidemia, chronic alcoholism and atrioventricular block with pacemaker.

He had transurethral resection of bladder tumor antecedent in 1999 and he presented polypoid recurrence 14 years later, diagnosed by ultrasound. For this reason he was
operated of papillary transitional cell bladder carcinoma, grade II (WHO) and stage pTa. Intravesical BCG instillation was indicated after the intervention.

He presented fever and malaise during the intravesical BCG instillation sessions, which disappeared at the end of the therapy.

One month after the end of intravesical BCG therapy, a chest X-ray (figure 4) was performed as a preoperative study requested by the surgical service. In this study, a micronodular pattern was observed, so a thorax CT was carried out, confirming this pulmonary pattern. The CT (figure 5) showed numerous pulmonary micronodules, randomly and diffuse distributed in both lungs.

At the moment the patient did not have any respiratory symptomatology or fever and the blood tests were completely normal.

Given the history of intravesical BCG instillations, suspicion of miliary tuberculosis was suspected. For this reason, microbiological studies, bronchoscopy with bronchoalveolar lavage and transbronchial biopsy are performed, which are negative for miliary tuberculosis.

In the transbronchial biopsy showed an unspecific pattern of lymphohistiocytic aggregates with perivascular location, and without signs of vasculitis. Thus, the conclusion was a pulmonary immunological reaction secondary to intravesical BCG instillations.

No treatment was given because the patient was asymptomatic. A HRCT of lung control was indicated at 6 months, in this study (figure 6 y 7), the number of micronodules slight decreased and the patient remained asymptomatic.

Images for this section:
Figure 1. Axial section from thorax CT. The image shows numerous small and well-defined pulmonary micronodules, randomly distributed throughout both lungs. The patient was treated with intravesical bacillus Calmette-Guerin instillation eight months ago.

**Fig. 1:** Axial section from thorax CT. The image shows numerous small and well-defined pulmonary micronodules, randomly distributed throughout both lungs.

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Figure 2. Coronal reconstruction of thorax CT with endovenous contrast. The image shows multiple pulmonary micronodules, which are uniform in size, well-defined and randomly distributed.

**Fig. 2**: Coronal reconstruction of thorax CT with endovenous contrast. The image shows multiple pulmonary micronodules, which are uniform in size, well-defined and randomly distributed.

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Figure 3. Axial section image shows almost complete resolution of micronodular pattern. This thorax CT was done 12 months after having found an accidentally micronodular pattern.

**Fig. 3:** Axial section image shows almost complete resolution of micronodular lung pattern. This thorax CT was done 12 months after having found an accidentally micronodular pattern.

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Figure 4. Chest radiograph shows a small nodular lung opacities randomly distributed in both lungs correspond to micronodular pattern. Also this image show a dual chamber pacemaker with lead in right atrial and the ventricular lead in the region of the right ventricular apex.

**Fig. 4:** Chest radiograph a small nodular lung opacities randomly distributed in both lungs correspond to micronodular pattern.

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Figure 5. Axial section from thorax CT. Numerous and well-defined pulmonary micronodules, randomly and diffuse distributed in both lungs, correspond to micronodular lung pattern, after starting the intravesical BCG instillation 7 months ago.

**Fig. 5:** Axial section from thorax CT. Numerous and well-defined pulmonary micronodules, randomly and diffuse distributed in both lungs, correspond to micronodular lung pattern, after starting the intravesical BCG instillation 7 months ago.

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Figure 6. Axial section from HRCT chest. The image shows decrease in the number of micronodules described in the previous study.

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Figure 7. Coronal reconstruction from HRCT lung. The image shows a numerous, small, well-defined micronodules randomly distributed throughout both lungs. In comparison with the previous study these have decreased in number.

Fig. 7: Coronal reconstruction from HRCT lung. The image shows a numerous, small, well-defined micronodules randomly distributed throughout both lungs. In comparison with the previous study these have decreased in number.

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Conclusion

The intravesical bacillus Calmette-Guerin (BCG) instillation, as therapy for bladder tumor, has side effects at local and systemic level. The pulmonary involvement is one of this systemic side effect and has different forms of presentation. One of these is the pulmonary immune reaction.

The diagnosis of pulmonary immune reaction after intravesical BCG instillation is uncommon.

The suspicion is based on the presence of a micronodular pattern in chest radiographs or HRCT in a patient with history of intravesical BCG administration as therapy for bladder cancer, whether or not symptomatic.

Its main differential diagnosis is miliary tuberculosis.

The treatment in symptomatic patients are corticosteroids with or without antituberculosis drugs, depending on the clinical presentation.

The interesting about these cases is that patients did not have any respiratory or general symptoms, being accidental image findings.

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References