A mycotic aneurysm of the abdominal aorta caused by *Mycobacterium bovis* after intravesical instillation with bacillus Calmette-Guérin

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ABSTRACT

Intravesical administration of bacillus Calmette-Guérin (BCG), a live attenuated strain of *Mycobacterium bovis*, plays an important role in adjuvant treatment of superficial bladder cancer. Severe adverse events due to this treatment are rare. Complications of varying character and severity have been described, including rare BCG-related vascular infections. In this writing, we present a case of mycotic abdominal aneurysm caused by *M. bovis* infection related to prior intravesical BCG instillation. (J Vasc Surg Cases and Innovative Techniques 2018;4:122-5.)

Bacillus Calmette-Guérin (BCG) is a weakened strain of *Mycobacterium bovis*. BCG is used as adjuvant intravesical therapy in non-muscle-invasive bladder cancer.

Adverse events occur in <5% of cases, ranging from mild local symptoms to severe sepsis and death.[1] It can be challenging to link previous intravesical BCG instillation to a patient's symptoms. We describe a case of mycotic aortic aneurysm caused by *M. bovis* infection after intravesical BCG instillation 2 years earlier. The patient agreed to publication of his case.

CASE REPORT

A 73-year-old man with lower back pain, severe fatigue, and 20-kg weight loss was analyzed by the Department of Internal Medicine. His history included early-stage transitional cell bladder cancer with invasion of the submucosa in 2012, treated with transurethral resection and intravesical mitomycin. Recurrence of disease was diagnosed in 2013. Transurethral resection of a low-grade non-muscle-invasive tumor was performed. Adjuvant therapy with intravesical BCG solution was administered once weekly for 6 weeks. No adverse events or immunocompromising conditions were noted during this period.

On examination for the aforementioned symptoms two years later, peripheral edema of the lower extremities and pain on palpation cranial to the left iliac crest were noted. Examination of the abdomen and spine showed no abnormalities. Because occult metastatic disease was a possible explanation for the symptoms, a positron emission tomography scan was performed showing pathologic activity of the abdominal aorta and left iliopsoas muscle (Fig 1, *a* and *b*). A thoracoabdominal computed tomography (CT) scan showed a pseudoaneurysm of the abdominal aorta and surrounding infiltration (Fig 1, *c*). As this seemed suggestive of a mycotic aneurysm, the Department of Vascular Surgery was consulted.

As the patient had not experienced septic episodes, he was not acutely ill, and indicators of infection remained only mildly elevated, it was decided to perform elective open aorta reconstructive surgery at short notice.

The operation was performed in February 2016. No preoperative antibiotics were administered. Intravenous perioperative antibiotic prophylaxis with cephalosporin and metronidazole was decided on. Postoperative antibiotic treatment would depend on culture specimens taken during the operation.

The aneurysm began just caudal to the renal arteries. A neoaortoiliac system bypass was considered. However, because of the limited infected area and limited experience with this procedure, reconstructive repair was performed with a bovine (pericardial) tube graft. The infected aneurysmal segment was excised. A collection of softened, infected mushy tissue was noted on the left side of the aneurysm. Culture and biopsy specimens from the aorta and surrounding tissue were taken. All tissue showing signs of infection was excised. A resorbable sponge impregnated with 130 mg of gentamicin was left behind in the cavity after removal of the aneurysm and surrounding infected tissue. Rifampicin was also directly applied to the cavity. The graft was sutured in the conventional manner and covered with a greater omentum wrap plasty.

Three samples of para-aortic tissue were cultured. One sample contained *M. bovis*. Pathologic evaluation showed extensive granulomatous and necrotizing inflammation of the aorta. However, histologic Ziehl-Neelsen staining used to identify acid-fast organisms such as *M. bovis* was negative.

DNA analyses showed that the cultured strain of *M. bovis* was identical to the one used for the BCG solution administered in 2013. The conclusion was that this BCG solution was the source

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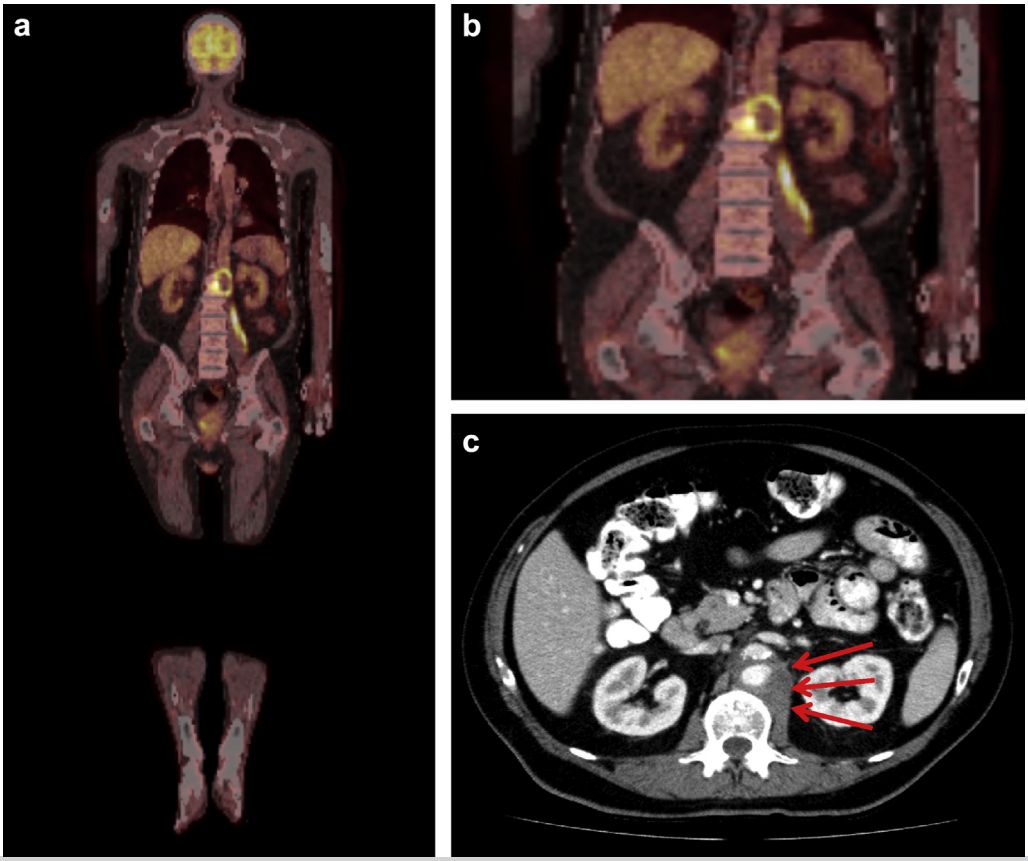

Fig 1. a, Positron emission tomography-computed tomography (CT): frontal section of whole body showing pathologic activity at the abdominal aorta and left psoas muscle. **b,** Positron emission tomography-CT: magnification of lumbar area discussed in **(a)**. **c,** CT: transverse section showing aneurysmal characteristics of the abdominal aorta (*arrows*).

of the *M. bovis* infection resulting in the mycotic aortic aneurysm. The Dutch Institute for Public Health notified the manufacturer of the BCG strain about this case. To our knowledge, no other cases of mycotic aneurysm have been linked to this BCG strain.

At first, the exact resistance-related characteristics of the mycobacterium in this patient were unknown. Therefore, initial antimicrobial treatment consisted of rifampicin, ethambutol, isoniazid, and pyrazinamide. As soon as it became clear that *M. bovis* had caused the infection, pyrazinamide was dropped from the treatment regimen.

Postoperatively, the patient developed severe inflammatory response syndrome and was admitted to the intensive care unit. Furthermore, acute-on-chronic renal insufficiency developed, for which he received hemodialysis. His postoperative course was also complicated by paralytic ileus and accumulation of chylous ascites. The chylous ascites was treated with a combination of paracentesis, total parenteral nutrition, and administration of octreotide. His condition gradually improved and hemodialysis could be stopped. Production of chylous ascites diminished substantially, and the ileus resolved.

The patient was transferred to the general surgery ward. His condition improved, and he was transferred to a rehabilitation center 2 months after surgery. Antimicrobial treatment with rifampicin, ethambutol, and isoniazid had to be continued.

Three months after discharge, the patient was again admitted with fever, generalized weakness, and malaise. Physical examination showed no abnormalities apart from fever and tachycardia. Blood tests showed an elevated C-reactive protein level (43 mg/L) and leukocytosis (18.2 $\times$ 10^9/L). A CT scan showed a fluid collection on the left dorsolateral side of the bovine aorta tube graft extending into the left psoas muscle (Fig 2). CT-guided drainage was performed, and 60 mL of fluid was sent for culture. Analyses showed mycobacterium in the aspirated fluid.

Initially, it was unclear whether the collection resulted from active *M. bovis* infection or from paradoxical abscess formation during antituberculosis therapy.[2] The patient's case was discussed with a tertiary tuberculosis center. The team decided to initiate treatment for both active infection and paradoxical abscess formation. The antibiotic treatment regimen was changed to rifampicin, ethambutol, and moxifloxacin. The paradoxical abscess formation was treated with drainage and dexamethasone.

The patient's condition improved substantially, and a follow-up CT scan showed a significant decrease of the collection, so the

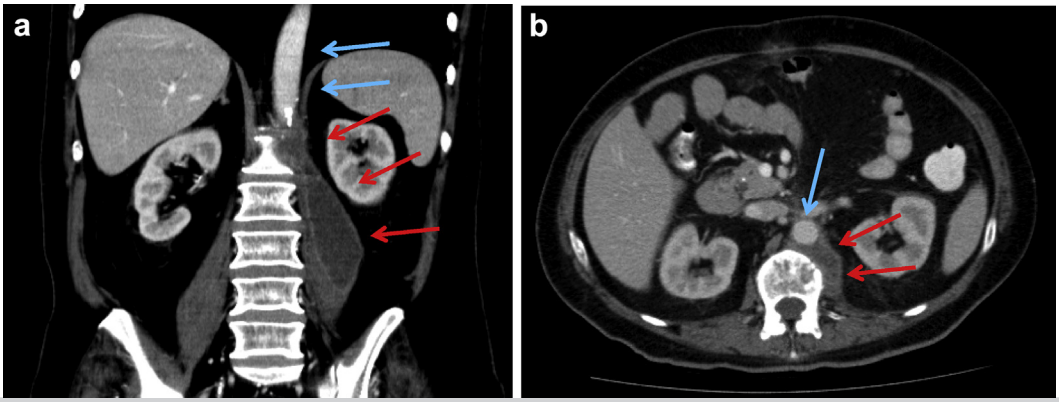

Fig 2. a, Computed tomography (CT) of the abdomen: frontal section showing the aorta (*blue arrows*) and recurrence of fluid collection with significant extension into the left psoas muscle (*red arrows*). **b,** Transverse section showing the left dorsolateral extension and the orientation of the collection (*red arrows*) with respect to the aorta (*blue arrows*).

patient was discharged. Awaiting the definite mycobacterium cultures, he will be monitored in an outpatient setting.

DISCUSSION

BCG is a live attenuated strain of *M. bovis* and is widely accepted as bladder instillation therapy for non-muscle-invasive bladder cancer. The mechanism of antitumor activity is not completely understood but seems to involve immune system stimulation resulting in release of tumor necrosis factor and apoptosis of tumor cells. The most common adverse effects described are fever, hematuria, granulomatous pneumonitis, and hepatitis and, less often, BCG sepsis.

Although it is a rare complication, increasing cases of aortic aneurysm secondary to *M. bovis* infection after intravesical BCG therapy have been reported, mainly in the past two decades.[3-12] Leo et al reviewed 20 cases and noted that patients often present with unspecified symptoms (weight loss, fatigue, malaise) that are often misinterpreted. They also noted a substantial spread in the time interval from BCG treatment to symptoms, ranging from 14 to 77 months.

The exact pathomechanism remains unclear. Although risk factors for reactivation of mycobacterial disease have been described, no risk factors specific for vascular complication after BCG treatment have been identified so far.[13] No imaging studies had been performed that could rule out a pre-existing aortic aneurysm. It remains unclear whether a pre-existing aneurysm had been infected or a primary infection of a normal aorta had occurred.

CONCLUSIONS

Infection of an aortic aneurysm is a potentially life-threatening complication of BCG therapy. The rarity, late appearance, unspecific clinical signs, and low awareness create challenges in diagnosis of this complication. In all patients with a history of BCG therapy and unspecified clinical signs, a mycotic aneurysm of the aorta must be ruled out. Furthermore, we advise additional research into the risk factors contributing to this complication.

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