An unusual case of a tuberculous granuloma of the liver presenting thirteen years after intravesical BCG therapy for bladder cancer

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ABSTRACT: The authors present the case of a female patient with a tumor of segment VII of the liver, which was postoperatively identified as a tuberculous granuloma. The patient was admitted for elective surgery for a liver tumor, which had been diagnosed a few months before. Computed tomography and nuclear magnetic resonance were performed, based on which focal nodular hyperplasia was suspected. Thirteen years prior to admission the patient had undergone a transurethral resection of superficial bladder carcinoma, followed by adjuvant intravesical Bacillus Calmette-Guérin (BCG-therapy). Upon surgery, segment VII of the liver was resected; postoperative course was uneventful. After the identification of granuloma, the patient was referred to a phthisiatric clinic for further diagnostics and treatment. The authors have deemed this case worthy of reporting primarily due to the exceptionally long period between the completion of BCG therapy and the onset of hepatic tumor.

KEYWORDS: BCG therapy, bladder carcinoma, liver, tuberculous granuloma

ABBREVIATIONS

BSG – Bacillus Calmette-Guérin
CT – computed tomography
FNH – focal nodular hyperplasia
NMR – nuclear magnetic resonance
PCR – polymerase chain reaction
SIRS – Systemic inflammatory response syndrome
USG – ultrasound

INTRODUCTION

Since the 1970s, the treatment of superficial malignant neoplasms of bladder has involved the use of enemas with Bacillus Calmette-Guérin (BCG) suspension. The efficacy of such therapy is estimated at as much as 70–90% for in situ papillary carcinoma. That said, treatment is burdened with considerably high risk of adverse events, both local (bladder, testes, epididymis, penis or prostate gland) and generalized, which include: fever, pneumonia, miliary tuberculosis, osteomyelitis, arthritis and (extremely rarely) systemic inflammatory response syndrome (SIRS). The incidence of more severe and long-term complications is estimated at 5% [1–3]. Hepatobiliary complications are observed in 0.7–3% of patients [4, 5]. The authors present a case report of tuberculous granuloma of the liver diagnosed extremely late, thirteen years after the end of BCG treatment.

CASE REPORT

In January of 2014, a 49-year-old female patient with an unclear segment VII tumor of the liver, detected in July 2013 during abdominal ultrasound due to pain in the right upper abdomen, was admitted to the Department of Liver and General Surgery, CM UMK in Bydgoszcz. CT and NMR (Fig. 1.) revealed a focal lesion in segment VII of the liver, with radiographic features of focal nodular hyperplasia, or FNH. During history taking in 2000, the patient had abdominal ultrasound due to non-specific symptoms of dyspepsia and general malaise. The examination revealed a bladder tumor identified as an early malignant lesion (Carcinoma urotheliale papillare non invasivum; G2). Electroresection of tumor was performed and supplemented with ten BCG intravesical infusions. There were no early treatment complications. The patient remained under urological observation for the following six years. In 2006, she underwent elective surgery to remove a right breast lump (fibroadenoma). On January 16, 2014, the patient had anatomic hepatic resection of segment seven. She was discharged on day 6 after surgery with the wound healed by primary intention. After consulting at the pulmonary center, no treatment was undertaken in this regard. During further follow-up until April 30, 2019, the patient’s health had remained unchanged.

RESULTS

The sample sent for histopathological examination after hepatic resection (segment VII with tumor) contained a lesion measuring 2 x 2.6 x 2 cm. Macroscopically visible solid, grayish mass. Microscopic examination revealed numerous granulomas with small foci of caseation necrosis, surrounded by fibrous tissue, containing: Langhans giant cells, epithelial histiocytes and...
life-threatening vascular fistulas [2, 7]. According to published literature, all those complications are observed quite early, within a few hours to a maximum of several months after administration of BCG infusion. Gonzales et al. published a literature review on adverse events associated with BCG therapy and presented data from their own clinical material. On this basis, they distinguished between early complications (occurring up to three months) and late complications (at least one year after starting BCG treatment) [8]. The authors of this report conducted their own search of the available literature and found no description of an equally long latency period before the onset of a complication after BCG treatment. Due to the exceptionally rigorous observation of the patient (annual abdominal ultrasound and chest X-ray every two years) for the first six years after the end of urological treatment and two years of close follow-up after an excision of a breast lump, it can be established with a high probability that at this time, the patient did not develop any pathological changes until July 2013.

**DISCUSSION**

The authors present a case report of tuberculous granuloma of the liver, a distant complication of treatment with BCG enemas of superficial bladder cancer, done thirteen years earlier. Since the completion of treatment, the patient has remained under close urological monitoring, including regular abdominal ultrasound.

BCG adjuvant therapy in superficial bladder cancer was introduced in 1976 by Morales et al. [6]. The mechanism of therapeutic effect has not been fully clarified; we consider the induction of phagocytosis with the subsequent activation of the cytokine cascade (IL12, interferon, TNF), leading to the activation of T lymphocytes, including the so-called natural killer cells [6]. As already mentioned, the complication rate for this therapeutic method is estimated at 3–5%. Severe, generalized complications such as miliary, pneumonia or granulomatous hepatitis are less common (0.7–3%). There are also reports of eye changes and hepatic triads in the surrounding liver parenchyma, there was lymphatic infiltration.

Ziehl-Neelsen staining was performed to identify the etiological factor of the granulomas; Mycobacterium tuberculosis was not identified. In order to analyze the morphology of granulomas and the surrounding parenchyma, additional histochemical and immunohistochemical stains were performed: Gomori, CD68, CD3, CD4, CD8, CD20, IL-1 and TNF-α (Fig. 1B–1H.). Gomori trichrome stain showed significant fibrosis obliterating the granulomas and a moderate degree of fibrosis around the liver parenchyma. Immunohistochemical staining for CD68, IL-1 and TNF-α was positive in epithelial histiocytes and Langhans giant cells. Moreover, all lymphocytes expressed TNF-α and IL-1. T (CD4+) and B (CD20+) cells were widely dispersed within the granulomas. The presence of CD3+ and CD8+ T cells was found in the cells surrounding the granulomas. Macro- and microscopic imaging in conjunction with clinical data gave grounds to establish a final diagnosis of granuloma with most likely tuberculous etiology.
liver resections due to suspected hepatocellular carcinoma were analyzed; the authors found eight cases of non-neoplastic tuberculosis tumors, in their conclusions highlighting the diagnostic challenges of such cases [10]. Percutaneous biopsy of the tumor may be helpful in establishing the diagnosis. In the case presented, biopsy was not performed due to: history of malignant neoplasm, ambiguous description of the imaging examination and extensive experience of the center in hepatic and biliary surgery. Macroscopic imaging revealed hepatic tuberculosis characterized by a broad range of morphological changes, including serous and non-keratinizing epithelial granulomas as well as caseation necrosis without component of granulomatous inflammation. Other possible histopathological findings include macrophage hyperplasia, the presence of lymphocytic infiltrates in hepatic triads, and necrotic hepatocytes. Some authors note that in the course of plasm, ambiguous description of the imaging examination and percutaneous biopsy was not performed due to: history of malignant neoplasm, uncertain diagnosis, and local form. In conclusion, the authors wish to emphasize that granulomatous disease caused by Bacillus of Calmette-Guérin as a local adjuvant treatment compliancy during BCG maintenance therapy for non-muscle-invasive bladder cancer. Int J Urol, 2005; 12(2): 145–151.

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To conclude, the authors wish to emphasize that granulomatous changes in the liver may occur even many years after completion of BCG therapy.

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