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A rare case of bone marrow BCG-itis responding to second-line anti-tuberculosis treatment

Intravesical administration of liquid bacille Calmette-Guérin (BCG) suspensions is widely used for malignant urothelial superficial papillomas, and serious adverse events have rarely been reported. We describe the case of a patient with bladder cancer who underwent transurethral resection, followed by BCG immunotherapy, and developed serious systemic BCG infection (BCG-itis), mainly affecting the bone marrow.

A 69-year-old male patient with a history of arterial hypertension, smoking, alcohol abuse and bladder cancer was transferred to our unit from a rural hospital with persistent high fever ($\geqslant$39°C). Onset of fever followed the fifth BCG instillation, which was reported as traumatic. He remained hospitalised for 12 days and received broad-spectrum antibiotics, with no response. Due to high clinical suspicion of BCG-itis, antibiotics were switched to isoniazid (INH) plus rifampicin (RMP), which were withdrawn 3 days later because of mild leukopaenia.

In the emergency department, the patient was febrile (40°C) with rigour, tachypnoeic (20 breaths/min) and had altered mental status (Glasgow Coma Scale E4V4M6). Blood pressure was 138/64 mmHg, oxygen saturation 96% in room air and heart rate 116 beats/min. Clinical examination revealed diffuse bilateral rhonchi, macroscopic haematuria and bilateral ankle pitting oedema. Soft painless liver tip was palpable 3 cm below the costal margin.

Laboratory tests showed anaemia (haemoglobin 10.8 g/dl), leukocytopaenia (white blood cell count 2290/ml, polymorphonuclear neutrophil leukocytes/lymphocytes 62.8%/23.9%), borderline platelet count (142 100/ml), cholestatic liver injury (serum glutamic oxalacetic transaminase 56 international units (IU)/l, serum glutamic pyruvic transaminase 40 IU/l, alkaline phosphatase [ALP] 184 IU/l, gamma glutamil transpeptidase 299 IU/l) and elevated inflammation markers (C-reactive protein [CRP] 16.12 mg/dl, procalcitonin 3.28 ng/ml). Neither consolidations nor miliary pattern were identified on chest computed tomography, while abdominal scan revealed hepatosplenomegaly and focal splenic lesions, probably corresponding to infarcts.

Diagnostic work-up for infectious diseases associated with pancytopaenia and hepatosplenomegaly was negative. Bone marrow aspiration and biopsy were also performed. Microscopy of the aspirate revealed only reactive changes. A triple regimen consisting of INH, RMP, and ethambutol (EMB) was initiated due to high clinical suspicion of BCG-itis.

Severe conjugated hyperbilirubinaemia and international normalised ratio (INR) prolongation were observed. Malnutrition, history of excessive alcohol intake and baseline ALP elevation, all present in our patient, are considered major risk factors for anti-tuberculosis treatment-associated drug-induced liver injury.[1] Triple therapy was discontinued and both INR and total bilirubin decreased.

A biopsy of bone marrow finally revealed multiple non-caseating granulomas, composed of epithelioid histiocytes, Langhan's giant cells and small T-lymphocytes (Figures 1 and 2). BCG-itis was the definitive diagnosis, and taking into consideration the abovementioned complication, second-line treatment with levofloxacin, amikacin, cycloserine and EMB was initiated.

A marked decrease in CRP was noticed and the patient was afebrile by day 20. His general condition and laboratory tests gradually improved, and he was discharged 29 days after admission.

As the classic first-line anti-tuberculosis drugs have significantly higher eradication rates, a successful attempt was made to gradually switch the patient to triple therapy consisting of INH, RMP and EMB after treatment initiation with second-line drugs.

According to the European Association of Urology, BCG immunotherapy reduces the risk of tumour recurrence and progression in patients with bladder cancer.[2] However, BCG administration is associated with numerous complications, either local, exclusively involving the genitourinary tract, or systemic.[3] Less

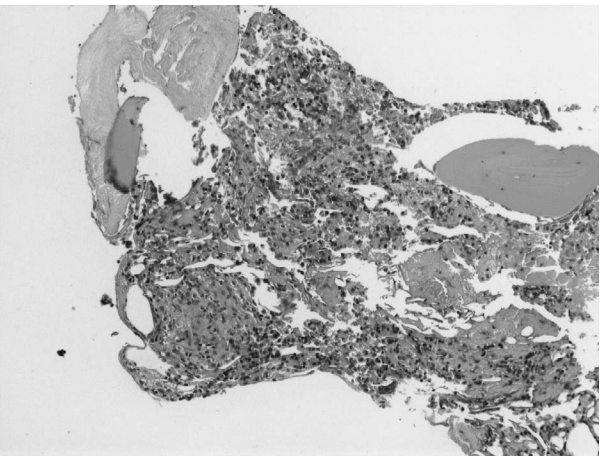

Figure 1 A non-caseating granuloma (bottom left) with epithelioid histiocytes and sparse small lymphocytes (338 × 254 mm).

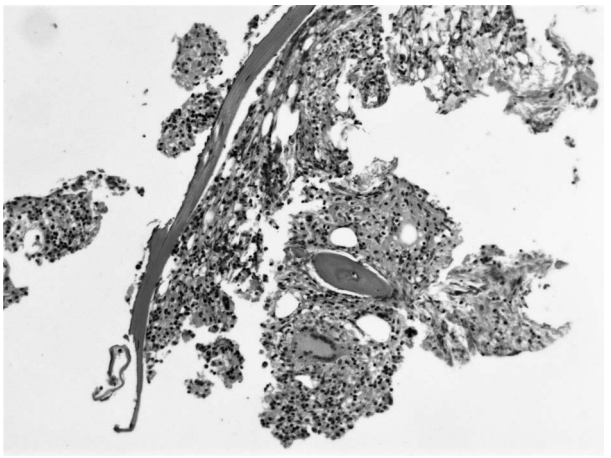

Figure 2 Another part of the biopsy with an isolated Langhan's giant cell (338 × 254 mm).

than 5% of treated patients experience major adverse events.[4,5] Most patients are males, with a mean age of 66.6 years, smokers, with hypertension or diabetes mellitus. Predisposing risk factors are traumatic instillation or concurrent urinary tract infection.[5]

Although histological examination is not the gold standard, it may contribute more to the diagnosis of BCG-itis than microbiological testing (<50% sensitivity). Fortunately, most patients respond well to standard drug treatment.[5]

This is one of the very few well-described cases of BCG-itis affecting the bone marrow and manifesting with cytopaenia (0.1% in the largest retrospective analysis[4]), and the first in which second-line treatment achieved complete response.

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