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CASE REPORT

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Diabetic ketoacidosis shortly after COVID-19 vaccination in a non–small-cell lung cancer patient receiving combination of PD-1 and CTLA-4 inhibitors: A case report

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Abstract

We describe a case of diabetic ketoacidosis (DKA) shortly after the SARS-CoV-2 (COVID-19) vaccination in a 65-year-old woman with non–small-cell lung cancer under a combination treatment of programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors. She had no history of diabetic mellitus. A few days after the second shot of COVID-19 vaccination, she developed DKA. We speculate that the immune-related adverse event and immunogenicity of vaccination synergistically induced DKA.

KEYWORDS

COVID-19 vaccination, diabetic ketoacidosis, immune checkpoint inhibitor, immune-related adverse event

INTRODUCTION

Over the last years, immune checkpoint inhibitors (ICIs) brought about a paradigm shift for the treatment in various types of cancer. Recently, the combination of nivolumab and ipilimumab (NIC) was shown to improve the prognosis in patients with non–small-cell lung cancer (NSCLC) compared to cytotoxic chemotherapy, irrespective of the tumor programmed death-ligand 1 (PD-L1) expression level in the first line setting (CheckMate 227).[1] ICIs cause immune-related adverse events (irAE), including type 1 diabetes mellitus (DM). In the CheckMate 227 trial, endocrine disorders of any grade were seen in 23.8% of the NIC therapy group and in 13.0% of the nivolumab monotherapy group.

SARS-CoV-2 infection (COVID-19) is currently a worldwide pandemic. The safety of vaccination in cancer patients receiving ICIs remains unknown.

We describe a case of diabetic ketoacidosis (DKA) shortly after the second shot of BNT162b2 mRNA COVID-19 vaccine (Comirnaty, Pfizer/BioNTech SE) in a patient with NSCLC who had no history of DM.

CASE REPORT

A 65-year-old woman was diagnosed with lung adenocarcinoma with brain metastases. She had no candidate driver oncogene for targeted therapy. PD-L1 tumor proportion score was negative. Although she had intraductal papillary mucinous carcinoma (IPMC), she did not have DM at the diagnosis and thereafter. IPMC was closely observed. Because asymptomatic panhypopituitarism due to metastatic lung cancer was detected at the diagnosis, she started hydrocortisone, levothyroxine, and desmopressin. Thereafter, the NIC therapy was introduced. She received 6 cycles of the treatment over 7 months and the disease was totally controlled (Figure 1(a)). She was vaccinated for COVID-19 twice within a 3-week interval. After the first shot, she had a low-grade fever and painful joints, and erythema appeared around the injection site. A few days after the second shot, she complained of fatigue, appetite loss, and extensive erythema on the trunk. As shown in Table 1, the laboratory tests indicated DKA. Although plasma C-peptide level was within the normal range (0.8–2.5 ng/mL), urine C-peptide level, which normally ranges 42.0 to 79.0 μg/day, was

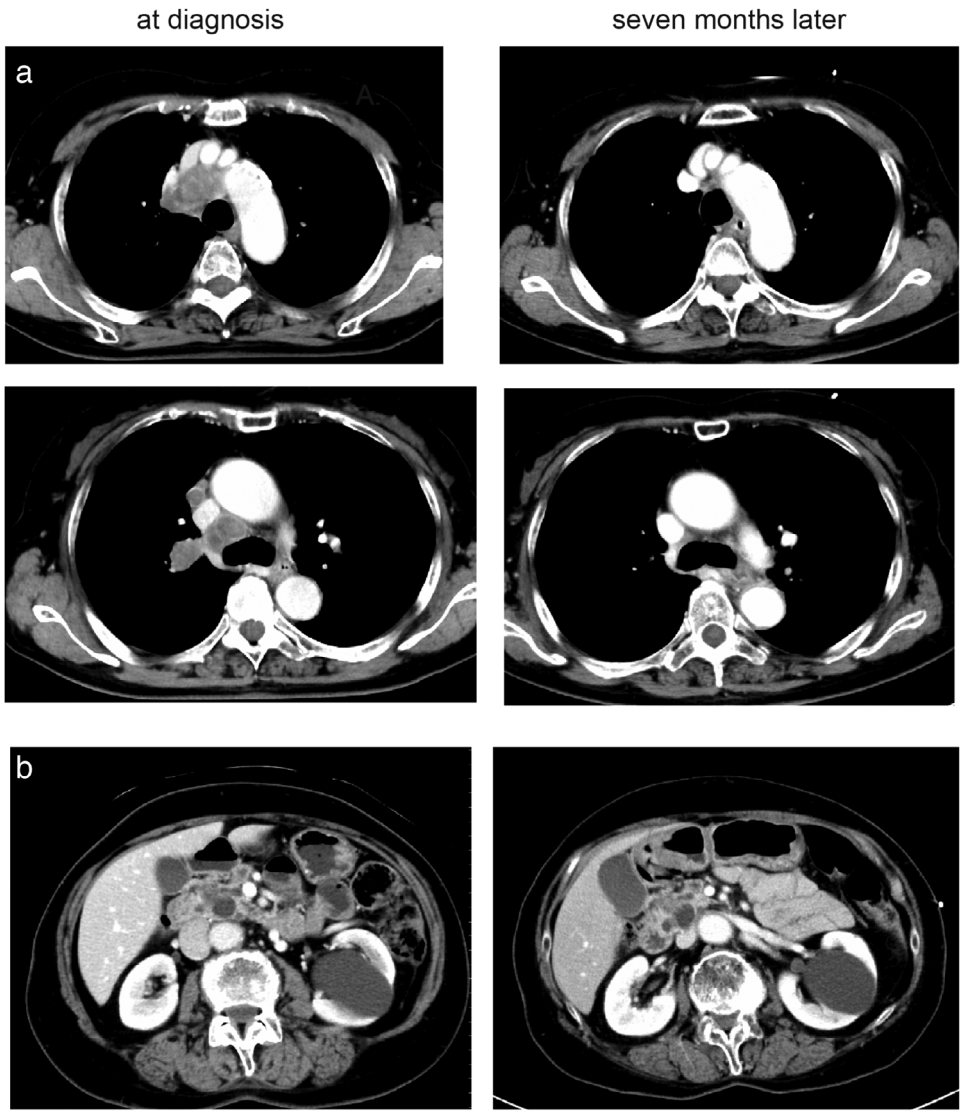

FIGURE 1 CT images of the thoracic lesion and IPMN at diagnosis and 7 months after the introduction of ICIs. (a) CT images of the thoracic lesion at diagnosis (on the left side) and 7 months after introduction of ICIs (on the right side). NSCLC was totally controlled after 6 cycles of the combination therapy with nivolumab and ipilimumab. (b) CT images of IPMN lesion at diagnosis (on the left side) and 7 months after introduction of ICIs (on the right side). No progression of IPMN was observed over 7 months

markedly decreased. All levels of serum anti-IA-2 (insulinoma-associated protein-2), insulin, and glutamic acid decarboxylase (GAD) antibody were normal. Serum anti-zinc-transporter 8 and islet cell antibody was not acquired. These data suggest acute onset of type 1 DM. Computed tomographic images of the abdomen revealed no progression of IPMN (Figure 1(b)). We concluded that DKA was immune-related and attributable to COVID-19 vaccination during the NIC therapy, not to IPMN. She was finally discharged with insulin-dependent DM. She reassumed receiving nivolumab monotherapy. Thus far, she has not presented with any other irAEs.

DISCUSSION

BNT162b2 mRNA COVID-19 vaccine is the first approved COVID-19 vaccine, containing lipid nanoparticles that encapsulate mRNA encoding SARS-CoV-2 spike protein. Once penetrating the cell surface, mRNA is translated into the spike protein, whereby degraded peptides are presented by MHC molecules and trigger an immune response. The clinical trial demonstrated that efficacy in preventing COVID-19 was 95%, and the incidence of severe adverse events was low.[2] However, cancer patients accounted for only 4% of the participants. The safety of this vaccine in cancer patients, especially receiving ICIs, has not been fully evaluated. Recently, short-term safety of the vaccine in these patients were reported.[3] The proportion of manifestation regarding the systemic side effects after the second inoculation increased in the subjects receiving ICIs compared to healthy subjects. However, irAE was not described. Recently, six cases developing irAEs after COVID-19 vaccination have been reported.[4] DM has not been described. Our present case and the previous report had in common that the duration from initiation of ICIs to the irAE events is no less than a few months and irAEs occurred within a few days after COVID-19 vaccination. According to 4-year data from CheckMate 227 trial, DM occurred in 0.9% (17/1994) of patients who received nivolumab monotherapy and 2.7%

TABLE 1 Laboratory findings on admission

Blood counts	Biochemistry
WBC, 8900/μL	TP, 7.9 g/dL
Hb, 16.1 g/dL	Na, 121 mEq/L
Plt, 192 × 10^3 /μL	K, 6.0 mEq/L
	Cl, 86 mEq/L
Arterial blood gas analysis	BUN, 35 mg/dL
pH, 7.27	Cr, 1.1 mg/dL
pCO_2, 15.0 mm Hg	AST, 15 IU/L
pO_2, 90.0 mm Hg	ALT, 18 IU/L
HCO_3^-, 7.2 mmol/L	Blood glucose, 837 mg/dL
	HbA_1C, 9.4%
Serology	Plasma osmolality, 315 mOsm/kg
Anti-GAD antibody, negative	Urine osmolality, 551 mOsm/kg
Immunoreactive insulin, 3.3 μU/mL	Urine C-peptide, 2.9 μg/day
Plasma C-peptide, 0.96 ng/mL	Urinary glucose, ≧500 mg/gCr
ACTH, <1.5 pg/mL	Urinary ketone, 2+
Cortisol, 0.16 μg/dL	
Anti-IA-2 antibody, >30 U/mL	
Anti-insulin antibody, <125 nU/mL	

(15/666) of patients who received NIC therapy, respectively.[5] DKA occurred in two patients of the monotherapy group and none of the patients in the combination therapy group. In the endocrine disorders, DKA is extremely rare. On the other hand, COVID-19 vaccination was reported to cause immune-mediated diseases (IMD) resembling irAEs.[6] Three cases presenting with DKA or hyperosmolar hyperglycemic syndrome just after COVID-19 vaccination were also reported.[7] In the report, all three of the cases finally withdrew insulin. In our present case, the patient became insulin-dependent permanently. This indicated that the deterioration of DKA in our case was not simply due to transient adverse event by vaccination. We speculated that the sudden onset of DKA and permanent insulin dependency might be induced by synergy of irAE and vaccination immunogenicity. The French Society for ImmunoTherapy of Cancer (FITC) raises an alert that cancer patients under ICIs receiving vaccination should be monitored closely.[8] There are two hypotheses for IMD. One hypothesis is that ICIs might have boosted the vaccine immunogenicity. Mucosal-associated invariant T (MAIT) cells, which exert innate immune response against viruses, are reported to be circulating in the blood of patients responding to ICIs. This might accelerate the vaccine immunogenicity.[9] The other hypothesis is that vaccination boosts irAEs. Moreover, COVID-19 influenza vaccination of cancer patients receiving ICIs are reported to be at possible risk for irAEs.[10] During tumor cell death, neoantigen as well as self-antigen epitope spread, followed by antigen presentation. During epitope spreading with checkpoint therapy, not only tumor immunity, but also autoimmunity against nonmalignant tissues are induced.[11] Furthermore, immunization was shown to boost production of antibodies including autoantibodies leading to irAEs.[12]

CONCLUSION

We demonstrated the non–small-cell lung cancer patients under nivolumab and ipilimumab combination therapy who developed diabetic ketoacidosis shortly after COVID-19 vaccination. We should pay more attention to the immune-mediated diseases after COVID-19 vaccination in cancer patients under immunotherapy.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

All authors have read and approved the final manuscript. All authors have contributed significantly and abided with the latest guidelines of the International Committee of Medical Journal Editors. T.M. prepared the manuscript. H.T., T.F., and K.T. treated and observed the patients in Hirosaki University. S.T. and S.T. reviewed the manuscript.

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REFERENCES

1. Hellmann MD, Paz-Ares L, Bernabe Caro R, Zurawski B, Kim SW, Carcereny Costa E, et al. Nivolumab plus Ipilimumab in advanced non–Small-cell lung cancer. N Engl J Med. 2019;381(21):2020–31.
2. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020;383(27):2603–15.
3. Waissengrin B, Agbarya A, Safadi E, Padova H, Wolf I. Short-term safety of the BNT162b2 mRNA COVID-19 vaccine in patients with cancer treated with immune checkpoint inhibitors. Lancet Oncol. 2021;22(5):581–3.
4. Chen Y-W, Tucker MD, Beckermann KE, Iams WT, Rini BI, Johnson DB. COVID-19 mRNA vaccines and immune-related adverse events in cancer patients treated with immune checkpoint inhibitors. Eur J Cancer. 2021;155:291–3.
5. https://news.bms.com/news/details/2021/Four-Year-Data-from-Phase-3-CheckMate–227-Trial-Show-Durable-Long-Term-Survival-with-Opdivonivolumab-Plus-Yervoy-ipilimumab-in-Patients-with-Non-Small-Cell-Lung-Cancer-with-PD-L1-Expression-1/default.aspx
6. Watad A, De Marco G, Mahajna H, et al. Immune-mediated disease flares or new-onset disease in 27 subjects following mRNA/DNA SARS-CoV-2 vaccination. Vaccine. 2021;9(5):1–23.
7. Lee HJ, Sajan A, Tomer Y. Hyperglycemic emergencies associated with COVID-19 vaccination: a case series and discussion. J Endocr Soc. 2021;5(11):1–6.
8. Gauci M-L, Coutzac C, Houot R, Marabelle A, Lebbé C. SARS-CoV-2 vaccines for cancer patients treated with immunotherapies: recommendations from the French society for ImmunoTherapy of cancer (FITC). Eur J Cancer. 2021;148:121–3.

9. Malek AE, Cornejo PP, Daoud N, Alam M. The mRNA COVID-19 vaccine in patients with cancer receiving checkpoint inhibitor therapy: what we know and what we don't. Immunotherapy. 2022;14(2):91–4.
10. Läubli H, Balmelli C, Kaufmann L, et al. Influenza vaccination of cancer patients during PD-1 blockade induces serological protection but may raise the risk for immune-related adverse events. J Immunother Cancer. 2018;6(40):1–10.
11. June CH, Warshauer JT, Bluestone JA. Is autoimmunity the Achilles' heel of cancer immunotherapy? Nat Med. 2017;23(5):540–7.
12. Kwek SS, Dao V, Roy R, Hou Y, Alajajian D, Simko JP, et al. Diversity of antigen-specific responses induced in vivo with CTLA-4 blockade in prostate cancer patients. J Immunol. 2012;189(7):3759–66.

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