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REVIEW

Infection of the acromioclavicular joint with *Mycobacterium bovis* following intravesical instillation of Bacillus Calmette-Guerin: a case-based review

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Abstract

Purpose Osteoarticular infections caused by intravesical BCG are rare and poorly characterized. This study presents a case of acromioclavicular joint infection caused by *Mycobacterium bovis* BCG, alongside a systematic review aimed at improving our understanding of the infection's clinical features, diagnosis, treatment and outcomes.

Methods This systematic review included all published cases of osteoarticular infections due to *M. bovis* BCG following intravesical BCG instillation, as identified through a PubMed search conducted up to 1 May 2025. The search used combinations of keywords related to 'BCG', 'bladder', and 'osteoarticular infection'. One additional case from our institution was added. Clinical, biological, radiological, treatment and outcome data were extracted and analyzed.

Results We reviewed 67 cases, classified as vertebral ($n=45$), prosthetic joint ($n=18$), and native joint ($n=4$). The affected patients were predominantly men (98.5%), with a mean age of 74.1 ± 9.2 years. The median delay in months between the first instillation and the diagnosis was 23 [IQR 13.0–48.0]. Fever was uncommon (20.5%), while elevated C-reactive protein levels were frequent (80%). Imaging (CT/MRI) played a key role in diagnosis by showing images consistent with infection in all cases in which it was used. Treatment typically involved rifampicin and isoniazid for 12 months, alongside ethambutol for two months. Outcomes were favorable in 90.6% of cases, with one death attributed to the infection.

Conclusion Though rare, *M. bovis* BCG osteoarticular infections should be considered in patients with unexplained joint symptoms following BCG therapy. Early diagnosis and appropriate therapy are essential for optimal management.

Keywords *Mycobacterium bovis* · BCG therapy · Osteoarticular infection · Acromioclavicular joint · Calmette-Guerin · Bladder cancer

Introduction

The use of Bacillus Calmette-Guérin (BCG) to treat non-muscle invasive bladder cancer (NMIBC) was first described by Morales in 1976 [1]. His promising results led to further validation through randomized controlled trials funded by the National Cancer Institute, which confirmed that adjunctive BCG immunotherapy significantly reduced cancer recurrence compared to transurethral surgery alone [2, 3]. BCG is now widely recognized as the most effective intravesical immunotherapy for superficial bladder cancer, significantly improving patient outcomes.

However, despite its effectiveness, BCG therapy is not without risk. Adverse effects can range from local irritations, such as bladder infections, to rare but serious systemic

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complications, including disseminated infections involving distant organs. Osteoarticular infections caused by *Mycobacterium bovis* after intravesical BCG therapy are rare, particularly when involving native joints without prosthetic material. Infections at other sites, such as the lungs, liver, and urinary tract, are far more common than osteoarticular infections [4, 5].

We describe a rare case of *M. bovis* BCG infection in a native acromioclavicular joint without a history of prosthetic implantation or trauma. In addition to reporting this delayed and unusual presentation, we conducted a literature review of osteoarticular infections caused by *M. bovis* BCG following BCG instillation.

Case presentation

A 64-year-old man presented in September 2024 with persistent right acromioclavicular joint pain lasting for several months. Prior to presentation, in January 2022, he underwent transurethral resection (TUR) of bladder polyps, which confirmed the diagnosis of high-grade papillary urothelial carcinoma, staged as pT1. Two months after TUR, he started induction therapy with 6 weekly instillations of intravesical BCG. Three months after the last instillation, a follow-up cystoscopy was performed and showed no suspicious lesions. He then underwent twice the maintenance regimen, one injection per week for 3 consecutive weeks, with a follow-up cystoscopy after 3 months. Both cystoscopies were reassuring.

In July 2023, a follow-up cystoscopy revealed a bladder polyp. The patient then underwent a second TUR, which

Fig. 1 The image shows a syringe containing thick purulent fluid obtained from a joint aspiration. Due to the specimen's high viscosity, a cell count, and differential leukocyte count could not be performed. However, direct microscopic examination revealed numerous neutrophils. The Gram stain did not reveal any germs. The sample was subsequently submitted for microbiological culture

confirmed a recurrence of the malignancy. A few weeks later, a thoracic CT-scan showed multiple peripheral lung opacities, which were hypermetabolic on PET-scan. A lung biopsy was performed, and pathological analysis revealed the urothelial origin of the lung lesions, confirming that they were metastases. Given the presence of metastatic disease, the patient was switched to systemic chemotherapy.

In June 2024, the patient complained of right shoulder pain which did not respond to conservative treatment, including corticosteroid infiltration, which provided temporary relief. The X-ray of the right shoulder was unremarkable and did not show any evidence of injury to the bones or joints.

Over time, the joint became increasingly swollen, tender and erythematous, raising concern of an underlying infectious process. The patient had joint aspiration, which revealed the presence of purulent material shown in Fig. 1. Based on these findings, septic arthritis was confirmed. The patient underwent surgical debridement and was started on broad-spectrum intravenous antibiotics (piperacillin-tazobactam 4 g four times daily for 7 days). Following intravenous treatment, the patient was started on oral moxifloxacin 400 mg once daily for a further 21 days.

At this time, the patient had a C-reactive protein (CRP) at 40 mg/L without leukocytosis, bacterial cultures remained negative 10 days after inoculation. As no pathogen could be identified using conventional techniques, a request for 16 S rRNA PCR was sent to an external laboratory (Institute of Pathology and Genetics).

Less than 14 days after surgical debridement, the scar became purulent, suggesting a recurrence of the infection. A second surgical debridement was then performed, with intra-operative findings confirming significant purulence, indicative of recurrent septic arthritis.

During this period, 16 S rRNA PCR testing identified *Mycobacterium tuberculosis complex* genome, in the first perioperative specimen. Following this result, direct examination of the second perioperative pus samples using auramine–rhodamine (AR) staining and fluorescence microscopy demonstrated the presence of acid-fast bacilli (AFB), further supporting the diagnosis of infection with *M. tuberculosis complex*.

To determine the exact species of the pathogen, a positive culture was sent to the National Reference Center in Belgium, Sciensano. Whole Genome Sequencing (WGS) was performed on it without success [6]. However, identification within the complex was achieved using line probe assay (GenoType® MTBC, Hain Lifesciences, Germany). Sciensano confirmed the presence of *Mycobacterium bovis sub-species BCG*.

This finding linked the infection to the patient's previous intravesical BCG therapy for bladder cancer, administered

approximately two years earlier. The patient started anti-tuberculous therapy (isoniazid, rifampicin, ethambutol, pyridoxine) which was administered for 12 months, with ethambutol being discontinued after 2 months. Six months after starting treatment, the patient reported no residual shoulder pain and had regained full shoulder mobility. He is currently undergoing an additional six months of anti-tuberculous therapy with isoniazid and rifampicin. A timeline of the patient's clinical course is presented in Fig. 2.

Methods

A targeted literature review was conducted using the PubMed database to identify case reports of osteoarticular infections associated with intravesical BCG therapy for bladder cancer. The search strategy combined two predefined keyword queries using Boolean operators, targeting both peripheral/prosthetic and vertebral infections.

The first query focused on peripheral joint involvement, including prosthetic infections:

((osteoarticular[Title/Abstract] OR osteomyelitis[Title/Abstract] OR prosthetic[Title/Abstract] OR arthroplasty[Title/Abstract] OR joint[Title/Abstract]) AND (BCG[Title/Abstract] OR Calmette[Title/Abstract] OR Guerin[Title/Abstract]) AND (bladder[Title/Abstract] OR instillation[Title/Abstract] OR intravesical[Title/Abstract])).

The second query targeted vertebral infections:

((spondylodiscitis[Title/Abstract] OR spondylitis[Title/Abstract] OR osteomyelitis[Title/Abstract] OR discitis[Title/Abstract]) AND (BCG[Title/Abstract] OR Calmette[Title/Abstract] OR Guerin[Title/Abstract]) AND (bladder[Title/Abstract])).

The results from both queries were combined. After duplicate removal, a total of 114 references were screened, and 55 articles were identified as reporting cases of *M. bovis* BCG osteoarticular infections following intravesical instillation [7–61]. Additional cases were included from other sources: 8 from a previous review [62–69], 3 cases reported by Cadiou et al. [35]. , 1 case identified via ScienceDirect [70], and the case we present, leading to a total of 67 cases reviewed. The final search was conducted on May 1, 2025.

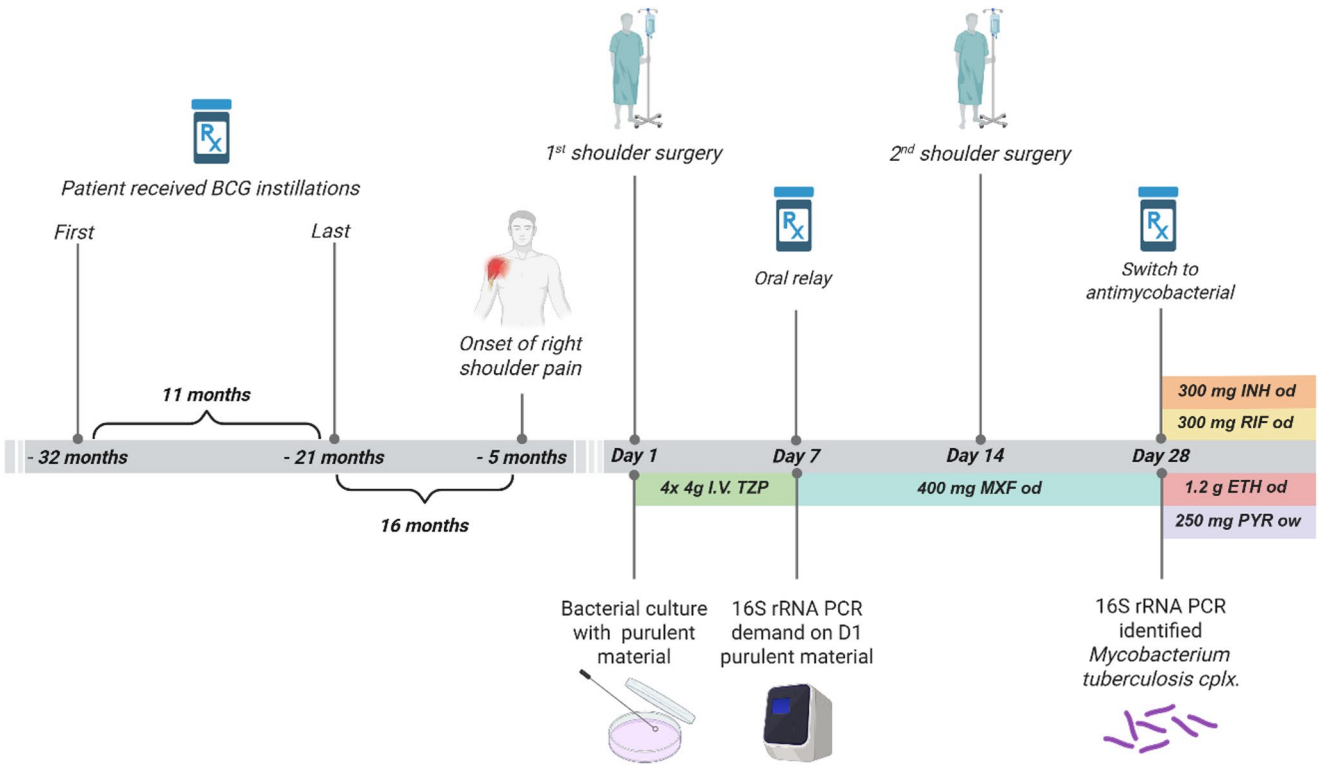

Fig. 2 Timeline of the clinical course, treatments, and microbiological investigations. The patient received a total of 12 doses of intravesical BCG therapy between March 2022 and February 2023. Sixteen months after the last instillation, the patient started to complain of right shoulder pain that did not respond to conservative treatment, including corticosteroid infiltration, which provided only temporary relief. Over time, the joint became increasingly painful, swollen, and erythematous, raising concern of an underlying infectious process. After five months of persistent symptoms, he underwent surgical debridement which retrieved purulent material. Initial cultures remained negative, but 16 S rRNA PCR on the purulent material identified *Mycobacterium tuberculosis complex*. Line Probe assay later confirmed *Mycobacterium bovis subsp. BCG*. The patient was subsequently treated with a 12-month course of antimycobacterial therapy

A Preferred Reporting Items for Systematic Reviews and MetaAnalyses (PRISMA) flow diagram summarizing the search and selection process is provided in Fig. 3.

Review

We reviewed 67 cases of osteoarticular infections caused by *M. bovis* after intravesical BCG instillation (66 literature cases and ours). These were divided into three groups: vertebral infections ($n=45$), prosthetic joint infections ($n=18$), and native joint infections ($n=4$). All the results are presented in Table 1.

Elderly men (98.5%, mean age 74.1 ± 9.2 years) were predominantly affected by the infection. The median number of BCG instillations was 8.0 [IQR 6.0–12.0], with a median diagnosis delay of 23 months [IQR 13.0–48.0] from the first and 14 months [IQR 6.0–30.0] from the last instillation, respectively. Clinically, the fever was rare (20.5% of cases), and biologically, the CRP was elevated in 80% of cases, while leukocytosis was rare (2.3%). Tuberculin skin tests and QuantiFERON® assay were rarely positive (16.7% and 7.7%, respectively).

Radiological imaging played a central role in the diagnostic work-up of *M. bovis* osteoarticular infections after intravesical BCG instillation. Radiographic findings compatible with infection were reported in 77.4% of cases (24/31), with a higher frequency in vertebral (88.2%) and prosthetic joint (81.8%) infections, whereas no abnormalities were noted in native joint infections. Computed tomography (CT) and magnetic resonance imaging (MRI) both demonstrated high diagnostic sensitivity, with infection-compatible findings reported in all cases (29/29 for CT and 42/42 for MRI). CT was particularly effective for diagnosing spinal and

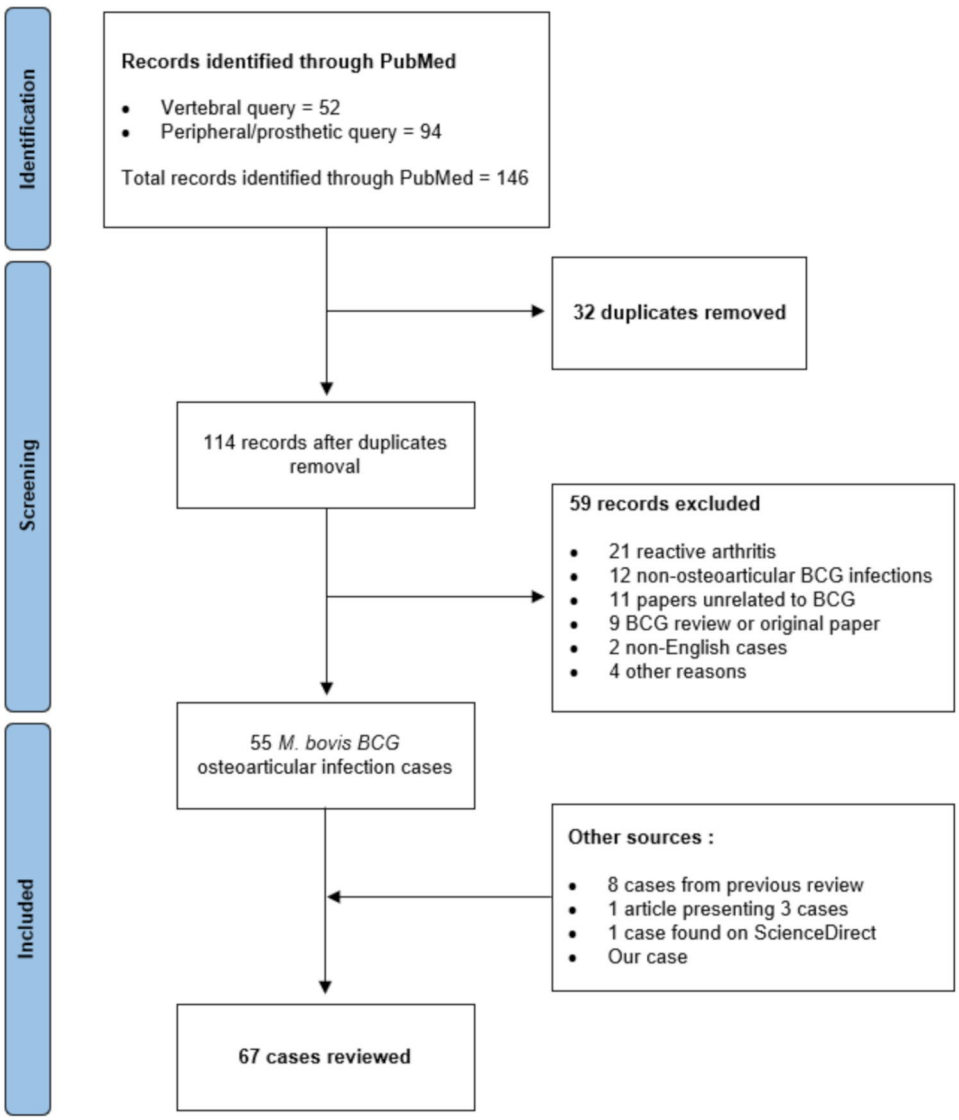

Fig. 3 PRISMA flow diagram of the literature search strategy. A total of 146 records were identified through two PubMed queries targeting vertebral and peripheral/prosthetic osteoarticular infections following intravesical BCG instillation. After removal of 32 duplicates and screening of 114 articles, 55 publications were included. Additional cases were identified by other sources, resulting in a total of 67 cases being reviewed

Table 1 Clinical, biological, radiological characteristics, treatment and outcomes of osteoarticular *M. bovis* BCG infections following BCG instillation, by infection site. This table summarizes the main characteristics of 67 cases of osteoarticular infections due to *M. bovis* following intravesical BCG instillation, categorized into vertebral ($n=45$), prosthetic joint ($n=18$), and native joint infections ($n=4$). Quantitative variables are presented as means ± standard deviations (SD) or medians with interquartile ranges (IQR). Qualitative variables are presented as number (percentage). For each variable, the number of patients for whom the data were available is indicated as n/N, where n is the number of cases reporting the data, and N is the total number of patients in that category

	Vertebral infections cases ($n=45$)	Prosthetic joint infections cases ($n=18$)	Native articulation infections cases ($n=4$)	All osteoarticular infections ($n=67$)
Clinicals characteristics				
Men, n (%)	45 (100.0%)	17 (94.4%)	4 (100.0%)	66 (98.5%)
Age in years (mean) ± SD	74.6 ± 8.0	76.4 ± 8.2	58.3 ± 13.1	74.1 ± 9.2
Number of instillations, median [IQR]	8.0 [6.0–12.0] (23/45)	8.5 [6.0–12.0] (12/18)	12.5 [10.2–13.0] (4/4)	8.0 [6.0–12.0] (39/67)
Median time [IQR] (in months) between diagnosis and				
First BCG instillation	20.0 [12.2–40.5] (34/45)	32.8 [19.0–48.0] (18/18)	14.5 [11.8–69.0] (4/4)	23.0 [13.0–48.0] (60/67)
Last BCG instillation	13.5 [6.2–23.8] (41/45)	24.0 [7.5–36.0] (17/18)	6.0 [1.0–36.0] (4/4)	14.0 [6.0–30.0] (63/67)
Fever, n (%)	4/27 (14.8%)	1/3 (33.3%)	1/3 (33.3%)	8/39 (20.5%)
Biological characteristics				
CRP > 5 mg/L, n (%)	19/26 (73.1%)	11/12 (91.7%)	2/2 (100.0%)	32/40 (80.0%)
CRP (mg/L), median [IQR]	28.1 [9.4–49.8] (19/45)	70.3 [33.5–121.5] (11/18)	50.0 [45.0–70.3] (2/4)	40.0 [18.0–76.9] (33/67)
Leukocytosis > 10 000/µL, n (%)	1/30 (3.3%)	0/11 (0.0%)	0/3 (0.0%)	1/41 (2.3%)
WBC (/µL), median [IQR]	6600 [5800–8200] (12/45)	8580 [7450–9450] (7/18)	6085 [5678–8125] (2/4)	7000 [6075–8745] (22/67)
Tuberculin skin test positive, n (%)	1/5 (20.0%)	0/0 (0.0%)	0/1 (0.0%)	1/6 (16.7%)
Quantiferon, n (%)	1/11 (9.1%)	0/1 (0.0%)	0/1 (0.0%)	1/13 (7.7%)
Radiological characteristics				
X-ray compatible with infection[A], n (%)	15/17 (88.2%)	9/11 (81.8%)	0/3 (0.0%)	24/31 (77.4%)
CT-scan compatible with infection[A], n (%)	23/23 (100.0%)	6/6 (100.0%)	0/0 (0.0%)	29/29 (100.0%)
MRI compatible with infection[A], n (%)	40/40 (100.0%)	1/1 (100.0%)	1/1 (100.0%)	42/42 (100.0%)
PET-scan compatible with infection[B], n (%)	5/5 (100.0%)	2/2 (100.0%)	0/0 (0.0%)	7/7 (100.0%)
[A]*Signs of bone lysis, prosthesis dehiscence, abscesses (epidural, psoas, etc.)*				
[B]*Increased uptake on bones and/or joints*				
Treatment				
Rifampicin, n (%)	41/41 (100.0%)	17/17 (100.0%)	4/4 (100.0%)	62/62 (100.0%)
Isoniazid, n (%)	40/41 (97.6%)	16/17 (94.1%)	4/4 (100.0%)	60/62 (96.8%)
Ethambutol, n (%)	34/41 (82.9%)	13/17 (76.5%)	4/4 (100.0%)	51/62 (82.3%)
Pyridoxine, n (%)	10/41 (24.4%)	1/17 (5.9%)	1/4 (25.0%)	12/62 (19.4%)
Other, n (%)	4/41 (9.8%)	6/17 (35.3%)	0/4 (0.0%)	10/62 (16.1%)
Median duration [IQR] of ethambutol tratment (in months)	2.0 [2.0–2.0] (12/45)	2.0 [2.0–2.2] (4/18)	2.5 [2.0–2.5] (2/4)	2.0 [2.0–2.0] (19/67)
Median duration [IQR] total tratment (in months)	12.0 [9.0–12.0] (26/45)	12.0 [8.8–12.0] (16/18)	9.0 [9.0–12.0] (3/4)	12.0 [9.0–12.0] (46/67)

Table 1 (continued)

	Vertebral infections cases ($n=45$)	Prosthetic joint infections cases ($n=18$)	Native articulation infections cases ($n=4$)	All osteoarticular infections ($n=67$)
Outcome				
Favourable outcome, n (%)	30/33 (90.9%)	15/17 (88.2%)	3/3 (100.0%)	48/53 (90.6%)
Died because of mycobacterial infection	0/33 (0.0%)	1/17 (5.9%)	0/3 (0.0%)	1/53 (1.9%)
Died for another reason (MI, cancer…)	3/33 (9.1%)	1/17 (5.9%)	0/3 (0.0%)	4/53 (7.5%)

Abbreviations: CRP, C-reactive protein; WBC, white blood cells; IQR, interquartile range; MRI, magnetic resonance imaging; CT, computed tomography; PET, positron emission tomography; MI, myocardial infarction

prosthetic infections, as it offers excellent resolution and is less affected by metal implants than MRI. In contrast, although MRI is highly sensitive, it was rarely used for prosthetic joint infections, probably due to signal artefacts that limit its usefulness in the presence of hardware. Positron emission tomography (PET) scans were positive in all cases but were rarely used (7/7).

Vertebral involvement was most common ($n=45$), predominantly lumbar (48.9%), followed by thoracic (40.4%). There are 5 reported cases on multi-level lesions, 3 thoracic-lumbar [10, 12, 18] and 2 lumbar-sacral [59, 61]. There are no reported cases of cervical infection. Of the 18 prosthetic joint infections, the most common sites involved were the hip prosthesis (72.2%) and the knee prosthesis (16.7%). One case involved a shoulder prosthesis [50] and one case involved both a hip and knee prosthesis [70]. Four native joint infections were reported, involving the elbow [71], the first tarsometatarsal joint of the foot [45], the carpal joint of the wrist [44], and the present case involving the acromioclavicular joint of the shoulder.

Treatment consisted of prolonged multidrug antimycobacterial therapy. The drugs used were rifampicin (100% of cases), isoniazid (96.8% of cases) and ethambutol (82.3% of cases). The median duration of treatment was 12 months [IQR 9.0–12.0]. Ethambutol was usually given for 2 months and then stopped. The use of pyridoxine was reported in 19.4% of cases.

Mortality due to mycobacterial infection was rare, with only one case (1.9%) reporting that the patient died in hospice care because of their infection [50]. Four other cases reported a fatal outcome, but the patients died of unrelated causes such as stroke [7], myocardial infarction [11], pneumonia [61] and lung cancer [13]. In most cases, the outcome was favorable (90.6%).

Discussion

Intravesical BCG is one of the most effective adjunctive treatments for superficial bladder cancer, significantly reducing tumor recurrence and progression compared to intravesical chemotherapy, especially when used in maintenance regimens. Its mechanism relies on a complex immune response involving Th1-mediated activation, cytokine production, and both innate and adaptive immunity. BCG therapy is generally well tolerated, but mild side effects such as cystitis, low-grade fever, and pelvic discomfort are common. More rarely, severe systemic complications may occur [72–74].

To our knowledge, this is the first reported case of *M. bovis BCG* infection involving the acromioclavicular joint. The infection developed twenty-one months after the last

intravesical BCG instillation, which contributed to the delay in diagnosis. According to *Cabas et al.*, the infectious complications after BCG treatment with the greatest delay in presentation are muscular, osteoarticular and vascular infections, with median times to onset of 93 [IQR 29–156], 68 [IQR 14–156] and 52 [IQR 20–104] weeks respectively. In contrast, infections involving organs such as the lung or liver tend to occur much earlier, with median delays of 1 [IQR 1–6] and 1 [IQR 1–4] weeks after the last instillation, respectively [5]. The delay observed in our case is consistent with that reported for osteoarticular presentations both in the review by *Cabas et al.* and in our own review of the literature, reinforcing the plausibility of this late presentation characteristic of osteoarticular complications.

The culture of *M. bovis* in laboratories require specialized media, long incubation times, and handling at biosafety level 3. These are not routinely used unless tuberculosis, or an atypical mycobacterial infection, is suspected. Consequently, if clinicians do not consider the possibility of a BCG-related infection, laboratories are unlikely to perform the necessary cultures, meaning the diagnosis may be missed. In contrast, molecular techniques such as 16 S rRNA PCR are useful when the pathogen is unknown, as they can identify a broad range of bacterial or mycobacterial DNA directly from clinical specimens. BCG-related infections are probably underdiagnosed because they are not considered during the initial diagnostic workup. It is therefore crucial to maintain awareness of past BCG therapy when evaluating patients with clinical or biological signs of an infection that cannot be explained, even many months or years after bladder cancer treatment.

The management of adverse effects related to BCG therapy has been the subject of recommendations by a working group of urologists from the European Association of Urology (EAU) in 2008 [75], as well as a literature review published in 2015 by *Decaestecker and Oosterlick* [76]. However, these recommendations are not supported by prospective clinical trials and are based primarily on literature reviews and expert consensus. Furthermore, they do not provide clear guidance on how to manage systemic BCG infections, including osteoarticular ones.

According to current clinical practice guidelines issued by the Infectious Diseases Society of America (IDSA), in collaboration with the Centers for Disease Control and Prevention (CDC), the American Thoracic Society (ATS), and the European Respiratory Society (ERS), treatment for *M. bovis* infection usually involves rifampicin, isoniazid and ethambutol, taken for at least nine months. This extended duration, compared to the standard six-month regimen used for *M. tuberculosis*, is necessary because pyrazinamide is excluded due to *M. bovis*'s intrinsic resistance. Ethambutol is generally discontinued after the initial two months [77]. Similarly, the World Health Organization (WHO) recommends a 12-month regimen for osteoarticular tuberculosis, comprising a two-month intensive phase (rifampicin, isoniazid, ethambutol and pyrazinamide), followed by a 10-month continuation phase (rifampicin and isoniazid). In the case of *M. bovis*, pyrazinamide is omitted [78]. These recommendations align with the outcomes of our review, indicating that BCG-related osteoarticular infections typically require an extended course of multidrug antituberculosis therapy. The most reported regimen includes rifampicin, isoniazid and ethambutol, with a median treatment duration of 12 months (IQR 9–12). Ethambutol is typically discontinued after two months, as recommended.

Osteoarticular infections caused by *M. bovis* following BCG therapy usually have a favorable outcome when promptly diagnosed and adequately treated. In our review of 67 cases, only one patient (1.9%) died, possibly because of the BCG infection. This is consistent with the findings of *Liatsos et al.*, who reported a mortality rate of 0% for isolated osteoarticular infections, compared to 18.9% for disseminated forms, 12.5% for vascular forms, and 8.3% for pulmonary forms [73]. Although mortality is rare, morbidity remains significant. Due to delayed diagnosis, patients often present with an advanced infection or joint destruction, which often require invasive procedures and may result in long-term functional impairment. Early recognition and appropriate therapy are therefore essential to avoid long-term functional impairment.

Conclusion

We presented a rare case of *M. bovis* BCG infection affecting the native acromioclavicular joint, which has not been documented in previous literature. The infection occurred 21 months after the last intravesical BCG instillation, highlighting the diagnostic challenges posed by the delayed and atypical presentation of BCG infections. This case highlights the importance of considering BCG-related complications in patients presenting with chronic arthritis and a history of bladder cancer immunotherapy. Molecular diagnostics, including 16 S rRNA PCR, line probe assay or whole genome sequencing, are essential for timely identification.

Although mortality in osteoarticular BCG infections is low, morbidity can be considerable. Delayed diagnosis often leads to joint destruction requiring surgery and can result in functional impairment. Early recognition and targeted treatment are crucial to improve outcomes. There is a need for greater awareness of such rare complications. Encouraging the early consideration of mycobacterial infection and the appropriate use of molecular diagnostics could

help to improve the recognition and management of these uncommon presentations.

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Data availability The data sets that were used and/or analyzed in the current study are available on reasonable request from the corresponding author.

Declarations

Competing interests The authors declare no competing interests.

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