Back pain following instillations of BCG for superficial bladder cancer is not a reactive complication review of 30 Mycobacterium bovis BCG vertebral osteomyelitis cases

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Case Based Review

Back pain following instillations of BCG for superficial bladder cancer is not a reactive complication: review of 30 *Mycobacterium bovis* BCG vertebral osteomyelitis cases.

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Abstract

Introduction: *Mycobacterium bovis* BCG instillations are used in bladder cancer treatment. Adverse effects can occur. Osteoarticular complications are mainly reactive arthritis, but true infections have been described, such as vertebral osteomyelitis.

Methods: We made a review of *M. bovis* BCG vertebral osteomyelitis after instillations for bladder cancer using PubMed search. We added 3 new French cases.

Review: Twenty-seven cases of BCG vertebral osteomyelitis had been reported on PubMed. Of the 30 cases, all were male, averaging 73.4 ± 8.7 year-old. Median time between diagnosis and first and last instillation was 22.5 months and 14 months respectively. Half of vertebral osteomyelitis was thoracic, and lumbar in the other half. Sensitivomotor deficit was present at diagnosis in 42% of cases. Other infectious locations were common, mainly infectious abdominal aortic aneurysms (20%). Rifampicin, ethambutol and isoniazid were the usual therapy. Poor outcomes were reported with 50% of one or more spine surgery.

Conclusion: *M. bovis* BCG vertebral osteomyelitis following bladder instillation for bladder cancer is a rare complication. However, the late onset of back pain after instillations differentiates them from reactive arthritis. Concomitant septic location such as infectious abdominal aortic aneurysms must be known.

Keywords: Bladder cancer, BCG-instillation, *Mycobacterium bovis*, vertebral osteomyelitis, Interferon-γ release assay

1. Introduction

Mycobacterium tuberculosis is the most frequent pathogen of vertebral osteomyelitis worldwide [1], and represent half of osteoarticular tuberculous infections [2]. In the past decades in developed countries, the incidence of tuberculosis in spinal infections decreased, involving 6% of vertebral osteomyelitis[3].

Bacillus Calmette-Guérin (BCG) is a strain obtained from *Mycobacterium bovis,* used for vaccination and immunotherapy for bladder cancer since 1976 [4]. Complications of bladder instillations occur in about 5% or less of patients [5], mainly with local urinary adverse effects such as pollakiuria, cystitis or haematuria.

Systemic reactions with spinal involvement such as Reactive Arthritis (ReA) [6] can appears in weeks following instillations. Two principal clinical patterns were described: symmetric or asymmetric polyarthritis (involving small or large and upper–lower joints are more common than asymmetric mono-oligoarthritis the large joints of lower limbs (especially, knee and ankle). Actually, ReA after BCG bladder instillations cannot be fully integrated in the spondyloarthritis concept, because clinical patterns are less correlated with HLA B27 status, if compared with ReA from enteric and urogenital infections, and the sacro-iliac or spinal involvement are rarer [6].

However, ReA after BCG bladder instillations are not the only osteoarticular events described in literature, and true infections such as mycobacterial vertebral osteomyelitis have also been described. Therefore, we performed a literature review of 27 cases previously published [7–33], and we had three original French cases.

2. Original cases

A. Case 1

A 65-year-old male was admitted to Pontoise hospital in January 2014 for low back pain which lasted for three months. His medical history included weaned smoking, hypertension, and a non-infiltrating urothelial carcinoma of the bladder. He was treated from December 2012 to March 2013 with six BCG instillations. Low back pain began rapidly, 6 months after the end of BCG instillation without any other triggering factor. He had lost eight kilos in three months and developed night sweats. A first X-ray showed moderate osteoarthritis of the spine. In December 2013, Magnetic Resonance Imaging (MRI) was performed. An inflammatory signal of L3 and L2 vertebral bodies and L2-L3 discs was found, with slight soft tissue reaction. Metastatic bone involvement was first suspected.

The physical examination on his admission in the rheumatology unit showed limited multidirectional lumbar mobility of the lumbar spine, without neurological deficit. The rest of the medical examination was normal. C-reactive protein (CRP) was high, at 123 mg/L. A PET-scan was performed. It showed an intense uptake of L2 and L3 vertebral bodies. Finally, an L3 bone biopsy was performed showing non-specific osteitis without granuloma. Acid-fast bacillus (AFB) testing and bacterial cultures including Lowenstein and Coletsos were negative. in February 2014, a second MRI demonstrated a typical image of L2-L3 spondylodiscitis with pre- and paravertebral abscesses. A new biopsy did not show histological abnormalities, but two samples were positive for *Staphylococcus epidermidis*. Antibiotics were started, without biological improvement. During hospitalisation, the patient became confused and developed pyramidal signs, without neurological deficit. A new MRI demonstrated vertebral fracture of L2 with retreat of the posterior wall, mild epidural involvement, partial compression of cauda equina, associated with a right psoas abscess (**Figure 1**).

At needle aspiration of the psoas abscess direct examination for acid-fast bacilli (AFB) was positive, A 4-drug anti-tuberculosis therapy was then initiated. PCR identified *M. tuberculosis* complex (MBTC), and cultures revealed six weeks later *M. bovis*, finally identified as *M. bovis* BCG by the French national reference center for tuberculosis. Pyrazinamide was discontinued. Surgical treatment was performed due to neurological signs and vertebral instability, consisting of L2 vertebrectomy, posterior laminectomy of L3 and T11-L5 arthrodesis. Ethambutol was stopped after two months. Isoniazid and rifampicin were continued for a total duration of three years because of persisting images in the psoas on MRI. Clinical, biological and radiological outcome was good. Thirteen months after discontinuing treatments, the patient was considered to be cured.

B. Case 2

A 73-year-old man was hospitalised in Rennes University Hospital in July 2017 for low back pain for 11 weeks. His medical history only reported a urothelial carcinoma, treated with transurethral resection of bladder tumor (TURBT) and 9 instillations of BCG, ended in December 2016. He was a retired veterinarian. Low back pain onset was reported as brutal, triggered by a bending effort. Secondarily, he developed anorexia, weight loss and asthenia.

Before his hospitalisation, he was examined with a CT-scan showing an osteolysis of L1 vertebral body. He was referred to his oncologist and had a PET-scan as part of a metastatic hypothesis. It showed an uptake of L1 and L2 vertebral bodies (**Figure 2**), with possible epiduritis. For further explorations, he had lumbar spine

MRI two months after the first symptoms (**Figure 2**). A typical vertebral osteomyelitis of L1 and L2 vertebral bodies was found, with centro-somatic erosion suggesting a *Mycobacterium* infection.

The physical examination at his admission only showed limited multidirectional lumbar mobility, and no neurological impairment. Laboratory analysis showed a normal white blood cell (WBC) count, and a high CRP level of 70 mg/L. A first discovertebral puncture was negative on direct examination, MBTC PCR was negative, and cultures were sterile after seven days. A puncture of the right psoas abscess showed AFB on direct examination. MBTC was identified in a culture six days later. The search for mutation of *rpoB* that confers resistance to rifampicin was negative, and an anti-tuberculosis quadritherapy was started. *M. bovis* BCG was finally identified by PCR and pyrazinamide was stopped. In June 2018, the patient had an excellent evolution, with a good tolerance of his nine months of triple therapy.

C. Case 3

A 77-year-old man, with a history of gastric adenocarcinoma (1996), urothelial carcinoma (2011) and chronic alcoholism, was hospitalised in August 2017 in the rheumatology department of the Saint Philibert hospital (Lomme) for insidious onset of low back pain a few weeks earlier. He had been diagnosed with a bladder papillary urothelial carcinoma (pTa high-grade) in 2011, treated by transurethral resection in July 2011, followed by intravesical BCG therapy from September 2011 to August 2014. He reported inflammatory back pain evolving since 2016, without radiculalgia. There was no weight loss. He experienced fever at 38.2°C, associated with an increase of CRP levels of 126 mg/L.

Spine MRI showed an L4-L5 vertebral osteomyelitis with fluid collection developed in the epidural space, sheathing the right L5 and S1 roots. A discovertebral biopsy was performed, showing AFB on direct examination and the MTBC was detected using real-time PCR. Other tests were unremarkable (negative HIV serology, CD4 cell count was normal, no hypogammaglobulinemia, no hypocomplementemia). The thoraco-abdomino-pelvic CT scan did not find another tuberculous localisation. Blood cultures were sterile and the interferon-gamma release assays were negative. The culture was sterile. The patient did not report any contact with tuberculosis. Antituberculosis therapy with isoniazid, rifampicin and ethambutol was introduced. Evolution was favourable after 12 months of treatment, with a decrease in pain and fever, and a decrease in acute phase reactants. At the end of follow-up, he was just diagnosed with lung cancer.

3. Methods

Based on PubMed research on the 1st January 2019, we used to identify *Mycobacterium bovis* BCG vertebral osteomyelitis the following keywords: “osteomyelitis AND BCG AND bladder”, “spondylodiscitis AND BCG AND bladder”, “spondylitis AND BCG AND bladder”. Seventy-five articles had been identified. We also used the keywords “aneurysm AND BCG AND bladder”, and looked for vertebral osteomyelitis due to overlap with *M. bovis* BCG infectious aneurysms, identifying 42 articles.

A total of 117 articles had been identified, and 24 cases had been included. Three other articles had been identified through previous reviews (**Figure 3)**. We had three original French cases.

4. Review

Since 1992, 25 cases of *M. bovis* BCG vertebral osteomyelitis following instillations for bladder cancer have been reported in English literature [7–31] and two cases in non-English literature [32, 33]. Other articles with *M. bovis* BCG infection and spinal pain have been published [34–36], but they were not consistent with a vertebral osteomyelitis diagnosis. The frequency is possibly underestimated knowing the possible difficulties in documenting such an infection, as in two other publications [27, 37].

A. Clinical characteristics

We have collected information from 30 cases (27 literature cases and our 3 new cases), and we have listed the main features in **Table 1**. Diagnostic characteristics are resumed in **Table 2**. Case 3 was included in our review, given the recently proven usefulness of interferon-γ release assay in vertebral osteomyelitis infection with *Mycobacterium tuberculosis* [38], and its recommendation by the IDSA (Infectious Diseases Society of America) [39].

We have estimated from these articles the period of time between the first and the last BCG instillation and the diagnosis (i.e. bacteriological diagnosis). When the dates mentioned in the article were not sufficiently detailed, we considered the first and the last instillation time-lap as the same. The median time between diagnosis and first or last instillation was 22.5 ± 28.5 months and 14 ± 25.5 months, respectively. At mean, patients received 9.4 ± 4.6 instillations of BCG. There was not enough information about the BCG strains to establish a difference between them. Seven of 30 cases had a cancer in their medical past history. No one had received immunosuppressive therapy between instillation and vertebral osteomyelitis diagnosis. Neoplasia was

considered as cured, in remission [20], or localized [10, 23]. No patients had received DMARDs for rheumatic condition, and one had psoriasis without musculoskeltal disorder.

All *M. bovis* BCG vertebral osteomyelitis cases occurred in men of 73.4 ± 8.7-year-old. Twenty-six cases involved two contiguous vertebrae, and two cases one vertebra. Half of infections affected the thoracic spine (from T1-T2 to T12-L1), and the other half affected the lumbar spine (from L1-L2 to L5-S1). No cervical osteomyelitis was reported. Back pain was almost always present (97%). The median of back pain duration at diagnosis was 5 (1-9) months, and the median period of time between the last instillation and back pain was 5 (0-16.5) months. No peripheral skeletal involvement had been reported.

Clinically, fever was reported only in 20% of cases, 75% developed anorexia and/or weight loss and/or asthenia. Sensitivo-motor deficit was present at diagnosis in 42% of cases.

On imaging (CT scan and/or MRI) 70% had epiduritis or epidural abscesses **(Figure 1)**, and 47% had paravertebral/psoas abscesses **(Figure 1 and 2)**. Other infectious locations occurred in nine cases, mostly abdominal aortic aneurysms.

Biologically, 77% of patients had CRP > 5 mg/l, and 21% an elevated WBC count. The tuberculin test was negative for 5 out of 6 patients, and the seven IFN-gamma tests were all negative (only one patient receive both tests, both negative). Biopsy showed a granuloma in 60% of cases, of which 56% was necrotic. *Mycobacterium bovis* BCG was almost always identified through cultures.

The direct exam was positive in 55% of bacteriological samples. All molecular tests and PCR were positive. Bacteriological identification was done through CT-guided biopsy with 79% positivity, and through surgical biopsy or abscess puncture which were always positive. When CT-guided biopsies were negative, diagnosis was made with surgical biopsy in two cases, and with abscess puncture in two cases. Abscess puncture was the only procedure used in four cases.

B. Treatment and outcomes

Frequently, the classical anti-tuberculosis therapy was started, and then Pyrazinamide was stopped when BCG was identified due to BCG natural resistance[40]. Isoniazid, rifampicin and ethambutol were normally used throughout the treatment period. Nevertheless, antibiotic modalities were heterogeneous (**Table 1)**. Treatment duration, known for 20 cases, was 12.1 ± 7.0 months.

The outcome was known for 14 patients with 18.5 months of mean follow up: 12 cases were considered cured, and 2 died from cardiovascular causes without vertebral osteomyelitis symptoms. Fifty percent had one or more cases of spine surgery, (ranging from one to three surgeries). Among them, five patients had spinal arthrodesis during the follow-up: three for neurological worsening, one for persistent root pain, and one for vertebral instability.

C. Comparison of M. bovis BCG with M. tuberculosis

Compared to vertebral osteomyelitis due to *M. tuberculosis* [41], *M. bovis* BCG vertebral osteomyelitis seems to involved an older population with a male predominance, probably due to the bladder cancer population. However, we noticed that all cases in this review were men, while 74.1% of non-muscle-invasive bladder carcinoma in the United States are male [42]. About clinical presentation, lumbar and thoracic involvement of BCG vertebral osteomyelitis were consistent with literature, but no cases of nonadjacent multiple-level involvement were reported with BCG after bladder instillation. Neurological complications at diagnosis and psoas abscesses prevalence seems to be higher in BCG than tuberculosis.

In contrast of tuberculosis, there was no other sites of *M. bovis* BCG vertebral osteomyelitis infection, whereas vertebral Pott's disease is frequently associated to pulmonary tuberculosis at diagnosis. We assumed that's it's probably due to the gateway of *Mycobacteria:* through airway contamination leading to pulmonary tuberculosis, and through catheterization leading to local urinary reaction or systemic reaction which are sometimes treated with antituberculosis treatment, decreasing risk of other infection.

D. Pathogenesis discussion

BCG instillations are a cornerstone for superficial bladder carcinoma treatment, and they have changed the prognosis of this disease [4, 5]. Septic side effects are rare, between 0.4% and 1/15,000 according to Lamm [5], and the benefit of the treatment remains higher than the risk of such events. However, other distant infections are described in the literature, mostly vascular aneurysms in a recent literature review [43], but also disseminated infections also called BCGitis [44], small-vessel central nervous system vasculitis [45] and even nosocomial infections, including vertebral osteomyelitis [46]. Some risk factors of distant infections could be suggested: a traumatic catheterisation during instillation [5], haematuria, instillations in the few days around an urological trauma [28] (pelvic radiation, surgery, bladder resection), arterial catheterisation [13], and general immunosuppressive factor such as HIV infection.

Pathogenesis of *M. bovis* BCG-associated infections following instillations can be supported in three

ways. First, through the pelvic lymphatic drainage system, particularly for psoas abscesses. Even if iliopsoas abscess pathogenesis is not clear, haematogenous or lymphatic spread is commonly admitted [47]. Such abscesses can be linked to BCG spread from bladder to the lymph nodes, particularly those closely related to the iliopsoas muscle, such as the common iliac and paravertebral lymph nodes. However, an exclusive lymphatic pathogenesis underlies an infection by contiguity only with vertebrae which have an anatomical relationship with iliopsoas, i.e. T12 to L4. Secondarily, as recently suggested [28], through the vertebral venous plexus (known as Batson's venous plexus). Once again, a venous spread of BCG does not explain thoracic osteomyelitis. Finally, through an arterial route: Higashi *et al.* [43] suggested a septic aneurysm pathogenesis from *vasa vasorum,* or directly by adhesion on atherosclerotic degeneration in a review of 29 cases (including three common cases of patients with vertebral osteomyelitis and infectious aneurysm).

Considering these vascular infections and the pathogenesis of haematogenous spread in vertebral osteomyelitis, arterial dissemination seems to be the principal way, as suggested by Civen *et al.* [10] who described a positive blood culture of BCG. However, there seems to be an association between infectious aneurysm and vertebral osteomyelitis: among the 17 cases including L1 to L4 vertebral involvement (i.e., vertebrae having a direct anatomical relationship with the abdominal aorta), there were five out of six cases of infectious aneurysm, and only one thoracic osteomyelitis was associated with infectious aneurysm. This higher frequency of aneurysms in lumbar osteomyelitis suggests pathogenesis other than the arterial route for aneurysms. Finally, a simultaneous infectious aneurysm may also seem to be associated with cardiovascular risk, because of a more frequent cardiovascular medical history **(Table 1)**.

Mycobacterium bovis BCG identification is crucial in *M. bovis* BCG associated osteomyelitis. Culture is the first step, but a specific identification has to be done. Oldest cases used high-pressure liquid chromatography (HPLC), which has been nowadays replaced by molecular technics. Multiplex PCR targeting specific regions of *Mycobacterium spp.* genomes can now differentiate with a total specificity [48] *M. bovis* BCG from the others mycobacteria. It means that, when vertebral osteomyelitis is suspected in a patient with medical history of BCG instillations for bladder carcinoma, AFB on direct examination or positive culture for MTBC must have the biologist carry out the precise identification of the strain by mutliplex PCR, including BCG detection, the therapeutic impact being significant.

Other related events following BCG instillations were described, such as ReA [6] with a HLA-B27 (or B51 in the Japanese population) association, suggesting a Th17 response. On the other hand, the anti-tumour effect of BCG therapy is based on a Th1 response [49] as well as the anti-infectious response. Tumour recurrence could not be evaluated in this review but occurred in eight patients. Based on purely immunological considerations, we assume that there could be a link between tumour recurrence and these signalling pathways. *M. bovis* BCG associated infections could be correlated to a lack of Th1 lymphocyte polarisation, and thus an increased risk of recurrence, making *M. bovis* BCG-associated infections a risk factor for the inefficacy of BCG instillations. In the same way, Th17 polarisation observed in ReA could reduce a Th1 response (because of the exclusive nature of the polarisation [50]). Such assumptions need more specific studies to evaluate correlations between tumour recurrence, infections and immunological reactions.

In conclusion, when vertebral osteomyelitis is suspected in a man with a medical history of bladder carcinoma treated with BCG instillations, *M. bovis* BCG osteomyelitis must be sought even if the last instillation was months before. A direct exam showing AFB and positive cultures followed by multiplex PCR are used for bacteriological diagnosis. The presence of aneurysms at osteomyelitis diagnosis should be investigated because of its potential life-threatening complications. The treatment is not codified, but the pyrazinamide resistance must be known. The duration of anti-tuberculosis therapy is heterogeneous, and individual adaptation has to be done, regards to the septic severity, neurological deficit, or treatment adverse effects.

Disclosure of interest
The authors declare that they have no competing interest.

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Figure 2. ***(a)*** *MRI Axial T1 with Fat Sat sequence and Gadolinium injection showing epiduritis with partial cauda equina compression, and voluminous right psoas abscesses* ***(b)*** *MRI Sagittal T2 with Fat Sat, showing hypersignal of L1 and L2 vertebral body with a vertebral fracture of L2 and retreat of posterior wall.*

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Table 1. Clinical, biological, bacteriological and imaging features of 30 reported cases of *M. bovis* BCG vertebral osteomyelitis after instillations of BCG for bladder cancer.

	Results
Clinical Characteristics	
Men, n (%)	30 (100%)
Age (years) mean ± SD	73,4 ± 8,7
Back pain, n (%)	29/30 (97%)
Duration of back pain (months), median ± IQR	5 ± 4 (22/30)
Median time (in months ± IQR) between diagnosis and:	
- first instillation of BCG	22.5 ± 28.5 (30/30)
- last instillation of BCG	14 ± 25.5 (30/30)
Period of time between last instillation and back pain (in months), median ± IQR	5 ± 11.5 (22/30)
Number of instillations, mean ± SD	9.4 ± 4.6 (19/30)
Fever, n (%)	4/20 (20%)
Weight loss, n (%)	12/20 (60%)
Night sweats, n (%)	3/20 (15%)
Sensitivo-motor deficit, n (%)	11/26 (42%)
Other infectious locations:	9/30 (30%)
- infectious aneurysm, n (%)	6/30 (20%)
- others	3/30 (10%)
Biological Characteristics	
ESR > 20 mm/1st h, n (%)	8/14 (57%)
High WBC, n (%)	4/19 (21%)
CRP > 5 mg/l, n (%)	10/13 (77%)
Morphological Characteristics	
CT scan and/or MRI:	
- epidural involvement	21/30 (70%)
- paravertebral	5/30 (17%)
- psoas abscess	10/30 (33%)
Bacteriological Characteristics	
Positive bacterial identification/number of procedures:	
- abscess puncture	9/9 (100%)
- CT guided biopsy	15/19 (79%)
- surgical biopsy	13/13 (100%)
Positive bacterial identification/number of tests:	
- acid-fast bacilli	11/20 (55%)
- cultures	28/30 (93%)
- molecular tests	14/14 (100%)
Histological biopsy:	
- presence of granuloma, n (%)	9/15 (60%)
- necrotizing granuloma, n (%)	5/9 (56%)
Antibiotics therapy duration (months), mean ± SD	12.1 ± 7.0

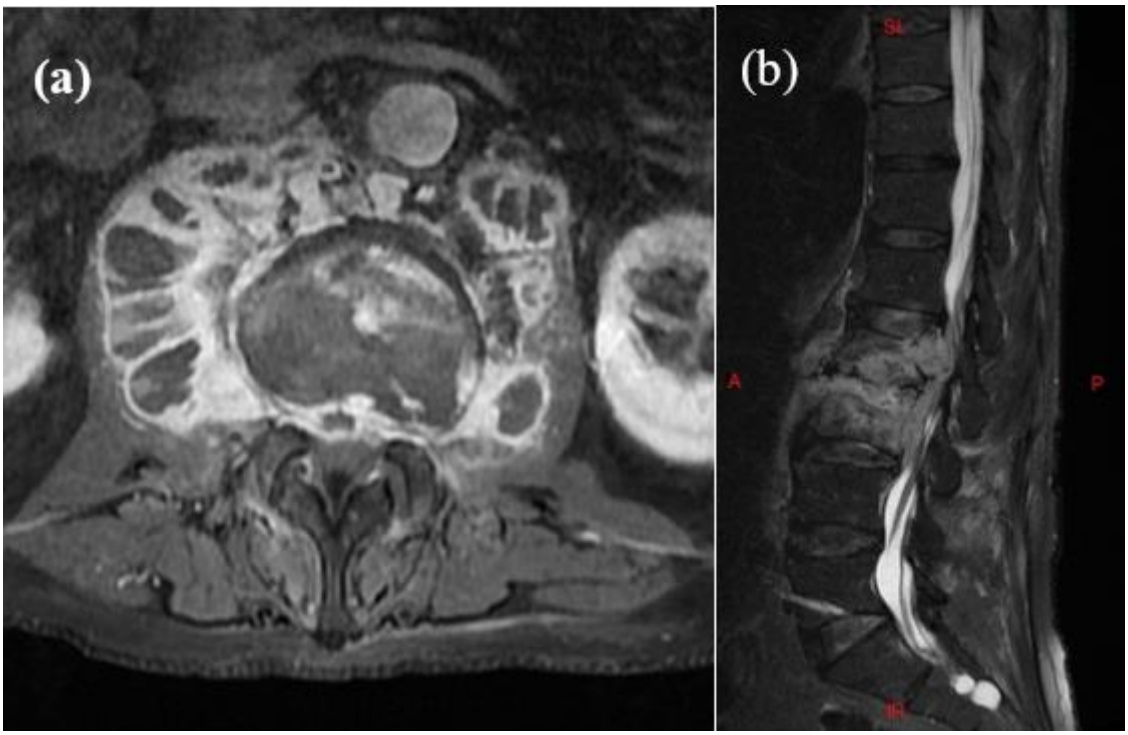
SD: standard deviation; IQR: interquartile range; ESR: erythrocyte sedimentation rate; WBC: white blood cell count; CRP: C-reactive protein.

Table 2

Table 2. Description of 30 cases of *M. bovis* BCG vertebral osteomyelitis after instillations of BCG for bladder cancer.

Authors	Year of article	Age / Sex	Comorbidities	Period of time (months) between instillation and diagnosis #		Back pain duration (months)	Number of instillations	Involved Levels	Other BCG infection	CRP (mg/L)	Anti-tuberculosis therapy	Treatment duration	Neurological symptoms on admission	Spine surgery
				First	Last									
Katz and al.	1992	66 / M	Smoking	15	3	NR	12	L4-L5	-	NR	INH + RIF	NR	Yes	Yes
Stone and al.	1993	80 / M	Coronary artery bypass, Ventricular fibrillation	5	3,5	3	6	L5-S1	Pacemaker	NR	INH + RIF then INH + ETH	4	NR	No
Fishman and al.	1993	90 / M	-	16	15	1	6	T11-T12	-	NR	INH + RIF + ETH	NR	No	No
Civen and al.	1994	81 / M	HBP, Atrial fibrillation, Prostate cancer	7	3,5	1	8	T12-L1	Blood Culture	NR	INH + RIF	12	No	Yes
Morgan and Iseman	1996	77 / M	Traumatic fracture of T12	80	8,5	6	12	T12-L1	-	NR	INH + RIF, then quadritherapy and then INH + RIF	25 (10+9+6)	NR	Yes
Rozenblit and al.	1996	76 / M	Myocardial infarction, Hearth failure	69	69	1	NR	L4	AAA	NR	INH + RIF	NR	No	No
LaBerge and al.	1999	75 / M	Coronary artery disease	22	22	2	NR	L3-L4	AAA	NR	NR	NR	NR	No
Aljada and al.	1999	79 / M	HBP, Smoking, Parkinson's disease, Myocardial infarction, Peripheral arterial disease	30	14	18	20	L3	-	NR	Quadritherapy then INH + RIF	12	Yes	Yes
Abu-Nader and Terrell	2002	76 / M	Benign prostatic hypertrophy, Psoriasis	84	84	6	6	T6-T7	-	NR	Quadritherapy then INH + RIF + ETH	12	Yes	No
Dahl and al.	2005	69 / M	Appendicitis, colorectal cancer, AAA	12	12	NR	NR	L3-L4	AAA	NR	Quadritherapy then INH + RIF	9	Yes	Yes
Nikaido and al.	2007	86 / M	HBP	23	21	NR	8	T12-L1	-	16	INH + RIF + ETH	NR	No	No
Mavrogenis and al	2009	72 / M	Benign prostatic hypertrophy, lumbarthrosis	120	105	6	12	L3-L4	-	NR	Quadritherapy then INH + RIF + ETH	12	Yes	Yes
Colebatch and Mounce	2010	67 / M	Testicular cancer	60	60	36		L4-L5	-	Normal	Quadritherapy then INH + RIF	7	NR	No
Josephson and al.	2010	75 / M	Mycosis fungoides	35	6	6	21	L1-L2	Cerebral tuberculoma	NR	Quadritherapy, INH + RIF + ETH and then INH + RIF	12 (2+10)	Yes	No
Patel and al.	2010	66 / M	-	9	8	5	6	T10-T11	-	NR	INH + RIF + ETH	12	No	No
Obaid and al.	2011	67 / M	-	11	9,5	5	6	L1-L2	-	NR	INH + RIF + ETH	9	No	Yes
Samadian and al.	2013	94 / M	Chronic kidney disease, Prostate cancer	23	23	18	NR	L1-L2	AAA	Normal	NR	NR	No	No
Stahl and al.	2013	60 / M	Clear cell carcinoma	23	23	NR	NR	T11-T12	-	NR	NR	NR	No	No
Santbergen and al.	2013	58 / M	Myocardial infarction, ischemic stroke et prostatectomy	39	39	NR	NR	T8-T9	AAA	10	Quadritherapy + moxifloxacin, then RIF + INH + moxifloxacin	12	No	No
Newman and al.	2014	80 / M	-	41	17	5	NR	T9-T10	-	NR	INH + RIF + ETH and then INH + RIF	8 (2+6)	Yes	Yes
Lara-Oya and al.	2015	78 / M	Parkinson disease, vertebral osteomyelitis of T11-T12 (*S. aureus*)	36	36	NR	NR	T11-T12	-	61	INH + RIF + ETH	12	Yes	Yes
Dabrowska and al.	2015	67 / M	HBP	10,5	6	5	9	T10-T11	-	Normal	INH + RIF + ETH, then INH + RIF	NR	Yes	Yes
Białecki and al.	2016	66 / M	-	60	60	NR	NR	T10-T11	-	30	Quadritherapy, then INH + RIF + PZA	NR	Yes	Yes
Mackel and al.	2016	64 / M	-	11	6	6	5	T11-T12	-	40	INH + ETH + rifabutine + cycloserine + moxifloxacin + capreomycin	12	No	Yes
Miyazaki and al.	2016	82 / M	-	16	14	2	8	T5-T6	-	7,5	INH + RIF + ETH	6	No	Yes
Seegobin and al.	2017	62 / M	-	14	3	1	12	T4-T5	-	NR	INH + RIF + ETH	9	Yes	Yes
Kusakabe and al.	2018	76 / M	Cervical laminoplasty, Idiopathic skeletal hyperostosis, HBP, Diabetes	14	12.5	5	6	L2-L3	AAA		INH + RIF + ETH	NR	No	Yes
Case n°1	-	65 / M	Weaned smoking, HBP	12	9	3	6	L2-L3	-	123	Quadritherapy, then INH + RIF + ETH	9	No	Yes
Case n°2	-	71 / M	Atrial fibrillation	11	7	2	9	L1-L2	-	70	Quadritherapy, then INH + RIF + ETH and then INH + RIF	36 (2+1+33)	No	No
Case n°3	-	77 / M	Gastric adenocarcinoma, Alcoholism	82	48	NR	NR	L4-L5	-	126	INH + RIF + ETH	12	No	No

Periods of time are the same when the dates mentioned in the article were not enough detailed; HBP Hyper Blood Pressure; NR: not reported; AAA: abdominal aortic aneurysm; INH: isoniazid; RIF: rifampicin; ETH: ethambutol;



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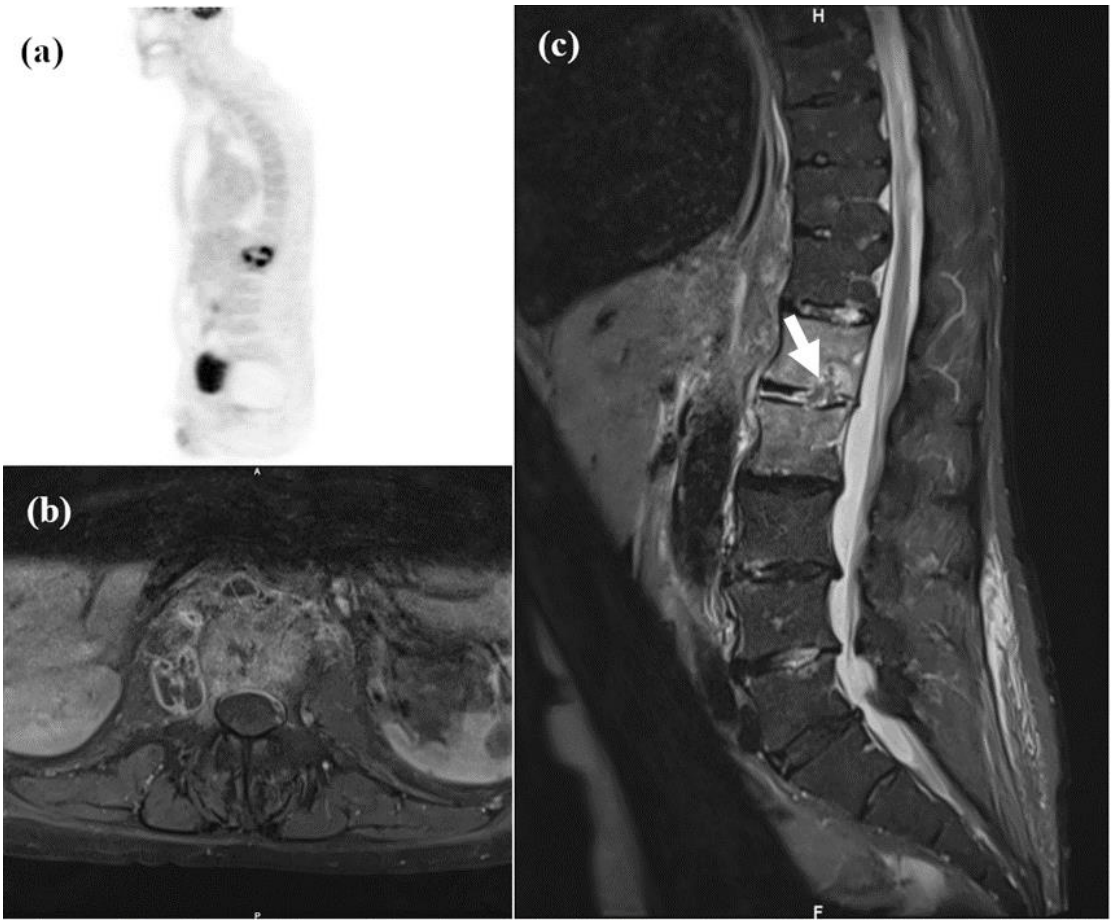

Figure 2. ***(a)****18F-FDG PET-CT showing FDG uptake on L1-L2 vertebral bodies* ***(b)*** *MRI Axial T1-weighted with contrast showed hypersignal of L2 body and a well circumscribed right psoas abscess with Gadolinium enhancement, without epiduritis.* ***(c)*** *MRI Sagittal STIR sequence of the lumbar spine showed hypersignal of L1 and L2 vertebral bodies, with hypersignal in the L1-L2 disc confirming the discitis. White arrow: centro-somatic erosion suggesting a Mycobacterium infection*[60].

Figure 3. Flow chart of literature review