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Case report

Spinal tuberculosis with severe neurological symptoms as a complication of intravesical BCG therapy for carcinoma of the bladder

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ABSTRACT

Introduction: Non-invasive bladder cancer is effectively treated with intravesical BCG therapy. The administration of the BCG vaccine is to destroy the neoplastic lesion or prevent further recurrences. The activity of the vaccine involves boosting the immune system through the stimulation of the inflammation in the bladder. Adverse reactions after this immunotherapy are rare.

The aim of the study was to present complications in the form of spinal tuberculosis and serious neurological symptoms that occurred during intravesical BCG immunotherapy for carcinoma of the bladder. The manuscript also describes a method for neurosurgical spinal cord decompression of the thoracic spine.

Material and methods: In the first patient, aged 66, after intravesical BCG therapy for bladder carcinoma, back pain and spastic paralysis of the lower limbs were observed. The MRI and CT revealed destruction of the intervertebral disc and vertebral endplates Th11–Th12. *Mycobacterium tuberculosis* complex bacilli were cultured from the material obtained by puncture aspiration. In the second patient, aged 35 years, during intravesical BCG immunotherapy for carcinoma of the bladder, girdle thoracic spine pain was observed. The MRI and CT of the spine showed visible lesions characteristic of tuberculosis. Immobilization in a plaster corset and implementation of antituberculous treatment resulted in quick relief of the pain and healing of the tuberculosis focus in the spine.

Conclusion: The cases described in the work are the first documented reports in the Polish literature of spinal tuberculosis which occurred as a complication of intravesical administration of bacilli Calmette–Guérin. The diagnosis was based on the finding of BCG vaccine bacillus with molecular methods or PCR. Full antimycobacterial treatment was implemented.

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1. Introduction

The BCG vaccine in the form of intravesical instillation is used to treat bladder cancer. The vaccine contains live attenuated (malignancy deprived) BCG mycobacteria. BCG as a vaccine against tuberculosis was developed by A. Calmette and G. Guérin in 1921 [1]. This strain lost its virulence as a result of passaging and never returned to its starting level. In Poland, BCG Moreau mycobacteria are used, derived from a Brazilian substrain manufactured by the Serum and Vaccine Production Plant in Lublin. The activity of BCG mycobacteria as a drug consists in stimulating the immune system of the patient and also the inflammation of the bladder wall. Intravesical administration of the BCG vaccine is to destroy the cancerous lesion, prevent further recurrences or delay their occurrence. The efficacy of BCG immunotherapy for the prevention of relapse is estimated at 70–90%. The BCG vaccine is used to treat superficial, epithelial, non-invasive bladder cancer lesions (Ta, Tis, T1). The discoverer of this method is considered to be Alvaro Morales who in 1976, together with his colleagues, announced the first results of the intravesical application of BCG in nine patients with bladder cancer [2]. In Poland, the BCG vaccine was introduced for the treatment of superficial bladder cancer by Mazurek et al., and the preliminary results were then presented in 10 patients [3]. It is believed that the cause of complications developing in organs at the time of intravesical immunotherapy is blood-derived spread of BCG bacilli. In the literature, such complications are described as single cases, while spinal tuberculosis following intravesical BCG therapy is extremely rare. The occurrence of undesirable effects is estimated at 1–10 per million of immunizations made almost exclusively in patients with impaired immunity. The laboratory diagnosis of mycobacterium is very difficult due to the fact that its genetic structure is not fully known.

2. Description of cases

Case 1. Patient K.J., 66 years old, treated for 5 years because of papillomas of the bladder with intravesical BCG immunotherapy was admitted to the Orthopedic Department, Subdivision of Bones and Joints Tuberculosis at Medical Centre of Postgraduate Education in Otwock, and diagnosed with tuberculosis of the spine in March 2014. During the examination, the patient reported back pain encircling the chest and progressive paralysis of the lower limbs. The neurological examination revealed weakness of the superficial sensation in the lower limbs, positive Babinski reflex on the right side, 3+ muscle strength on the Lovett scale and features of spasticity in both legs. X-ray and 3D CT imaging of the spine before the first operation (Fig. 1A–D) showed on the lateral view of the spine visible kyphus of Th10/Th11 caused by the destruction of endplates and the intervertebral disc. The CT-3D (Fig. 1C and D) showed extensive damage to the vertebral body with the osteosclerotic foci within the endplates.

In the pre-surgery thoracic spine MRI (Fig. 2A–C), destruction of the intervertebral disc Th10/Th11 with angled bend of the spine axis was observed. There was low signal in the T1-dependent image (Fig. 2A) and mixed signal in T2-dependent images (Fig. 2B). There was also noted an abscess in the spinal canal (Fig. 2B and C) exerting pressure on the spinal cord.

The chest X-ray showed no changes. The parameters of inflammation were moderately elevated: OB 40 mm, CRP 30 mg/l ($N < 6$). Fine needle puncture of the focus score in the spine was performed at the Department of Neurosurgery at the Medical University of Gdańsk and *Mycobacterium tuberculosis* was cultured during the first stage of bacteriological diagnosis. During the surgery performed at the Orthopedic Department, Subdivision of Bones and Joints Tuberculosis at Medical Centre of Postgraduate Education, the focus score was

Fig. 1 – (A) The lateral view of the spine revealed visible destruction of Th10/Th11 caused by the destruction of endplates and the intervertebral disc. The CT-3D (B), (C) and (D) showed extensive damage to the vertebral body with the osteosclerotic foci within the endplates.

Fig. 2 – Destruction of the intervertebral disc Th10/Th11 with angled bend of the spine axis. Low signal in the T1-dependent image (A) and mixed signal in T2-dependent images (B). An abscess in the spinal canal (B and C) exerting pressure on the spinal cord.

removed, leading to spinal cord decompression from the anterolateral access through costo-transversectomy (01 April 2014). The chemotherapeutic treatment was continued with Rifamazid 2×1 capsule, Ethambutol 1×5 capsules, Pyrazinamide 3 capsules. The histopathological examination revealed inflamed granulation tissue with Langhans giant cells. *M. tuberculosis* complex was cultured with the Bactec method. Also, the PCR result was positive. In the postoperative period, the symptoms of back pain and spasticity of the lower limbs slowly subsided. The patient was put in a plaster corset and transferred to the Department of Neurological Rehabilitation. After a month stay at the Department of Rehabilitation no improvement was obtained. In July 2014, the patient again reported back pain and neurological deterioration that resulted in almost total paralysis of the lower limbs. In August 2014, there appeared visual disturbances in the form of blurred vision and color vision disorders. The patient was diagnosed at the Department of Neurology with toxic neuropathy of the optic nerves that most likely occurred as a result of the treatment with Ethambutol. Ethambutol administration was then discontinued, which stopped the progress of visual impairment. Imaging diagnostics was performed, namely X-ray, MRI and CT of the spine.

In MRI (Fig. 3A–D), in the area of Th10/Th11, low signal in the T1-dependent image was observed (Fig. 3A) and at T2-dependent image, there was noted mixed signal (Fig. 3B). The signal became enhanced after administration of gadolinium (Fig. 3C and D). There was also observed deterioration in the form of increased peri-vertebrae infiltration and high signal

covering the vertebral arches, where it was found that there occurred higher reduction in vertebral bodies Th10 and Th11 compared with the previous testing and destruction of the intervertebral disc and epidural infiltration within the spinal canal from the lower part of the vertebral body Th9, accompanied by significant canal stenosis. Due to the deterioration of the neurological state, the patient was readmitted to the Department of Orthopedics in Otwock. Increased neurological disorders were manifested by impaired feeling in the area from Th12/L1. Additionally, upper and middle abdominal reflexes were weak, and lower were not observed at all. There was noted paraparesis with increased spastic muscle tension and bilateral Babinski reflex. On 29 September 2014, there was performed revision of the Th11/Th12 focus score and core decompression at this level. With the patient laying on the left side, the cut in an old scar was used to reach the spine at the level of Th9/Th12. Just beneath the skin, abscess was discovered with curdy masses penetrating to the spine. The spinal cord was surrounded by curdy masses and inflammatory granulation tissue. The bacteriological examination found tubercle bacilli and the histological examination revealed tubercular granulation tissue. Additional molecular tests allowed to establish an infection with the BCG vaccine. This test is regarded as determining the cause of the infection. To deepen the imaging diagnostics concerning the extent of the damage of the vertebral bodies related to the tuberculosis process, CT was performed (Fig. 4).

The 3D CT examination gave the following results: on selected layers A and B visible damage to the intervertebral

Fig. 3 – In the area of Th10/Th11, low signal in the T1-dependent image (A) and mixed signal at the T2-dependent image (B). The signal became enhanced after administration of gadolinium (C and D). Deterioration in the form of increased peri-vertebrae infiltration and high signal covering the vertebral arches, where there occurred higher reduction in vertebral bodies Th10 and Th11 compared with the previous testing and destruction of the intervertebral disc and epidural infiltration within the spinal canal from the lower part of Th9, accompanied by significant canal stenosis.

disc with the fragmentation of the vertebral bodies Th10/Th11. One rib missing on the right side after surgical removal of the focus score.

Case 2. Patient C.R., aged 35, treated with intracavitary attenuated *Bacillus Calmette-Guérin* therapy due to non-invasive malignancy at the Department of Urology in Zabrze. During the 18 months of treatment, no relapse of the cancer

symptoms was observed. After another intravesical administration of bacilli Calmette-Guérin (March 2014), the patient reported girdle chest pain. No changes in the lungs were found and the CT scan of the spine and MRI showed foci of destruction at Th5/6 with an intracanal abscess. A detailed description is contained in Figs. 5 and 6.

In the lateral projection at the Th5-Th6 level, there was a small focus score with the destruction of endplates and the destruction of the rear part of the Th5 vertebral body. The image of destruction is more visible on the selected layer of the volume transformation of the thoracic spine Fig. 5C. The cross-section Fig. 5B shows an area of more severe osteolytic lesions affecting the Th5 vertebral body. The thoracic spine MR results are shown in Fig. 6A-C.

The T1-dependent sequence showed marrow edema in the Th5/T6 vertebral bodies with foci of destruction of endplates, without any reduction of the height of the vertebral bodies (Fig. 6A). The signal in the T1-dependent images was enhanced after contrast administration (Fig. 6B). There was observed mixed signal in the T2-dependent images. Visible moderate cord compression at Th5/Th6 was noted as well (Fig. 6C).

The patient was diagnosed with Th5/T6 spondylitis, most likely due to tuberculosis and was sent to the Subdivision of Bones and Joints Tuberculosis at Orthopedic Department. The neurological examination revealed only the positive Babinski reflex, which resolved after the antimycobacterial treatment was implemented (Rifamazid, Ethambutol, Pyrazinamide) and relieving the spine in bed. No diagnostic puncture biopsy was performed. It was concluded that the probability of the spine infection can also be determined based on a number of indirect symptoms such as: (1) establishing a causal link of the infection during the treatment with BCG, (2) positive MTX test, (3) low parameters of inflammation characteristic of the

Fig. 4 – The 3D CT examination: on selected layers A and B visible damage to the intervertebral disc with the fragmentation of the vertebral bodies Th10/Th11. One rib missing on the right side after surgical removal of the focus score.

Fig. 5 – In the lateral projection at the Th5–Th6 level, a small focus score with the destruction of endplates and of the rear part of the Th5 vertebral body. The image of destruction is more visible on the selected layer of the volume transformation of the thoracic spine (C). The cross-section (B) shows a more severe osteolytic lesions affecting the Th5 vertebral body.

tuberculous infection of the skeletal system, (4) vertebral bodies osteoporosis visible on the CT scan, and (5) effective TB treatment.

Relieving the spine in bed was continued for 3 weeks. The parameters of inflammation in the blood considerably decreased. Then the patient wore a plaster corset while walking with support for the mandible and occiput. After that, the patient was discharged home and his state was controlled in the outpatient clinic (October). Another spinal X-ray showed healing of the inflammation by blocking and kyphotic reconstruction.

3. Discussion

Extra-bladder complications after intravesical BCG immunotherapy for carcinoma of the bladder are rare. Accurate diagnosis and determination of the type of bacillus is difficult. In one of the first reports in the literature, the infection was diagnosed in lumbar vertebrae in a 79-year-old man, who received with intravesical BCG immunotherapy 2.5 years earlier. The diagnostics was based on culturing the bacillus from the focus in the spine, while determination of the strain of *Mycobacterium bovis* was based on Bactec culture, chromatographic tests and the test for PZA resistance [4] since *Tuberculosis bovis* is resistant to PZA. Currently, the diagnostics methods are more accurate and require the use of isotopic,

genetic and chromatographic tests [5,6]. Genetic testing should be considered as complementary and should not substitute the non-genetic methods. Also the PCR technique has its limitations, because it detects both viable and nonviable bacilli. A relatively new test is the so-called MTDT commercial test (*M. tuberculosis* Direct Test, Gen-probe, USA). It allows for the detection of even one bacillus cell in the examined material. Another molecular test (sensitive) is GTMD (Genotype *Mycobacteria* Direct) [7,8]. This test does not require any prior culturing of bacillus.

The observed side effects are rare [3,9,10]. They can be divided into: (1) infectious (infection) and (2) non-infectious (inflammation). Noninfectious complications occur more frequently. In the literature, they are characterized by pollakiuria (in 80% of patients), hematuria (40%), and sub-febrile temperature (40%). These reactions are mild and disappear after 48 h. Intravesical BCG therapy may also lead to BCG spreading around the organism. Microdamages of the bladder are the gates through which BCG mycobacteria can spread across the surrounding tissue via the circulatory system. The risk factors are considered to include the degree of bladder tumor malignancy, cigarette smoking and advanced age. The risk factors of mycobacteria spreading are as follows: epithelial damage during catheterization, deep tumor resection, urethra injury during intravesical bacillus Calmette–Guérin instillation, bladder outlet obstruction, pelvic X-irradiation and other forms of severe inflammation of the

Fig. 6 – The T1-dependent sequence showed marrow edema in the Th5/T6 vertebral bodies with foci of destruction of endplates, without any reduction of the height of the vertebral bodies (A). The signal in the T1-dependent images enhanced after contrast administration (B). Mixed signal in the T2-dependent images. Visible moderate cord compression at Th5/Th6 (C).

bladder and conditions of impaired immunity [11]. Transurethral resection of the prostate or bladder biopsy performed two weeks before BCG administration also predispose patients to complications. The occurrence of serious complications after BCG immunotherapy is found in 0.4% of patients [12]. Lamm, in the report published in 2000, stated that the complications were very rare [13] and appeared in 5% of 2602 patients treated with intravesical bacillus Calmette-Guérin instillation. The patients manifested fever (1.9%), miliary TB (0.9%), inflammation of the lungs and liver (0.7%), arthralgia (0.5%), rash (0.3%), renal abscess (0, 1%), sepsis (0.4%), and anemia (0.1%) [12,25]. The complications described in literatures related primarily to miliary tuberculosis [9,10,12,14–17].

Our cases are exceptional. The available literature describes only six cases of spinal tuberculosis which occurred following the intravesical administration of bacilli Calmette-Guérin [4,11,18–21]. In the first case presented by the authors, the clinical diagnosis did not raise any doubts. The microscopic examination of the material obtained from the focus score

in the spine by fine needle puncture showed the presence of *M. tuberculosis* complex. Also the PCR test of the surgical material was positive, since even from one bacterium it is possible to obtain a whole series of identical copies of the genetic material of a mycobacterium [9]. However, the most important examination determining the etiology was the molecular method used to detect a BCG vaccine mycobacterium. The case report by Rogoziński et al. concerning granulomatous lung inflammation following bladder cancer treatment with BCG vaccine informed of the presence of granulation with “caseating tubercles”, curdy tissue necrosis resembling Langhans’ cells in the situation when genetic testing of the case for tuberculosis brought negative results [22]. Despite this, the patient was treated with antimycobacterial drugs in accordance with the recommendation [23]. In our second case (spondylitis after intravesical BCG therapy), we failed to identify the presence of a mycobacterium. It was decided not to perform the diagnostic fine needle puncture, since the probability of tuberculous infection of the spine, very rapid therapeutic effect after administration of full TB

treatment and the temporal relationship between the intravesical BCG administration and the occurrence of spondylitis confirmed the validity of this diagnosis.

Polish literature describes two cases of complications following the BCG vaccine treatment of bladder cancer [22,24]. In one case, granulation tissue was found in the patient's epididymis [24]. In the second case, suspicion of the BCG infection led to extending the diagnostics with genetic and bacteriological testing, and during the examination of the histopathological material taken by videothoracoscopy, the presence of granulation tissue and curdy masses was revealed [22]. Histopathological examination can only determine tuberculosis, but the type of bacillus is still unknown. The patient was diagnosed with granulomatous inflammation of the lungs. Nevertheless, it was decided that the best course will be the full antimycobacterial treatment for 9 months as in the case of bone tuberculosis. Zwolska et al. described five cases concerning children, in whom prophylactic vaccination with BCG caused a number of adverse reactions [6,9]. In the material collected for bacteriological examinations from suspicious areas and organs in children, the National Mycobacterium Reference Laboratory found *Mycobacterium bovis* [6,9].

Japanese and other authors reported that miliary tuberculosis is the most common organ complication (0.9%) induced by intravesical BCG immunotherapy for carcinoma of the bladder [9,10,12,14–17,25]. Cough, X-ray and CT examination of the lungs, transbronchial biopsy of the lung tissue and detection of *M. tuberculosis* determine the definitive diagnosis and tuberculostatic treatment leads to recovery. However, in some cases, allergic reactions associated with miliary tuberculosis require additional administration of steroids [16]. The treatment of adverse organ complications after intravesical administration of bacilli Calmette–Guérin was developed by the International Bladder Cancer Group [23]. These authors recommend discontinuation of the intravesical bacillus Calmette–Guérin instillation and the use of antimycobacterial drugs, and in the case of particularly severe allergic reactions, also the additional application of steroids [16]. In our cases, there was no need for such therapy, because in the first case, the neurological symptoms manifested through paraparesis were associated with mechanical compression of the spinal cord and required operative decompression. Complications during intravesical BCG administration such as miliary pulmonary tuberculosis and hepatitis are rare, and tuberculous spondylitis – as in our case – is even rarer. The key role is played by early diagnosis and proper treatment, and careful qualification of patients for BCG therapy and assessment of risk factors on the basis of the guidelines will make it possible to avoid serious complications.

Zwolska determined that bacilli of *Mycobacterium bovis* are morphologically, physiologically, biochemically and genetically similar to other species of mycobacterium belonging to *M. tuberculosis* complex [6,9]. Such tests were not performed in our cases. Zwolska also stated that each instance of complications after the use of BCG mycobacteria should be reported to the National Mycobacterium Reference Laboratory, where it is possible to determine the infection with *Mycobacterium bovis* BCG. That was the case concerning the first patient described by the authors.

The authors presented a detailed description of the clinical diagnostics and the relationship of the infection with intravesical BCG immunotherapy for the carcinoma of the bladder and the orthopedic therapeutic intervention. In the first case described by the authors, the patient was treated surgically for neurological deficits caused by pressure on the spinal cord. The probability of spinal tuberculosis caused by the BCG vaccine was described in detail in the text.

4. Conclusion

Intravesical BCG vaccine therapy is a proven treatment for carcinoma in situ of the bladder. Complications during the treatment with the BCG vaccine are rare and may affect both the bladder and other organs such as lungs, liver and also prostate adjacent to the bladder, epididymis and testicles. On the other hand, spinal tuberculosis is extremely rare. The most certain and reliable diagnosis of spinal tuberculosis is finding the bacillus in the focus score using fine needle puncture or in the material obtained during surgery and having determined whether it is *Mycobacterium bovis* by the National Mycobacterium Reference Laboratory. Preventing the side effects consists predominantly in disseminating the education/knowledge of such complications, and – during the therapy – applying the proper technique of BCG vaccine administration into the bladder. Full antimycobacterial treatment is mandatory and if there occurs compression of the spinal cord, it is necessary to perform anterolateral spinal decompression surgery.

Conflict of interest

None declared.

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None declared.

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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