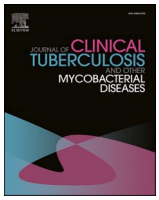
Journal of Clinical Tuberculosis and Other Mycobacterial Diseases 35 (2024) 100438

Contents lists available at ScienceDirect

Journal of Clinical Tuberculosis and Other Mycobacterial Diseases

journal homepage: www.elsevier.com/locate/jctube



Case Report

Chest wall tumor following intravesical BCG instillation for non-muscle invasive bladder cancer

Marc Hartert [a,1,*], Claudia Deppe [b,1], Ludger Fink [c], Jutta Kappes [b]

[a] Department of Thoracic Surgery, Katholisches Klinikum Koblenz-Montabaur, Koblenz, Germany
[b] Department of Internal Medicine and Pneumology, Katholisches Klinikum Koblenz-Montabaur, Koblenz, Germany
[c] Institute of Pathology, Cytopathology, and Molecular Pathology, Supraregional Joint Practice for Pathology, Member of the German Center for Lung Research, Wetzlar, Germany

ARTICLE INFO

Presented at the 63rd Annual Congress of the German Society for Pneumology and Respiratory Medicine, March 29th – April 1st 2023, Düsseldorf, Germany.

Keywords:
Mycobacterium bovis bacille Calmette-Guérin (BCG)
Intravesical therapy
Non-muscle invasive bladder cancer
Chest wall tumor
Diagnosis
Treatment

ABSTRACT

Mycobacterium bovis bacille Calmette-Guérin (BCG) is the most effective intravesical immunotherapy for non-muscle invasive bladder cancer (NMIBC), administered after its transurethral resection. Although its instillation is generally well tolerated, BCG-related infectious complications may occur in up to 5% of patients. Clinical manifestations may arise in conjunction with initial BCG instillation or develop months or years after the last BCG instillation. The range of presentations and potential severity pose an imminent challenge for clinicians. We present a case of an isolated subcutaneous chest wall abscess in an immunocompetent 52-year-old patient nearly two years after intravesical BCG instillation for NMIBC, an absolute rarity. As the enlarging chest wall tumor may be misinterpreted as malignancy, its expedient diagnosis and prompt treatment are of critical importance.

1. Introduction

The intravesical administration of bacillus Calmette-Guérin (BCG), an attenuated live strain of *Mycobacterium bovis,* is an established standard adjunctive therapy for non-muscle invasive bladder cancer (NMIBC) [1,2]. Even though generally well tolerated, up to 5 % of local and systemic BCG-related infectious complications may occur. The most common presentations are (1) disseminated infections (i.e. miliary tuberculosis, persistent fever, bone marrow and/or liver infiltration), (2) genitourinary complications (i.e. bladder involvement, penile lesions, prostatitis, kidney involvement, epididymo-orchitis), and (3) osteomuscular manifestations (i.e. mono-, oligo- or polyarthritis affecting the extremities, spondylodiscitis) [3]. We present a case of an isolated subcutaneous chest wall abscess in an immunocompetent 52-year-old patient nearly two years after intravesical BCG instillation for NMIBC, which is an absolute rarity. As the progressively enlarging chest wall tumor may be misinterpreted as malignancy, its expedient diagnosis and prompt treatment represent a major challenge for clinicians.

2. Case report

A 52-year-old man presented with a three-month progressively growing chest wall tumor under the right costal arch. On visual examination, the tumor measured approximately eight centimeters in diameter. The patient expressed a sensation of pain and a feeling of pressure at the tumor site. He worked as a construction worker, was a chronic smoker (35 pack-years), and denied persistent cough, fevers, chills, hemoptysis, dyspnea, weight or appetite changes, sick contacts, or recent travel. He also denied taking medications. Relevant medical history was an NMIBC nearly two years before, which was treated by transurethral resection of the bladder tumor (TURBT) in March 2020, followed by six cycles of intravesical BCG therapy (from late April until early June 2020). There were no *peri*-interventional abnormalities, particularly any traumatic BCG instillations with subsequent intense

* Corresponding author at: Department of Thoracic Surgery, Katholisches Klinikum Koblenz-Montabaur, Rudolf-Virchow-Str. 7-9, 56073 Koblenz, Germany.
E-mail address: m.hartert@bbtgruppe.de (M. Hartert).
[1] Equally contributed to the manuscript.

https://doi.org/10.1016/j.jctube.2024.100438

Available online 9 April 2024

hematuria. The tumor after-care was unremarkable. Initial symptoms of the chest wall tumor appeared at the beginning of November 2021. A biopsy was taken from the chest wall tumor at a secondary care hospital by the end of December 2021, which histologically demonstrated active and partially resolving inflammation with several epithelioid cells. A microbiological analysis of the sample was not done, and no therapy was initiated afterward. Laboratory tests done in February 2022 on admission at our lung center were normal (in particular inflammatory values and blood count) with a negative interferon-gamma release assay (QuantiFERON-TB Gold in tube, QFTG-IT; Quiagen, Hilden, Germany). A tuberculosis skin test (TST) was not performed. Sonographically, the chest wall tumor appeared as a deep solid mass with a perifocal liquid margin. Magnetic resonance imaging (MRI) revealed the extent of the chest wall tumor with no additional abnormalities in the lungs or mediastinum (Fig. 1a). Further investigation included a punch biopsy of both solid tumor mass and perifocal edema for further microbiological and histological investigations. The pathology revealed a slightly active inflammatory reaction with sarcoid-like epithelioid cell granulomas (Fig. 2). The microbiology testing could not identify bacteria on either Gram stain, Kinyoun stain, aerobic or anaerobic bacterial culture. Furthermore, M. tuberculosis-specific DNA was not detectable by PCR (FluoroType® MTB VER 1.0, Hain Lifescience GmbH, Nehren, Germany). A bronchoscopy was performed based on histologically proven sarcoid-like epithelioid cell granulomas with inconspicuous findings, including no growth of mycobacteria in the bronchoalveolar lavage culture.

Based on the suspected diagnosis of actinomycosis, treatment with amoxicillin and clavulanic acid (2 g/d) was started. On the 31st day of incubation, microbiologic culture of the punch biopsy samples identified growth of *Mycobacterium bovis* bacille Calmette-Guérin (BD BACTEC^{TM}MGIT^{TM} 960 Supplement Kit and BD BBL^{TM} MGIT^{TM} Mycobacteria Growth Indicator Tubes, Becton, Dickinson and Company, Sparks, MD, USA; Loewenstein-Jensen Medium and Stonebrink Medium, Fisher Scientific GmbH, Schwerte, Germany). A culture-based drug susceptibility testing was not performed. Nucleic acid hybridization with a desoxyribonucleic acid probe identified the *Mycobacterium tuberculosis* complex (GenoType MTBC VER 1.X, Hain Lifescience GmbH, Nehren, Germany). Additional molecular tests excluded rifampicin and isoniazid

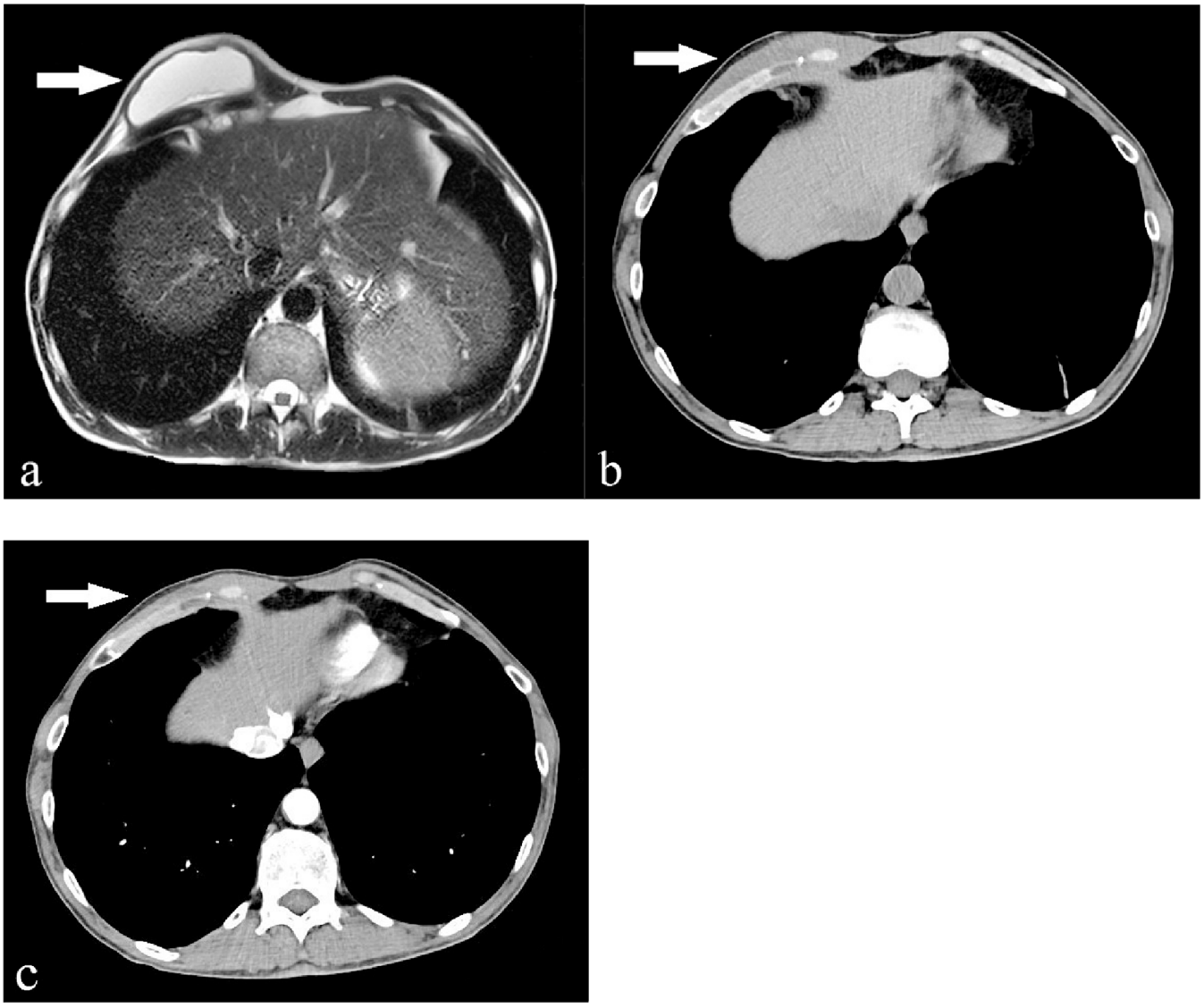


Fig. 1. a) Pretherapeutic magnetic resonance imaging (MRI) revealed the extent of the chest wall tumor caudal to the right costal arch (arrow) with no additional abnormalities of the lungs or mediastinum (T2-weighted half Fourier single-shot turbo spin-echo [T2-HASTE] sequence). b) As early as three months after initiation of therapy, the tumor has vanished clinically with only small remnants (arrow) on non-contrast-enhanced computed tomography (CT) scan. c) Nine months after initiation of antimycobacterial treatment the remaining CT-findings had normalized (arrow pointing to formers tumors site).

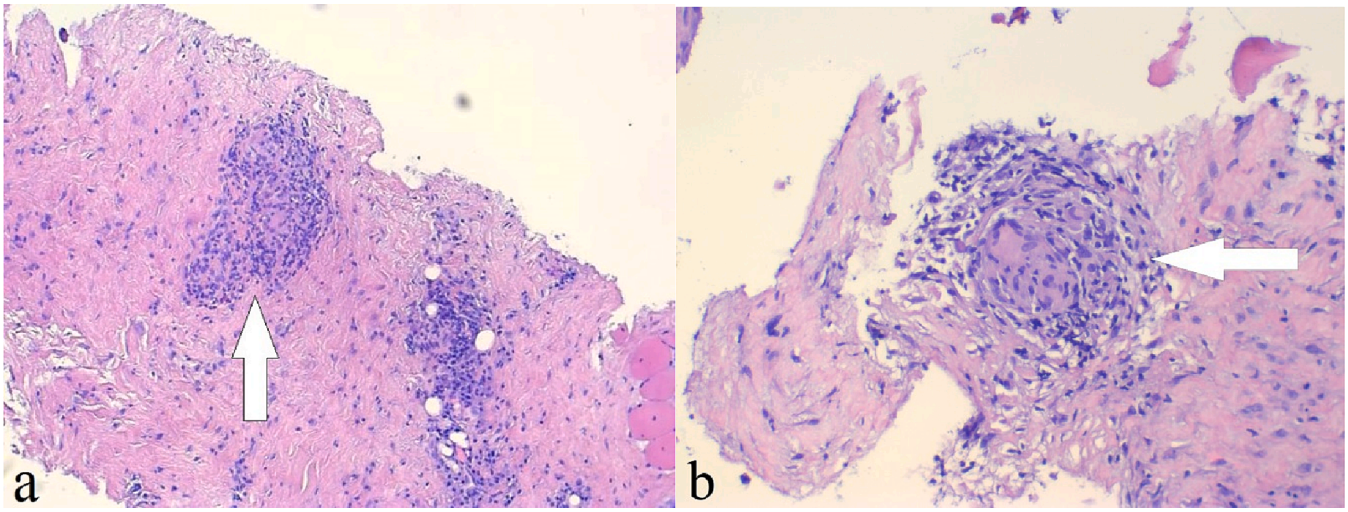


Fig. 2. Histopathological examination presented sarcoid-like epithelioid cell granulomas with Langhans-type giant cells (arrows), surrounded by inflammatory cells composed of a mixture of neutrophils and eosinophils (a: magnification 40×, b: magnification 100×; hematoxylin and eosin (H&E) staining).

resistance (GenoType MTBDRplus VER 2.0, Hain Lifescience GmbH, Nehren, Germany). Consequently, amoxicillin and clavulanic acid were discontinued and therapy with isoniazid (5 mg/kg of body weight), rifampicin (10 mg/kg), and ethambutol (15 mg/kg) was initiated. Pyrazinamide, which is part of the standard therapy for tuberculosis, was not administered as *Mycobacterium bovis* is intrinsically resistant to this drug. Because of the size and location of the tumor in bradytrophic tissue, we decided to extend the duration of the initial triple therapy from two to four months. After that, double therapy with isoniazid and rifampicin was continued for an additional five months (total duration of therapy = 9 months). The antimycobacterial therapy was well tolerated. While the initial treatment with amoxicillin and clavulanic acid for a putative Actinomyces infection was ineffective, the size of the tumor regressed under antimycobacterial combination therapy. The tumor had vanished clinically with only small remnants on a computed tomography (CT) scan after three months of treatment with isoniazid, rifampicin and ethambutol (Fig. 1b). Nine months after initiation of antimycobacterial therapy, the remaining CT-findings also normalized (Fig. 1c). A clinical follow-up six months after the end of therapy was unremarkable.

3. Discussion

For nearly 40 years, intravesical BCG therapy has been the standard of care in patients with high-risk NMBIC and an optional treatment for intermediate-risk NMIBC [4]. BCG induces a complex immunological cascade of innate and adaptive immune responses resulting in cell-mediated tumor-specific destruction of urothelial carcinoma cells [5]. Furthermore, it decreases the probability of tumor recurrence and reduces the rate of disease progression after TURBT. Compared with BCG vaccination, the number of bacteria given for intravesical therapy is orders of magnitude higher ($\sim 10^6$ bacilli for vaccination; $\sim 10^9$ bacilli for bladder cancer) [6]. Despite a beneficial safety profile, intravesical BCG instillation carries the potential for serious adverse events as it consists of viable attenuated mycobacteria [7,8]. Most of the information on BCG-related infection comes from case reports [9]. Few observational cohort studies aimed at determining its incidence [3,10]. The most obvious limitation is the difficult distinction between actual infection and self-limited post-instillation symptoms, as no accurate diagnostic criteria exist yet. When BCG adheres to the bladder urothelium, the immune response stimulates cytokine production and boosts local migration of leukocytes and macrophages, ultimately leading to tumor cell death [11,12]. Comprehensibly, many patients endure irritable voiding symptoms (urgency/frequency, dysuria, suprapubic pain, and hematuria) and flu-like signs (mild fever and malaise within 48 h after BCG instillation) [3]. This clinical picture must be seen less as an adverse event and more as a marker for an adequate antitumor BCG effect [11].

Traditionally, variable terms have been used to label the incidence of adverse events following intravesical BCG immunotherapy, like *BCGitis*, *hypersensitivity reaction*, *tuberculosis*, *granulomatous complication*, or *M. bovis infection*. The heterogeneity of this nomenclature reflects the incomplete understanding of the pathogenetic mechanisms for the development of localized or systemic complications following intravesical BCG instillation. In principle, the adverse events can be categorized as follows: (1) localized complications due to direct contact with the bacilli (i.e. infection of the genitourinary tract) and (2) systemic complications due to hematogenous dissemination (i.e. miliary tuberculosis) or cross-reactivity between the tissue self-antigens and mycobacterial antigens (i.e. reactive arthritis, so-called Reiter syndrome). The hypothesis of hypersensitivity reaction is affirmed by the histological finding of granulomas in the absence of detectable microorganisms. In contrast, the hypothesis of active mycobacterial infection is supported by finding viable bacilli in various tissues [12]. In addition, some conditions may result in hematogenous BCG dissemination (e.g. impairment of the urothelial barrier due to traumatic urinary catheterization, early instillation after TURBT, or concurrent urinary tract infection), but the role of subclinical immunosuppression still needs to be addressed [13].

Subcutaneous abscesses and other dermatological complications are well documented after Bacillus Calmette-Guérin vaccination [14]. Most commonly, they represent a local reaction at the BCG injection site. In these cases, the time frame from BCG vaccination to the development of skin lesions ranges from several months to years. In contrast, dermatological complications after intravesical BCG instillation are an absolute rarity [15–17]. Again, the spread of mycobacteria to cutaneous sites could be explained by either hematogenous spread from systemic absorption of intravesical bacilli or direct inoculation into cutaneous tissue. In our case, it is rather implausible that viable intravesical mycobacteria could have gained access to an open sore by urinary contamination. Although the *peri*-interventional course of our patient was reportedly unremarkable in terms of traumatic BCG installation, the *"bacteria invasion hypothesis"* is more likely.

The incidence of systemic BCG infection ranges from 1 % to 5 % [3,11]. However, this should be interpreted cautiously, as prompt diagnosis and treatment may be hampered by the variability of clinical features and the delayed appearance of clinical signs and symptoms of complications, which takes months to years following the last BCG instillation. As documented in the literature, the largest time interval

between BCG instillation and onset of complication (in the case of epididymo-orchitis) was 17 years [18]. Nevertheless, the period between BCG instillation and the onset of localized complications (e.g. genitourinary tract) is even longer [19].

Apart from the most frequently reported systemic BCG infections (miliary tuberculosis, sepsis, or fever associated with organ involvement), there is a wide range of different clinical manifestations like anecdotes of prosthetic joint infection, parotid gland tuberculosis, endogenous endophthalmitis with infiltrative retinitis, and lymphocytic meningitis [3,10]. As anecdotal manifestations are often not adequately appreciated, BCG infections are frequently ignored in the differential diagnosis in most cases until microbiological testing shows *M. bovis* by culture. This highlights the requirement of keeping delayed BCG infection in mind based on a preceding history of BCG exposure.

Predisposing factors for localized and systemic BCG infection following intravesical BCG instillation are still to be determined. Traditionally, the most relevant risk factors were a poor technical procedure with traumatic instillation (i.e. inappropriate urinary catheterization) or concurrent urinary tract infection [3]. A specific predisposing factor for systemic BCG infections is a disruption in the bladder mucosal barrier at the moment of BCG instillation [7]. Furthermore, the mycobacterial dissemination from the lower urinary tract via the so-called Batson venous plexus to the spinal column – historically misdiagnosed as spinal metastasis – might be an additional pathogenesis mechanism for BCG spread [3]. Theoretically, immediate intravesical BCG instillation following preceding TURBT would highly favor a direct BCG entrance to lymphatics and bloodstream via the disrupted urothelial mucosa [7]. Practically, there seems to be no significant difference in the period between short-term versus long-term BCG instillation and the onset of BCG-related complications [3,10]. Against this background, the recommended interval between the preceding TURBT and the initial BCG instillation is roughly 30 days [20]. Besides, there are no significant differences in dosing regimens of BCG instillation (i.e. split vs. full dose regimens) with respect to toxicity frequency or treatment discontinuation rate due to adverse events [21]. Our patient received the BCG instillations more than 30 days after the TURBT. Even though there were no documented *peri*-interventional abnormalities – in particular, any traumatic BCG instillations with subsequent intense hematuria – it is worth mentioning that our patient tended to be reserved. There is a chance that a traumatic BCG instillation with postinterventional hematuria was undisclosed. Synoptically, BCG-related complications most likely depend on the recipient's characteristics (i.e. major bladder mucosal damage or specific underlying conditions) or the BCG instillation technique rather than BCG dosage, quantity of treatment courses, or time from the preceding TURBT [3].

As the immune system is less effective with aging in its innate and adaptive responses, older patients, especially those older than 70 years, would theoretically face an increased risk of BCG-related complications [21]. However, there is no difference in the occurrence of severe adverse events in patients over 80 years, with a moderately lower disease-free rate when compared to a younger patient group [3]. The average age of patients diagnosed with BCG-related infections is 66.6 years, which is close to the age of patients undergoing an uneventful course of BCG therapy for NMIBC. Otherwise, a positive purified protein derivative (PPD) test before BCG instillation might predict both subsequent systemic adverse side effects and positive antitumor activity [22]. Our patient was much younger than the defined cut-off age of $>$ 70 years, which is reported in the literature as a relevant *peri*-interventional risk factor.

As microbiological cultures often remain negative (up to 60 %), the cornerstone in diagnosing BCG-related infections comprises excluding other entities and the rapid response to antimycobacterial treatment [3]. The low sensitivity of microbiological swabs is explained by fast immunologic control of BCG replication due to the attenuated BCG virulence and the preexisting delayed-type hypersensitivity causing granuloma formation [7]. Nevertheless, a representative tissue biopsy has the best chance for BCG detection by conventional culture and is, therefore, particularly relevant in the diagnostic workup for BCG infection. Conversely, the positive predictive value of *M. bovis* isolation from urine samples in case of systemic BCG infection is notably low [3]. However, urine analysis should be routinely performed in patients with suspected BCG-related infections to rule out urinary tract infections caused by conventional uropathogens [23]. Molecular-based techniques (e.g. PCR assay) have gradually modified the diagnostic opportunities and increased the overall rate of proven BCG-related infections [3]. A sample of *M. tuberculosis* complex DNA obtained from a site distant to the genitourinary tract (such as the lung, liver, aortic wall, or periprosthetic hip joint) affirms the hypothesis of direct BCG invasion and/or hematogenous spread rather than a mere hypersensitivity reaction [3,7]. Since BCG belongs to the *M. tuberculosis* complex, nucleic acid amplification (NAA) tests (Xpert MTB/RIF assay or Xpert MTB/RIF ultra) have an acceptable sensitivity and specificity in diagnosing BCG infections in non-respiratory samples like tissue biopsy or purulent material. Compared to culture, the sensitivity and specificity of Xpert MTB/RIF ultra and Xpert MTB/RIF assay were 100 % and 72.3 %; 92.6 % and 88.3 %, respectively. In comparison with composite microbiological reference standard (CRS), these were 98.9 % and 100 %; 57.5 % and 100 %, respectively [24]. In our case, nucleic acid hybridization (GenoType MTBC VER 1.X) successfully identified the *M. tuberculosis* complex. Moreover, an additional molecular test (GenoType MTBDRplus VER 2.0) excluded rifampicin and isoniazid resistance. Interferon-gamma release assays (IGRA) use antigen targets like ESAT-6 and CFP-10, whose gene loci were deleted during *M. bovis* BCG strain development (so-called "region of difference", RD1). Consequently, the IGRA is (1) positive in the case of *M. bovis* infection and (2) negative in the case of *M. bovis* BCG infection or after vaccination [6]. In our case, an additional TST was not performed. In contrast with typically negative IGRA in patients with BCG infections, TST could be positive in these cases [25].

Based on the standard therapy for *M. tuberculosis*, the most commonly administered drug cocktail consists of isoniazid and rifampicin for six months, with an initial 2-month "intensive 3-drug-phase" including ethambutol. The administration of pyrazinamide is avoided as BCG – an attenuated derivative of *M. bovis* – is intrinsically resistant to it. Furthermore, the different BCG strains (i.e. Connaught, Tice, and RIVM) are also resistant to cycloserine. Depending on the exact BCG strain, some patients benefit from additional, though less common, use of fluoroquinolones (like ofloxacin, ciprofloxacin, moxifloxacin, and levofloxacin) [26]. The use of corticosteroids within antimycobacterial treatment in patients with disseminated BCG infection highlights its presumptive underlying pathogenetic etiology of both hypersensitivity reaction and active infection. Currently, the optimal antimycobacterial regimen and its duration for treating BCG infections are not well-defined. Most of the experience comes from case reports, where the duration depends on disease severity and clinical response. In our case, the 9-month treatment duration is based on the size and location of the tumor in bradytrophic tissue and the fact that BCG is resistant to pyrazinamide which, in turn, is extrapolated from the treatment of *M. bovis*. However, BCG is an attenuated strain, and previous reported cases have been successfully treated with 6-month regimens.

The overall prognosis of BCG infection is favorable despite circulating reports of BCG-attributable mortality and morbidity rates of 5.4 % and 7.4 %, respectively [3]. Until now, no precise risk factor has been clearly identified to predict BCG-related complications. There is some evidence to support linking three factors to an increase in mortality: (1) age at diagnosis $\geq$ 65 years, (2) disseminated infection, and (3) vascular involvement (e.g. mycotic aneurysm or infected vascular prosthetic grafts). Since this association has not been proven, it is crucial to rely on prevention strategies for treating high risk patients for intravesical BCG therapy (i.e. old patients and those with pre-existing atherothrombotic aneurysms). A promising decrease in the rate of post-BCG instillation systemic complications has been seen with the prophylactic use of

ofloxacin after each BCG instillation [27].

Even in centers for thoracic oncology, chest wall tumors of any etiology (malignant neoplasms vs. abscesses) represent an absolute rarity. Primary chest wall sarcomas (typically chondrosarcomas and fibrosarcomas in approximately up to 80 % of cases) and recurrent breast cancers account for the most common malignancies [28]. The leading infectious causes for chest wall tumors comprise extrapulmonary tuberculosis and actinomyces (<5% of cases) [29,30]. In either case, a pre-therapeutic biopsy is mandatory. Surgery is primarily used in complicated cases or when percutaneous drainage or excisions for diagnostic purposes are indicated for chest wall abscesses. As a general rule, like in the present case, targeted antibiotic treatment leads to restitutio ad integrum [30]. In contrast with other bacterial abscesses, where surgical drainage is the cornerstone treatment, it is usually avoided in cases of mycobacterial abscesses as healing is hindered and medical treatment is indispensably needed anyway. In terms of extended investigation, special attention must be paid to a thorough medical history, as patients do not regularly report all their diseases or treatments received. We recommend that clinicians critically consider and thoroughly assess all aspects of such cases and, if needed, go beyond conventional paradigms and common diagnostic pathways. A good clinical sense is an indispensable component of diagnosing rare entities. It entails (1) taking both malignant and infectious etiologies into account, (2) quickly collect a sample for work-up, and (3) obtain an extended and thorough medical history.

In conclusion, currently, there are no precise predictors to identify patients at risk of developing BCG infections following its intravesical instillation. Extrapulmonary manifestation of *M. bovis* BCG infection can be a long-term medically serious complication of guideline-conforming intravesical *M. bovis* BCG instillation in NMIBC patients. The diagnosis is based on both micro and molecular biological examinations. Histopathological findings of necrotizing epithelioid cell granuloma can be a clue. Infections with *M. bovis* BCG have a good prognosis if adequately treated. Antimycobacterial treatment should span at least a 6-month period.

CRediT authorship contribution statement

Marc Hartert: Writing – review & editing, Writing – original draft, Project administration, Methodology, Conceptualization. **Claudia Deppe:** Writing – review & editing, Project administration, Conceptualization. **Ludger Fink:** Writing – review & editing, Methodology, Investigation, Data curation. **Jutta Kappes:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors thank Christoph Lange, MD, PhD (Division of Clinical Infectious Diseases, Medical Clinic, Research Center Borstel, Borstel, Germany; German Center for Infection Research (DZIF) Tuberculosis Unit, Borstel, Germany; Respiratory Medicine and International Health, University of Lübeck, Lübeck, Germany; Global TB Program, Baylor College of Medicine and Texas Children's Hospital, Houston, TX, USA) for his excellent suggestions while drafting the manuscript, Peter Kleemann, MD (MVZ für Laboratoriumsmedizin und Mikrobiologie Koblenz-Mittelrhein, Koblenz, Germany) for the provision of microbiological test information, and Philip A. Haddad, MD, MPH, MHA, MSHCI (Professor, LSUHSC-S/Feist-Weiller Cancer Center, Chief of Hematology/Oncology & Research, Overton Brooks VA Medical Center, Shreveport, LA, USA) for proofreading and his friendship.

Ethics approval and consent to participate

Ethics approval was not required. Written informed consent was obtained from the patient reported in this study. All methods were performed in accordance with the Declaration of Helsinki.

Consent for publication

The patient provided informed consent for the publication of this report and any accompanying images.

Availability of data and materials

Materials of the current study are publicly available from the corresponding author upon a reasonable request.

Funding

No funding was obtained for this study.

References

[1] Lobo N, Brooks NA, Zlotta AR, Cirillo JD, Boorjian S, Black PC, et al. 100 years of Bacillus Calmette-Guérin immunotherapy: from cattle to COVID-19. Nat Rev Urol 2021;18:611–22.
[2] Babjuk M, Burger M, Capoun O, Cohen D, Compérat EM, Dominguez Escrig JL, et al. European Association of Urology Guidelines on Non-muscle-invasive Bladder Cancer (Ta, T1, and Carcinoma in Situ). Eur Urol 2022;81:75–94.
[3] Pérez-Jacoiste Asín MA, Fernández-Ruiz M, López-Medrano F, Lumbreras C, Tejido Á, San Juan R, et al. Bacillus Calmette-Guérin (BCG) infection following intravesical BCG administration as adjunctive therapy for bladder cancer: incidence, risk factors, and outcome in a single-institution series and review of the literature. Medicine (Baltimore) 2014;93:236–54.
[4] Flaig TW, Spiess PE, Abern M, Agarwal N, Bangs R, Boorjian SA, et al. NCCN Guidelines® Insights: Bladder Cancer, Version 2.2022. J Natl Compr Canc Netw 2022;20:866–78.
[5] Pettenati C, Ingersoll MA. Mechanisms of BCG immunotherapy and its outlook for bladder cancer. Nat Rev Urol 2018;15:615–25.
[6] Lange C, Aaby P, Behr MA, Donald PR, Kaufmann SHE, Netea MG, et al. 100 years of Mycobacterium bovis bacille Calmette-Guérin. Lancet Infect Dis 2022;22:e2–12.
[7] Liu Y, Lu J, Huang Y, Ma L. Clinical spectrum of complications induced by intravesical immunotherapy of bacillus Calmette-Guérin for bladder cancer. J Oncol 2019;2019:6230409.
[8] Shakhssalim N, Dadpour M, Sharifiaghdas F, Narouie B, Askarpour Kabir S, Sepehran E, et al. Evaluating the effectiveness of intravesical instillation of BCG by modified maintenance method in patients with high-risk Ta and T1 bladder cancer: a randomized clinical trial. Clin Med Insights Oncol 2023;17:11795549231184682.
[9] King B, Singh D, Rathore A, Flenner R, Flemmer M. Case report with systematic literature review on vascular complications of BCG intravesical therapy for bladder cancer. J Clin Med 2022;11:6226.
[10] Green DB, Kawashima A, Menias CO, Tanaka T, Redelman-Sidi G, Bhalla S, et al. Complications of intravesical BCG immunotherapy for bladder cancer. Radiographics 2019;39:80–94.
[11] Donin NM, Lenis AT, Holden S, Drakaki A, Pantuck A, Belldegrun A, et al. Immunotherapy for the treatment of urothelial carcinoma. J Urol 2017;197:14–22.
[12] Han J, Gu X, Li Y, Wu Q. Mechanisms of BCG in the treatment of bladder cancer-current understanding and the prospect. Biomed Pharmacother 2020;129:110393.
[13] Rey-Cárdenas M, Guerrero-Ramos F, Gómez de Liaño Lista A, Carretero-González A, Bote H, Herrera-Juárez M, et al. Recent advances in neoadjuvant immunotherapy for urothelial bladder cancer: what to expect in the near future. Cancer Treat Rev 2021;93:102142.
[14] Kigawa T, Kawai M, Yamaoka H, Kondoh A, Tojo M, Mabuchi T. Two cases of subcutaneous tuberculous granuloma associated with BCG vaccination. Tokai J Exp Clin Med 2020;45:136–8.
[15] Ng YH, Bramwell SP, Palmer TJ, Woo WK. Cutaneous mycobacterial infection post intravesical BCG installation. Surgeon 2006;4:57–8.
[16] Kureshi F, Kalaaji AN, Halvorson L, Pittelkow MR, Davis MD. Cutaneous complications of intravesical treatments for bladder cancer: granulomatous inflammation of the penis following BCG therapy and penile gangrene following mitomycin therapy. J Am Acad Dermatol 2006;55:328–31.
[17] Keijsers RR, Bovenschen HJ, Seyger MM. Cutaneous complication after BCG vaccination: case report and review of the literature. J Dermatolog Treat 2011;22:315–8.
[18] Serretta V, Scalici Gesolfo C, Alonge V, Cicero G, Moschini M, Colombo R. Does the compliance to intravesical BCG differ between common clinical practice and international multicentric trials? Urol Int 2016;96:20–4.

[19] Gonzalez OY, Musher DM, Brar I, Furgeson S, Boktour MR, Septimus EJ, et al. Spectrum of bacille Calmette-Guérin (BCG) infection after intravesical BCG immunotherapy. Clin Infect Dis 2003;36:140–8.
[20] Compérat E, Amin MB, Cathomas R, Choudhury A, De Santis M, Kamat A, et al. Current best practice for bladder cancer: a narrative review of diagnostics and treatments. Lancet 2022;400:1712–21.
[21] Kamat AM, Li R, O'Donnell MA, Black PC, Roupret M, Catto JW, et al. Predicting response to intravesical bacillus calmette-guérin immunotherapy: are we there yet? A systematic review. Eur Urol 2018;73:738–48.
[22] Niwa N, Kikuchi E, Matsumoto K, Kosaka T, Mizuno R, Oya M. Purified protein derivative skin test prior to bacillus Calmette-Guérin therapy may have therapeutic impact in patients with nonmuscle invasive bladder cancer. J Urol 2018;199:1446–51.
[23] Poletajew S, Zapała P, Radziszewski P. Safety and efficacy of intravesical bacillus Calmette-Guérin immunotherapy in patients with non-muscle-invasive bladder cancer presenting with asymptomatic bacteriuria: a systematic review. Urol Int 2017;99:1–5.
[24] Nasrin R, Uddin MKM, Kabir SN, Rahman T, Biswas S, Hossain A, et al. Xpert MTB/RIF Ultra for the rapid diagnosis of extrapulmonary tuberculosis in a clinical setting of high tuberculosis prevalence country and interpretation of 'trace' results. Tuberculosis 2024;145:102478.
[25] Druszczynska M, Seweryn M, Wawrocki S, Pankowska A, Godkowicz M, Kowalewska-Pietrzak M. The interferon-gamma release assay versus the tuberculin skin test in the diagnosis of mycobacterium tuberculosis infection in BCG-vaccinated children and adolescents exposed or not exposed to contagious TB. Vaccines 2023;11:387.
[26] Del Giudice F, Asero V, Bologna E, Scornajenghi CM, Carino D, Dolci V, et al. Efficacy of different bacillus of Calmette-Guérin (BCG) strains on recurrence rates among intermediate/high-risk non-muscle invasive bladder cancers (NMIBCs): single-arm study systematic review, cumulative and network meta-analysis. Cancers (Basel) 2023;15:1937.
[27] Numakura K, Kobayashi M, Ishida T, Okane K, Suzuki K, Shimoda N, et al. Effect of levofloxacin on the efficacy and adverse events in intravesical bacillus Calmette-Guerin treatment for bladder cancer: results of a randomized, prospective, multicenter study. Eur Urol Focus 2022;8:1666–72.
[28] Dai Z, Maihemuti M, Sun Y, Jiang R. Resection and reconstruction of huge tumors in the chest wall. J Cardiothorac Surg 2022;17:116.
[29] Alzarrad A, Naeem S, Rovida S. Sonographic features of a tuberculous cold abscess: a case report and literature review. POCUS J 2023;8:48–51.
[30] Hartert M, Wolf M, Ferber J, Huertgen M. Thoracoabdominal actinomycosis - Chameleon through kaleidoscope. Respir Med Case Rep 2020;31:101281.