CASE REPORT

Systemic BCG infection in a patient with pancytopenia and fever 9 years after intravesical BCG administration for bladder cancer

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SUMMARY

BCG is an attenuated live strain of *Mycobacterium bovis* that is used as an intravesical immunotherapy for superficial bladder cancer. Although generally well tolerated, BCG instillation can lead to systemic diseases. We present a case of a 75-year-old man who was treated for recurrent localised transitional cell carcinoma (TCC) of the bladder with intravesical instillation of BCG in 2006. His medical history included Parkinson's disease. The patient reported worsening of Parkinson symptoms in the preceding month. In addition, he had progressive pancytopenia and a bone marrow biopsy showed a granulomatous inflammatory infiltrate. Cultures from bone marrow aspiration grew *M. bovis*. He was successfully treated with tuberculostatic drugs and made a full recovery. In addition, there was partial amelioration of the Parkinson symptoms. This case shows that physicians should be aware that BCG instillation for TCC can cause systemic disease even years after treatment.

BACKGROUND

BCG is an attenuated live strain of *Mycobacterium bovis*. It has been developed for vaccination against tuberculosis. It has also shown effectiveness as an intravesical immunotherapy for superficial bladder cancer. Although generally well tolerated, BCG instillation can lead to systemic diseases, often referred to as BCG-itis. This usually occurs within weeks after intravesical instillation, although longer latency periods have been described. We present a case of systemic BCG infection presenting 9 years after BCG treatment.

CASE PRESENTATION

A 75-year-old man of Italian descent was admitted in July 2015 because of deterioration of his general health. The patient reported progressive gait disturbance and weight loss in the preceding months. His medical history included epilepsy, lower body Parkinson's disease and recurrent localised transitional cell carcinoma (TCC) of the bladder. In 2005, he had undergone endoscopic resections of the TCC and, 1 year later, recurrent lesions were treated with intravesical instillation of BCG. In November 2014, he was evaluated for unexplained weight loss. Positron emission CT/CT imaging showed a mycotic abdominal aneurysm, and surgical aneurysm repair was performed. Perioperative

cultures remained negative and the pathological examination showed unspecific inflammation.

At admission in 2015, the physical examination was unremarkable except for cachexia and signs of Parkinson's disease.

INVESTIGATIONS

Laboratory investigation showed a C reactive protein of 30 mg/L, a normal haemoglobin count (13.3 g/dL), thrombocytopenia of $70 \times 10^9/L$ and leukocytopenia of $3.0 \times 10^9/L$.

During observation at our ward, intermittent fever up to 38.7°C was recorded.

Urine analysis, chest X-ray and abdominal echography were unremarkable. Serological investigation for HIV, syphilis, brucellosis, bartonellosis and Q fever was negative. Repeated blood cultures and extended cultures for brucellosis remained negative. During admission, the patient had an evolution towards pancytopenia, with a 10.8 g/dL haemoglobin level, a $2.1 \times 10^9/L$ white cell count and a $49 \times 10^9/L$ platelet count.

Subsequently, a bone marrow biopsy and aspiration for bone marrow cultures were performed. The biopsy showed a granulomatous inflammatory infiltrate (figure 1). Mantoux and Interferon-γ Release Assays were performed, both remained negative. Bone marrow cultures and mycobacterial blood cultures later became positive with *M. bovis*.

TREATMENT

The patient was treated with isoniazide, rifampicin and ethambutol for 2 months, followed by isoniazide and rifampicine for an additional 7 months.

Figure 1 Bone marrow biopsy showing granulomatous inflammation (H&E, ×20).

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OUTCOME AND FOLLOW-UP

The patient experienced full recovery with normalisation of blood counts and general condition. Of interest, we also witnessed partial amelioration of the Parkinson symptoms.

DISCUSSION

Instillation of BCG in patients with TCC triggers a local immune response leading to the production of proinflammatory cytokines and influx of leucocytes, ultimately leading to lysis of tumour cells.¹ Many patients experience an episode of dysuria and flu-like symptoms, including low-grade fever and malaise. The episodes are self-limiting and last only for a few days. However, BCG immunotherapy has long been known to cause prolonged systemic complications. These occur in 3–7% of patients and comprise disseminated infection, reactive immune phenomena (eg, reactive arthritis) or a combination of both.^{2–4} The true incidence of disseminated infection is unknown. A pooled analysis of the literature of all the cases published from January 1975 to April 2013 identified 282 patients with systemic complications of BCG instillation.⁴ Disseminated infection was described in 97 cases (34.4%). Mycotic aneurysms were seen in 13 patients (4.6%). In less than half the patients, the micro-organism was identified by culture or PCR and only in three patients was *M. bovis* recovered from bone marrow specimen. The time interval between instillation and onset of related symptoms can be up to several months or even years. To the best of our knowledge, there are only two cases reported in the literature, with an interval between BCG instillation and systemic disease that is longer than in our patient: one case of epididymo-orchitis that occurred after 17 years⁵ and a case of spondylodiscitis 11 years after BCG instillation.⁶ In retrospect, the mycotic aneurysm that our patient suffered from 8 months before admission may have been caused by *M. bovis*.

Learning points

- ▶ Intravesical instillation of BCG is an effective and generally safe treatment for transitional cell carcinoma of the bladder.
- ▶ However, in rare cases, intravesical BCG can cause systemic disease several years after exposure.
- ▶ Progressive pancytopenia can be a clinical manifestation of disseminated BCG infection.

Competing interests None declared.

Patient consent Obtained.

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