Clinical Note

Intravesical Mitomycin C and Pulmonary Fibrosis

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Abstract

Mitomycin C is a chemotherapeutic agent used for various kinds of carcinoma. It has been used for more than a quarter century for superficial bladder carcinoma, administered in intravesical instillations.

It is a relatively safe drug; however, adverse effects associated with systemic administration have been described, such as bone marrow suppression, anemia, renal toxicity, and, less frequently, pulmonary fibrosis.

We present the case of one patient with a respiratory picture compatible with interstitial lung disease that progressed to severe respiratory failure and death after the intravesical administration of mitomycin C; this is an exceptional adverse effect for this route of administration.

Key words: Mitomycin C. Pulmonary fibrosis.

Various therapeutic strategies are used for treating bladder carcinoma, including intravesical instillations of substances such as mitomycin C. Like other treatments, mitomycin C is not exempt from adverse effects. One of these effects is the possibility of triggering pulmonary fibrosis, which although uncommon at the low doses used in the intravesical route, must be considered as a possible diagnosis in patients with compatible respiratory symptomology after initiation of the treatment.

We present the case of a patient with bladder carcinoma treated with intravesical mitomycin C. After the first few treatment sessions, the patient presented progressive dyspnea and x-ray images compatible with pulmonary fibrosis.

CLINICAL CASE

The patient was a 67-year-old retired male who had worked as a bus driver; he was a moderate smoker with no criteria of chronic obstructive pulmonary disease, with a history of duodenal ulcer 20 years before. He visited the urologist for a first episode of painless gross hematuria. The cystoscopy revealed several papillary neo-formations in the bladder that were treated with transurethral resection. The anatomopathological examination reported a grade II-III transitional cell carcinoma with no infiltration of the muscle layer. After surgery, the patient started a protocol of intravesical instillations of mitomycin C (40 mg once a week for 8 weeks).

Around the time of the fourth instillation session, the patient noticed exertional dyspnea that progressed to resting dyspnea, accompanied by non-productive cough and no other symptoms; the patient was hospitalized ten days after the onset of his symptoms. The instillation of mitomycin C was discontinued immediately upon hospitalization, and he did not receive the fifth instillation.
Laboratory tests showed no hematologic or biochemical abnormalities; the arterial blood gas test showed hypoxemia (pO₂ 61.8 mmHg), normocapnia (pCO₂ 35 mmHg), pH 7.42, and bicarbonate 24 mEq/L.

The patient had not been in contact with any suspicious inhaled substance, had no pets or habitual contact with animals, nor had he previously had had any fibrous lung-associated disease such as lupus, collagenosis or sarcoidosis.

The physical examination revealed only a reduction in the vesicular breath sounds which was more significant in the right lung.

The chest x-ray taken upon admission showed a bilateral diffuse interstitial infiltrate that was more intense in the right pulmonary field, which had not been observed in preparatory x-rays. (Fig. 1).

**FIGURE 1. Chest x-ray upon admission: Interstitial infiltrate that is more intense in the right pulmonary field.**

The following tests were ordered to complete the studies, and were all negative: immunoglobulins, angiotensin converting enzyme (sarcoidosis), ANA (lupus anti-nuclear antibodies), ANCA (antineutrophil cytoplasmic antibodies for Wegener's granulomatosis), Human Immunodeficiency Virus (HIV), auramine in sputum (pulmonary tuberculosis), precipitins (bronchopulmonary aspergillosis), and sputum cytology.

The pulmonary function tests showed a restriction of pulmonary volumes with no evidence of air flow obstruction, with a slight diffusion deficit.

A computed tomography of the chest confirmed the presence of reticular interstitial lung disease with asymmetrical involvement of both pulmonary fields; the right lung was affected the most and had a honeycomb appearance (Fig. 2).
The patient was treated with oxygen therapy and systemic corticoids. The Urology service was consulted, and after reviewing the case they recommended discontinuing the instillation of intravesical mitomycin C since there was a possible association between this and the development of the respiratory symptomology.

After suspending the instillation of mitomycin C and initiating treatment, the patient experienced clinical and gasometric improvement the first week, with dyspnea persisting with moderate exertion; imaging tests showed fibrous scar tracts in the right pulmonary field. On the third week after admission the patient's condition worsened due to a possible respiratory infection; his progress was poor despite treatment, and evolved to severe respiratory failure and death.

DISCUSSION

Mitomycin C is a substance with antibiotic and cytotoxic properties; it was first isolated in 1955 by the Japanese researcher Hata. It is produced by *Streptomyces caespitosus*, and has DNA-alkylation activity.

Due to its cytotoxic properties, mitomycin C is administered in intravesical instillation in patients with superficial bladder carcinoma; it reduces the number of relapses after transurethral resection of the tumor.

Its high molecular weight (334 Dalton) compared to other intravesical cytostatic agents allows a very limited absorption through the urothelium (<1% of all instilled mitomycin C).

The most common adverse effects of the intravesical administration include local inflammatory reaction in the form of eosinophilic cystitis\(^1-3\) and incrustcd cystitis\(^4\). Less frequently there is myelosuppression, anemia, renal failure, bleeding, skin reaction\(^5,6\), and interstitial lung disease, which is exceptional for this intravesical route and has been reported in very few published cases\(^1,7\).

A rare post-systemic administration of mitomycin has been described: the kidneys are compromised with nephrotic syndrome associated with microangiopathic hemolytic anemia and pulmonary hypertension. In the case published, treatment with corticosteroids and plasmapheresis was not effective and the patient died six months after onset\(^8\).

Lung toxicity after treatment with mitomycin C is uncommon during systemic administration, and even more exceptional with intravesical administration; it manifests as a respiratory
clinical picture characterized by progressive dyspnea or worsening of a prior pulmonary pathology.

The pathogenic mechanism is believed to be of immune origin, with development of immune complexes that are deposited in the lung parenchyma and produce a local inflammatory reaction with a tendency to progress towards fibrosis. The clinical process and pulmonary lesions may be reversed, at least partially, upon early discontinuation of the drug and rapid initiation of anti-inflammatory treatment to stop the immune reaction.

The doses used in intravesical instillation are relatively low compared to those used in systemic chemotherapy, and have a very low urothelial absorption due to the drug's high molecular weight; thus, cases of lung involvement are even more rare when this route is used. In the exceptional cases reported, the dose threshold after which the probability of lung compromise increases is 20 mg/m² of mitomycin C9,10.

The pulmonary interstitial involvement caused by the inflammatory process produces a restrictive pattern in the spirometry tests, with a reduction of the pulmonary volumes and a decreased elasticity of the lung parenchyma. From the beginning there are gasometric abnormalities with marked hypoxemia due to the involvement of the pulmonary gas exchange membrane.

The clinical picture may be superimposed to other pulmonary interstitial inflammatory processes, with dyspnea progressing with increasingly smaller exertion which may be accompanied by dry and unproductive cough. The condition appears usually during the first weeks after initiating mitomycin C treatment, which facilitates the diagnosis; however, because of the rarity of this condition, a causal relationship should not be ruled out even with a less insidious presentation. Imaging tests show a reticular pattern that may progress to a reticular-nodular pattern with severe fibrosis and honeycomb lung, and important and irreversible loss of the pulmonary volume11.

Chest computerized tomography is the imaging test that provides the most information in this condition, as it detects even incipient fibrocatricial processes that are difficult to see with other techniques.

Treatment is based on anti-inflammatory therapy with the purpose of stopping the immune reaction in the lungs and preventing subsequent fibrosis. Steroids are the therapeutic basis. In severe cases, or cases in which the side effects of steroids are undesirable or contraindicated, immunosuppressors such as cyclophosphamide may be used. In cases with poor progress despite medical treatment, with a worsening of the pulmonary function, the last resource is lung transplantation.

CONCLUSIONS

In patients receiving intravesical mitomycin C, the potential adverse effects of this drug must always be considered. One of these effects is the development of acute or subacute respiratory failure, which even though rare, should always be borne in mind due to the possibility of developing irreversible pulmonary fibrosis which, as in the case we present here, may end with the patient's death.

The patients at higher risk, such as those who have had a prior lung or immune diseases, should be more closely monitored in this respect during instillations, being alert to the possibility of triggering an inflammatory immune reaction in the lungs that would worsen the prior pathology.

Immediate discontinuation of mitomycin C is essential when a potentially severe adverse effect such as this one is detected. The speed of the onset of the process depends on early immunosuppressor and anti-inflammatory treatment and on the response to this treatment.

It should be always kept in mind that mitomycin C is a drug not exempt from risks, and when it is used in patients with superficial bladder carcinoma, we must keep in mind that the intravesical instillation could trigger a potentially lethal pulmonary fibrosis, even though this is exceptional for this route of administration and for the low doses used.
REFERENCES


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