

INFEZIONE DISSEMINATA DA MYCOBACTERIUM BOVIS DOPO TERAPIA CON INSTILLAZIONI INTRAVESICALI DI BCG

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Riassunto

La terapia endovesicale con *Bacillus Calmette-Guérin* (BCG) è un trattamento adiuvante efficace per il carcinoma uroteliale non muscolo-invasivo della vescica, ma può raramente causare un'infezione disseminata. Un uomo di 75 anni, portatore di una protesi vascolare aortica e affetto da carcinoma uroteliale ad alto grado, trattato con resezione transuretrale seguita da terapia endovesicale con BCG, ha sviluppato febbre persistente, alterazione dello stato mentale, perdita di peso e aumento degli indici infiammatori. La PET/TC ha evidenziato una captazione patologica a livello epatico e della protesi aortica. La biopsia epatica ha documentato un'epatite granulomatosa, con identificazione del complesso *Mycobacterium tuberculosis*, successivamente supportata da colture ematiche e urinarie positive per micobatteri. Sebbene la terapia antibiotica abbia determinato una rapida risoluzione della febbre e la

normalizzazione degli indici infiammatori, il ritardo diagnostico è stato seguito da un progressivo deterioramento clinico e funzionale. Questo caso sottolinea l'importanza di riconoscere precocemente un'infezione disseminata da BCG.

Introduction

Intravesical *Bacillus Calmette-Guérin* (BCG) therapy is an established adjuvant treatment for intermediate- and high-risk non-muscle-invasive bladder cancer following transurethral resection [1]. It consists of intravesical instillation of an attenuated strain of *Mycobacterium bovis* and induces a local immune response against tumour cells, reducing tumour recurrence and progression.

BCG therapy is generally well tolerated. Local inflammatory reactions, commonly referred to as BCGitis, are relatively frequent, whereas disseminated BCG infection (BCGosis) is a rare but potentially severe complication resulting from systemic spread of *M. bovis* [2]. As *M. bovis* belongs to the *Mycobacterium tuberculosis* complex, disseminated BCG infection can clinically resemble tuberculosis and may involve distant organs, including the liver, lungs, bones, and vascular structures [3]. Diagnosis can be challenging because clinical manifestations are often nonspecific and may occur weeks to years after BCG instillation.

Case presentation

A 75-year-old man with a history of aorto-biliac endoprosthesis placement in 2021 for an asymptomatic abdominal aortic aneurysm, ischaemic heart disease treated with coronary artery bypass grafting and ascending aortic replacement, and high-grade urothelial carcinoma treated by transurethral resection of the bladder tumour was undergoing intravesical BCG adjuvant therapy. His last BCG instillation had been administered two months before

presentation. He had no history of diabetes mellitus and had no known conditions associated with immunosuppression.

He was brought to the emergency department by ambulance because of altered mental status, severe rigors, profuse sweating, and fever up to 39°C, which had persisted for approximately one week. Laboratory investigations showed elevated C-reactive protein (39 mg/L) and lymphopenia ($0.51 \times 10^9/L$). An acute cerebral event had previously been excluded by cranial CT. The patient had recently undergone cystoscopy following his last BCG instillation and had been started on empirical antibiotic therapy by his general practitioner for suspected urinary tract infection. He was admitted for further investigation and intravenous ceftriaxone therapy.

Over the following weeks, fever persisted despite antibiotic treatment, with persistently elevated inflammatory markers (maximum C-reactive protein, 77 mg/L) and progressive liver enzyme abnormalities (alanine aminotransferase 108 U/L, aspartate aminotransferase 110 U/L, alkaline phosphatase 258 U/L, and gamma-glutamyl transferase 404 U/L). Significant weight loss and persistent altered mental status were also observed. Blood and urine cultures for common bacterial pathogens remained negative, potentially influenced by prior antibiotic exposure. Serological and molecular testing for *Brucella*, *Coxiella burnetii*, *Bartonella henselae*, *Treponema pallidum*, and *Borrelia burgdorferi* was negative. HIV testing was also negative. Cerebrospinal fluid analysis and transoesophageal echocardiography did not identify an alternative source of infection.

Given the persistent fever and progressive clinical deterioration despite broad-spectrum antibiotics, antibacterial therapy was discontinued and

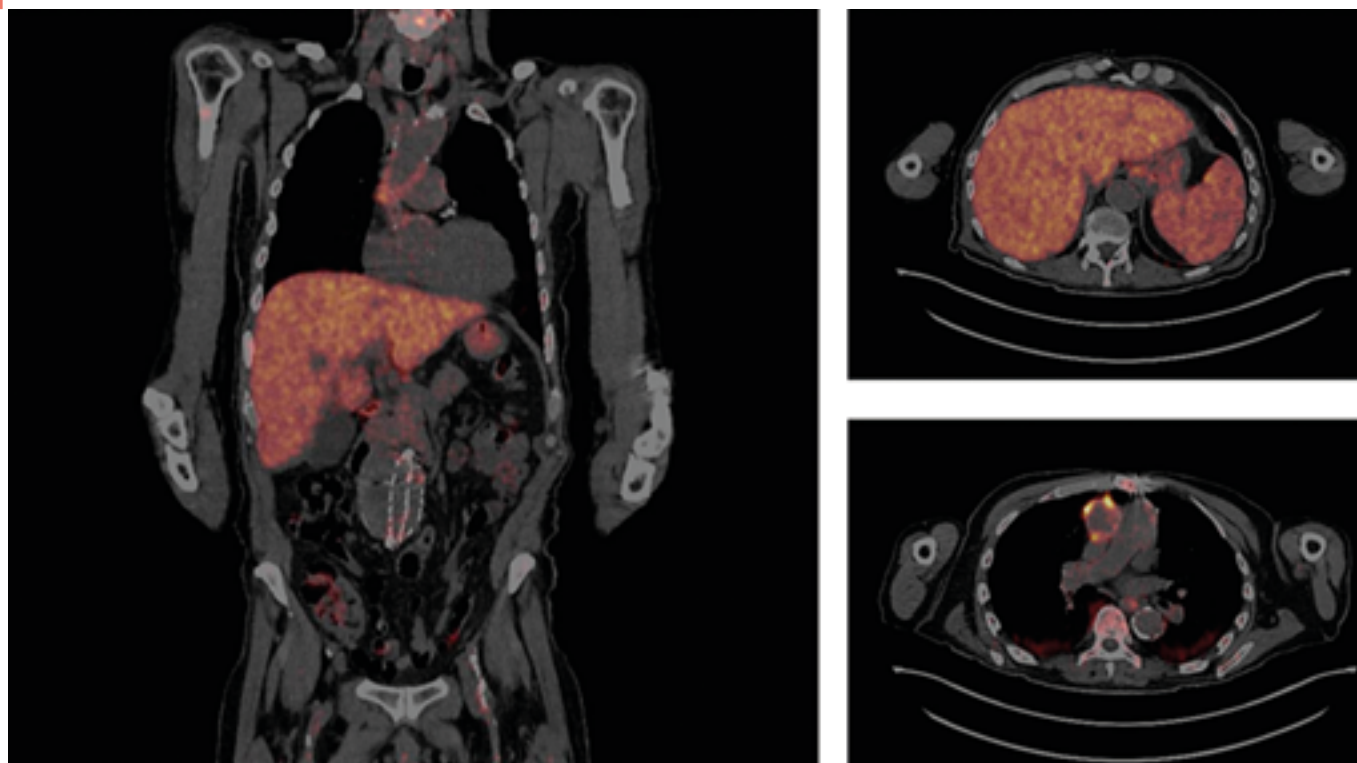


Fig 1: Whole body PET/CT scan showing aortic and hepatic uptake

further investigations were pursued. PET/CT demonstrated increased uptake involving the aortic endoprosthesis and focal hepatic uptake in segments VII–VIII, with no pathological uptake in the bladder or regional lymph nodes (Fig 1).

Following multidisciplinary discussion with nuclear medicine specialists, the hepatic uptake was considered pathological and prompted liver biopsy. Histological examination demonstrated granulomatous hepatitis, with molecular testing identifying *M. tuberculosis* complex. In the context of the previous intravesical BCG therapy, these findings raised suspicion of disseminated BCG infection, prompting specific mycobacterial cultures of blood and urine, which subsequently became positive. In the context of the patient's clinical history and these findings, disseminated BCG infection was suspected,

prompting specific mycobacterial cultures of blood and urine. Two to three weeks later, both cultures became positive for mycobacteria. The overall clinical, radiological, histological, and microbiological findings were consistent with disseminated BCG infection involving the liver and aortic endoprosthesis, with associated aortitis.

Treatment with isoniazid (5 mg/kg), rifampicin (10 mg/kg), and ethambutol (25 mg/kg) was initiated for two months, followed by dual therapy with isoniazid and rifampicin for a total treatment duration of nine months.

Following initiation of antimycobacterial therapy, body temperature and inflammatory markers rapidly normalized. Despite microbiological and inflammatory improvement, however, the patient experienced persistent functional deterioration, with severe cachexia and loss of au-

tonomy, ultimately requiring nursing home care.

Discussion

Disseminated BCG infection is a rare but potentially life-threatening complication of intravesical BCG therapy. It should be distinguished from BCGitis, the local inflammatory response commonly observed following treatment. Because *M. bovis* BCG belongs to the *Mycobacterium tuberculosis* complex, disseminated infection may resemble tuberculosis and involve multiple organs. Vascular involvement is particularly uncommon but can have severe consequences when prosthetic material is affected. A review of 73 cases of BCG-related vascular infection reported prosthetic graft or endoprosthetic involvement in 15%, with a reported risk of rupture of approximately 35% and mortality of 10% [4]. The interval between BCG instillation and diagnosis may be prolonged, with previ-

ous reviews reporting median or mean intervals of 17 and approximately 24 months, respectively [5-6], potentially contributing to delayed diagnosis.

In the present case, the aortic endoprosthesis represented a potential site of *M. bovis* infection, with concomitant hepatic involvement causing granulomatous hepatitis. Persistent fever, weight loss, systemic deterioration, and negative conventional cultures prompted further investigation. PET/CT was pivotal in identifying abnormal uptake at the aortic endoprosthesis and liver and guided targeted tissue sampling. Liver biopsy demonstrated granulomatous hepatitis and identified *M. tuberculosis* complex by molecular testing, prompting specific mycobacterial cultures of blood and urine, which subsequently became positive.

This case highlights the importance of considering disseminated BCG infection in patients with unexplained systemic symptoms following intravesical BCG therapy, particularly in the presence of vascular prosthetic material. PET/CT may be valuable when conventional investigations are inconclusive, both for identifying sites of involvement and guiding biopsy. Early multidisciplinary assessment is important because vascular infection may lead to severe complications and require prolonged antimycobacterial therapy and, in selected cases, surgical intervention. Despite microbiological and inflammatory improvement, the patient experienced substantial functional decline and ultimately required nursing home care, illustrating that control of infection does not necessarily result in recovery of functional status when diagnosis and treatment are delayed.

Conclusion

Disseminated BCG infection is a rare but potentially life-threatening complication of intravesical BCG therapy. Persistent unexplained fever and systemic deterioration should raise suspicion for BCG dissemination, particularly in patients with vascular prosthetic material. PET/CT may facilitate the identification of involved sites and guide tissue biopsy when conventional investigations are inconclusive. Early recognition and multidisciplinary management are essential to limit potentially severe complications.

rimborsato dalle casse malati

Rheumalix® forte Gel [RFG] / Rheumalix® forte Spray [RFS] / Rheumalix Gel [RG]. C: RFG: 1 g (RFS: 1 ml; RG: 2 g) contiene 100 mg di etofenamat. I: stati dolorosi e flogistici e tumefazioni in caso di distorsioni, contusioni e strappi. Trattamento locale di supporto dei disturbi reumatici. P: (RFG: 10 cm di gel corrispondono a circa 300 mg di etofenamat); (RFS: 1 erogazione equivale a 0,1 ml e contiene 10 mg di etofenamat); (RG: 10 cm corrispondono a 150 mg di etofenamat). RFG/RG: applicare più volte al giorno circa 5-10 cm di gel e massaggiare finché penetra nella pelle. RFS: 4-7 volte al giorno, fino a un massimo di 9 erogazioni (in base alle dimensioni dell'area interessata). Massimo 1200 mg di etofenamat al giorno. C: ipersensibilità (anche all'anamnesi) al principio attivo, a un altro FANS, all'acido flufenamico o a una delle sostanze ausiliarie secondo la composizione. Non utilizzare nel 3° trimestre di gravidanza e in lattanti, bambini piccoli, bambini e adolescenti. Non applicare sulle membrane mucose/occhi. Non applicare sulla cute lesa. PR: non applicare su aree estese per periodi prolungati. In caso di eruzione cutanea interrompere il trattamento. Contiene glicole propileno. Rischio di asma e reazioni cutanee da analgesici. Evitare il solarium. IA: rischio trascurabile. GA: nel primo e nel secondo trimestre di gravidanza solo se chiaramente necessario, controindicato nel terzo trimestre e durante l'allattamento. Et: reazioni cutanee locali, respiro affannoso, fotosensibilizzazione, gravi reazioni di ipersensibilità (anche dopo la prima applicazione). CO: tubi da 40 g e 100 g, flacone spray da 50 ml. (D). Per informazioni dettagliate consultare www.swissmedinfo.ch. Sdi: RFG/RFS: aprile 2024, RG: agosto 2021. **Drossapharm SA, 4002 Basilea.**

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Disseminated *Mycobacterium bovis* Infection after Intravesical BCG instillation therapy

Abstract

Intravesical Bacillus Calmette-Guérin (BCG) therapy is an effective adjuvant treatment for non-muscle-invasive bladder cancer but may rarely cause disseminated infection. A 75-year-old man with an aortic vascular graft and high-grade urothelial carcinoma developed persistent fever, altered mental status, weight loss, and elevated inflammatory markers following BCG therapy. PET/CT revealed pathological uptake in the liver and aortic prosthesis. Liver biopsy demonstrated granulomatous hepatitis, with identification of *Mycobacterium tuberculosis* complex, subsequently supported by positive mycobacterial blood and urine cultures. Although antimycobacterial therapy rapidly controlled the infection, delayed diagnosis was followed by progressive clinical and functional deterioration. This case highlights the importance of early recognition of disseminated BCG infection and its diagnostic challenge.

Keywords: Intravesical BCG, *Mycobacterium bovis*, Disseminated BCG infection, Aortitis, Granulomatous hepatitis

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Declarations

- Authors' role in the preparation of the manuscript: All authors contributed to the conception and design of the manuscript, reviewed and critically revised the manuscript, and approved the final version.
- Conflicts of interest: none declared.
- Written informed consent for publication was obtained from the patient's wife, as the patient lacked decision-making capacity
- Data availability statement: Anonymized data supporting this case report are available from the corresponding author upon reasonable request.
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