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Case Report

Mycotic aortic aneurysm due to intravesical BCG immunotherapy: Clinical manifestations and diagnostic challenges

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ABSTRACT

A live, attenuated form of *Mycobacterium bovis*, bacillus Calmette–Guérin (BCG), is commonly used as intravesical immunotherapy for non-invasive urothelial bladder carcinoma. While complications are rare, dissemination can occur. A case of mycotic aortic aneurysm following BCG administration with recovery of *Mycobacterium bovis* in culture is reported. A review of the published experience with this problem is also presented.

1. Case report

A 64-year-old man presented to our hospital with a four-week history of progressive back pain that began six weeks after he underwent extensive dental work. His past medical history included gastroesophageal reflux disease, asthma, ten pack-years of smoking, and high-grade bladder cancer that had been treated with bacillus Calmette–Guérin (BCG), the live, attenuated form of *Mycobacterium bovis*, five months previously. On admission, his body temperature was 36.5 °C; cardiovascular and abdominal exams were normal and without bruits. There was no tenderness over the thoracic and lumbar spines. Initial laboratory testing demonstrated a white blood cell count of 6.0×10^3/cu mm (reference $4.5–11.0 \times 10^3$/cu mm); a chemistry panel was within reference ranges. Computed tomographic (CT) scans of the chest, abdomen, and pelvis revealed a large, proximal aortic aneurysm (8.4 cm in transverse diameter) beginning at the level of the diaphragmatic crus, with an associated lobulated, saccular outpouching arising from the proximal abdominal aorta (Fig. 1). A psoas muscle abscess was contiguous with the posterior inferior margin of the aneurysm (Fig. 2).

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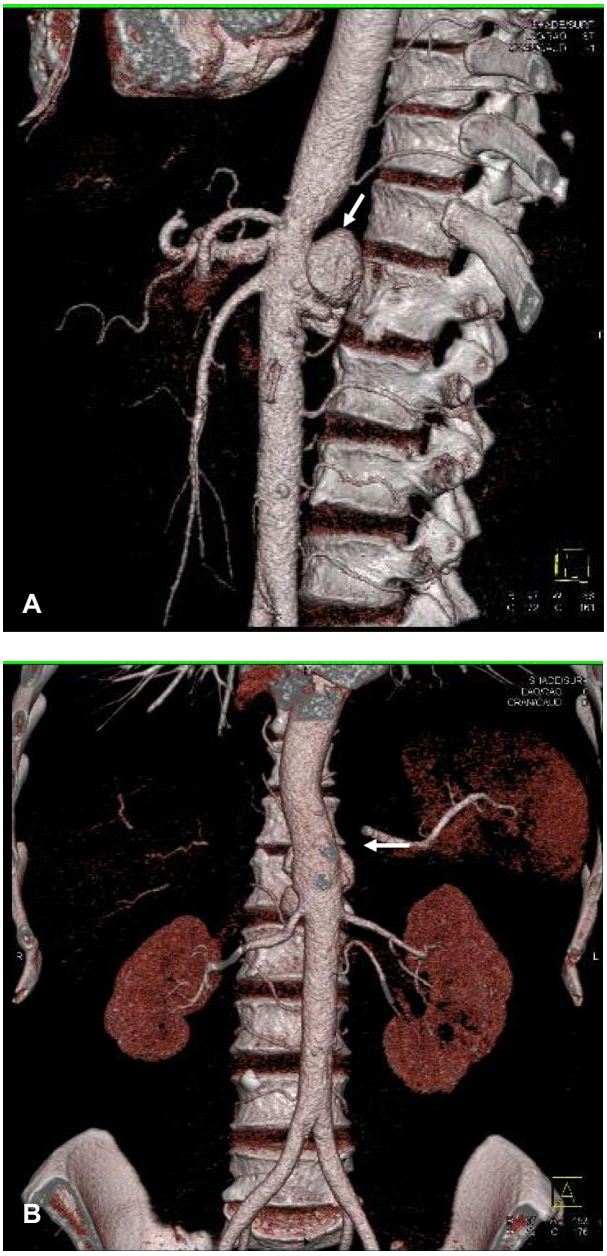

Fig. 1 – Image of the suprarenal aortic aneurysm (8.4 cm transverse diameter) with associated saccular outpouching [(4.7 cm cephalocaudal × 2.2 cm anteroposterior × 3.7 cm transverse diameter), white arrows] using 3-dimensional CT angiography: (A) sagittal view, (B) coronal view.

Initial bacterial blood cultures, blood cultures for acid fast bacilli (AFB), and a culture of fluid aspirated from the psoas muscle collection were negative. Empiric treatment with rifampin, isoniazid, pyrazinamide, and ethambutol (RIPE) was initiated. Transthoracic echocardiography showed no valve pathology. Surgical consultation was obtained, RIPE was held for 72 h prior to surgery, and the patient underwent open surgical debridement and repair with a 24-mm rifampin-soaked, four-branched, Coselli vascular graft. The surgery was performed with partial left heart bypass and distal aortic perfusion. With this technique, the aorta could be clamped

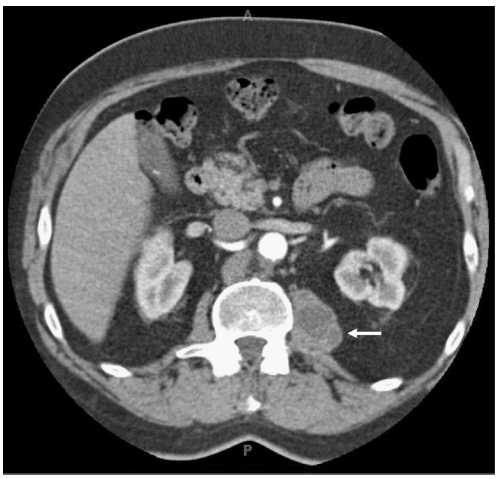

Fig. 2 – Image of psoas muscle abscess [(2.8 cm cephalocaudal × 3.1 cm anteroposterior × 6.1 cm transverse diameter), white arrow] using contrast-enhanced CT angiography.

and extensively debrided, while perfusion to the kidneys and lower extremities was maintained. Intraoperative examination revealed a contained rupture of the aorta surrounded by turbid fluid. Malodorous fluid was also noted within the left psoas muscle.

Cultures were collected for bacteria, fungi, and AFB from the aortic tissue, periaortic fluid, left psoas muscle fluid, and peripheral blood. Culture of the aortic tissue in Middlebrook media demonstrated growth of an organism identified as belonging to the *M. tuberculosis* complex by nucleic acid probe testing (AccuProbe, Gen-Probe, San Diego, CA). The final identification of BCG was obtained through high-performance liquid chromatographic (HPLC) identification of the mycolic acid profile (Sherlock®, MIDI, Inc., Newark, DE).

RIPE therapy plus vitamin B6 was re-initiated post-operatively; pyrazinamide was discontinued upon definitive identification of BCG. After three months of treatment, the patient developed peripheral neuropathy that was attributed to isoniazid, so this agent was stopped and replaced with moxifloxacin. One month later, he reported changes in his vision. He was evaluated by ophthalmology due to concern for ethambutol-associated optic neuritis. A diagnosis of cataracts was made; treatment with moxifloxacin and rifampin was continued, but ethambutol was discontinued. Repeat CT imaging of the chest and abdomen 6 months after surgery showed post-surgical changes superior to the diaphragmatic hiatus with a 4.5 × 2.3 cm fluid collection within the right diaphragmatic crus. Nine months after surgery, he developed posterior ankle pain. Achilles tendinopathy was diagnosed one month later and attributed to moxifloxacin. At that time, moxifloxacin and rifampin were discontinued. Repeat CT imaging of the chest and abdomen 10 months post-surgery was unchanged.

2. Discussion

Bacillus Calmette–Guerin is a live, attenuated strain of *Mycobacterium bovis* that was developed in the early 20th century as a vaccine against tuberculosis. It is now widely used in

the treatment of superficial bladder carcinoma [1] and as adjuvant therapy for malignant melanoma [2,3]. While its mechanism of action against bladder carcinoma is not fully understood, use of BCG has been shown to induce a multifaceted inflammatory response that is thought to result in antitumor effects [4].

Intravesical BCG instillation is associated with localized reactions, including hematuria (30–35% of treated patients) and lower urinary tract symptoms, such as urgency, frequency, and dysuria (30–60%) [5]. Other local complications, including granulomatous prostatitis and epididymo-orchitis (1–4%), are less common, but compel cessation of treatment. Systemic side effects, such as fever and malaise, are not uncommon (10–30%), but are typically transient. Potentially life-threatening complications are heralded by high, persistent fever and are either due to sepsis or a systemic immune response. Although uncommon (0–7%), these complications can occur years following BCG instillation.

Vascular complications are rare, with only 24 cases previously reported (Table 1) [3,6–26]. While men are 3–4 times more likely than women to develop urothelial bladder cancer [27], only men have been reported to develop aneurysms after urinary bladder BCG instillations. Although one case of a mycotic aneurysm occurring in a woman has been described, this was in the setting of BCG therapy for metastatic malignant melanoma [3].

The mean age of patients at the time of the mycotic aneurysm diagnosis is 71 years, with individuals as young as 58 years reported [3,6–26]. The mean reported aneurysm size is 5.2 cm in largest diameter, with a range of 1–8 cm. Mycotic aneurysms commonly appear saccular and thin-walled on radiographic imaging (Fig. 1) [6–11]. While vascular complications involving both large- and medium-sized vessels have been reported, 79% of mycotic aneurysms associated with BCG therapy have primarily involved the aorta. Of those 19 cases, one occurred at the aortic arch while the remaining 18 involved the abdominal aorta, and 15 occurred inferior to the renal vasculature. Four (22%) of the 18 reported cases of BCG-associated abdominal aortic aneurysms have been accompanied by rupture, and all four ruptures occurred in patients with infrarenal aneurysms. Extension of the infection into the psoas muscle occurred in 7 (39%) of 18 previously reported patients with BCG-related abdominal aortic aneurysms. These psoas muscle abscesses also occurred nearly exclusively in patients with infrarenal mycotic aneurysms (Table 1). The one notable exception is the case reported by Izes et al., where the patient presented with an aneurysm of the aortic arch and was subsequently noted to have an isolated psoas muscle abscess [12].

As with other complications of intravesical BCG therapy, mycotic aneurysms may come to attention long after treatment has been administered. Cases diagnosed between four months and over five years after completion of treatment have been described [11,13]. Symptoms of BCG-related mycotic aneurysms are non-specific. Weight loss is the most common constitutional sign, occurring in 33% of cases, followed by fever (20%) and night sweats (15%). In patients with site-specific symptoms, lumbago was most frequent, occurring in 8 (33%) of the previously reported cases, all of whom had an infrarenal aneurysm. Due to the rarity of the condition, the non-specific symptoms, and the potential for late-onset disease manifestations, a delay in accurate diagnosis of over a year occurred in four cases [3,9,14,15]. One patient who presented with constitutional symptoms of malaise and generalized weakness, for example, was found to have an elevated erythrocyte sedimentation rate and was presumptively diagnosed with polymyalgia rheumatica. Only after the development of abdominal and back pain did a CT scan of the abdomen lead to the definitive diagnosis [16]. Since bladder cancer and aortic aneurysms tend to affect patients of similar ages, the aortic aneurysm may be initially misjudged as incidental [17].

Accurate identification of BCG in culture presents a diagnostic challenge. Many microbiology laboratories only speciate these organisms to the level of the *M. tuberculosis* complex using nucleic acid probe testing. Additional methods, such as biochemical testing for nitratase activity and thiophen-2-carboxylic acid hydrazide susceptibility, HPLC identification of the mycolic acid profile, and/or susceptibility testing for pyrazinamide mono-resistance, are needed to distinguish *M. tuberculosis* from BCG. Molecular techniques have also been developed, including multiplex PCR to detect deletion of genomic region RD1 [28] and ETR-D spacer sequencing [29]. However, these methods are not commercially available and are not routinely performed in microbiology laboratories, particularly in regions with a low prevalence of tuberculosis. Thus, a high clinical index of suspicion based upon a history of BCG instillation is necessary to guide laboratory identification of the organism.

Treatment of BCG-related mycotic aneurysms has commonly involved combined antimycobacterial therapy with surgical placement of rifampin-soaked aortic graft material. Currently, there are no formal guidelines for the duration and selection of antimicrobial treatment of BCG-associated mycotic aneurysms; however, the most frequently utilized regimen for reported cases includes a minimum of 9 months of isoniazid and rifampin (Table 1). There is no role for pyrazinamide in the treatment of BCG-related infections because of inherent resistance owing to a lack of pyrazinamidase and nicotinamidase, enzymes necessary for activation of the drug [30]. BCG is also susceptible to the fluoroquinolone moxifloxacin *in vitro* [31] and has been employed with partial success in previous cases where first-line agents were contraindicated [13] and [14].

Since BCG has been recovered in culture in a minority of cases, the roles of host and pathogen in the formation of mycotic aneurysms remain unclear. Furthermore, BCG is not a single entity, as multiple bladder instillation protocols using different strains of BCG are currently utilized. While prior studies have been designed to establish equivalent antitumor efficacy among strains [32], recent research has elucidated divergence between BCG strains, including differences in antibiotic susceptibility patterns [33]. Further investigation of relative virulence and risk of dissemination may guide future therapy protocols.

This report expands the limited data on vascular complications related to BCG therapy. This case is unique in that it is the first reported case where an aneurysm superior to the renal vasculature was contiguous with a psoas muscle abscess. Further, the three dimensional imaging presented here

Table 1 – Reported cases of BCG-related vascular complications.

Case	Age	Anatomical site[a]	Position	Size[b]	Rupture	Presenting symptoms[c]	Surgical repair[d]	Antibiotic regimen[e]	Outcome
Woods[f,g]	62	AA	Infrarenal	4.5 cm	No	LBP	Primary	RI	Lived
Bornet[g]	74	Bilateral FA	N/A	N/A	Yes	Rupture	Primary	RIE × 3 mo; IE × 9 mo	Lived
Deresiewicz[g]	67	AA, EIA	Infrarenal	8 cm	No	Pulsatile mass, WL	Primary	None	Died
Izes[g]	69	Aortic Arch, PM	N/A	5 cm	No	WL, Fatigue, Confusion	None	None	Died
Wolf[g]	80	AA, PM	Infrarenal	NR	Yes	LBP, RDP, NS, malaise	Primary	RIE × 20 mo	Lived
Hellinger[g]	71	AA, PM	Lower[h]	6 cm	No	Fever, malaise	Primary	RIE × 2 mo; IE × 10 mo	Lived
Rozenblit[g]	76	AA, PM, OM	Infrarenal	NR	No	LBP, WL, RDP	EVAR	RIE + FQ	Died
Damm[g]	71	AA	Infrarenal	NR	Yes	Abdominal pain, fever	Primary	RI	Lived
Seelig[g]	72	Left FA bypass graft	N/A	N/A	No	Groin pain	Primary	RIE	Lived
Seelig[g]	58	AA	Infrarenal	6 cm	No	LBP, Fever, WL	Primary	IE × 12 mo	Lived
Seelig[g]	71	AA	Infrarenal	6 cm	No	Extremity wound, fever	Primary	RIE × 2 mo, RI × 10 mo	Lived
Farber[g]	74	Left FA	N/A	N/A	No	Leg pain, pulsatile mass	Primary	ER	Lived
LaBerge[g]	75	AA, PM	Infrarenal	NR	No	LBP	Primary after EVAR	NR	NR
Geldmacher[g]	68	CA fistula	N/A	NR	No	Bleeding	Primary	NR	NR
Kamphuis[g]	65	AA	Suprarenal	NR	No	AP, WL, Nausea	Primary	None	Died
Witjes[g]	67	Left PA	N/A	NR	No	Fever, knee pain	None	RIE × 12 mo	Lived
Wada[g]	75	AA, PM, Left FA	Infrarenal	5 cm	No	LBP	Primary	None	Lived
Dahl[g]	69	AA, PM, SP	Infrarenal	4.5 cm	Yes	LBP, NS, RDP, Malaise	Primary	RI × 12 mo	Lived
Harding[g]	80	AA	Infrarenal	7.6 cm	Yes	Fever, WL, Malaise	Primary	RIE × 12 mo	Lived
Safdar[g]	79	AA	Infrarenal	3 cm	No	Fever, NS, WL, Malaise	Primary	RIE × 12 mo	Lived
Costiniuk[g]	75	AA, FA	NR	6.5 cm	No	LBP, AP	Primary	RIE × 12 mo	Lived
Coscas[g]	79	Descending TA, AA, Left EIA, Left PTA	Infrarenal	1 cm	No	Painful neck mass	Primary	RIE × 2 mo; RI × 7 mo	Died[i]
Maundrell	75	AA	Suprarenal	5 cm	No	Fever, NS, WL	Primary	RIE	Died
Santbergen	58	AA, PM, SP	Infrarenal	NR	No	LBP	EVAR	RI + FQ × 12 mo	Lived
Present case	64	AA, PM	Suprarenal	8.4	No	LBP	Primary	R × 9 mo; FQ × 6 mo; E × 4 mo; I × 3 mo	Lived

a AA: Abdominal Aorta; CA: Carotid Artery; EIA: External Illiac Artery; FA: Femoral Artery; OM: Osteomyelitis; PA: Popliteal Artery; PM: Psoas Muscle; PTA: Posterior Tibial Artery; SP: Spondylitis; TA: Thoracic Aorta.

b CM: Largest Diameter in Centimeters; NA: Not Applicable; NR: Not reported.

c AP: Abdominal Pain; LBP: Low Back Pain(Lumbago); NS: Night Sweats; RDP: Radiculopathy; WL: Weight Loss.

d EVAR: Endovascular Repair.

e E: Ethambutol; FQ: Fluoroquinolone; I: Isoniazid; R: Rifampin.

f Immunotherapy for Malignant Melanom.

g Case previously tabulated by Coscas et. al.

h Not further specified.

i Died of bladder cancer.

depicts the characteristic appearance of these aneurysms. While data regarding evaluation and management are limited, this report is the most comprehensive review to date. Based on characteristics of previous cases, it is recommended that any individual with a history of BCG instillation therapy who subsequently develops sustained constitutional symptoms, including new-onset lumbago, should be evaluated for the presence of mycotic aneurysm. Additionally, surgical evaluation and medical management with 2 months of isoniazid, rifampin, and ethambutol followed by a minimum of 7 months of isoniazid and rifampin seems prudent.

Conflicts of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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