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Granuloma of epididymis in a patient treated with intravesical BCG therapy — complication of BCG therapy or tuberculosis?

Ziarnina stwierdzona w najądrzu chorego leczonego dopęcherzowymi wlewkami BCG — powikłanie leczenia BCG czy gruźlica?

Abstract

We present a case of a 72-year-old man treated for superficial bladder carcinoma from the year 2007. The patient underwent a surgical intervention for transitional cell carcinoma of the bladder, followed by intravesical BCG immunotherapy. Two years later, the right testis and epididymis were found to be enlarged. A resection was carried out. Histological examination revealed granulomatous infiltration with eosinophilic necrosis in cauda epididymis. No bacteriologic tests of the resected material were performed. Due to a suspected BCG infection or TB, the patient was transferred to the Institute of Tuberculosis and Lung Diseases in Warsaw, for pulmonary evaluation. Chest X-ray, chest CT scan and bronchoscopy were performed but apart from scars in the bronchi suggesting a history of TB, they did not contribute to the diagnosis. Tuberculin skin test was 21 mm. Diagnosis was determined by spoligotyping which found genetic material of *Mycobacterium tuberculosis* in specimens preserved in a paraffin block. Tuberculosis of the right epididymis and past pulmonary tuberculosis were diagnosed. The patient was treated with rifampin, isoniazid and pyrazinamid.

Key words: BCG infection, male genital tuberculosis, spoligotyping

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Introduction

Infection with *Mycobacterium tuberculosis* may involve any organ. Extrapulmonary tuberculosis constituted 7.1% of all new registered cases in Poland in the year 2009. Genitourinary system is the fourth most common location of tuberculosis (TB), after the pleura, lymph nodes, bones and joints. In Poland, 62 cases of urinary tract tuberculosis and 18 cases of genital tuberculosis were diagnosed in 2009, which constituted 10.6% and 2.7% (respectively) of all cases of extrapulmonary

tuberculosis [1]. The lesions are mostly found in the epididymis (9–42%) and prostate gland (11–58%) [2–5]. The infection spreads with the bloodstream or it may ascend from an infected genitourinary tract [4].

Bacillus Calmette-Guerin (BCG), an attenuated strain of *Mycobacterium bovis*, is the world's only vaccine used in anti-TB vaccination. The strain of BCG is a live bacterial vaccine, in which the active ingredient is bovine bacillus, which was devoid of virulence by repeated passaging. The strain due to deletions and/or multi-point mutation in the

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genome has lost its virulence and never returned to its original virulence [6]. It is now known that the loss of virulence is associated with the deletion of the RD1 region which encodes a 9.5-kb fragment, containing at least 8 open reading frames.

Intravesical BCG is used in the treatment of the superficial bladder carcinoma [7, 8]. The immune mechanism activated by BCG may not only influence the urinary bladder, but also cause some local adverse reactions in other organs of the genitourinary system, such as the prostate, testes, epididymides, and kidneys. It may also result in some distant lesions, including granuloma in the lungs, liver, and other parenchymal organs, as well as bone inflammation [9–14]. Case reports on miliary BCG infection are reported in the literature. It is believed that adverse effects of BCG are rare and concern less than 5% of patients. Lesions of the lungs and/or liver are found in 0.7%, of joints in 0.5%, of kidneys in 0.1%, of prostate in 0.9%, and of epididymides in 0.4% of subjects treated with BCG [5, 15].

Microbiological diagnostic work-up of extrapulmonary tuberculosis is very difficult and requires careful sampling of the material from the patient and choosing an appropriate diagnostic method. The diagnostics of extrapulmonary tuberculosis is hindered by such factors as: a very long growth time of bacilli, disease course connected with a low number of bacilli, presence of inhibitors of genetic reactions, difficulties with sampling/obtaining the material for bacteriological examinations.

Many forms of extrapulmonary tuberculosis require an invasive diagnostic methods of material sampling (tissue sections, bone marrow, pericardial effusion, pleural effusion, cerebrospinal fluid), which leads to a situation in which only one specimen is delivered to laboratory and the whole diagnosis is based on it. Therefore, the recognition of such forms of tuberculosis requires an application of the modern microbiological diagnostic methods, available in some laboratories only.

The development of molecular biology and tests of nucleic acid amplification allowed for an improvement of the methods of TB bacilli detection directly in the clinical material, without their incubation. Unique sequences of nucleic acids of *Mycobacterium* can be detected directly in the clinical material, with a higher sensitivity than in case of bacterioscopic methods, and in a much shorter time than in case of cultures.

The spoligotyping (spacer oligonucleotide typing) method uses polymorphism of the chromosomal DR (direct repeat) region of bacilli of *M. tu-*

berculosis complex type. The number and position of spacer sequences in the DR region constitute criteria of differentiation between particular strains. Synthetic oligonucleotide probes are used to identify spacer sequences. They are complementary to 43 known, sequenced spacer regions identified in *M. tuberculosis* strains [16]. Spoligotyping as a method based on PCR (polymerase chain reaction) requires only small amounts of DNA. Owing to that, it may be used to detect and identify *M. tuberculosis complex* directly in the clinical material, without a need for bacilli culture. Such results can be obtained within 1–2 days. As it was shown, this method may also be used for identification of *M. tuberculosis* strains in microscopic examinations or tissue sections embedded in paraffin [16].

The obtained genetic patterns of *M. tuberculosis* were compared with patterns collected in the international spoligotyping database (SpolDB4) and qualified to specific molecular families.

Case report

A 72-year-old patient with urinary bladder cancer diagnosed in 2007, received intravesical BCG therapy after electroresection of the lesions. After approx. two years, the left testicle and epididymis were resected due to pain and hard swelling in the testicular region. The postoperative wound healed without complications. Histological examination found regions of irregular eosinophilic necrosis in the epididymis, surrounded by a palisade of fibroblasts and histiocytes, with giant cells and abundant lymphoid infiltrates. No culture of the urine or semen was performed. The histological material was not sent for bacteriological examination either. The patient was referred to the Institute of Tuberculosis and Lung Diseases in Warsaw, with BCG infection suspected on the basis of the histopathological image.

At the time of admission, the patient did not have any respiratory signs or symptoms. He denied fever, loss of body mass or chest pain. The physical examination did not find any abnormalities either. The tuberculin skin test was 21 mm. Chest CT performed in another institution showed band-like densities in the lower lobe of the right lung, segmentally contiguous to the thickened pleura. CT of the chest performed 5 months later at the Institute didn't reveal any new lesions and didn't show any radiological features of active tuberculosis.

Due to lack of bacteriological examinations performed on the resected testicle and epididymis, it was attempted to confirm the aetiology of dise-

ase with a different methods. Urinalysis did not show any abnormalities suggestive of tuberculosis. The cultures were negative as well. Bronchoscopy showed anthracotic incrustations in the bronchi and scars due to perforations of the lymph nodes, which was suggestive of past tuberculosis. However, the bronchial secretion did not contain any genetic material of *M. tuberculosis*. No acid-fast bacilli were grown either.

The preserved pathological specimens were examined with spoligotyping method, which showed the presence of genetic material of *M. tuberculosis*. The obtained hybridisation patterns were compared to patterns registered in the international spoligotyping database (SpolDB4). As a result — *M. tuberculosis* strain of molecular family T153, was identified.

This led to the diagnosis of tuberculosis of the right epididymis in the patient with a history of pulmonary tuberculosis. Rifampin, isoniazid and pyrazinamid were administered, according to the therapeutic regimen used at that time.

Discussion

Diagnosing extrapulmonary tuberculosis may be difficult, as its symptoms are nonspecific. Tuberculous infection of the pleura is usually diagnosed more easily than tuberculosis of the bones and joints due to the severity of the clinical symptoms and probably also availability of the bacteriological material [17]. Bacteriological confirmation is difficult in case of extrapulmonary location. In Poland, in 2009, only 32% of cases of extrapulmonary tuberculosis were confirmed with positive bacteriological results; for pulmonary tuberculosis, this rate amounted to 65.8% [1]. Owing to that, extrapulmonary tuberculosis is usually diagnosed in late clinical course or not diagnosed at all during lifetime. It is believed that 20–50% of extrapulmonary tuberculosis cases are revealed during autopsy. This rate amounts to 5% for lung tuberculosis [18, 19].

Tuberculosis of epididymis is mostly found in young and sexually active men. Before era of anti-tuberculous treatment, tuberculosis of epididymis had concerned mostly men aged 16–40 years. At present, over 70% of patients are older than 35 years, and 15–20% are over 65 [20]. Most of the patients (70%) reveal features of past TB at a different location [4]. Usually (as in the presented case) the lesions occur in the respiratory system. In 2/3 of cases, the disease course is acute. Local symptoms prevail, but they may be accompanied by fever, sweating, decreased appetite and loss of body

mass [4]. Epididymis becomes enlarged and tends to be painful. Pain may radiate to the kidney. With time, the pathological lesions spread to testes. Abscesses may form in the head and tail of the epididymis, leading to fistulas in the scrotal skin [2, 20]. The lesions are mostly unilateral, as in the presented case, but approx. 1/3 of the patients develop bilateral changes [20].

Complications of vesical BCG treatment may be related to immune response to BCG treatment or BCG infection. Distant lesions (in the lungs, liver, or joints) are believed to be a result of immune response, in majority of cases. They appear early in the disease course — 3–6 months after BCG treatment. Histological examination occasionally reveal the presence of granuloma, however, BCG infection is confirmed by bacteriological tests in 30% of cases only, which (according to many authors) suggests the immune mechanism of the disease in the remaining cases. Local lesions appear after at least 6 months following BCG administration. In approx. 70% of lesions, BCG was identified, which proves their infectious aetiology [21]. Gonzales et al. [21] observed infectious complications caused by BCG in 8 patients aged 44–77 years (mean of 63.8). General symptoms are rare. Local oedema and pain are usually observed. The symptoms are usually interpreted as cancer-related. Therefore, very often, sampling of the material for histopathological examination is performed. Tuberculosis-like granuloma of male genitals may have different causes. They include (apart from tuberculosis) infections with nontuberculous bacilli, such as *M. kansasii*, *M. avium-intracellulareae*, *M. fortuitum*. Other infectious causes include leprosy, brucellosis, actinomycosis, and fungal infections. Noninfectious aetiological factors include sarcoidosis and vasculitis. A positive tuberculin skin test does not differentiate tuberculosis from BCG infection.

Growing the bacilli is the only method to establish a certain diagnosis. The sampling material may include tissue from biopsy, urine, or semen. In case of TB suspicion, the material from the respiratory tract (sputum, bronchial secretion, bronchoalveolar lavage, i.e. BAL) should be cultured as well. Therefore, in the presented case, cultures of the material collected from the respiratory system were performed. In the study by Garcia et al., reporting on 8 cases of tuberculosis of the epididymis and testicle, the disease was confirmed bacteriologically in 6 individuals with the use of urine and in two patients with the use of needle biopsy [2].

However, other physicians than pulmonologists rarely take tuberculosis into consideration in the differential diagnosis. Therefore, bacteriologi-

cal tests for TB are too seldom (as it was shown in the presented case as well, in which culture of the resected material was not carried out at all, and urine culture was performed only after the resection of the pathological lesions).

In the diagnostics of extrapulmonary tuberculosis, which is often based on tissue material with few bacilli, it is difficult to confirm the disease with standard microbiological techniques. In order to maximize the sensitivity of the tests, molecular methods were introduced. They allow for detection of *M. tuberculosis* not only in the material collected directly from the patient but also in tissues embedded in paraffin blocks. In the presented case, one of the proofs of the pathological process was the histological material including granuloma. The use of molecular methods in tissue specimens allowed for detection of *M. tuberculosis* in a short time, and did not confirm the BCG infection.

Establishing the proper diagnosis is important, as the therapies for tuberculosis and BCG infection are different. Tuberculosis must be treated. A standard therapeutic set includes rifampin, isoniazid and pyrazinamid. In case of infection caused by BCG bacilli, resection of the local lesions may be sufficient. Distant lesions require the use of drug regimens without pyrazinamid (BCG bacilli are resistant to this drug).

The presented case showed difficulties connected with TB diagnosis and its differentiation from BCG infection. It was proved that the diagnosis cannot be based on history or clinical and histopathological picture. Only the bacteriological test allows for a certain diagnosis in such cases. The presented case illustrates the usefulness of the modern techniques of microbiological tests in a difficult to diagnose form of tuberculosis.

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