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ORIGINAL ARTICLE

Destructive Mono-Arthritis Caused by *Mycobacterium bovis* during Treatment with Pembrolizumab in a Patient Previously Treated with BCG Instillations for Bladder Cancer: A Case Report

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Abstract

Immune checkpoint inhibitor (ICI) treatment is an integral part of second line treatment of patients with urothelial carcinoma (UC) as well as in first line in cisplatin-ineligible patients with PD-L1 positive tumours. A substantial proportion of patients with bladder cancer have been treated with intravesical *Mycobacterium bovis* BCG in the past. Although it is rare, disseminated infections with *Mycobacterium bovis* have been described, but not in association with ICI treatment. We herein report a case of destructive monoarthritis caused by *Mycobacterium bovis* in a patient previously treated with intravesical BCG and a recent initiation of the ICI pembrolizumab in first line for metastatic UC. A culture of synovial fluid from the involved wrist was positive for *Mycobacterium bovis*. Based on whole genome sequencing based-subtyping, the identified Mycobacterium was shown to be related with the previous BCG instillations. Because of severe complaints and progressive destruction of the patients' wrist, it was decided to interrupt the pembrolizumab. At that moment, following the seventh cycle of pembrolizumab, evaluation showed a partial disease response. Following systemic treatment with triple combination therapy (Isoniazid, Rifampicin, Ethambutol) and surgery, the complaints of the wrist gradually improved. This is the first report describing a disseminated Mycobacterium bovis infection in a patient treated with an ICI and previous BCG instillations for bladder cancer. This is of relevance, because an increasing number of bladder cancer patients, previously treated with BCG instillations, will be treated with an ICI in advanced disease setting.

Keywords

Immune Checkpoint inhibitor, Bacillus Calmette-Guerin, *Mycobacterium bovis*, Arthritis, Bladder cancer

List of Abbreviations

BCG: Bacillus Calmette-Guérin; CIS: Carcinoma *in situ*; ICI: Immune checkpoint inhibitor; CTCAE: Common Terminology Criteria for Adverse Events; PD-1: Programmed death-1; SNPs: Single nucleotide polymorphisms; TBC: Tuberculosis; TNF: Tumor necrosis factor; TURB: Transurethral resection of the bladder; UC: Urothelial carcinoma

Background

Patients with non-muscle invasive urothelial cancer can be treated with intravesical administration of Bacillus Calmette-Guérin (BCG), a live attenuated strain of *Mycobacterium bovis* (*M. bovis*). In general, this treatment is well tolerated, although disseminated BCG infection can occur. This is uncommon but a well-recognized complication of intravesical BCG treatment [1-4]. The underlying mechanism by which intravesical BCG leads to systemic infections is not fully understood. The rate of osteoarticular side effects after intravesical BCG therapy ranges from 0.5 to 1 percent [5].

Despite treatment with intravesical BCG and TURB, approximately 40% of the patients progress to muscle invasive disease and progression to metastatic urothelial cancer occurs in 20 to 30% of these patients [6,7]. In patients with metastatic urothelial cell carcinoma with progressive disease following or during first line platinum based chemotherapy, the FDA approved treatment

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Table 1: Differences in SNPs (number) based on WGS.

	NLA001900744	*M. bovis* BCG vaccin strain 1	*M. bovis* BCG vaccin strain 2	*M. bovis* BCG installation strain	WGS fingerprint type
NLA001900744	-				A003
A004	27	-			A004
A005	61	46	-		A005
A003	5	24	58	-	A003

A003: *M. bovis* BCG installation strain; A004: *M. bovis* BCG vaccin strain 1; A005: *M. bovis* BCG vaccin strain 2; NLA001900744: *M. bovis* strain of the patient

with an immune checkpoint inhibitor (ICI) targeting PD1 or PD-L1 (pembrolizumab, atezolizumab, durvalumab, avelumab, nivolumab) as second line treatment [8-12]. There have been only a few reports of a flare of tuberculosis in patients treated with immune checkpoint inhibitors (ICIs), but no reports of *M. bovis* related infections [13-17].

Here, we present a patient previously treated with intravesical BCG who developed a fulminant *M. bovis* related mono-arthritis during treatment with pembrolizumab for advanced bladder cancer.

Case Presentation

Our 64-year-old Caucasian male patient was diagnosed in January 2017 with a non-invasive papillary carcinoma of the urinary bladder (cTaG3). He was treated with 6 cycles of intravesical BCG. In May 2017 a re-transurethral resection of the bladder (TURB) showed a T1G3 urothelial cell carcinoma for which he received re-induction with 6 cycles of intravesical BCG. Unfortunately, the patient developed metastatic disease in June 2019. As a results of preexisting grade 2 tinnitus the patient was deemed to be cisplatinum ineligible and therefore PD-L1 expression was assessed by immunohistochemistry on tissue derived from the earlier TURB by using the Dako PD-L1 IHC 22C3 test. Based on a combined positive score (CPS) result of >10, the patient was candidate to be treated with pembrolizumab. In July 2019, treatment with pembrolizumab 200 mg (q3w) was initiated. Response evaluation following cycle 4 showed a partial response based on RECIST 1.1. [18]. Adverse events were fatigue grade 1 and a rash grade 1 according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 [19]. The patient reported also increasing pain and impaired movement of his left wrist.

Six months before the initiation of the pembrolizumab the patient presented at the outpatient rheumatology clinic with a slight synovial swelling of the left wrist without impairment of the joint. Retrospectively the first complaints of the wrist started some 18 months before and gradually evolved over time. Analysis revealed a markedly positive IgM-rheumatoid factor and a negative anti-CCP and no abnormalities were seen with plain radiography of the wrist. Treatment with a non-steroidal anti-inflammatory drug (ibuprofen) was initiated. Because of an insufficient effect, the patient was subsequently treated with a triamcinolone injection of the wrist. The working diagnosis of his rheumatologist was a monoarthritis either as a first sign of a starting rheumatoid arthritis or otherwise a paraneoplastic syndrome. Awaiting further diagnostic procedures and the subsequent decision concerning the treatment of the patients' advanced urothelial carcinoma, it was decided not to start disease modifying ant rheumatic drugs but to continue with local intra-articular triamcinolone injection when indicated. Two weeks following the first cycle of pembrolizumab, the patient developed a clear increase of complaints of his wrist for which he received an intra-articular triamcinolone injection again. This time without significant effect. Plain radiography of the wrist showed an increasing osteopenia. An MRI scan and a diagnostic puncture with aspiration of the synovial fluid of the left wrist were performed. The MRI scan showed a very active synovial inflammation and serious erosive changes of the intercarpal and carpometocarpal joints. The culture of the synovial fluid turned out to be positive with *M. bovis*. The identified *M. bovis* strain was compared with the *M. bovis* strain used in BCG instillations, by using whole genome sequencing (Table 1). In this analysis WGS patterns were compared between 2 available BCG vaccination strains, 1 BCG instillation strain and the strain of our patient. The latter and the BCG instillation strain turned out to differ only 5 single nucleotide polymorphisms (SNPs). To show a correlation, strains should differ less than 12 SNPs. Based on the performed analysis, it can be concluded that the arthritis in our patient was caused by an *M. bovis* infection as a consequence of his previous treatment with BCG instillations.

Triple combination treatment was started with Isoniazid, Rifampicin and Ethambutol, with discontinuation of Ethambutol after one month based on the resistance pattern of the identified M. bovis. Unfortunately, two months later the complaints aggravated caused by an ongoing bacterial arthritis with extension to the ulnocarpal, intercarpal and carpometocarpal joints with secondary abscess formation for which the patient underwent surgical debridement and synoviectomy. After recovery from surgery, the patient remained free of complaints. Isoniazid and Rifampicin were discontinued 9 months after initiation. The pembrolizumab was kept interrupted and 8 months later there still is an ongoing partial response of this treatment.

Discussion and Conclusions

Serious systemic side effects of treatment with intravesical BCG installations are rare, with an incidence of pneumonitis or hepatitis of 0.7% and osteoarticular side effects of 0.5% [20,21]. Although one study reported an incidence of 4.3% of systemic BCG infection [22], disseminated BCG-induced infections can manifest many years later [21]. It has been reported that BCG can persist in the bladder for more than one year after intravesical BCG installation [20]. Osteoarticular side effects are mostly manifested by reactive arthritis, but an infectious arthritis by *M. bovis* can also occur, predominantly in the lower extremities [22-26].

The mechanism of action of BCG-induced systemic infections is unclear. Even the exact working mechanism of treatment with intravesical of BCG is unknown. It is assumed that BCG installation triggers a variety of local immune responses, which includes the following: Induction of mononuclear cell infiltrate, consisting of CD4 T cells and macrophages; increased expression of interferon gamma) in the bladder; direct suppression of tumor growth; elevating urinary cytokine levels including interleukin-1, -2, -8 and 12, interferon-gamma, tumor necrosis factor (TNF) alpha and tumor necrosis factor apoptosis inducing ligand [27]. In synovial fluid and tissue in patients with BCG arthritis antigen-specific CD4+ and CD8+ T cells have been found [24].

To the best of our knowledge reactivation of latent *M. bovis* infection has not been described in patients treated with an ICI. Aggravation of latent mycobacterium infections during treatment with an ICI is a concern of clinicians. It has been described that reactivation of latent *M. tuberculosis* (TBC) infections in patients treated with PD-1 targeted therapy is possible. One article summarized 11 case reports documenting patients treated with PD-1 inhibitors developing acute pulmonary tuberculosis [16]. In our patient there were no signs of pulmonary involvement. Patients with latent TBC seem to develop reactivation and symptoms within 6 months of PD-1/PD-L1 inhibition [15]. This was also the case in our patient. A retrospective analysis showed an association between the use of PD-1/PD-L1 inhibitors and increased TBC and atypical mycobacterial infection, with a reporting odds ratio of 1.79 and 5.49 respectively [17].

There are hypotheses about potential mechanisms of TBC reactivation caused by immune checkpoint inhibition. It has been hypothesized that progression from latent TBC to an active infection is a consequence of failure of the immune system, as demonstrated by increased incidence in patients with an HIV infection or after anti-tumor necrosis factor treatment. PD-1 inhibition has been suggested as a host-directed therapy in TBC, on the basis that the PD-1 pathway may inhibit an effective host response [14]. In mouse models enhanced CD4 activity in absence of PD-1 surveillance exacerbates tuberculosis. In human patients with active TBC, PD-1 was described to be increased on CD4+ T cells but not on CD8+ T cells compared to healthy controls, while effective anti-tuberculosis treatment was associated with downregulation of PD-1 on CD4+ T cells [28,29]. One study suggests TNF-alpha may be the driver of TBC reactivation associated with PD-1 inhibition [30].

In conclusion, we present a patient with a proven BCG-instillation related *M. bovis* mono-arthritis in whom a relatively indolent inflammation changed into a fulminant and severe arthritis during treatment with an immune checkpoint inhibitor. The aggravation of the inflammation could be a result of the ICI used. To our knowledge this is the first case in literature. Clinicians should be aware of this complication since an increasing number of patients will be treated with ICI in advanced urothelial cancer setting after previous treatment with BCG instillations.

Compliance with Ethical Standards

Conflict of interest

The authors declare that they have no conflict of interest.

Informed consent

Written informed consent was obtained from the patient for publication of this case report.

Declarations

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Availability of date and material

Not applicable.

Code availability

Not applicable.

Authors' Contributions

DR, SH and PL treated the patient. CE and DR wrote the case report. All authors made substantial contributions to discussion, review and revision. All authors read and approved the final manuscript.

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