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Infection of an axillo-bifemoral bypass graft following intravesical bacillus Calmette–Guerin (BCG) immunotherapy for urothelial cancer due to *Mycobacterium bovis* and *Staphylococcus aureus*

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ABSTRACT

We report a case of occult *Mycobacterium bovis* left axillary-bifemoral bypass graft infection, with superimposed acute methicillin-susceptible *Staphylococcus aureus* (MSSA) infection in an 82 year old male following intravesicular bacillus Calmette–Guerin (BCG) for adjuvant therapy of urothelial cancer. The patient underwent partial removal of the bypass graft and treated with antimycobacterial therapy—rifampin and isoniazid for 9 months, and intravenous cefazolin followed by oral cephalexin for chronic suppressive therapy for MSSA. This presentation highlights the need to consider indolent infection masquerading as mechanical erosion, even when an alternate infection is present.

Case

An 82 year old Caucasian male with aortic atherosclerosis and left axillary femoral bypass graft with a femorofemoral crossover, presented to our institution with rigors, progressive weakness, weight loss, and hypotension with an open wound over the graft. He underwent aortobifemoral graft placement 28 years before, with subsequent bowel perforation and infection of the graft necessitating removal of the graft and placement of a left axillary to iliac bypass graft 7 years later. Six year prior to presentation, he underwent left nephroureterectomy and transurethral resection of bladder tumor for a noninvasive grade 2 out of 3 papillary urothelial carcinoma. He had evidence of recurrence 3 years prior to presentation. Pathology revealed noninvasive grade 3 out of 3 carcinoma. He received bacillus Calmette–Guerin (BCG) therapy for three treatments weekly, every 6 months, with excellent response to this therapy on repeat cystoscopies without evidence of tumor in the bladder.

Approximately 3 years later (2 months prior to presentation), he noticed erythema and skin blisters over the graft without systemic symptoms. Of note, his last BCG therapy and cystoscopy was 4 months prior. Several weeks later, he developed weakness, loss of appetite, weight loss, and an open wound with purulent drainage over the graft. In the following 1–2 weeks, he had fevers, rigors, progressive weakness and presented to the emergency department where he had a blood pressure of 70/40, temperature 38.3 °C, and a pulse rate 139 bpm. Blood cultures on admission grew methicillin-susceptible *Staphylococcus aureus* (MSSA). A wound culture obtained from the graft also grew MSSA. He was started on intravenous vancomycin and piperacillin/tazobactam. Physical examination was remarkable for a 2 cm open lesion over the left lateral abdomen through which the graft was visible with a small surrounding area of erythema. Laboratory studies revealed a white blood cell count of 10,700 cells/mm^3 (90% neutrophils), hemoglobin 11.1 g/dL, sodium 128 mmol/L, creatinine 0.9 mg/dL, AST 43 U/L, ALT 33 U/L, and alkaline phosphatase 167 U/L.

Ultrasound of the bypass graft and computer tomography angiogram of the abdominal aorta showed complete occlusion of the left axillary to bilateral common femoral artery bypass graft and an open wound in the left flank extending to the graft (see Fig. 1). An Indium-111 white blood cell scan revealed abnormal radiotracer localization along the left axillary to left common femoral artery graft consistent with an infected bypass graft. He was diagnosed with *S. aureus* graft infection with secondary bloodstream infection. However, the subacute erythema over the graft developing about 8 weeks prior to admission raised the possibility of a more indolent infection leading to graft erosion through the skin. Given previous BCG therapy, disseminated BCG infection was also considered.

The following day, he underwent explantation of the graft with closure of the left axillary proximal anastomosis over a stump of the graft, and closure of the distal right femoral anastomosis and left femoral anastomosis, leaving a small rim of incorporated

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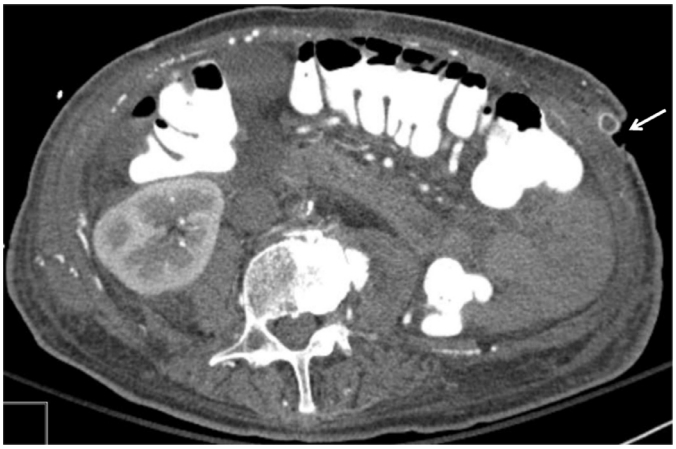

Fig. 1. Open wound in the left flank extending to the graft.

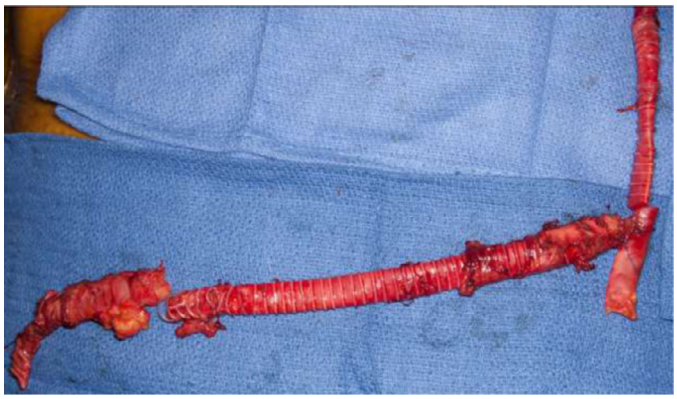

Fig. 2. Explanation of the infected left axillofemoral bypass graft.

graft (see Fig. 2). Transesophageal echocardiogram was performed and did not show any evidence of valvular vegetations. Bacterial cultures of the explanted graft revealed MSSA and antibiotic therapy was narrowed to IV cefazolin to complete 4 weeks of therapy followed by chronic oral antibiotic suppression with cephalexin 500 mg twice daily, given the residual graft present. Pathology of the graft material showed acutely inflamed fibrous tissue without identifiable microorganisms on tissue Gram and Gomori methenamine silver stains.

Approximately 2 weeks after explantation, mycobacterial cultures grew *Mycobacterium tuberculosis* complex on 5 out of 5 surgical specimens obtained. Acid-fast smears were negative on all cultures. Mycobacterial blood cultures remained negative at 60 days. Identification by high-performance liquid chromatography revealed *Mycobacterium bovis*, BCG strain. Susceptibilities demonstrated resistance to pyrazinamide with mutation detected in pncA on sequencing, and sensitivity to rifampin, ethambutol, and isoniazid. He was treated with oral isoniazid and rifampin for 9 months. He was seen in follow up 3 months following completion of antimycobacterial therapy and had no fevers or chills, and his only complaint was claudication after walking two to three blocks.

Discussion

We report a rare case of *Mycobacterium bovis* infection of a vascular bypass graft in a patient receiving intravesical BCG therapy. Our patient developed a skin and soft tissue infection that progressed over an 8-week period with exposure of the bypass graft and ultimately MSSA bloodstream infection. He was treated with anti-staphylococcal antibiotic therapy and underwent surgical removal of the graft. However, given the indolent course, which would be unexpected for *S. aureus*, the provider requested additional cultures (fungal, mycobacterial) considering alternative diagnoses given the history of previous BCG therapy. This ultimately led to our finding of *M. bovis*. We hypothesize the patient developed BCG infection of the bypass graft that led to subacute wound breakdown and exposure of the graft with secondary infection from skin flora (MSSA) leading to bacteremia. Our patient improved following graft removal and antimicrobial therapy—IV cefazolin for 4 weeks followed by chronic suppression with oral cephalexin 500 mg twice a day, and oral isoniazid and rifampin for 9 months.

BCG is a live attenuated strain of *Mycobacterium bovis* that has become the treatment of choice in patients with superficial urothelial cancer [1]. Intravesical BCG therapy reduces disease progression, the need for cystectomy, and prolongs survival [2]. It is well tolerated by >95% of patients. However, both local and systemic complications can occur following BCG therapy such as dysuria, hematuria, fever, and malaise for up to 48 h following instillation [3,4]. The anti-neoplastic mechanism is thought to be due to immune stimulation of both cell-mediated immunity and cytokines, which results in the death of cancer cells [2,3,5–7]. In one study of over 2600 patients, 4.8% of patients developed severe, systemic complications including sepsis, cytopenia, renal abscess, pneumonia, fever, and granulomatous prostatitis [2]. In an analysis of 282 patients with BCG infection, disseminated BCG infection (miliary tuberculosis, fever with bone marrow and/or liver infiltration, and sepsis with multiorgan failure) was the most common manifestation, occurring in 34.4% of patients. Less common manifestations included osteomuscular infection including prosthetic joint infections (19.9%), hepatitis (5.7%), mycotic aneurysms (4.6%), and infection of a vascular bypass graft (0.7%) [3].

The risk profile of patients who develop complications from intravesical BCG therapy is unknown. It has been suggested that early BCG instillation following disruption of the urothelial barrier, presence of underlying immunosuppression, advanced age [6], and early BCG instillation after transurethral resection of bladder cancer [3,8,9]. Our patient received intravesical BCG therapy for approximately 3 years, starting at the age of 79 and presented with BCG involvement of the vascular bypass graft at the age of 82. His last BCG instillation was approximately 4 months prior to the development of infection. Heiner and Terris [6] caution against providing maintenance BCG therapy in patients 70 years and older, and suggest altogether avoidance in patients over age 80.

There has been only one case report in the literature of *M. bovis* infection of an axillary-femoral bypass graft following intravesical BCG therapy [10]. This patient was a 62 year old male with non-invasive urothelial carcinoma who received BCG instillations over a 10 month period. He underwent removal of the bypass graft and received isoniazid, rifampin, and ethambutol for 9 months [10]; however, there was no follow-up available for their patient. Our patient underwent surgical removal of the entire axillo-bifemoral bypass graft except there was a small rim of incorporated graft. The treatment course was 9 months for *M. bovis* with oral rifampin and isoniazid, and IV cefazolin followed by oral suppression with cephalexin for MSSA. He was followed up in clinic 13 months post-hospitalization, doing well without fevers or chills.

This case illustrates the importance of having a high-index of suspicion for occult infection with BCG infection, even when an alternate pathogen is present. Surgical explantation of the bypass graft, and anti-staphylococcal and antimycobacterial therapy, resulted in a favorable outcome in this case.

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