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Case report

A thoracic tuberculous spondylodisctis after intravesical BCG immunotherapy of bladder cancer – Case report and literature review

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ABSTRACT

We report a rare case of tuberculosis of the thoracic spine caused by *Mycobacterium bovis* infection as a complication of BCG (Bacillus Calmette-Guérin) intravesical immunotherapy, which is a well known and acknowledged treatment of superficial bladder cancers applied since 1976. Although this therapy is broadly used in urology and considered to be safe and well tolerated, one should be aware of the potential local and systemic side effects as in the case of our patient, who developed tuberculous spondylodiscitis after intravesical BCG therapy.

1. Introduction

Low back pain is one of the main causes of medical consultations and the fifth most common reason of all physician visits in the USA [1]. The lifetime prevalence of spinal pain has been estimated at as high as 54% to 80% of population and its frequency raises with age [2]. This most common form of this pain is mainly associated with mechanical and degenerational changes of various spinal structures. Nevertheless, in the minority of cases the low back pain may be a symptom of severe and even life-threatening disorders, one of them is spondylodiscitis – the inflammation of the vertebral bodies and intervertebral disk space, caused by various pathogens. Its incidence is estimated at 0.4–2.4/100,000 [3]. *Mycobacterium tuberculosis* is responsible for even 17–39% of all the cases of spondylodiscitis [4]. Musculoskeletal tuberculosis is generally rare in comparison to other forms of the disease, but among its cases the spine is the most frequently affected and accounts for 1–3% of all tuberculous infections [5].

Although in a significant percentage of tuberculous spondylodiscitis the primary infection is not evident, in the

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majority of cases, it results from a haematogenous seeding of the mycobacterium from a latent pulmonary focus [6]. It can spread also by contiguous or lymphatic way [4]. Other possible, but very rare routes of spreading the bacteria in patients without primary infection, such as BCG osteomyelitis, are vaccinations (the risk is one in a million, with very infrequent spine involvement [7] or intravesical immunotherapy (the exact prevalence is unknown [8]).

BCG is an attenuated strain of *Mycobacterium bovis* and its use is broadly approved in medical practice both as a vaccine and anticancer agent [9]. Intravesical application of BCG immunotherapy is an established and effective treatment of bladder carcinomas and carcinomas in situ (CIS) [10]. It is considered to be a safe procedure, however sometimes serious complications may occur. We present a case of a 67-year-old patient with spondylodiscitis following BCG intravesical treatment as an example of a very rare, but severely dangerous side effect of this therapy.

2. Case report

A 67-year-old man was admitted to the neurological ward with the history of low back pain lasting about six months and a 5 kg weight loss. His past medical history included arterial hypertension and bladder cancer of papillary type. He underwent a few transurethral resections of tumor during 10 years after initial diagnosis and the procedure was repeated due to neoplasm recurrences. In order to prolong time between the subsequent relapses the patient finally received a full cycle of BCG immunotherapy (6 applications administered at weekly intervals) with 3 additional applications administered at monthly intervals. One month after the last intravesical installation he noticed the appearance of low back pain. An out-patient lumbar radiograph showed the scoliosis of thoracic and lumbar spine segments with no other significant pathologies. The cytoscopy examination performed 6 months after finishing the BCG immunotherapy did not show tumor. Despite using anti-inflammatory and analgesic medications prescribed by general practitioner the pain was debilitating and finally the patient was admitted to hospital. He denied any trauma, did not have fever, nor night sweats. His basic blood tests were normal, including white blood cells count, ESR (erytrocyte sedimentation rate) and CRP (C-reactive protein). He had no previous history of tuberculosis infection.

Physical examination on admission showed the following neurological symptoms: mild proximal weakness of lower limbs and slight hypoaesthesia below the L1 dermatome level, but he was still able to walk. CT (computed tomography) showed destruction of T10 and T11 vertebraes with fractures of terminal laminas, disk interspace involvement and the formation of the epidural abscess (Fig. 1). MRI (magnetic resonance imaging) scan of the spine confirmed the destruction of the T10-11 vertebraes and their interspace (Fig. 2). Diagnosis of osteomyelitis or metastatic changes was suspected by radiologist.

In the subsequent CT scan of the whole trunk (thorax and abdomen) neither features of tuberculosis, nor of active neoplasm or metastatic process were found. The examination also did not reveal any other sources of inflammation. Based on the preasumptive diagnosis of discitis the neurosurgeons were requested to perform a biopsy of the involved spine segment. As they initially refused to perform this procedure, it resulted in a10-day delay between the admission and surgical intervention. Due to uncertainty of the diagnosis empirical treatment was applied (ceftriaxone 2 × 1 g i.v. and lincomycin 3 × 600 mg i.v.), as recommended for the discitis.

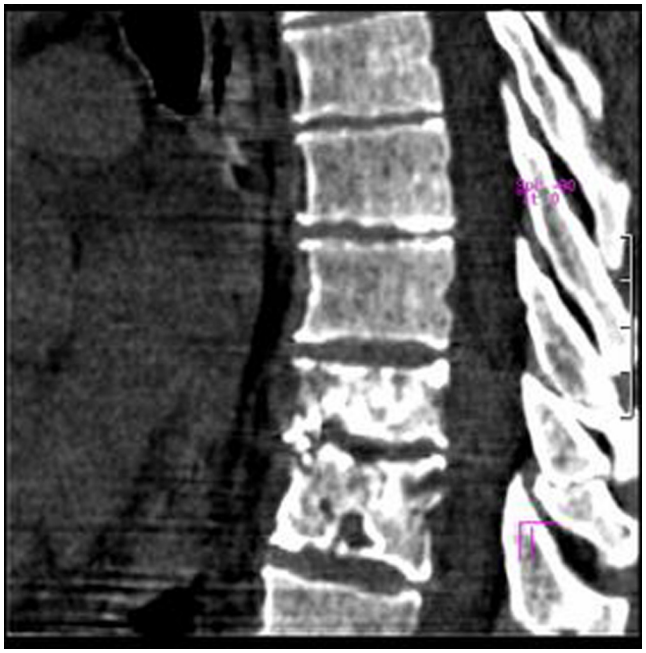

Fig. 1 – A CT scan of the spine with degenerational process of Th10-11 vertebraes and intervertebral space.

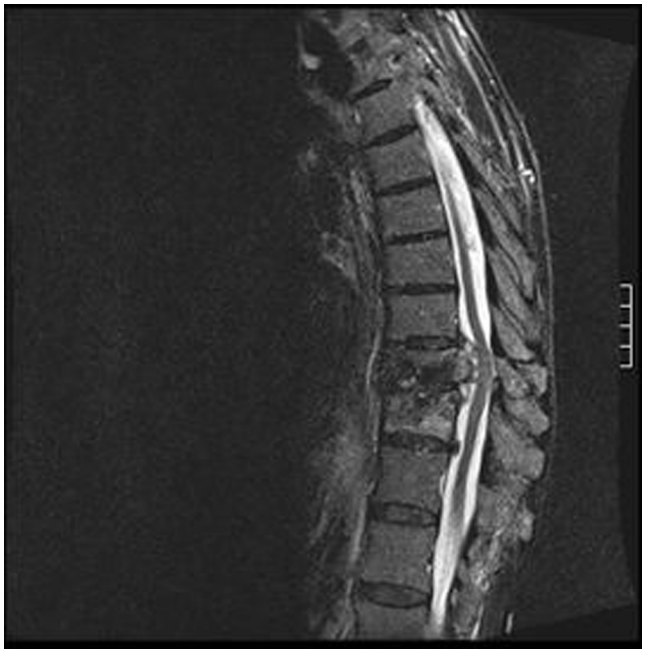

Fig. 2 – T2-weighted MRI scan with the destructive process of Th10-11 vertebraes and intervertebral space, epidural abscess and spinal cord compression.

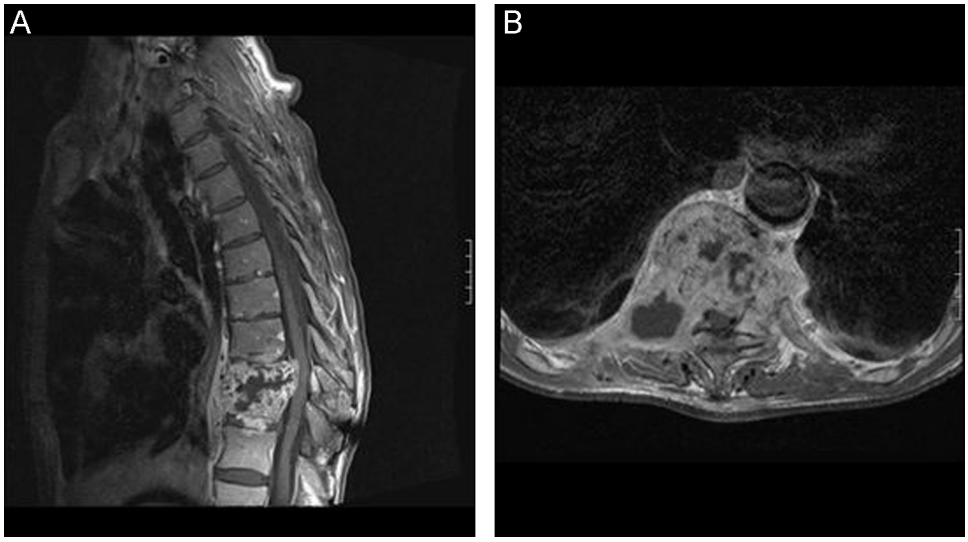

Fig. 3 – T1 MRI scans after first surgery showing bone block with necrolysis, epidural abscess and spinal cord impression: (A) sagittal, (B) axial images.

Histopathological assessment of the biopsy specimen did not show neoplastic cells, but four weeks later the microbiological cultures revealed the acidoresistant bacillus infection, further reported as *M. tuberculosis* complex. The therapy was changed to antimycobacterium treatment. The sensitivity was tested and showed that the bacterium may response to rifampicyne, isoniasid, ethambuthol and streptomycin and is resistant to pyrazinamide (which raised our suspicion that the strain could be *M. bovis*, due to the resistance of this pathogen to that antibiotic, earlier reported in the literature [9]). Subsequent PCR (polymerase chain reaction) confirmed that the bacterium was *M. bovis* BCG strain.

Patient was referred to Polish Referral Center of Treating Tuberculosis of Bones and Joints in Otwock/Warsaw, where the surgical intervention was performed. He underwent the debridement of inflammatory changes with decompression of the spinal cord. Unfortunately, postoperative recovery was complicated and several weeks after the procedure the patient still suffered from severe back pain and the progression of paraparesis. He was unable to walk or even stand. He also complained of vision lost. He was again admitted to the neurological department. The ophthalmological examination revealed drug related toxic neuropathy, which was confirmed by VEP (Vision Evoked Potentials). The NCS (nerve conduction studies) showed features of axonal polineuropathy probably also due to antituberculosis treatment. The control MRI scan (Fig. 3) showed the inflammatory compression of the thoracic spine and subsequently the second surgery was performed with the excision of abscesses and decompression of the spinal cord (Fig. 4).

Three months after the second surgical procedure the general condition of the patient improved: the pain relieved

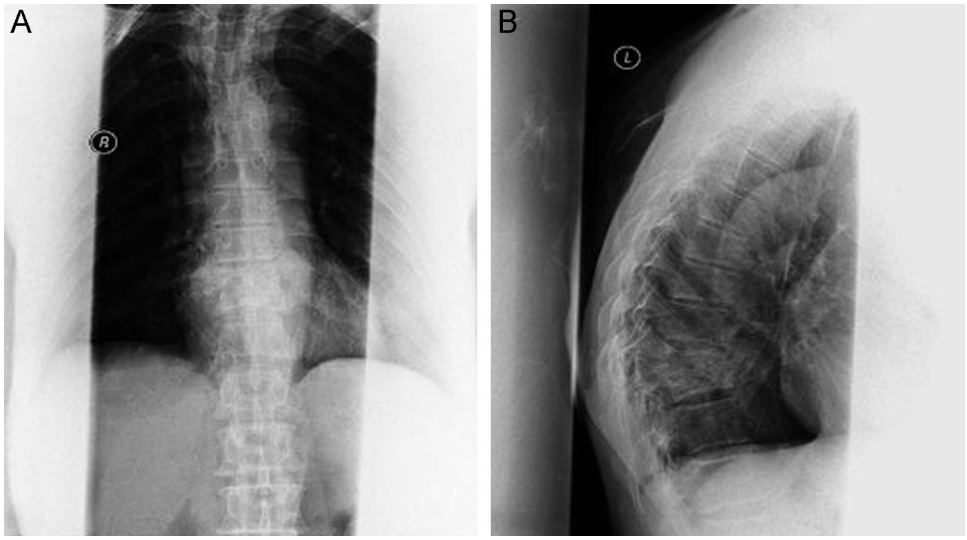

Fig. 4 – The X-ray of the spine after second surgery.

completely and he put on weight slightly. He moves with the use of a wheelchair, but recently at the rehabilitation department he started to stand and walk. He still continues anti-tuberculosis chemotherapy regimen (isoniazid 300 mg and rifampicin 600 mg/daily). The ethambutol was discontinued previously due to drug-related toxic neuropathy of optic nerves.

3. Discussion

M. bovis is a component of the *M. tuberculosis* complex, which refers to a genetically related group of Mycobacterium species that can cause tuberculosis in humans or other organisms. It includes *M. tuberculosis*, *Mycobacterium africanum*, *M. bovis* and the Bacillus Calmette-Guérin strain, *Mycobacterium microti*, *Mycobacterium canettii*, *Mycobacterium caprae*, *Mycobacterium pinnipedii*, *Mycobacterium mungi* [11]. A live attenuated strain of *M. bovis* BCG has been used in medicine since 1921 when it was initially applied as a vaccine in order to prevent tuberculosis infection [12]. Later, in 1976 Morales et al. [13] made use of the BCG strain in a new therapeutic approach to the treatment of superficial bladder neoplasm. It was a significant breakthrough in uro-oncology as the rate of tumor recurrence was very high (it had occurred in approximately 88% of patients) and BCG immunotherapy reduced it on average by about 40%, which also led to a decrease in mortality [14]. Nowadays BCG is the initial treatment of choice for the carcinoma in situ and it is still used as a main adjunctive therapy after surgical resection of tumor [10,15]. The standard induction schedule consists of 6 intravesical installations administered at weekly intervals [13]. BCG therapy stimulates the local immune system and cell-mediated activity plays a major role in this response, which results in the inflammation and eradication of tumor cells [16]. This treatment is generally considered safe and in >95% of patients it is well tolerated [14]. However, unpleasant side effects due to the inflammatory reaction are relatively common. The patients often experience irritative bladder symptoms (urgency, dysuria, frequency of voiding) accompanied by low-grade fever and malaise for less than 24–48 h after installation [17,18]. This phenomenon is not regarded as an adverse event, it is rather treated as a marker for adequate anticancer effect exerted by the BCG [19]. Nevertheless, other infrequent extravesical and systemic complications may also occur such as: fever (2.9%), hematuria (1%), prostatitis (0.9%), urethral obstruction (0.3%), renal abscess, granulomatosus involvement of various organs and the most dangerous of them – systemic septic reaction with the incidence of 0.4% [14]. Another possibly fatal side effect is tuberculous spondylodiscitis, which seems to be an exceptionally rare complication, accordingly to the paper of Newman [20] only 15 previous cases had been described in the literature till 2014. This list can be supplemented by 3 new cases recently published. All published reports are summarized in Table 1. In contrast to the frequency of this therapy worldwide, it seems to be a rather low number.

Table 1 – The reported cases of spinal *M. bovis* infection following BCG intravesical therapy (according to Obaid et al. [10] modified and supplemented).

Authors	Age/sex	Time to onset	Level of infection	Clinical presentation	Surgery	Outcome
Obaid et al. [10]	67, M	11 m	L1/L2	LBP, right leg mild weakness	+	Complete recovery
Katz et al. [21]	67, M	16 m	L4/L5	LBP, anorexia, right L5 & S1 radiculopathy	+	No long term follow-up
Abu-Nader [9]	76, M	7 y	T6/T7	LBP, anorexia, bilateral parentheses & paraparesis	– percutaneous biopsy	Improvement of symptoms
Aljada et al. [22]	79, M	2.5 y	L3	LBP, left hip pain, left leg weakness	+	After 1 year still leg weakness
Morgan and Iseman [23]	77, M	0.5 m	T11/L1	LBP, kyphosis	+	Functional after 1 year
Nikaido et al. [12]	86, M	2 y	T12/L1	LBP	– percutaneous biopsy	Complete recovery
Samadian et al. [24]	94, M	5 m	L1/L2	LBP, malaise	– percutaneous biopsy	No long term follow-up
Colebatch et al. [25]	67, M	2 y	L4/L5	LBP	– percutaneous biopsy	No long term follow up
Civen et al. [26]	81, M	7 m	T12/L1	LBP, weight loss	+	Complete recovery.
Fishman et al. [27]	90, M	1 m	T11/T12	LBP	+ (open biopsy)	Not specified
Patel et al. [28]	66, M	5 m	T10/T11	LBP	– percutaneous biopsy	In 3 months follow-up symptoms improved.
Mavrogenis et al. [29]	72, M	11 y	L3/L4	LBP, anorexia, L2-L5 radiculopathy	+	Remission of pain at 18 months
Rozenblit et al. [30]	76, M	6 y	L4	LBP, right leg pain, weight loss	– percutaneous biopsy	Asymptomatic at 8 months.
Dahl [31]	69, M	1 y	L3/L4	LBP	+	Complete recovery
Newman [20]	80, M	3 y	T9/T10	Fatigue, weight loss	+	Unknown
Santbergen [8]	58, M	3 y	T8/T9	LBP	– percutaneous biopsy	Complete recovery
Sugita et al. [32]	71, M	2 m	T7	LBP	+	Not specified
Josephson et al. [33]	75, M	6 m	L1/L2	LBP, fatigue	– percutaneous biopsy	No long term follow-up

LBP, low back pain; m, moths; y, years.

It is supposed that haematogenous spread is the most probable way of bacteria's dissemination after the procedure. This hypothesis can be supported by observations that *M. bovis* was identified in all the previously reported cases [10] (and also in our patient) and indirectly supported by the published cases of the large vessel mycotic vasculitides following BCG bladder [8,34]. The possible risk factors have been associated with this way of dissemination: the injury of the bladder during catheterization, deep tumor resection, urethral trauma during BCG installation, outer obstruction of bladder, previous pelvic radiation, transurethral prostate resection or bladder biopsy within 2 weeks before starting BCG therapy and all immunocomprised states [9,10] It was also reported that sometimes bacilli may persist in the urinary tract for over one year following the treatment [35]. It may explain why some patients remain at risk of disseminated infection for many months and even years after BCG therapy as in the case reported by Mavrogenis et al. in which the reactivation appeared 12 years after the initial treatment [29]. The genetic factors predisposing to those complications may be related to a deletion in the gene encoding interferon gamma or interleukin 12 receptor which can be responsible for the decreased host defense against mycobacterial infections [36].

Diagnosis of the tuberculous spondylodiscitis is often delayed or even missed [37]. The time between the onset of symptoms and final diagnosis ranges from 2 months to 4 years [4]. The disease onset is often insidious, tuberculous spondylodiscitis has much slower and less painful clinical evolution in comparison to pyogenic infections. It is due to microbiological characteristic of mycobacterium which grows slowly and does not present proteolitic enzymes activity. Fever is often absent (was reported in less than 40% of cases) and was not reported in our case either [4]. The most common clinical symptom reported in many studies is the back pain (more than 80% of patients) [37]. As it is a very common complaint, especially in older population, it may be missed. Regardless the inflammatory response, laboratory studies may not be helpful in differential diagnosis. CRP and white blood cells levels as in our case are usually normal in the majority cases [38]. ESR values are often found to be elevated [4], although in the case of our patient it was low, too. Among non-invasive studies, radiological methods are essential for diagnosis and management of the spine tuberculosis [39,40]. The major radiological findings reported by Maeda et al. were: osteolityc changes (86%), narrowing of disk space (73%), loss of vertebral body height (69%), erosion of the vertebral endplates (56%) [41].

Nevertheless, although MRI features are highly supportive in diagnosing skeletal tuberculosis, they are not pathognomonic [42] and require an active search for other sites potentially infected by mycobacteria and further differential diagnosing. Typically tuberculous spondylodiscitis affects the thoraco-lumbar hinge of the spine [43], which was also confirmed in our case.

In all the cases of the discitis and especially in those suspected of tuberculous spondylodiscitis, biopsy and pathogen isolation is the method of choice [4,44]. This procedure should be mandatory in all possible cases as it allows to find a specific pathogen and test antimicrobial sensitivity what results in an appropriate treatment [4]. In the case of our patient the microbiological diagnosis obtained from the biopsy specimen totally has changed the therapeutical approach. The increasing incidence of MDR TBC (multidrug-resistant tuberculosis) reported in many countries may encourage this approach [45]. It seems also important to distinguish *M. bovis* BCG from *M. tuberculosis*. This cannot be obtained by microscopic evaluation. Only sophisticated molecular methods may discern members of Mycobacterium complex, such as different PCR modifications with restriction enzymes analyses or gene sequencing [33].

The osteoarticular infections caused by BCG should be treated by standard triple-regimen anti-tuberculous therapy [46], with the exception of pyrazinamide because *M. bovis* strains are resistant to this drug [9,15,47]. It is a characteristic feature of this bacterium and can be an important diagnostic clue (as it was also in our patient). Hence, isoniazid and rifampicin with ethambutol should be used as first-line antibiotics for BCG infections for two months, then followed by isoniasid and rifampicin for the next 10 months [48]. Ethambutol may rarely complicate this treatment and cause severe optic nerve neuropathy leading even to the loss of vision [49]. Therefore, all patients undergoing the treatment should be monitored ophthalmologically. The early withdrawal of the antibiotic potentially allows for the recovery of vision [50], as it was shown in our patient. In tuberculous spondylodiscitis corticosteroids may also be added [48] to reduce the spinal cord compression. Our patient also underwent surgical intervention, which is considered to be necessary in almost all cases accompanied by either spinal instability or abscess formation [8,9,29]. The aim of the surgery is a radical debridement, decompression of the spinal cord and reconstruction of spinal stability [51].

In conclusion, the back pain following the BCG immunotherapy of bladder cancer, irrespective of the time interval between the onset of symptoms and last application should be suspected of spondylodiscitis. MRI followed by biopsy are the methods of choice to make a correct diagnosis and apply a proper treatment. Although the therapy is of long duration with possible complications, it may result in significant recovery. To avoid the irreversible spinal cord injury the diagnosis should be made as soon as possible.

Conflict of interests

None declared.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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