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Miliary tuberculosis complicating intravesical BCG therapy

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Abbreviations: BCG: Bacille Calmette Guerin; CT: Computed Tomography

Abstract

In April 2018, a 63-year-old patient was admitted due to general fatigue, dyspnea and continuous pyrexia. He was previously treated for several weeks with intravesical BCG for a bladder carcinoma. Chest computed tomography scan revealed bilateral miliary nodules. Microbiological findings including acid fast staining and urine cultures were all negative. Cytological examination of bronchoalveolar lavage was negative for malignant cells as well as bacteriological examination. Given the persistent cholestasis, it was decided to perform a liver biopsy. Pathology showed epitheloid granulomatous inflammation. BCG itis was suspected with pulmonary and hepatic manifestation. The patient was treated with Isoniazid, Rifampicin and Ethambutol. His symptoms improved fifteen days later and biological tests normalized after three months of treatment. Chest CT scan revealed complete regression of pulmonary nodules after six months of therapy. The present paper aimed to provide a better knowledge of a potentially fatal complication of intravesical BCG therapy: Miliary pulmonary tuberculosis.

Introduction

Immunotherapy with intravesical BCG is a well-established treatment adjuvant to endoscopic resection of non-invasive bladder carcinoma at intermediate and high risk of recurrence and progression [1,2]. Minor side effects usually consist of local infectious complications. BCG disseminated infections including miliary pulmonary tuberculosis are rare. However, misdiagnosis of this complication and inappropriate treatment may lead to fatal consequences. The aim of this paper was to provide a better knowledge and management of miliary pulmonary tuberculosis complicating intravesical BCG therapy.

Case presentation

A 63 year-old-patient was admitted with persistent fever, dyspnea and general fatigue. He was a former smoker and was diabetic treated with insulin. He underwent endoscopic resection of low-grade bladder urothelial carcinoma in October 2017 and in January 2018 (a complete resection PT1). A few days after the fourth weekly administration of intravesical BCG therapy, the patient had persistent fever and general fatigue. On examination, he was in fair condition over all. Chest radiograph suspected the presence of pulmonary micronodules. CT scan showed multiple micronodules randomly distributed with

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respect to lobular structures, consistent with miliary pattern (Figure 1). Intradermal Tuberculin Test was negative. Microbiological findings were all negative including acid fast staining and cultures. The cytological examination of bronchoalveolar lavage was negative for malignant cells as well as bacteriological examination. Mycobacterial cultures of the sputum and bronchial washing were negative. Biological tests revealed cholestasis (Alkaline phosphatase level was 298 IU/L and Gamma Glutamyl transferase level was 314 IU/L). Hepatitis serology was negative. It was decided to perform a liver needle biopsy. Histology revealed epitheloid granulomatous inflammation with intrahepatic cholestasis (Figure2). Mycobacterial culture of the liver biopsy was negative. The suspected diagnosis was BCG-itis with miliary pulmonary tuberculosis and hepatitis.

Fundus oculi examination as well as cerebral CT were normal. The patient was started on a regimen associating Isoniazid (300mg/day), Rifampicin (600mg/day) and Ethambutol (800mg/day). His weight was 65 kilograms.

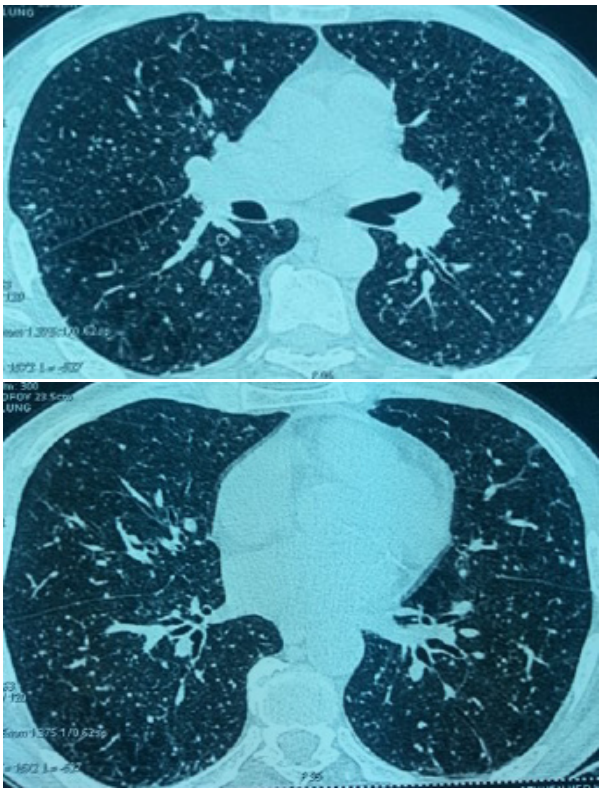
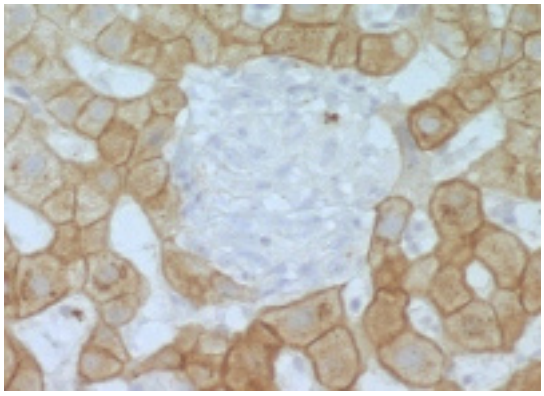


Figure 1: CT scan showed multiple micronodules randomly distributed with respect to lobular structures, consistent with miliary pattern.



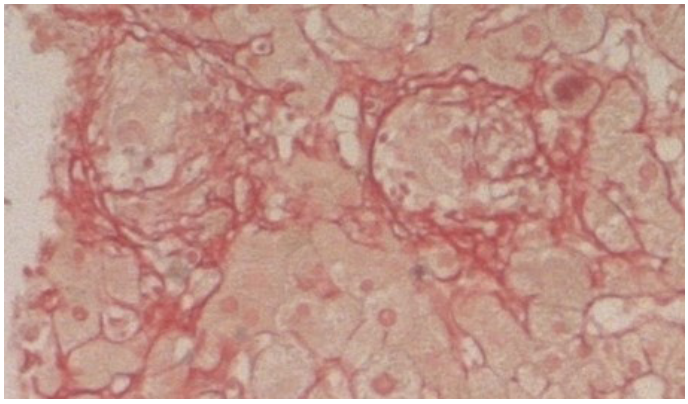


Figure 2: Histopathological findings of liver biopsy revealed an epitheloid granulomatous inflammation.

Outcome and follow up

15 days after treatment, his fever subsided and his dyspnea disappeared. Cholestasis markers normalized after 3 months of treatment and the patient gained 8 kg after 9 months of total treatment. Chest CT scan revealed complete regression of pulmonary nodules after 6 months of therapy (Figure 3).

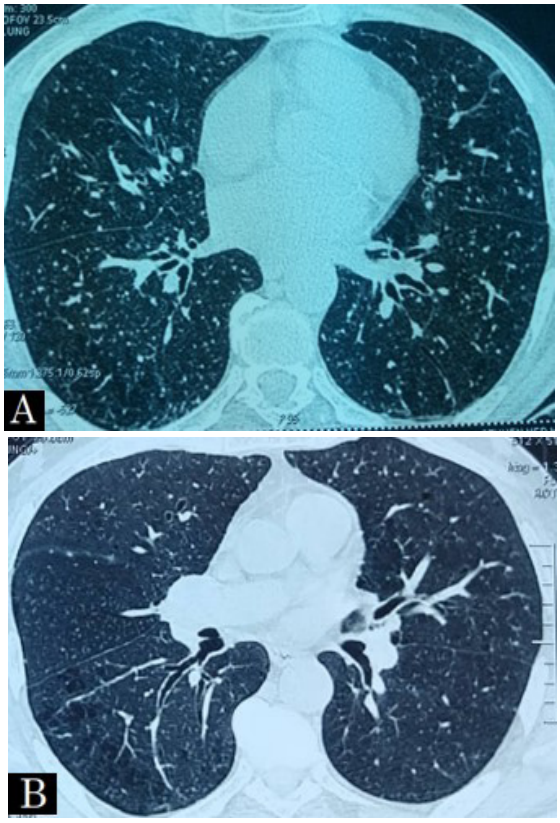


Figure 3: CT scan before treatment onset. CT scan after 6 months of treatment.

Discussion

Local BCG immunotherapy is a well-established treatment for early stages of bladder carcinoma. It is an adjuvant treatment to endoscopic resection that is indicated for tumors with intermediate or high risk of recurrence or progression [1,2]. It is generally well tolerated among immunocompetent patients [3]. Local side effects such as concurrent cystitis or mild systemic complications (general fatigue) were reported. They usually resolve within few days [4]. From the literature data, severe systemic complications including miliary pulmonary tuberculosis and hepatitis are rare <1% [5-7]. According to Rosati et al., at least 37 cases of miliary pulmonary tuberculosis related to BCG

instillation were noticed from literature [1,8]. The exact pathogenesis of systemic complications due to BCG immunotherapy is not fully known [9]. Two types are the most described: mycobacterial pneumonia and hypersensitivity [10]. Mycobacterial pneumonia is due to hematogenous spread of BCG. Type IV hypersentivity to BCG is suspected when microbiological findings are negative and granulomas are absent. Bacteriological tests including acid fast bacilli, the culture of lesions (lung or liver biopsy) are rarely positive (10 % of cases of hepatic tuberculosis) [11]. Hepatic tuberculosis is suspected when abnormal liver function result is not related to a drug use or another liver disease. In cases of suspected pneumonia, difficulties in isolation of acid fast bacilli made the diagnosis intriguing [12]. In our case, the negativity of microbilogical findings and cholestasis has led to further investigation with a liver needle biopsy. Mycobacterium Bovis is known to be resistant to pyrazinamide according to the literature data [1,13]. The most watched regimen is a 3-drug antitubercular association of Isoniazid, Rifampicin and Ethambutol for a period of 6 to 9 months [13]. In our case, the patient was treated for 9 months as recommended in the Tunisian National Guidelines of anti-Tuberculosis treatment in case of a 3-drug regimen. corticosteroids are added when hypersensitivity is highly suspected but particularly in the presence of severe clinical symptoms (a life-threatening risk) [14].

Conclusion

Systemic complications of BCG immunotherapy including miliary pulmonary tuberculosis are rare. However, misdiagnosis can lead to life-threatening consequences. A high index of suspicion is essential in order to early initiation of antituberculosis therapy.

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