Unexpected outcome (positive or negative) including adverse drug reactions

A cough conundrum in a patient with a previous history of BCG immunotherapy for bladder cancer

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Summary

We describe a non-smoker who presented with a persistent cough, weight loss and general malaise, and had a medical history of bladder carcinoma that had been successfully treated with intravesical BCG immunotherapy. Radiology revealed hilar lymphadenopathy, a predominantly mid-zone and lower-zone lung parenchymal nodular pattern with a perilymphatic distribution, a few thickened interlobular septae, and small pleural effusions bilaterally. The T-SPOT.TB blood test was negative. Video-assisted thoracoscopic surgery showed multiple pleural nodules, the histopathology of which showed multiple well-defined non-caseating granulomata. The patient was started on antituberculosis medication for presumed BCGosis—a systemic complication of previous BCG immunotherapy—and the patient showed an excellent clinical and radiological response. This case further adds to previous reports and reinforces the recommendation that all patients should be made fully aware of the potential systemic and delayed complications of BCG immunotherapy when they are consented for treatment.

CASE PRESENTATION

A 50-year-old Indian woman presented with an 8-week history of a dry, irritating cough that was progressively worsening. She reported two stone weight losses over the previous 2 months and felt generally unwell. There were no night-sweats or fever. There was no history of: occupation-related dust inhalation, asthma, recurrent chest infections, tuberculosis (TB) or recent foreign travel. She denied keeping pets and had never smoked or indulged in illicit drug use. There was no family history of respiratory disease. Three years previously, she had been diagnosed with superficial transitional cell carcinoma of the bladder (pT1, G3) plus multifocal carcinoma in situ, and this was successfully treated with six intravesical instillations of BCG (Connaught strain: ImmuCyst) 38 months prior to her current presentation. Catheterisation at the time was atraumatic and the treatment was completed without any side-effects. On examination, her body mass index was 18.1 kg/m², and her physical examination was normal.

INVESTIGATIONS

An ECG tracing was normal. The chest radiograph (figure 1) showed bilateral hilar lymphadenopathy associated with ground-glass shadowing in the mid/lower zones. There were one or two small ill-defined nodules in the lower zones. There was a trace of a pleural effusion at the bases. The full blood count, urea and electrolytes, including serum calcium, and liver function tests were all unremarkable. However, there were raised inflammatory markers, with a raised erythrocyte sedimentation rate at 50 mm/h (reference range: 0–14 mm/h) but a normal C reactive protein at 9 mg/l (reference range: 0–10 mg/l). The serum immunoglobulin G level was only mildly elevated in a polyclonal manner at 16.82 g/l (reference

range: 6.00–16.00 g/l). Serum ACE level was raised to 78 IU/l (reference range: 8–59 IU/l). Serum antinuclear antibodies and antineutrophilic cytoplasmic antibodies were undetected and rheumatoid factor was negative. Urine dip and microscopy were negative for blood. The T-SPOT.TB blood test (Oxford Immunotec Ltd, Abingdon, UK) was negative. Spirometry was normal. CT scan of the thorax (figure 2A–C) showed bulky bilateral hilar, subcarinal, precarinal and aortopulmonary window lymphadenopathy. Within the lung parenchyma there was a fine nodular pattern in all zones but with a mid-zone and lower-zone predominance. The nodules had a perilymphatic distribution. There were also a few thickened interlobular septae. Two soft tissue nodules of approximately 1 cm diameter were seen in the left lower lobe. There was a small pleural effusion bilaterally.

Transbronchial biopsy showed neither any signs of malignancy nor any signs of granulomatous inflammation, and broncho-alveolar lavage (BAL) was negative for acid-alcohol-fast bacilli. Left-sided video-assisted thoracoscopic surgery showed multiple pleural nodules on both lung and parietal surfaces. Histology of the biopsies is shown in figure 3A,B. No acid-alcohol-fast bacilli were seen after Ziehl-Neelsen staining and all final culture reports on biopsies, BAL, sputum and urine were negative for mycobacteria.

DIFFERENTIAL DIAGNOSIS

Table 1 shows a suggested diagnostic formulation, based on patient factors, radiological findings and clinical impression. The histopathology of the biopsies shows no evidence of a metastatic or neoplastic process, but, instead, multiple well-defined non-caseating granulomata, both in the pleura (figure 3A), and in the lung parenchyma (figure 3B).

Figure 1 Postero-anterior chest radiograph demonstrating prominent bilateral hilar shadows with associated perihilar reticular shadowing.

The most likely diagnoses based on this are: pulmonary sarcoidosis, TB, or BCGosis, owing to a complication of previous immunotherapy for bladder cancer. The histology is more suggestive of the former diagnosis and the negative T-SPOT.TB both reduces the likelihood that there is active TB, and is particularly useful in this patient because the assay uses two proteins (ESAT-6 and CFP10) encoded by a unique genomic sequence of *Mycobacterium tuberculosis* that is absent from the live-attenuated strain of *Mycobacterium bovis* (*M. bovis*) in BCG. Tissue *M. bovis* can rarely be identified by PCR, allowing for confirmation of the diagnosis (although this was not done for this case).

TREATMENT

A shared decision-making process between the patient and the multidisciplinary team led to the decision that she would be treated for BCGosis. On the one hand, she could have been treated with corticosteroids as if she had stage II pulmonary sarcoidosis, for which there is good evidence for a short-term to medium-term improvement in the 50% of patients that do not spontaneously resolve. However, if the diagnosis of sarcoidosis was wrong, and in fact the patient had BCGosis or TB, the outcome could be worse, owing to steroid-induced immunosuppression.

The patient was, therefore, initiated on a therapeutic trial of antituberculous medication using combination

preparations (Rifater four tablets daily, containing 120 mg rifampicin, 50 mg isoniazid and 300 mg pyrazinamide, together with ethambutol 700 mg once daily for 2 months; then, Rifinah-300 two tablets daily, containing rifampicin 300 mg and isoniazid 150 mg). Additionally, she took 10 mg pyridoxine supplementation daily. There is some debate as to what is the best regime for BCGosis, given the fact that *M. bovis* is resistant to pyrazinamide and the addition of corticosteroids may be of benefit, owing to putative hypersensitivity aetiology. This debate is compounded by the fact that there are no trial data to support these treatment regimes or the duration of treatment. In this case, it was felt reasonable to withhold prescribing concomitant corticosteroids, owing to the fact that the patient was stable and there were no large pleural or pericardial effusions. It was felt that it was more appropriate to use only one pharmacological approach, keeping all other things constant; adding two different agents could have led to the dilemma later in the management about which drug or drugs were responsible for the patient's improvement or any ill effects.

OUTCOME AND FOLLOW-UP

The patient's symptoms completely resolved while on treatment, and her 3 months post-treatment CT scan (figure 4) showed no sign of active disease within the thorax. The therapeutic trial of antituberculous

Figure 2 (A) Contrast-enhanced high-resolution CT of the thorax demonstrating hilar and mediastinal lymphadenopathy with a small pleural effusion bilaterally. (B) High-resolution CT of the thorax showing parenchymal nodules including involvement of the fissures (arrow) indicating a perilymphatic distribution. (C) High-resolution CT of the thorax demonstrating one of the larger left lower lobe nodules along with interlobular septal thickening (arrow).

Figure 3 (A) High-powered light microscopy of a pleural biopsy (H&E). (B) High-powered light microscopy of lung biopsy (H&E).

medication had worked, with the caveat that spontaneous remission of sarcoidosis was a possibility.

DISCUSSION

Intravesical administration of BCG, a live-attenuated strain of *M. bovis*, has become the mainstay of adjunctive therapy for treating multifocal, recurrent or especially invasive superficial transitional cell carcinoma of the bladder ever since it was first used by Morales.¹ The precise mechanism of drug action is unknown, but it probably stimulates a T-cell-mediated local cytokine immune response against malignant cells.^{2–5} Side-effects from the treatment are classified as local or systemic⁴ and they occur predominantly in the first few days of treatment.⁵ Accordingly, cystitis is reported in the vast majority of patients and low-grade fever is frequent. Side-effects can be severe in about 5% of patients⁶ and BCG sepsis, the most severe of systemic complications, is reported in around 0.4–0.7% of patients.⁵ Ten deaths have been attributed to BCG treatment to date,⁷ with one case occurring 3 years after BCG treatment that was associated with several months of oral corticosteroid medication.⁸ The majority of cases of sepsis were probably precipitated by physical disruptions in the bladder urothelium. Biopsies of

Table 1 Diagnostic formulation, based on patient factors, radiological findings and clinical suspicion

Diagnosis	Features in favour	Features against
Lymphangitis carcinomatosa	<ul style="list-style-type: none"> Interlobular septal thickening with nodularity Bilateral pleural effusions Mediastinal and hilar lymphadenopathy A history of bladder carcinoma 	<ul style="list-style-type: none"> The relative lack of septal thickening compared with perilymphatic nodularity The absence of any overt tumour between the bladder and the chest
Pulmonary sarcoidosis	<ul style="list-style-type: none"> Symmetrical bilateral hilar and mediastinal lymphadenopathy The perilymphatic pattern of parenchymal nodularity 	<ul style="list-style-type: none"> The presence of pleural effusions The mid-zone to lower-zone nodular distribution
Mycobacterial disease	<ul style="list-style-type: none"> Bilateral lymphadenopathy Bilateral pleural effusions The patient's ethnicity (in favour of pulmonary <i>Mycobacterium tuberculosis</i>) and urological treatment history with intravesical BCG (in favour of BCGosis) 	<ul style="list-style-type: none"> The perilymphatic nodular pattern

Figure 4 Thoracic high-resolution CT following antituberculosis treatment showing complete resolution of the large soft tissue nodules, the diffuse perilymphatic nodularity, the pleural effusions and the mediastinal and hilar lymphadenopathy.

liver and lung from such patients show non-caseating granulomata. Cultures are rarely positive, but tissue *M. bovis* can be sometimes identified by PCR.⁷ *M. bovis* is sensitive to all antituberculous medication, except for pyrazinamide and cycloserine,⁹ and it is also moderately sensitive to later generation fluoroquinolone antibiotics. During the acute phase of sepsis, murine models have shown that early corticosteroid administration can be a life-saving manoeuvre¹⁰ but their use clinically should be exercised with caution.

To our knowledge, this is the first reported case of a likely pulmonary reaction to BCG bladder immunotherapy to have occurred in an immunocompetent patient 3 years after the last instillation. The long interval and the development of respiratory symptoms in the absence of traumatic catheterisation at the time of treatment encourage the publication of more cases and further research into the mechanisms of action of BCG treatment. We suggest that all patients should be made fully aware of the potential delayed systemic complications of BCG immunotherapy when they are consented for treatment.

Learning points

- This was a difficult case, where the diagnosis was not certain. Working through the clinical, radiological and pathological evidence led to the creation of a reasoned diagnostic formulation, and a subsequent presumptive diagnosis of BCGosis.
- The T-SPOT.TB blood test, a relatively recent enzyme-linked immunosorbent spot (ELISpot) assay, which has a high sensitivity for active tuberculosis (TB, >90%¹¹), and a high specificity for *Mycobacterium tuberculosis* infection (>90%^{12 13}), is a useful ancillary test in patients who could have either active TB or BCGosis.
- BCG immunotherapy is an effective treatment for bladder cancer, but it can rarely give rise to BCGosis as a systemic complication, which may occur several years after treatment.

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Competing interests None.

Patient consent Obtained.

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