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Case Report

Multisystemic BCGitis: A rare complication of intravesical BCG immunotherapy for bladder cancer ☆,☆☆

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ABSTRACT

Intermediate- to high-grade non-muscle invasive bladder cancer is preferably treated with transurethral resection followed by adjuvant intravesical immunotherapy with Bacillus Calmette-Guérin (BCG). BCG acts as an immune stimulator, inducing a complex inflammatory response that selectively targets tumoral cells. Mild side effects of BCG instillation, such as fever, malaise, and bladder irritation are frequent, while severe treatment-associated complications of the genito-urinary tract are rare. "Distant" complications are even rarer and, since BCG is able to disseminate hematogenously, virtually all organs and systems can be involved, with the lungs, liver and musculoskeletal system being most commonly affected. Vascular complications of BCG immunotherapy are exceedingly rare and difficult to diagnose, because they can mimic other vascular infections and may occur several years after treatment. Knowledge of previous BCG immunotherapy and awareness about treatment-related complications is essential to avoid misdiagnosis, and to guide appropriate treatment.

CASE REPORT

A 71-year-old diabetic and hypertensive male was admitted to the Emergency Department (ED) two days after a BCG instillation session complaining of general malaise and anuria. He had been diagnosed with high-grade non-muscle invasive bladder carcinoma (NMIBC) 3 years prior and submitted to 3 transurethral resection (TURBT) procedures which were followed by adjuvant intravesical immunotherapy with BCG. So far treatment had been well-tolerated, without cancer recurrence on follow-up urinary cytology and cystoscopy.

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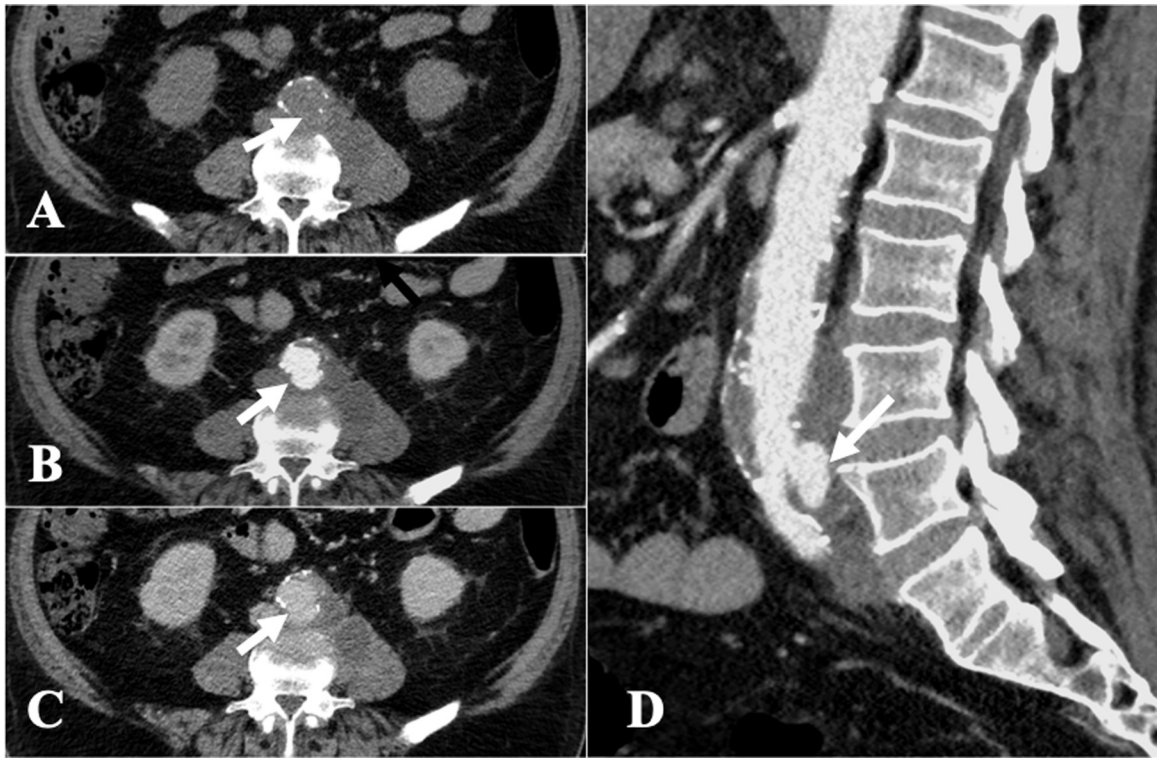

Fig. 1 – Abdomino-pelvic CT reveals a pseudoaneurysm of the distal abdominal aorta measuring 45 mm of maximal axial diameter. On non-enhanced CT images (A) a "fracture" of the calcium ring can be appreciated on the posterior aspect of the aorta (white arrow), a sign considered to be indicative of impeding aneurysmal rupture. On the arterial phase (B) a posterior outpouching of the distal aorta (white arrows) is seen, corresponding to the pseudoaneurysm. Its extension can be better appreciated on the sagittal plane image (D). On both the arterial (B; D) and venous phases (C) densification of the peri-aortic tissues is seen with loss of the fat planes between the aorta and the left psoas muscle. Signs of rupture, such as active contrast extravasation or retroperitoneal hematoma, were absent.

Laboratory studies performed at admission disclosed a significant elevation of serum creatinine and urea levels. Reno-vesical ultrasound excluded hydronephrosis or obstructive reno-vesical lesions. He was diagnosed with acute kidney injury (AKI) of undetermined etiology and admitted for urgent dialytic therapy and further study.

To exclude a vascular cause of AKI, an abdomino-pelvic Computed Tomography (CT) was performed which revealed normal permeability of both renal arteries. A pseudoaneurysm of the distal abdominal aorta, measuring 45 mm of maximal axial diameter, was detected (Fig. 1). Imaging features of impeding rupture, including fracture of the calcium ring (Fig. 1A) and loss of the fat planes between the aorta and left psoas muscle (Fig. 1B, 1C and 1D) were seen. No other relevant findings were reported at the time.

Endovascular aneurysm repair (EVAR) was successfully performed, with proper aneurysm exclusion, and no intra-operative complications.

The patient remained under close monitoring in an Intermediate Care Unit with significant improvement of its general condition and renal function. Renal biopsy was performed with no remarkable features other than acute tubular necrosis. Bacterial and mycobacterial microbiological work-up of renal biopsy and urinary specimens was negative.

Given his stable condition, he was moved to a medical ward on the 9th day of inpatient stay. A few days later, he started having febrile episodes which became more recurrent and vespertine over time. An elevation in hepatic cytolytic and cholestatic markers was also noted. Given the known medical history of BCG immunotherapy, sustained fever with no apparent cause and laboratory evidence of hepatitis, a control CT scan was performed. Numerous pulmonary micronodules distributed in a military pattern and involving both lungs were now visible (Fig. 2).

Adjacent to the excluded aortic aneurysm, an intra-muscular collection of the left psoas, measuring 30 mm of maximal axial diameter, was also found (Fig. 3).

The patient was then transferred to the Infectious Diseases Department and stated on tuberculostatic therapy with isoniazid (H), rifampicin (R), and ethambutol (E) for presumed disseminated BCGitis. An abdomino-pelvic Magnetic Resonance (MR) was performed to further characterize the abdominal findings, revealing marked densification and enhancement of the peri-aortic tissues and confirming the presence of an intra-muscular psoas abscess (Fig. 4). On T2-weighted images (Fig. 4A) marked thickening of the peri-aortic tissues and an intra-muscular liquid collection of the left psoas were seen. On T1-weighted fat-saturated contrast-enhanced images

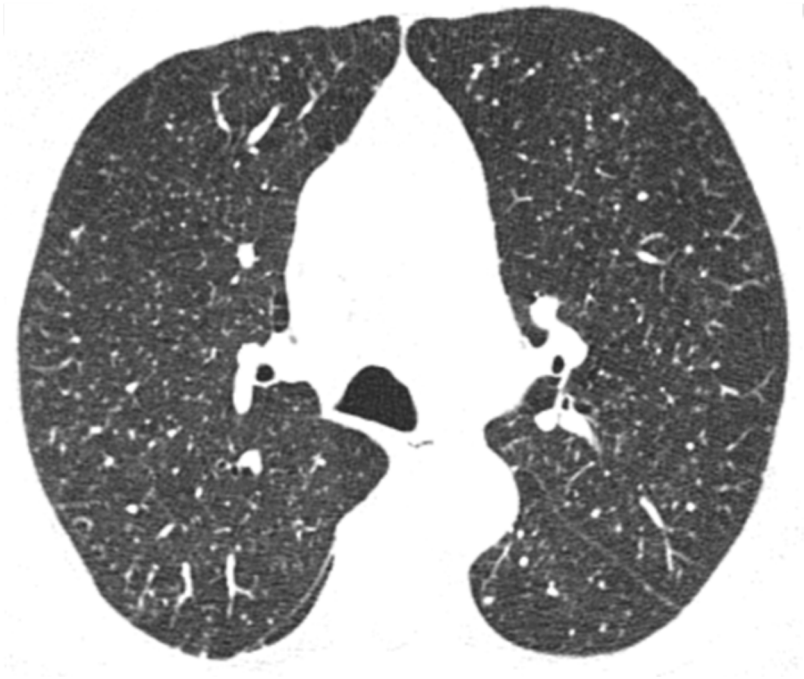

Fig. 2 – Thoracic CT reveals the presence of innumerable pulmonary micronodules with a miliary pattern of distribution involving all lobes of both lungs. Given the clinical setting, these findings were highly suggestive of infection.

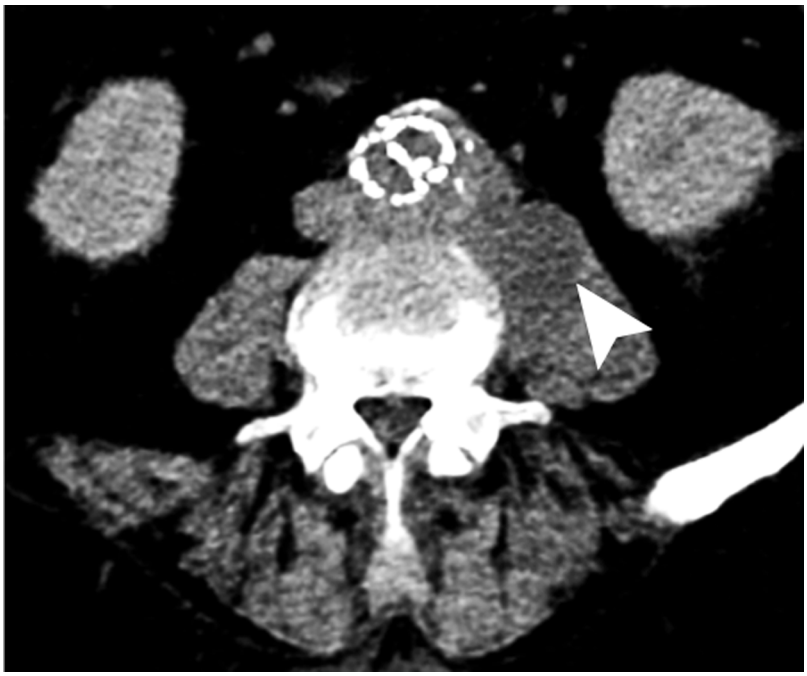

Fig. 3 – Non-enhanced abdomino-pelvic CT reveals an area of low / hydric density within the body of the left psoas muscle (arrowhead) adjacent to the treated aortic pseudoaneurysm. The findings were highly suggestive of an intra-muscular abscess.

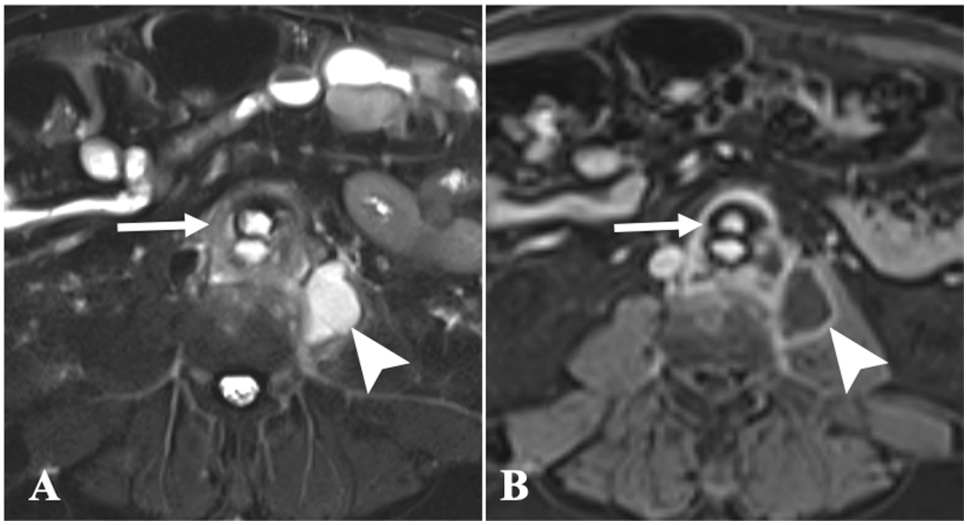

Fig. 4 – Abdomino-pelvic MRI. T2-weighted MR image (A) revealed marked thickening of the periaortic tissues (white arrow) and confirmed the presence of an intra-muscular liquid collection of left psoas (arrowhead). T1-weighted fat-saturated contrast-enhanced MR image (B) revealed marked enhancement of the periaortic tissues (white arrow), a finding that also supports the presence of significant inflammatory / infectious periaortic changes. Peripheral enhancement (arrowhead) of the psoas collection helped to confirm that it corresponded to an intra-muscular abscess.

(Fig. 4B) there was marked enhancement of the peri-aortic tissues and peripheral enhancement of the left psoas collection.

The presence of the psoas abscess was confirmed (Fig. 5A) which was then drained under CT control (Fig. 5B).The obtained samples revealed the presence of numerous acid-fast bacilli (AFB).

Nucleic acid amplification test was positive for *Mycobacterium tuberculosis complex* both in the abscess pus and sputum samples. The growth of a strain of BCG in the abscess specimens was later found, allowing the definitive diagnosis of multisystemic BCGitis to be made.

DISCUSSION

BCG is a live attenuated strain of *Mycobacterium bovis*. First developed in the early 20th century as a vaccine against tuberculosis, intravesical instillation of BCG is now widely used for the treatment of intermediate- to high-grade NMIBC [1]. Although its mechanism of action is not fully understood, BCG has been shown to induce local inflammatory and anti-tumoral effects [2], and it has now a well-established role as an adjuvant agent in the treatment of NMIBC following TURBT [1].

Mild side effects of BCG instillation, such as fever, malaise, and symptoms of bladder irritation are frequent, while severe treatment-associated complications of the genito-urinary tract are rare. “Distant” complications are even rarer and, since BCG is able to disseminate hematogenously, virtually all organs and systems can be involved, with the lungs, liver and musculoskeletal system being most commonly affected. There are several reports of systemic dissemination of the bacillus after intra-vesical immunotherapy, particularly in immunocompromised patients. The exact mechanism through which multisystemic infection with BCG (ie, BCGitis) develops is still unclarified [3]. Some authors agree it is a consequence of hematogenic dissemination of the instilled mycobacteria [4], while others suggest it results from a type IV hypersensitivity reaction to BCG [5]. In this case, mycobacterial growth in the collection surrounding the aortic pseudo-aneurysm is in accordance with the first theory, but both are acceptable explanations of its pathogenesis.

Several risk factors for BCGitis development have been described, including bladder trauma, immunosuppression, Diabetes *mellitus* and genetic susceptibility [6]. In this case, the combination of 2 risk factors – Diabetes *mellitus* and recent bladder biopsies – might have contributed for the reported outcome.

The diagnosis of systemic BCGitis is challenging, particularly because associated imaging findings are non-specific, being indistinguishable from those of cancer or non-mycobacterial infections [3]. Vascular complications of BCGitis most commonly involve the abdominal aorta and present as a saccular aneurysmor pseudoaneurysm. Signs of overt or impending rupture are commonly encountered. CT and MR findings of infection, such as densification and hyperenhancement of the peri-aortic tissues can be encountered but are non-specific, therefore radionuclide imaging is frequently necessary to confirm the diagnosis. [7] Paraspinal and psoas abscesses generally occur in association with BCG-spondylodiscitis, which was absent in this case, but can also result from the local dissemination of aortic infections [3]. On CT, pulmonary BCGitis typically presents with diffuse micronodules distributed in a miliary pattern. This appearance mimics that of miliary tuberculosis and fungal infections, and frequently leads to misdiagnosis of BCGitis [8]. Imaging findings of BCG-hepatitis are even more unspecific, and frequently only hepatomegaly and ascites are encountered on CT or MRI [9].

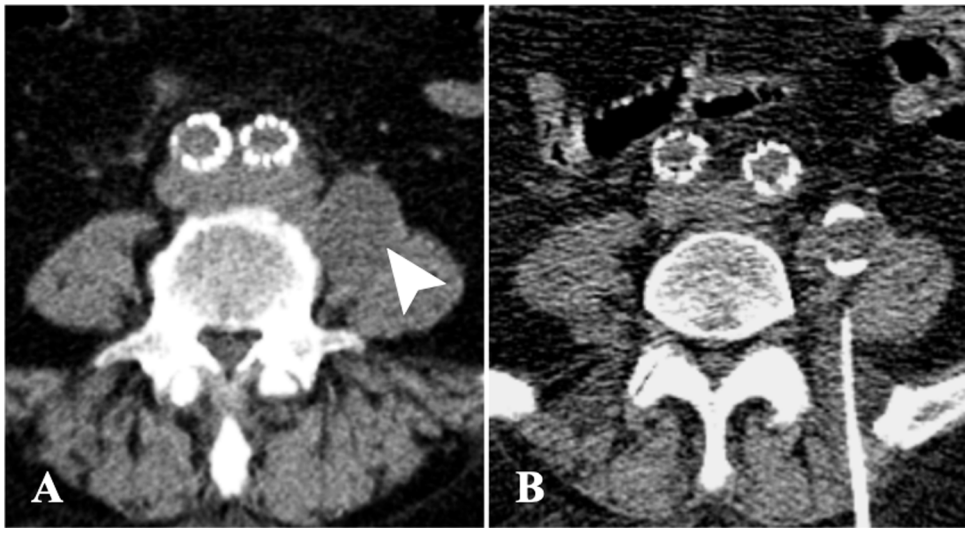

Fig. 5 – Non-enhanced CT (A) confirmed the presence of the left psoas abscess (white arrowhead), which was then drained under CT control (B). The growth of a strain of BCG in the pus allowed the confirmation of the diagnosis of multisystemic BCGitis.

Although there are no standard guidelines on the management of systemic BCGitis, care for these patients involves immunotherapy suspension and tuberculostatic therapy usually with an initial phase of HRE followed by a continuation phase of HR, similar to infections from other sources by *Mycobacterium bovis* [6].

In conclusion, systemic BCGitis is a rare but serious complication of BCG immunotherapy. Presentations can be diverse and are not always clear, particularly when multiorgan involvement is documented. Increased awareness among physicians is essential so that an early diagnosis can be achieved and optimal treatment instituted promptly.

Patient consent statement

The authors obtained written informed consent from the patient for publication of this case report.

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