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Case Reports and Series

Delayed-onset disseminated BCG disease causing a multi-system illness with fatal mycotic aortic aneurysm

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ABSTRACT

Case: We report a case of disseminated BCG infection, diagnosed two years after BCG infusion for bladder cancer. Our patient, a 74-year-old male, was referred with an 18-month history of fevers, weight loss and intermittent confusion. Prior to referral, the patient had multiple hospital admissions for evaluation of fever of unknown origin, confusion, and fatigue. He was treated for several acute infections, whilst extensive investigations did not identify a focal cause of the persistent fever. During this period two aneurysms, iliac and aortic, were found and stented. Both were presumed mycotic, but no positive microbiology arose from either.

He presented again with fever and confusion and was found to have a left sided pleural effusion, which was drained, and broad-spectrum antibiotics started, but his fever and inflammatory markers did not settle. *Mycobacterium tuberculosis* PCR on a pleural fluid sample returned a positive result, and later cultures from the same fluid grew *Mycobacterium* species which whole genome sequencing identified as *Mycobacterium Bacillus Calmette-Guérin* (BCG).

Despite a number of adverse events with anti-BCG medications, the patient was established on four medications (rifampicin/isoniazid/ethambutol/levofloxacin) with symptomatic improvement. He re-presented four months later with abdominal pain and was found to have an inoperable leaking thoracic aortic sac from deterioration of his mycotic aneurysm. Following discussion with the patient and his family he was managed palliatively and died two days later.

Discussion: The learning points from this case are to consider disseminated BCG in patients presenting with pyrexia of unknown origin following reported intravesical BCG treatment for bladder malignancy in the years prior to presentation. Mycotic aneurysms are a rare but serious complication of disseminated BCG with a high mortality.

Background

A 74-year-old Caucasian, UK born male was referred to our service with an 18-month history of unexplained fevers, weight loss and intermittent confusion. The patient had a past medical history of localised bladder carcinoma (in remission), chronic sinusitis, irritable bowel syndrome and previous glandular fever. His regular medications were amlodipine, aspirin, and folic acid, and he was allergic to clarithromycin and doxazosin.

Prior to his acute deterioration, the patient had been independent, active, and working as a writer. There was no travel outside Europe in the preceding five years. In the eighteen months prior to referral to our centre, the patient was admitted to three hospitals a total of five times for evaluation of fever of unknown origin, confusion, and fatigue. During these admissions, he was treated for several acute infections, including extended spectrum beta-lactamase producing (ESBL) E.coli urosepsis, and clinical presentations with cholecystitis and encephalitis. Radiological investigations, including computed tomography (CT) of the chest, abdomen and pelvis, and CT head and MRI brain did not elucidate a focal cause of the persistent fever. Cerebrospinal fluid (CSF) analysis showed a marginally raised protein. Antimicrobials administered during this period included ciprofloxacin, metronidazole and meropenem. After

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each antibiotic course there was demonstrable improvement in the patient's symptoms and inflammatory markers though these would then deteriorate when the drugs were discontinued.

During the patient's penultimate admission prior to review by our service, he was found to have a left iliac artery aneurysm. This was diagnosed on CT abdomen-pelvis as part of investigation of fever of unknown origin, when presenting to a new hospital with fever. He underwent endovascular stent repair and had a further course of meropenem.

One year after stenting of his left iliac aneurysm, the patient was readmitted to another hospital with ESBL bacteraemia. A CT-PET scan was performed to investigate the source of bacteraemia which identified a thoracic aortic aneurysm. A second endovascular procedure with stenting was undertaken, and the patient completed an extended course of oral co-amoxiclav (625 mg three times daily). The aetiology of both the iliac and aortic aneurysms was presumed to be mycotic, though microbiological sampling was not performed.

Admission

One month after the thoracic aneurysm repair, the patient presented to our centre with fevers up to 40 °C, confusion, fatigue, and significant weight loss of 18 kg (admission weight 57 kg compared to pre-morbid baseline of 75 kg). His exercise tolerance had fallen from unlimited outdoor hikes to less than 5 m. Admission blood tests showed raised inflammatory markers, with a white cell count of 8.3 $\times$ 10^9/L (neutrophils 6.7x 10^9/L) and CRP of 75 mg/L, haemoglobin of 73 g/L and platelets of 235 $\times$ 10^9/L. Liver function tests were deranged in a cholestatic picture, with ALT of 21 IU/L and ALP of 271 IU/L, bilirubin 16umol/L.

A chest radiograph showed a new left-sided pleural effusion. Thoracic ultrasound confirmed the presence of a moderate sized effusion with loculations, indicating an inflammatory aetiology. A 12 Fr intercostal chest drain was inserted in accordance with national guidelines. Pleural fluid results suggested pleural infection: pH 7.0, protein 48/L, glucose 2.7 mmol/L. Cytology demonstrated numerous granulocytes with an overall acute inflammatory picture. Pleural fluid was sent for bacterial and mycobacterial evaluation, and provisional results were negative. The patient was commenced on broad-spectrum antimicrobials to cover common causes of pleural infection (co-amoxiclav, escalated to piperacillin-tazobactam after five days of non-response to the initial management). Intrapleural fibrinolysis with tissue plasminogen activator was administered to breakdown the loculations and aid drainage. The chest drain was removed after nine days following drainage to dryness.

The patient's inflammatory markers and fever failed to improve despite drainage of the empyema. A CT chest, abdomen and pelvis demonstrated splenomegaly and mediastinal lymphadenopathy, with no clear source for infection, [Fig. 1.a]. Further serology to exclude vasculitic and infective causes, including antinuclear and antineutrophil cytoplasmic antibodies, HIV, hepatitis B and C, Brucella, Borrelia and syphilis serology and a fungal screen (beta-d-glucan and galactomannan), were negative, and immunoglobulins were in the normal range. No organisms were grown on nine peripheral venous bacterial blood cultures. The patient had a lumbar puncture due to intermittent confusion. CSF analysis on this admission was unremarkable, with a normal protein and glucose and negative bacterial cultures and polymerase chain reaction testing for *Herpes simplex*, *Varicella zoster* and enteroviruses.

A CT-positron emission tomography (PET) scan was performed. This demonstrated increased metabolic activity at the thoracic aortic stent-aneurysm surface, in keeping with a persistent mycotic infection, [Fig. 2.]. A six-week course of intravenous ceftriaxone to treat presumed bacterial infection was commenced.

Based on clinical suspicion, *Mycobacterium tuberculosis* PCR (using GeneXpert Ultra nucleic acid amplification test) was retrospectively performed on the pleural fluid specimen and was positive. Three weeks from sampling, mycobacterial cultures from the pleural fluid grew a *Mycobacterium* species that was MPT64 antigen negative (a positive test suggesting *M. tuberculosis*). Whole genome sequencing identified *Mycobacterium Bacillus Calmette-Guérin* (BCG), with predicted sensitivities to isoniazid, rifampicin, ethambutol and quinolones, and resistance to pyrazinamide. Pleural biopsies were obtained, which confirmed non-necrotising granulomatous inflammation, [Fig. 3.] Bone marrow trephine, performed during a preceding hospitalisation, demonstrated hypercellularity with granulomatous inflammation. During the lengthy diagnostic work-up, and prior to obtaining a positive TB PCR result, the patient's family made the treating team aware that BCG infusion was used for bladder cancer treatment two years previously (ie six months before the first onset of symptoms), further informing the diagnosis.

Treatment

The patient started treatment for systemic BCG infection (BCG-osis) with rifampicin, isoniazid, and ethambutol. The regimen was poorly tolerated, and he was readmitted to hospital a week later with worsening confusion, including auditory and visual hallucinations, and fatigue. MRI brain demonstrated multiple foci of enhancement (which were not seen on CT head a month earlier), suspicious for intracerebral BCG, [Fig. 4.]. Repeat CSF analysis returned negative MCS and AFB culture,

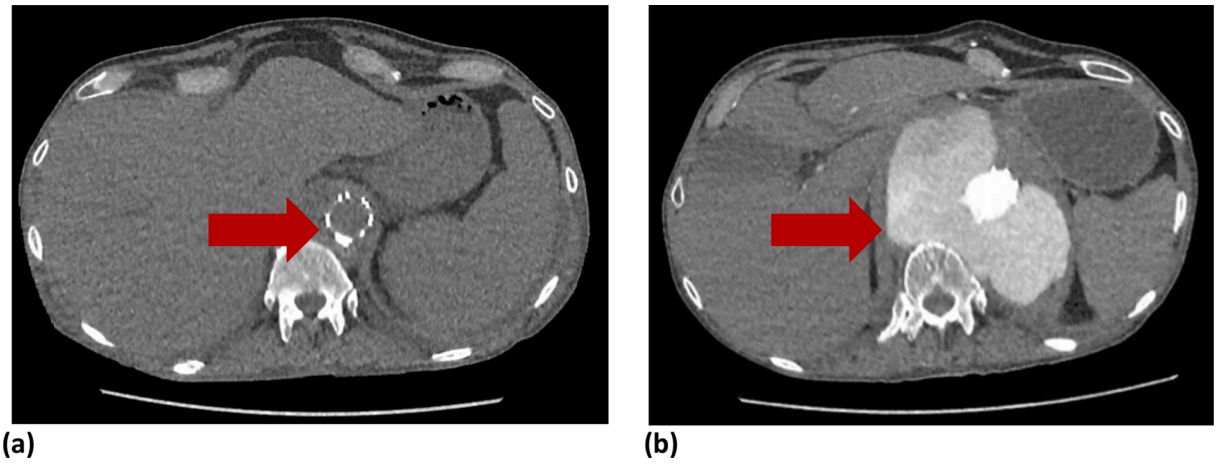

Fig. 1. a) Axial section of CT Abdomen showing aortic stent in situ following initial stent insertion. **1. b)** Axial section of CT Angiogram prior to death demonstrating enlarged aneurysmal dilatation around aortic stent with loss of fat plane between aorta and posterior structures, findings suggestive of aortic aneurysm rupture.

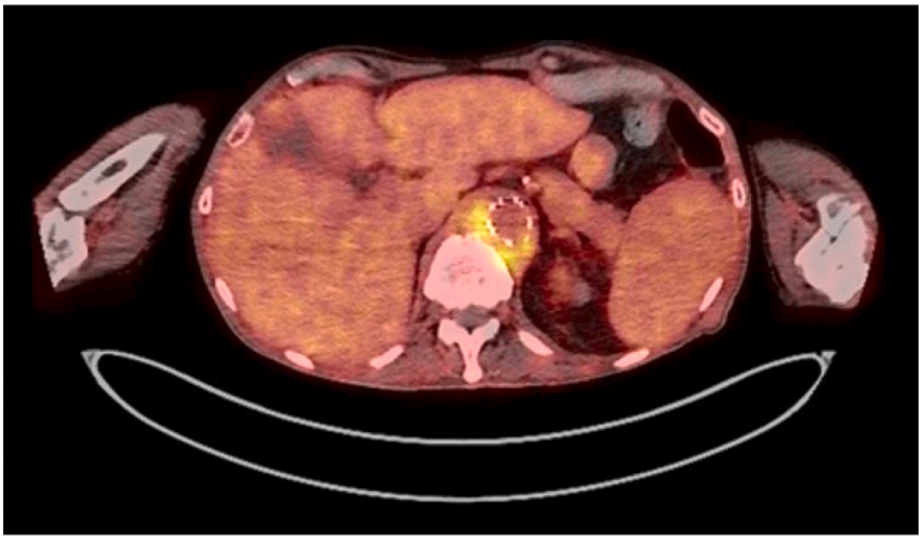

Fig. 2. Axial section of CT-PET demonstrating multifocal, non-circumferential intense metabolic foci at thoracic stent-aneurysm interface in keeping with mycotic infection.

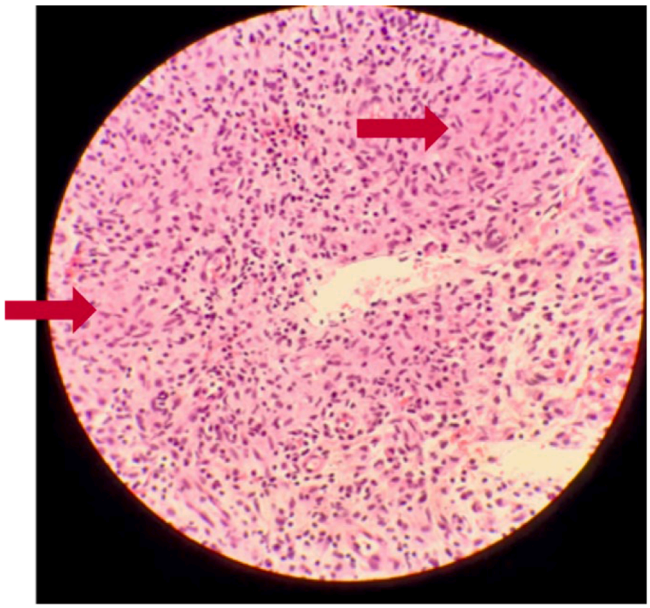

Fig. 3. Pleural biopsy histology microscopy: H&E stain, well-formed small non-necrotizing granulomas composed of epithelioid histiocytes (indicated by red arrows). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

however the protein was raised (0.9), similar to the first sample. He was also found to be hyponatremic (128 mmol/L) and was diagnosed with syndrome of inappropriate anti-diuretic hormone (SIADH), which was thought to be secondary to his possible CNS disease. This was managed with a 1.5L total daily fluid restriction. Isoniazid was substituted for moxifloxacin to address concerns about possible isoniazid-related encephalopathy. The patient was discharged after symptomatic improvement, and discontinued moxifloxacin seven days later, attributing new-onset deteriorating mood to this drug.

On further review, encephalopathy was felt to be unlikely, and there was concern about inadequate central nervous system penetration with the rifampicin/ethambutol regimen. Therefore, levofloxacin was added into the treatment regimen and isoniazid re-introduced. The regimen was tolerated, and he remained on four drugs (rifampicin/isoniazid/ethambutol/levofloxacin) until ethambutol was stopped after two

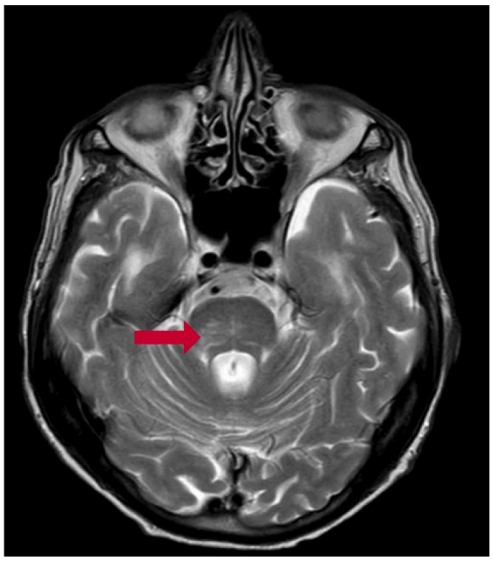

Fig. 4. Axial section T2 weighted MRI Brain demonstrating patchy hyperintensity within pons.

months. Following multidisciplinary team review with patient and family involvement that included discussion of fluoroquinolone use with pre-existing aortic aneurysm, a 12-month treatment regimen was planned with levofloxacin being discontinued at four months.

Over the early treatment phase, the patient reported increased energy and exercise capacity, and no further fevers. His weight increased by 12 kg, and his inflammatory markers fell. He re-presented after four months' treatment with a three-week history of abdominal pain, dysphagia, and worsening fatigue. A CT angiogram showed a leaking and enlarged distal thoracic aortic sac [Fig. 1. b], presumed due to continued deterioration of the mycotic aneurysm around the stent.

Extensive discussions were had with the patient and his family by the multidisciplinary medical, surgical and radiology teams involved in his care. It was felt that deployment of a further stent in a likely septic field would be a temporalizing measure, and that an open thoracic-abdominal operation in the context of significant frailty would have minimal chance of survival. The patient and his family opted for conservative management and palliative care. He died two days later, 26 months after

his first presentation to hospital with symptoms [Fig. 5].

Discussion

Mycobacterium Bacillus Calmette-Guérin (BCG) is derived from Mycobacterium bovis and is part of the Mycobacterium tuberculosis complex (hence being identified by the GeneXpert PCR test). Intravesicular BCG as a treatment for superficial bladder cancer is an established and effective therapy (Morales et al., 1976; Morales, 2017), which has been shown in multiple clinical trials to reduce tumour progression, and improve five year survival. However, the infusion of a live pathogen into the highly vascular bladder has recognised consequences (Green et al., 2019).

Our patient had disseminated BCGosis, with BCG the confirmed cause of pleural disease, a highly probable cause of aortic and iliac mycotic aneurysms and bone marrow infiltration, as well as radiological changes in the CNS compatible with mycobacterial disease.

In 2,602 patients treated with intravesical BCG there was a 2.9% incidence of high fever (>39 °C), 0.9% granulomatous prostatitis, 0.7% granulomatous pneumonitis/hepatitis and 0.4% life-threatening BCG sepsis (Lamm et al., 1992). In a pooled analysis of 282 cases of systemic BCG, disseminated (34.4%), genitourinary (23.4%), and skeletal (19.9%) infections were the most common presentations (Pérez-Jacoiste Asín et al., 2014). This study also reported mycotic aneurysms in 5.7% of systemic BCG cases and found that those with vascular involvement had a mortality rate roughly four times baseline (16.7% vs 4.5%). A study looking at 118 BCG cases reported to the US National Tuberculosis Surveillance System from 2004 to 2015 reported that genitourinary and skeletal systems were most commonly affected, with only 3% of cases having pleural, and none meningeal involvement (Wansaula et al., 2019).

Our patient had a presentation more than 6 months post-BCG infusion, and a diagnosis > 2 years post infusion). Published information on the time from last infusion to onset of symptoms or diagnosis is surprisingly limited, and in the eight cases discussed by Perez-Jacoiste Asin et al where the time from BCG infusion to diagnosis was documented, the mean time from last instillation to onset of complications was 8.3 days, with only two reported BCGosis diagnoses being made more than a year from BCG infusion (Pérez-Jacoiste Asín et al., 2014). Delayed-onset of mycotic aneurysms are reported, though appear rare overall (Wolf et al., 1995; Coscas et al., 2009; Leo et al., 2015), as is bone marrow infiltration by BCG (Ramalingam et al., 2021) – which may have acted as a reservoir for continued dissemination.

Later in his presentation pleural BCG disease was confirmed, which is rarely reported in the case literature (Rachakonda et al., 2017). His symptoms, radiological evidence on MRI brain of multiple foci of cerebral enhancement, and raised protein on repeated lumbar punctures, are also suggestive of possible BCG CNS disease, which appears to occur infrequently, with most cases being found in infants post-BCG vaccination (Furuichi et al., 2020; Sharifi et al., 2020), and only one describing tuberculomas post intravesicular infusion (Golub et al., 2011). These rarer presentations may reflect the prolonged period of probable BCG dissemination, indicated by the persistent high-grade fevers and elevations in inflammatory markers seen in our patient.

Adequate treatment of this case was a challenge with the patient experiencing numerous symptoms after starting anti-BCG medication such as confusion and low mood. It demonstrates the difficulty of finding effective treatment for disseminated BCGosis with a mycotic aneurysm, given its resistance to pyrazinamide, and concerns over use of fluoroquinolones. After initial reluctance we commenced moxifloxacin (and subsequently levofloxacin), alongside the initial three medications, and did see an improvement in the patient's weight, well-being, and inflammatory markers.

The learning points from this case are to consider disseminated BCG in patients presenting with pyrexia of unknown origin following specific enquiry into intravesical or systemic BCG treatment in the years prior to presentation, particularly in those who report previous bladder malignancy. Valuable tools that should be considered in the diagnostic work-up include CT-PET to highlight areas of increased metabolic activity and tissue sampling to confirm a microbiological, cytological, and histopathological diagnosis. Mycotic aneurysms are a rare but serious complication of disseminated BCG with a high mortality rate. Debate remains as to whether systemic BCG disease is a consequence of a hypersensitivity reaction or reflects mycobacterial growth. The histological findings from both pleural and bone marrow samples, as well as the positive mycobacterial PCR and culture suggest the latter.

Ethics approval and consent to participate

Not applicable

Consent for publication

The patient and next of kin agreed to have the case publicized, and next of kin consented formally. They fully understand the process and were in favour of this case being submitted for publication.

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Authors' contributions

LT & RH as joint first authors were responsible for the conceptualisation, data collection and interpretation, and the overall write-up of this manuscript. Appraisal and adjustments to the manuscript as well as involved clinical care were provided by ML & BD'C. AB, MD, AM, APa & APr provided input into the case as clinicians in the management of the care of this patient. They also appraised the data, interpretation, and the manuscript itself prior to submission. All authors read and approved and the final manuscript.

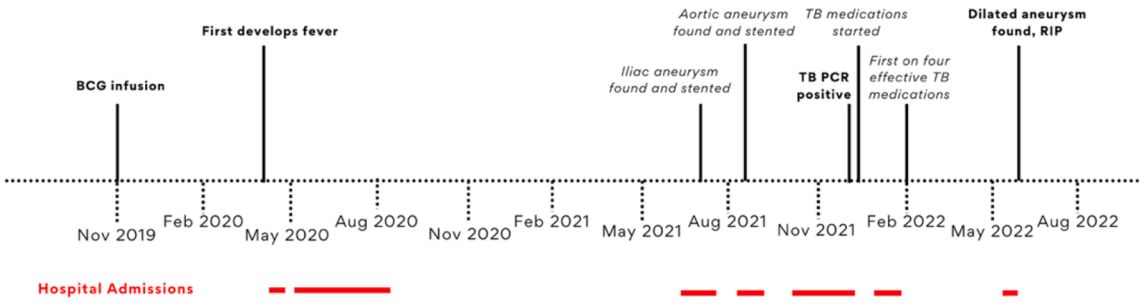

Fig. 5. Timeline of events of case.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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