Late Presentation of Disseminated Bacillus Calmette-Guerin Infection in an Immunocompetent Male

Virgil Vasile Captan, Pouneh Dokouhaki, Kim Solez, Artur Szkotak, Fraulein Morales

DOI: 10.22374/cjgim.v13i1.214

About the Authors

Virgil Vasil Captan is a general internal medicine subspecialty resident at the University of Alberta. Pouneh Dokouhaki is a clinical fellow in the Department of Laboratory Medicine and Pathology, University of Alberta. Kim Solez is a professor of pathology in the Department of Laboratory Medicine and Pathology, University of Alberta. Artur Szkotak is an assistant professor in the Department of Laboratory Medicine and Pathology, University of Alberta. Fraulein Morales is a clinical associate professor in the Department of Medicine, University of Alberta.

Submitted: May 30, 2017; Accepted: December 20, 2017. Published: March 5, 2018.

Abstract

Intravesical administration of Bacillus Calmette-Guerin (BCG) is a cornerstone of adjuvant treatment for low-grade urothelial carcinoma. Complications from administration are relatively rare and generally evident within one month. Systemic BCG infections are typically diagnosed within 14 days post BCG administration; however, cases have been reported of infections being diagnosed as late as 17 years after treatment. Here, we describe the unusual case of a 55-year-old immunocompetent male who was diagnosed with disseminated BCG infection 3 years after initial adjuvant treatment for urothelial carcinoma.

Résumé

L'administration intravésicale du bacille de Calmette et Guérin (BCG) est un principe de traitement d'appoint pour le carcinome urothélial à évolution lente. Les complications liées à l'administration sont plutôt rares et se manifestent en général en dedans d'un mois. Les infections systémiques causées par le BCG sont habituellement diagnostiquées dans les quatorze jours qui suivent l'administration du BCG; on a toutefois déjà rapporté des cas d'infection aussi tardivement que 17 ans après le traitement. Nous décrivons ici le cas peu commun d'un homme de 55 ans immunocompétent chez qui on a diagnostiqué une infection disséminée due au BCG 3 ans après un premier traitement d'appoint pour un carcinome urothélial.

Case Presentation

Mr. M. is an immune-competent 55-year-old male smoker diagnosed with low-grade urothelial papillary carcinoma. He underwent a transurethral resection of the bladder followed by 6 instillations of Bacillus Calmette-Guerin (BCG). Two-years later, he developed bilateral pedal edema, fatigue, exertional dyspnea, and frothy urine. In the two years between his BCG instillation and presentation to clinic he had no travel outside his native country of Canada. He also had no contact with farm animals. He seemed to have remained in good health and did not seek medical attention for any specific symptoms.

On initial assessment, he did not have constitutional symptoms of fever, weight loss, or night sweats. His past medical history was significant only for the above-mentioned bladder cancer and a clinical diagnosis of chronic obstructive pulmonary disease. He had no travel outside of Canada and no tuberculosis (TB) contacts or risk factors. His medications included furosemide, codeine, naproxen, symbicort, and iron supplements. He had

no known allergies. He is an active smoker with a 15-pack-year history and did not consume alcohol or illicit drugs. He worked as a furniture delivery man. His physical exam showed a normal blood pressure of 112/62, heart rate 74, Temp 37.2, Oxygen saturations of 96% and a body mass index of 22. His cardio-respiratory exam was suggestive of obstructive airway disease. Jugular venous pressure was 3–4 cm above the sternal angle. There was a normal S1, S2 with no extra heart sounds. Respiratory exam revealed clear breath sounds. He had a decreased laryngo-sternal height at 3 cm. There was symmetrical mild leg edema present. No lymphadenopathy or organomegaly was detected.

Initial investigations showed new proteinuria with a Protein:Creatinine ratio of 109 mg/mmol and a normocytic anemia with a Hgb 121 g/L. His iron indices showed an iron of 6 umol/L, total iron-binding capacity of 68 umol/L, iron saturation 0.09, and ferritin 204 ug/L. Thyroid stimulating hormone and vitamin B_{12} levels were normal. His creatinine clearance 4 weeks before initial evaluation was normal with a glomerular filtration rate (GFR) of 79 mL/min and a creatinine of 94umol/L. Albumin was 36 g/L. and a urine albumin:Cr ratio was elevated at 7.04 mg/mmol. Trasnaminases and inflammatory markers were not done at initial consultation. A chest radiograph showed mild pulmonary hyperinflation and peribronchial cuffing centrally, along with mild interstitial opacity bilaterally in lower lobes. EKG showed normal sinus rhythm at 66 bpm. A transthoracic echocardiogram suggested pulmonary hypertension with an RVSP of 60–65mmHg but preserved left sided function. Pulmonary function tests showed forced expiratory volume 1/forced vital capacity of 71, forced expiratory volume 1 of 87% predicted, total lung capacity 97% predicted, and transfer coefficient of 41% predicted. He underwent a computed tomography scan of the chest that revealed interlobular septal thickening, central bronchial wall thickening, and mosaic attenuation. A ventilation-perfusion scan showed no evidence of chronic thromboembolic disease. A positron emission topography scan showed a PET avid 1.6 cm ill defined soft tissue nodule at the left lateral margin of the left common iliac artery, diffuse increased bone marrow activity, and low-grade activity in the distal esophagus. Post scans, he was found to be in renal failure (presumed contrast induced nephropathy) with a GFR of 30 mL/min. He was treated conservatively, but over the next few months he had persistent leg edema, fatigue and dyspnea. He also developed weight loss (~25lbs over one year), anorexia, and dysphagia. A repeat cystoscopy showed no evidence of recurrent disease. His anemia became more profound and microcytic with absent reticulocytosis. He underwent a bone marrow biopsy that showed non-caseating granulomas, serous fat atrophy, and normal marrow iron stores (Figure 1A). Three and a half years after initial bladder cancer treatment the patient was becoming weaker and was admitted to the University of Alberta Hospital. In hospital, he had a gastroscopy and colonoscopy which showed evidence of gastropathy and a small bowel biopsy showed focal non-caseating granulomas (Figure 1B). His GFR was still suppressed at 30ml/min, and a kidney biopsy was performed which showed non-necrotizing granulomatous interstitial nephritis and, diffuse active tubulointerstitial nephritis on the background of hypertensive vascular changes, (Figure 1C). While the working diagnosis was sarcoidosis, specimens were sent off for acid-fast stains and cultures. Tuberculin skin test was negative, as was a QuantiFERON Release assay. Urine, blood, and sputum specimens grew *Mycobacterium bovis* within 16 days of incubation. Isolation of Mycobacterium chimera complex was done using the BACTEC mycobacterial growth indicator tube and identification was achieved by performing pyrosequencing of the 16s ribosomal ribonucleic acid gene. The patient's human immunodeficiency virus test was negative. Interestingly, while in hospital the patient also developed spontaneous bilateral pneumothoraces that were managed conservatively without chest tube insertion.

The patient was diagnosed with disseminated BCG infection; isoniazid, rifampin, vitamin B6 and moxifloaxacin were started. He had good symptomatic response associated with clearance of blood, urine, and sputum cultures.

Discussion

BCG is a live attenuated strain of *Mycobacterium bovis* that was isolated by Calmette in 1921.[1–3] BCG immunotherapy was proposed as an alternative to chemotherapy for treatment of bladder cancer in the 1970s,[4] and remains a cornerstone of adjuvant bladder cancer treatment.[5] Most patients experience lower urinary tract and flu-like symptoms in the first 48 hours post BCG instillation,[6] and these symptoms potentially indicate a favourable therapeutic response.[7] Both local and systemic complications have been documented post BCG instillation. Cystitis is the most common side effect and has been reported in 91% of patients; however, clinically significant complications have been estimated at less than 5%,[8] with disseminated BCG being reported in less than 1% of patients. Complications from BCG instillation are classified as early (within 3 months) or late (after 1 year). Early disease is characterized by systemic complications such as hepatitis, pneumonitis, osteomyelitis, mycotic vascular infections, endophthalmitis, or sepsis; whereas late disease involves focal infection of the genitourinary tract such as prostatitis, testicular masses, or bladder involvement.[9] Some complications have been thought to be secondary to hypersensitivity reactions and include granuloma formations in the liver, spleen, lungs, bone marrow, and lymph nodes.[10]

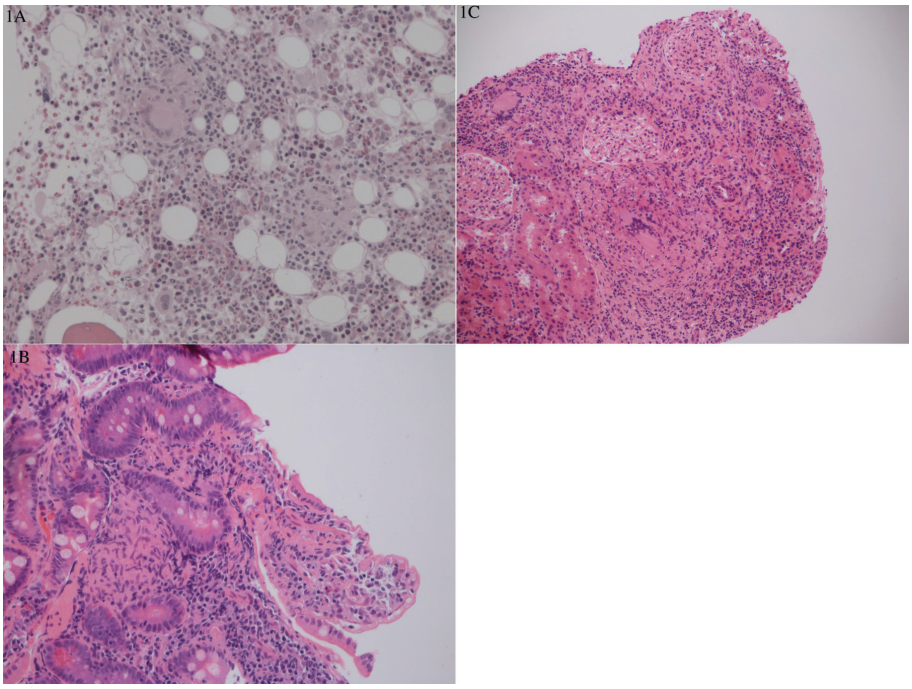

Figure 1. (A) Hematoxylin and eosin stain of bone marrow biopsy showing non-caseating granulomas. (B) Hematoxylin and eosin stain shows duodenal mucosal biopsy with a collection of epitheloid histiocytes forming small loose granuloma in the lamina propria (200× magnification). (C) Hematoxylin and eosin stain of kidney core biopsy with few multinucleated giant cells and mixed inflammatory infiltrate including many neutrophils in the interstitium (100× magnification).

However, other complications have been shown to be secondary to actual BCG infection.

Disseminated BCG infections described in case series have been predominantly documented as an early complication post BCG instillation. A recent case series of 11 patients reported the time interval between the last BCG instillation and the onset of complications to be 8.3 +/- 6.5 days.[1] The present case report is notable because of the two year gap between the last BCG instillation and subsequent symptom development. Review of the literature revealed one other case of disseminated BCG infection three years after initial bladder cancer treatment.[11] In contrast to our patient, that patient had marked constitutional symptoms at presentation associated with diffuse abdominal lymphadenopathy and splenomegaly.

In conclusion disseminated BCG infections present in a delayed and heterogeneous fashion and organ involvement. As such, a high index of suspicion must be maintained in anyone who presents with systemic complaints and a history of BCG adjuvant treatment.

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