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A severe Bacillus Calmette-Guérin vertebral osteomyelitis requiring spinal stabilization: a clinical and microbiological investigation

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Vertebral osteomyelitis

Dear Editor,

Bacillus Calmette-Guerin (BCG), an attenuated derivative of the virulent *Mycobacterium tuberculosis* var. *bovis*, is commonly used as treatment of non-muscle invasive bladder cancer, since it triggers an innate immunological reaction in the bladder wall that is protective against tumor recurrence and progression.[1] Nevertheless, in a high proportion of patients, the treatment is interrupted due to local or systemic (usually manageable) complications. Among these, vertebral osteomyelitis is one of the less frequent and more difficult events to treat, due to delayed diagnosis and early non-specific symptoms.[2]

An 80-year-old man, with no chronic diseases except hypertension, was evaluated because of fever and severe lower back pain with limited walking. Two years before, he was diagnosed with bladder cancer and treated with BCG instillation. After the third instillation, he developed fever and acute renal failure subsequently resolved. About one year later, he complained progressively worsening lower back pain. Antalgic lumbar infiltrations were performed, but pain worsened and fever appeared. Magnetic resonance imaging revealed high signal intensity compatible with lumbar (L1-L2) vertebral osteomyelitis (Fig. 1A). At time of our first evaluation, he had weakness motor and paresthesia of lower limbs, but was able to walk and afebrile. Routine laboratory test showed normal white cells count, mild anemia, erythrocyte sedimentation rate (99 mm/1st h) and increased C-reactive protein levels (185 mg/dl). Chest X-ray was unremarkable. Blood cultures and QuantiFERON-TB tested negative, as *Brucella* antibody detection. Diagnosis of vertebral osteomyelitis was confirmed by ^{18}F-Fludeoxyglucose–Positron Emission Tomography/Computed Tomography (PET-CT), and a CT-guided needle biopsy was performed. Histological examination revealed granulomatous infection, with no evidence of acid-fast bacilli; however, culture of the infected tissue allowed for identification of *M. tuberculosis complex (bovis)* by MALDI-TOF mass spectrometry (Becton Dickinson, US). Species confirmation was carried out by line probe assays using the GenoType CM and MTBC kit (Hain Lifescience, Nehren, Germany), coupled with whole genome sequencing (WGS) using the Nanopore MinION system (Oxford Nanopore Technologies, UK) (BioProject No. PRJNA841452). Molecular typing consistently yielded *Mycobacterium tuberculosis* var. *bovis* BCG.

An anti-mycobacterium treatment with isoniazid (300 mg/day), rifampin (600 mg/day), and ethambutol (1200 mg/day) was started for the first two months, and then continued with isoniazid and rifampin. After three months the patient improved, C-reactive protein was in the normal range (<5 mg/dl), but the spine was unstable with residual pain. A posterior spinal segmental instrumentation, decompression and fusion was necessary by a posterior approach with resolution of pain (Fig. 1B). Therapy with isoniazid and rifampin was continued for 12 months without adverse events.

Although the first clinical case of BCG vertebral osteomyelitis was described in 1992, with 32 cases reported so far,[3–5] its real prevalence is likely underestimated. Clinical diagnosis is difficult and often delayed because of the late

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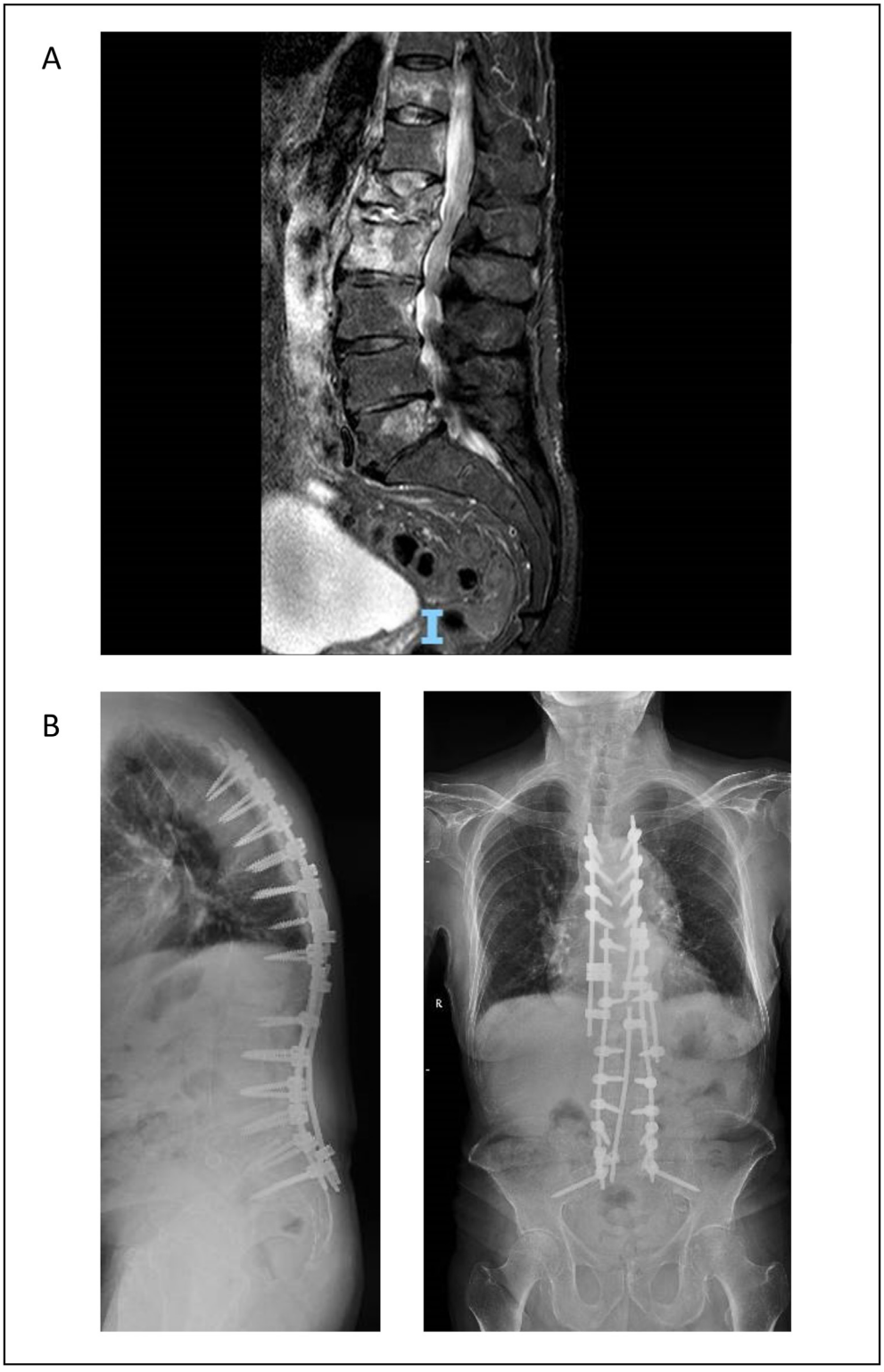

Figure 1. A) Magnetic resonance imaging of the spine showing high signal intensity in the L1-L2 vertebral body, compatible with lumbar osteomyelitis. B) Spine radiography after stabilization achieved by a posterior spinal segmental instrumentation, decompression and fusion, with bars and screws.

onset of back pain after instillation and early not-specific symptoms, with the risk of serious disabling outcomes.[2] Likewise, identification of *M. tuberculosis* var. *bovis* BCG is challenging for clinical microbiology laboratories, requiring advanced molecular approaches for a proper species identification within the *M. tuberculosis* complex. Nevertheless, it should be considered that negative interferon-γ release assay (unaffected by previous BCG vaccination) and a positive

culture for *M. tuberculosis* complex could also lead to suspicion, together with susceptibility data; indeed, *M. bovis* is susceptible to isoniazid, rifampin, and ethambutol but resistant to pyrazinamide, while *M. tuberculosis* is not.

Further genomic epidemiological investigations are warranted to uncover possible evolutionary trajectories of BCG strains causing adverse events, in order to identify genetic factors that may shape the BCG virulent behavior and clinical properties, including safety, immunogenicity, and protective efficacy.

Ethics approval

The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Written informed consent was obtained from the patient. Clinical and laboratory data was collected from the patient's medical record in the context of clinical routine. All information and metadata had been anonymized. Samples were coded and downstream retrospective analyses were performed with anonymized data.

Author contributions

Conceptualization: Giuliana Carrega, Anna Marchese, Vincenzo Di Pilato; Methodology: Patrizia Morelli, Ramona Barbieri, Vincenzo Di Pilato; Formal analysis and investigation: Giuliana Carrega, Patrizia Morelli, Davide Vallerga, Giovanni Riccio, Ramona Barbieri, Vincenzo Di Pilato; Writing - original draft preparation: Giuliana Carrega, Anna Marchese, Vincenzo Di Pilato; Writing - review and editing: Patrizia Morelli, Giovanni Riccio, Davide Vallerga, Ramona Barbieri; Resources: Anna Marchese, Vincenzo Di Pilato.

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Declaration of competing interest

None.

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Giuliana Carrega
Giovanni Riccio
Infectious Diseases and Septic Orthopedics Unit, ASL2 Pietra Ligure, Savona, Italy

Davide Vallerga
Orthopedic Unit, ASL2 Pietra Ligure, Savona, Italy

Patrizia Morelli
Microbiology Unit, ASL2 Pietra Ligure, Savona, Italy

Ramona Barbieri
IRCCS Ospedale Policlinico San Martino, Genova, Italy

Vincenzo Di Pilato*
Department of Surgical Sciences and Integrated Diagnostics (DISC), University of Genoa, Genoa, Italy

Anna Marchese
IRCCS Ospedale Policlinico San Martino, Genova, Italy
Department of Surgical Sciences and Integrated Diagnostics (DISC), University of Genoa, Genoa, Italy

*Corresponding author. Department of Surgical Sciences and Integrated Diagnostics (DISC), University of Genoa, V. Benedetto XV, No. 6, 16132 Genoa, Italy.
E-mail address: vincenzo.dipilato@unige.it (V. Di Pilato)

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