CASE REPORT

A late presentation of isolated lymph node tuberculosis postintravesical BCG therapy for superficial bladder cancer: a novel case

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SUMMARY

Intravesical BCG immunotherapy is commonly used in the treatment of superficial bladder cancer. We recount the case of an 82-year-old British man who completed a course of BCG immunotherapy in 2011 for superficial bladder cancer, and presented in January 2013 with a loss of appetite, loss of weight and severe back pain. CT scanning, followed by MRI displayed a 5.7 cm × 5 cm conglomerated necrotic, haemorrhagic mass of lymph nodes in the para-aortic region. A CT-guided biopsy revealed granulomatous inflammation, focal fibrosis and acid-fast bacilli consistent with *Mycobacterium tuberculosis* (TB). The patient was treated with combination antituberculous medication, and is recovering. To our knowledge, this is the only reported case of lymph node TB secondary to intravesical BCG immunotherapy. We suggest that in patients treated with postintravesical BCG with enlarged lymph nodes, a diagnosis of secondary TB should be considered.

symptoms, haematuria or pulmonary problems. He had never previously been diagnosed with tuberculosis (TB).

INVESTIGATIONS

We performed a series of blood tests including a full blood count, liver function tests, urea and electrolytes and prostate-specific antigen. His alkaline phosphatase was elevated at 1227 IU (normal range is 44–147 IU/L), with all the other results within normal limits. Further to this, he underwent a flexible cystoscopy which did not show any local recurrence of bladder cancer. Imaging was performed including a CT of the chest, abdomen and pelvis with a urogram phase revealing a 5.7 cm × 5 cm conglomerate mass of lymph nodes in the para-aortic region, inferior to the right kidney (figure 1). Initially, they were reported as being possibly malignant. The vertebral bodies of T6 and T7 demonstrated a likely reactive or infective discitis as opposed to a metastatic process. The complexity of this particular case necessitated a discussion at the multidisciplinary meeting (MDM), where differential diagnoses proposed were metastatic disease, lymphoma and TB. Subsequently, an MRI of the whole spine was performed with evidence of spondylodiscitis/infection at T5/T6 (figure 2A) and the lymph node mass compressing the inferior vena cava (figure 2B). The patient underwent a CT-guided biopsy of the nodal mass. The histology showed a focus of granulomatous inflammation and focal fibrosis with no evidence of malignancy in the specimen. Ziehl-Neelsen staining showed few

BACKGROUND

Systemic 'BCG-osis' and local effects of intravesical BCG immunotherapy are well documented in the literature. However, the isolated tuberculous involvement of retroperitoneal lymph nodes without any local bladder or pelvic effects of BCG, 2 years postintravesical BCG treatment has not previously been reported. This case also highlights the importance of timely imaging and image-guided biopsies in the management of patients where the aetiology of lymphadenopathy is unclear.

CASE PRESENTATION

In 2010, an 82-year-old British man was diagnosed with high-grade superficial transitional cell carcinoma (TCC) of the bladder, with carcinoma in situ (pTa G3 TCC+CIS). He had a full adjuvant course of intravesical instillation therapy using the Connaught substrain of BCG which is live attenuated *Mycobacterium bovis* (ImmuCyst 81 mg) with the final session in September 2011. The patient was then lost to follow-up as he moved from the vicinity. He later presented to his general practitioner (GP) with worrying symptoms of loss of appetite and a considerable amount of weight loss with night sweats and fevers. Additionally, he was suffering from severe back pain requiring regular strong analgesia resulting in impaired mobility. He was referred to us by his GP in January 2013. At that time, he denied any lower urinary tract

Figure 1 CT axial slice of the abdomen, displaying the necrotic lymph node conglomeration anteriorly and to the right of the abdominal aorta.

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Figure 2 (A) MRI sagittal slice of the spine, demonstrating the large lymph node mass abutting the spinal column resulting in spondylodiscitis. (B) MRI axial slice of the abdomen, displaying the same lymph node mass. Its proximity to the inferior vena cava is seen.

acid-fast bacilli (AFB) consistent with *M bovis* (figure 3A,B). H&E staining displayed the characteristic pattern of caseation necrosis (figure 4). Periodic acid-Schiff staining for fungi was negative. The results were rediscussed at the MDM and a diagnosis of TB lymphadenopathy secondary to intravesical BCG immunotherapy was made.

Figure 3 (A) Photomicrograph (×400) (A) showing acid-fast bacilli on Ziehl-Neelson staining and (B) displaying acid-fast bacilli on Ziehl-Neelson staining.

Figure 4 Photomicrograph (×400) displaying caseation necrosis on H&E staining.

DIFFERENTIAL DIAGNOSIS

- ▶ Infective focus of lymphadenopathy (reactive in nature)
- ▶ Metastases from originating TCC of the bladder
- ▶ Lymphoma
- ▶ Tuberculous lymphadenopathy

TREATMENT

The patient was referred to the respiratory physicians for appropriate treatment. He was started on combination antituberculous medication including Rifater five tablets: (rifampicin 120 mg, isoniazid 50 mg pyrazinamide 300 mg) and ethambutol 900 mg daily.

OUTCOME AND FOLLOW-UP

At recent follow-up 5 months after the start of medication, his symptoms including the back pain had resolved and he was gaining weight demonstrating clinical resolution. Additionally, follow-up imaging confirmed a reduction in the lymphadenopathy described (figure 5).

DISCUSSION

European Association of Urology guidelines advocate intravesical BCG for the management of high-risk superficial bladder tumours (G3/pT1/CIS) and in patients with intermediate-risk bladder cancer who have failed mitomycin C. In multiple pT1 G2 tumours, pTa/T1 G3 tumours with or without CIS and CIS alone, the advantages of intravesical BCG are more pronounced than in patients with intermediate risk, who are at a lower risk of progression.¹ BCG should not be instilled immediately after surgery because of the high rate of systemic complications and the recommended interval period is 2 weeks. In our case, all the recommended principles were adhered to. Side effects of intravesical BCG immunotherapy are multiple and commonly: aseptic cystitis and dysuria (80%), haematuria (40%) and low-grade fever.^{2,3} Granulomatous prostatitis is noted in about 1% of patients and less commonly, granulomas may occur in the lungs, liver and bones.⁴

Many cases of TB infection at sites distant to the bladder after BCG therapy are described. The incidental detection of mediastinal lymphadenopathy and granulomatous prostatitis has been illustrated previously by Ilgan *et al.*⁵ In this case, the prostatic lesion was detected on 18-fluoro-deoxyglucose positron emission tomography scanning and the mediastinal lymphadenopathy was seen on CT with a histopathological diagnosis made from prostate biopsies. The findings of mycotic tuberculous

Figure 5 CT sagittal slice of the abdomen, showing a significant reduction in size of the lymph node mass after 5 months of antituberculous treatment.

aneurysms and pseudoaneurysms have been described widely in the literature with more than 20 documented cases.^{6–8} Harding and colleagues discussed a case of ruptured mycotic abdominal aneurysm secondary to intravesical BCG, with a 2-year lag-time. Here, the diagnosis was made after material from the aneurysm was stained showing AFB. Wada and colleagues described a similar case in which the patient presented with high-grade fever and back pain due to a tuberculous abdominal pseudoaneurysm penetrating the left psoas muscle. Interestingly, here acid-fast stains were negative and the diagnosis was made from the histological and bacteriological examination of tissue obtained at the time of vascular reconstruction. The patient did not take antituberculous medication before or after surgery and made an uneventful postoperative recovery. Penile caseating lesions with granulomatous balanoposthitis have been shown in a patient who was later treated with isoniazid (300 mg/day) to good effect.⁹ In cases involving the penis, postulated mechanisms for inoculation included inadvertent trauma during catheterisation, spillage of the BCG-containing solution and splash back from voided urine.^{10 11}

Our case and those described above demonstrate that direct spread and hypersensitivity reactions contribute to the clinical manifestations of systemic BCG infection, and distant occurrence. However, the presence of a granulomatous lesion is not pathognomonic for disseminated infection. We propose that in patients who have received BCG instillation therapy for superficial bladder cancer in the past and who are found to have an enlargement of their lymph nodes, the possibility of TB in addition to metastatic and infective causes should be entertained. A biopsy should be performed if indicated, to rule out or diagnose TB in these patients. Additionally, all non-specific systemic symptoms such as, fever, malaise, weight and appetite-loss should be considered in the context of recent immunotherapy

and not merely attributed to disease spread, as chemotherapy for presumed metastases in such patients may be lethal. The present case is of relevance because the patient presented with tuberculous involvement of the para-aortic lymph nodes with clinical manifestations of TB, but no locoregional manifestations of TCC or BCG side effects at the time of treatment.

Learning points

- ▶ Clinicians should be aware of the possible systemic manifestations of intravesical BCG immunotherapy in the management of superficial bladder cancer, namely tuberculosis.
- ▶ Prompt CT/MRI to define the nature of suspicious lymphadenopathy is important and in conjunction, image-guided biopsies should be considered to obtain a histological diagnosis.
- ▶ A multidisciplinary approach to complex cases produces favourable outcomes for patients as demonstrated here with the involvement of urologists, radiologists and respiratory physicians, notwithstanding the care of specialist nurses and allied healthcare professionals.

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Contributors AMT has written the majority of the case report with input from BV and WM. The senior author was the consultant in charge of the patient's care and also helped with editing.

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