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Case Report

Pneumonitis secondary to intravesical Bacillus-Calmette-Guérin (BCG) immunotherapy ☆

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ABSTRACT

Intra vesical Bacillus Calmette-Guérin (BCG) instillation therapy is a well-established treatment for superficial bladder cancer, though it can occasionally lead to rare systemic complications. We report the case of a man in his early 80s who developed acute onset dyspnoea after receiving BCG therapy. Clinical evaluation supported by pathology and multi-modal imaging including X-rays, CTs and PET scans led to a diagnosis of BCG-induced pneumonitis, a rare but serious complication. The exact underlying mechanism is still not fully understood and thus no standardized treatment protocol exists. Success has been reported in the literature with the use of anti-tuberculous drugs in combination with steroids. Our patient was successfully treated with anti-tuberculous medication only, for 4 months. This case highlights the importance of maintaining awareness for systemic BCG findings in patients undergoing intra vesical BCG instillations.

Introduction

Intra vesical Bacillus Calmette-Guérin (BCG) is widely used in the treatment of superficial non-muscle invasive bladder carcinoma and is a well-established prophylactic immunotherapy used to prevent relapse [1,2]. Whilst most patients tolerate the treatment well with improved outcomes, associated local and systemic complications have been reported. Interstitial pneumonitis is a rare side effect believed to affect 0.7% of patients [3]. The time between treatment and clinical manifestation varies with some patients developing symptoms following 1 injection [4] or multiple injection cycles [5]. The exact pathophysiology of extra-vesical pulmonary manifestation remains unknown, although it is postulated to be due to either a hypersensitivity reaction or disseminated mycobacteria [6–9]. As a result, there is currently no established treatment regimen. Existing case reports have indicated that the most successful approach involves a combination of steroids and anti-tuberculous medications [10].

Case presentation

Written informed consent has been obtained.

☆ Competing Interests: 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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Symptoms

A man in his 80s presented with a month history of feeling unwell with lethargy and decreased appetite being the predominant symptoms. He developed an episode of acute onset dyspnoea and chest discomfort which prompted presentation to the emergency department. This was on a background of ongoing (11 months) intra-vesical BCG instillations for in situ transitional cell carcinoma of the bladder.

Imaging and clinical investigations

The admission chest X-ray (CXR) showed new patchy opacifications in the right mid lung zone and both lung bases reported as infective, whilst the CXR obtained 8 months prior (Fig. 1) was clear.

Considering his presentation and previous history of bladder and colonic malignancies, he underwent an enhanced CT of the Thorax Abdomen and Pelvis (TAP) and a CT urogram to exclude malignancy recurrence and metastatic disease.

The CT TAP revealed bilateral, right more than left, predominantly basally distributed uniform and small (<2 mm) pulmonary nodules in a miliary pattern with interlobular septal thickening and tree-in-bud appearances. There was no lymphadenopathy or pleural effusions. The liver was unremarkable with no focal lesions. Furthermore, there was no evidence of recurrence of the previous colonic malignancy; the CT Urogram showed resolution of previous seen right sided urinary bladder wall lesion as well. Comparison made with historic CT Thorax 2 years prior demonstrated normal lung parenchyma and architecture (Fig. 2).

Covid-19 swab, and tuberculosis interferon gamma release assay were both negative. No mycobacterium was isolated from 3 distinct sputum cultures obtained over several days. A flexible bronchoscopy and bronchoalveolar lavage revealed normal airway anatomy with no endobronchial or submucosal abnormality. Washings (180 mL) were obtained from the upper and lower lobes of both lungs. No acid-fast bacillus, fungi or other organism was detected in these samples. No malignant cells were seen on cytology; however, an abundance of acute inflammatory cells was detected.

The findings were discussed in a lung multi-disciplinary meeting (MDM). The Pneumologists and Radiologist agreed that the history of ongoing vesical BCG instillation, presentation, lab work and radiological findings suggested the diagnosis of BCG induced pneumonitis.

A 4-month course of anti-tubercular therapy (Rifampicin, Isoniazid and Moxifloxacin) was commenced.

An FDG PET CT 2 weeks after the start of treatment showed some resolution of the previously noted reticular nodular changes in both lungs (Fig. 3).

Both subsequent CT Thorax (4 months within anti-tubercular therapy) and CXR 6 months and 2 months after treatment cessation were unremarkable.

On admission, his common bile duct appeared mildly dilated and his liver function test were deranged. Further tests including an autoimmune liver screen (Anti-nuclear antibody, anti-mitochondrial antibody, anti-smooth muscle antibody and anti-liver-kidney microsomal antibody) were negative. His gastric parietal cell antibody titres were positive in keeping with his known pernicious anemia. The viral serology was negative for Hepatitis, CMV, EBV and HIV. In light of these findings, he underwent further investigations including an endoscopic ultrasound which revealed a bile duct stricture with no evidence of biliary tree stone.

His liver function tests improved during his admission as he was commenced on anti-tuberculous treatment with close monitoring of his liver function tests.

Differential diagnosis

The initial chest X-ray differentials were infection or malignancy recurrence.

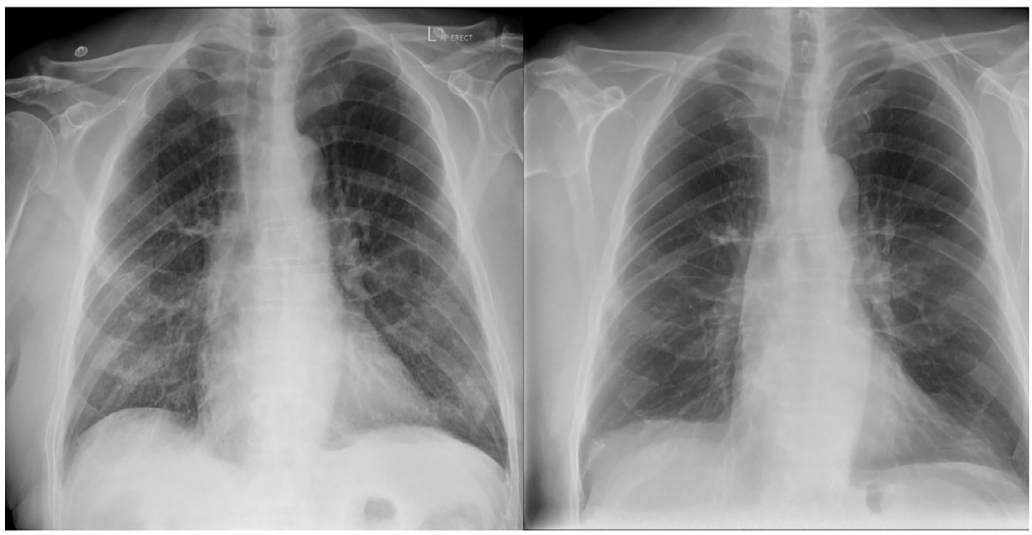

Fig. 1 – Admission chest radiograph (left) showing new patchy opacifications in the right mid and bilateral lower zones. Historical chest radiograph (right) showing unremarkable air spaces.

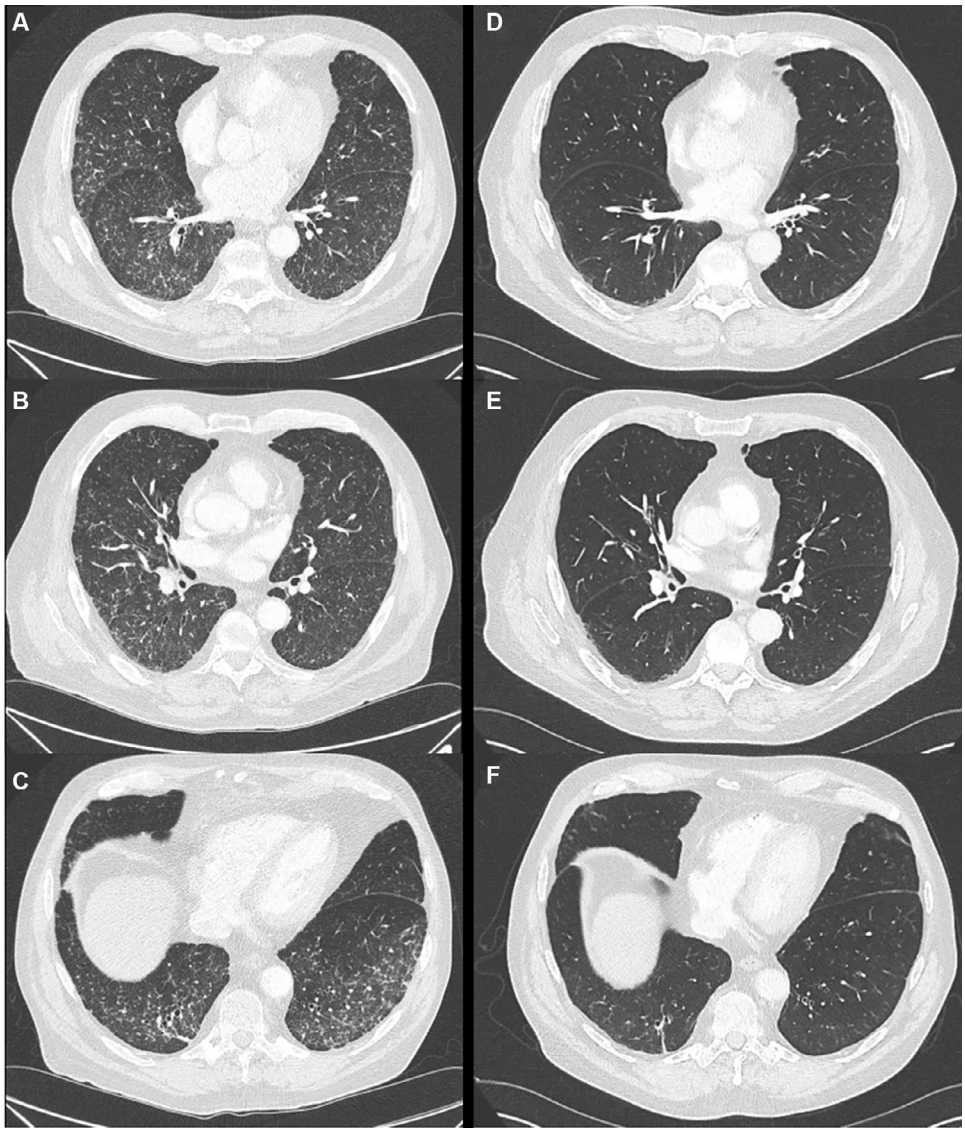

Fig. 2 – Selected axial CT Thorax images (A-C) showing a predominantly basally distributed widespread, uniform and small (<2mm) pulmonary nodules in a miliary pattern with interlobular septal thickening and tree-in-bud appearance. Selected axial CT thorax images (D-F) show historic CT thorax 2 years prior, demonstrating normal lung parenchyma and architecture.

The subsequent cross-sectional imaging demonstrated new widespread, right sided more than left pulmonary micronodularity in a miliary pattern, in a patient with ongoing BCG intra vesical instillations.

The clinical findings, lab work and imaging suggested a diagnosis of pneumonitis secondary to BCG immunotherapy (hypersensitivity reaction). Less likely differentials included miliary tuberculosis and micro metastases, pending histopathology and culture results.

Treatment

Following multi-disciplinary discussion a 4-month course of anti-tuberculous therapy comprised of once daily oral 600 mg rifampicin, 300 mg isoniazid and 400mg moxifloxacin. Mycobacterium bovis (MTB) is known to be resistant to pyrazinamide, thus it was not included as part of the anti-tuberculous regimen.

Outcome and follow-up

The patient improved rapidly and was discharged after being established on anti-tuberculous medications. He had an outpatient chest clinic follow a month later. His symptoms at this point had improved significantly with no reported dyspnoea and mobility had returned to baseline. He was aware of potential side effects from the 4-month anti-tuberculous regimen and he was compliant with blood monitoring under-

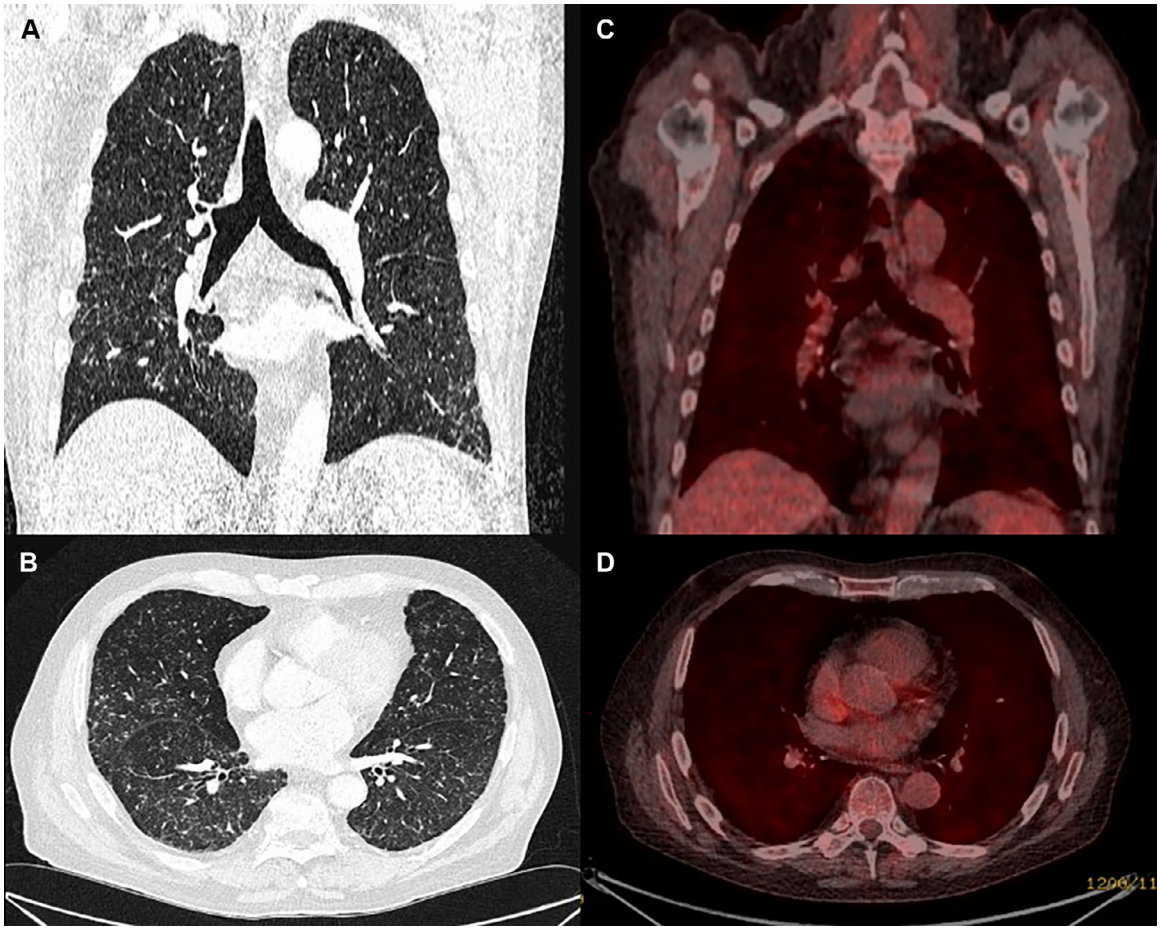

Fig. 3 – Axial and coronal FDG PET CT images 2 weeks after the start of treatment showing some resolution of the previously noted nodular changes in both lungs.

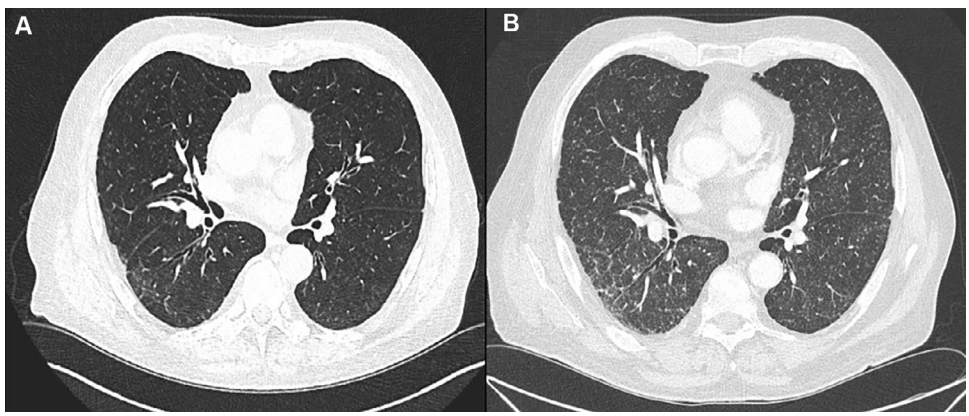

Fig. 4 – Selected axial images of CT thorax performed after completion of 4-month course of antituberculous therapy (left) demonstrating improvement with complete resolution of previously noted widespread micronodularity (right).

standing the importance of regular liver function monitoring by his General Practitioner.

He completed the 4-month course of anti-tuberculous therapy and underwent a repeat CT thorax which demonstrated complete resolution of previously noted widespread micronodularity (Fig. 4).

Discussion

In the UK, bladder carcinoma is the 11th most common cancer with an average annual incidence of around 10,300 cases [11]. Intra-vesical instillation of BCG is widely used in the manage-

ment of superficial nonmuscle invading bladder cancers [1,2]. Whilst the mechanism underpinning the development of BCG induced pneumonitis is not fully understood, it is believed to be related to a hypersensitivity reaction or disseminated MTB infection [12].

Although MTB was not isolated in our patient, this is not uncommon and widely reported in the literature [10]. There is a recognised technical difficulty in isolating and detecting MTB with many influencing factors ranging from tissue handling, culture techniques and number of organisms present which could be low in an immunocompetent host [13]. Thus, absence of MTB does not preclude disseminated infection as a diagnosis.

Following a comprehensive multidisciplinary team discussion, the patient was commenced on a 4-month course of anti-tuberculous treatment overseen by pneumologists. Upon completion of the treatment regime, a follow up CT Thorax was performed which demonstrated clear lungs with resolution of prior findings. The patient was subsequently reviewed in the respiratory clinic with no reported respiratory symptoms or concerns. Follow up CXR 2 months following cessation of treatment showed clear lungs.

Although the recommended treatment length for BCG-related pneumonitis typically involves a 6-month course of antituberculous medication [9] some cases may see improvement with treatment as short as 3 months. Our patient showed rapid clinical improvement and was symptom free at 3 months. A follow up CT Thorax done after 4 months of antituberculous medication demonstrated resolution of prior lung findings and no focal lung abnormality; antituberculous treatment was capped at 4 months; clinical and imaging follow-up were uneventful.

In patients with significant hypersensitivity component, steroids (like Prednisolone) may be used, tapered over weeks to months. In our patient steroids were not used with following reasoning:

- Concerns for immunosuppression and sepsis in an elderly patient with 2 prior cancers. Although in our patient no mycobacteria were isolated and the Tuberculosis Interferon Gamma Release Assay were negative, there was an ongoing concern for BCG infection and dissemination.
- There was no definite bronchoalveolar lavage or biopsy confirmed hypersensitivity.
- There was a brisk, favorable response to antitubercular therapy alone.

Conclusion

Although rare, the differential of BCG related pneumonitis is worthwhile to radiologists, lung and urology specialists, more so in patients undergoing intra vesical BCG immunotherapy for bladder carcinoma. This may allow early detection, treatment and improved outcomes. The clinical presentation, history of ongoing BCG instillations for bladder cancer, imaging and lab work findings, response to anti-tuberculous medication and exclusion of alternative diagnoses supported the diagnosis of BCG related pneumonitis in the case presented. There is currently no consensus on standard treatment of BCG induced pneumonitis; many report cases whereby patients achieved significant recovery following a combination of anti-tuberculous therapy and steroids [14]. The recommended treatment length for BCG-related pneumonitis typically involves a 6-month course of antituberculous medication. Additionally, if there is a significant hypersensitivity component, steroids (like Prednisolone) may be given, tapered over weeks to months to minimize the risk of recurrence. Some cases may see improvement with treatment as short as 3 months. Our patient had an excellent response and outcome with anti-tuberculous medication only for 4 months.

Patient consent

Written, informed consent for publication of the case was obtained from the patient for the case report titled: Pneumonitis secondary to intravesical Bacillus-Calmette-Guérin (BCG) Immunotherapy.

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