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Case Report

Combined Application of Nivolumab and Intravesical Bacillus Calmette-Guérin Led to Acute-Onset Type 1 Diabetes

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Keywords
Type 1 diabetes · Nivolumab · Lung cancer · Intravesical BCG · PD-L1

Abstract
We report a case of acute-onset type 1 diabetes due to combined application of nivolumab and intravesical Bacillus Calmette-Guérin (BCG). An 84-year-old woman underwent lung resection for pulmonary squamous cell carcinoma. She had been treated for type 2 diabetes and later experienced lung cancer recurrence. She was started on nivolumab treatment, and complete response was achieved for one year. However, during this time, she was diagnosed with superficial bladder cancer and underwent surgery but experienced recurrence. After one month of intravesical BCG instillation, the patient developed acute-onset type 1 diabetes. Thus, we recommend that combined application of nivolumab and intravesical BCG be avoided.

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Introduction

Nivolumab is a standard therapy for metastatic lung cancer. Type 1 diabetes mellitus (T1DM) is one of the side effects of nivolumab administration. Intravesical Bacillus Calmette-Guérin (BCG) is a standard therapy for high-risk superficial bladder cancer, major risk factors of which include smoking and lung cancer. We hypothesize that many patients have cancer of both the lung and bladder. These patients may be candidates for combined application of nivolumab and intravesical BCG. Here, we experienced a case of acute-onset T1DM after combined application of nivolumab and intravesical BCG. According to the drug information, the combination of BCG and nivolumab should be administered with caution. Thus, we report this case to attract attention to the risks of coadministration.

Case Report

An 84-year-old woman underwent lung resection for pulmonary squamous cell carcinoma in May 2016. She had been treated for type 2 diabetes with metformin and alogliptin and had a smoking history of 10 pack-years. In November 2016, pulmonary and left axillary lymph node metastases were found. The former shrank after administration of tegafur/gimeracil/oteracil; however, the latter increased. More than 75% of cancer cells stained positively for programmed cell death ligand 1 (PD-L1) using the PD-L1 IHC 22C3 pharmDx (Dako, Carpinteria, CA, USA). In September 2017, she was started on the programmed cell death 1 (PD-1) inhibitor, nivolumab (3 mg/kg) once every 2 weeks, and complete response was achieved (Fig. 1). In January 2018, macroscopic hematuria was found. Cystoscopy revealed superficial bladder cancer. Transurethral resection of the bladder tumor was performed, but relapse occurred. From September 2018, Immunobladder® 80 mg intravesical BCG (Japan BCG Laboratory, Tokyo, Japan) was instilled six times weekly to prevent recurrence. In September 2018, the patient suffered a left ischium fracture and took non-steroidal anti-inflammatory drug (NSAID) tablets. In October 2018, she suffered from herpes zoster, and valaciclovir (3,000 mg/day) was administered. On the first day of the 26th nivolumab administration, her plasma glucose was 448 mg/dL, which increased to 951 mg/dL 4 days later. Her consciousness was normal. Her serum C-peptide level was 0.2 ng/mL (reference range, 0.8–2.5 ng/mL), and her urinary C-peptide level was below 1.0 μg/L; however, ketoacidosis was not present. She tested negative for glutamic acid decarboxylase, and her glycated hemoglobin level was 6.5% (reference range, 4.6–6.2%). T1DM was diagnosed and insulin therapy was started, whereas nivolumab administration was stopped. After 6 months, lung cancer recurrence was not found (Fig. 2).

Discussion

Several cases of fulminant T1DM or acute-onset T1DM related to PD-1 inhibitors have been reported [1, 2]. PD-L1 is expressed on pancreatic endocrine beta cells as well as cancer cells. Peripheral immune tolerance is achieved between PD-L1 on pancreatic beta cells and PD-1 on T lymphocytes [3, 4]. In our patient, T1DM did not develop following 26 doses of nivolumab alone; however, following six combined administrations of nivolumab and intravesical BCG, T1DM developed.

Intravesical BCG mainly acts via the innate immunity. Toll-like receptors in the urinary bladder mucosa recognize lipopolysaccharides and lipoproteins on the BCG membrane. Subsequent cytokine expression activates neutrophils, dendritic cells, macrophages, and natural killer cells [5]. We suspected that peripheral immune tolerance between PD-1 and PD-L1 was blocked by nivolumab. Moreover, administration of intravesical BCG activated the innate immunity. As a result, activated T lymphocytes destroyed pancreatic beta cells, and T1DM developed. Viral infection has been thought to lead to T1DM, but we could not find a report on T1DM caused by herpes zoster.

Conclusion

We hypothesize that the combined usage of nivolumab and intravesical BCG increased the chance of side effects due to nivolumab. We recommend that the combined application of nivolumab and intravesical BCG be avoided.

Statement of Ethics

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

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors reviewed the manuscript and approved the final version of the manuscript.

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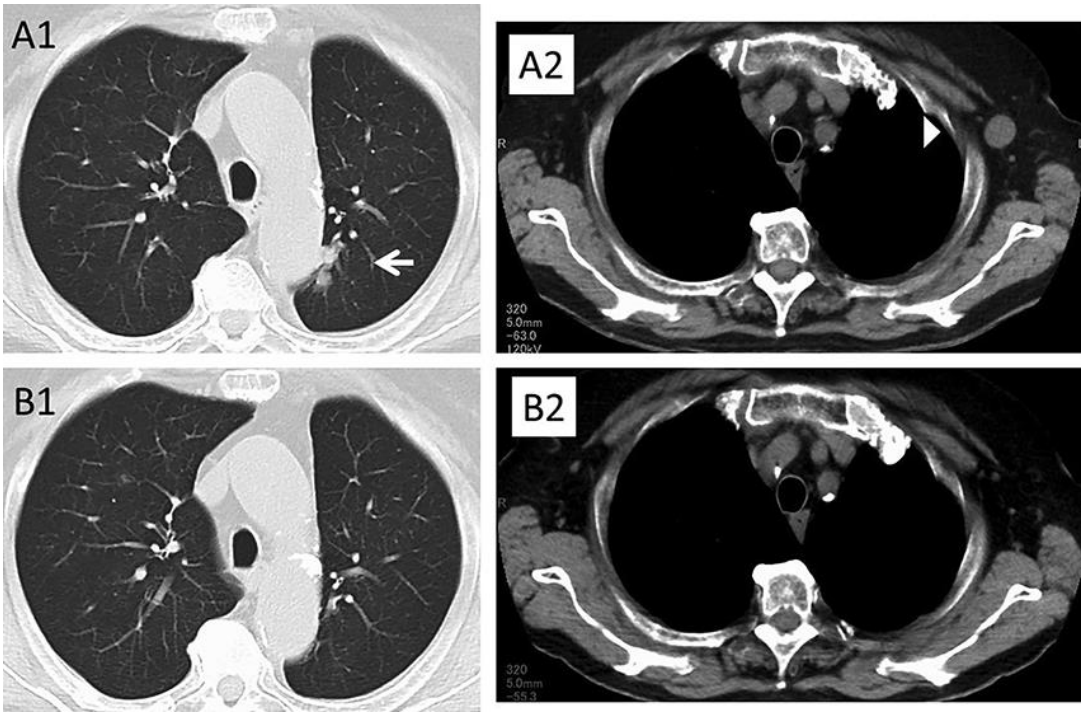

Fig. 1. Chest computed tomography (CT) before and after nivolumab administration. (**A1**, **A2**) CT image before nivolumab administration revealing pulmonary metastasis (arrow) and left axillary lymph node metastasis (arrowhead). (**B1**, **B2**) CT image 9 months after nivolumab administration.

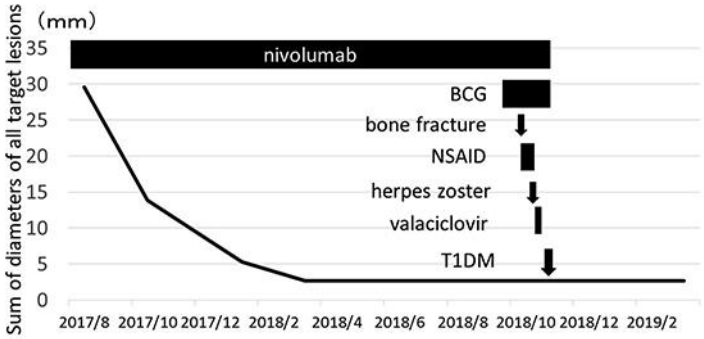

Fig. 2. Sum of diameters of all target lesions during administration of nivolumab and intravesical BCG. BCG, Bacillus Calmette-Guérin; NSAID, non-steroidal anti-inflammatory drug; T1DM, type 1 diabetes mellitus.