

Fulminant type I diabetes mellitus associated with nivolumab in a patient with relapsed classical Hodgkin lymphoma

Wataru Munakata¹  · Ken Ohashi² · Nobuhiko Yamauchi¹ · Kensei Tobinai¹

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Abstract We report the case of a patient with relapsed classical Hodgkin lymphoma who developed fulminant type I diabetes mellitus as a severe adverse event of treatment with the anti-programmed cell death-1 (PD-1) antibody, nivolumab. On the first day of the sixth cycle, the blood glucose level was markedly elevated (375 mg/dL). Although neither ketoacidosis nor ketonuria was detected, the markedly acute onset of the hyperglycemia was consistent with the typical clinical course of fulminant type I diabetes mellitus, and this diagnosis was supported by clinical data. All autoantibodies associated with type I diabetes mellitus were negative. The endogenous insulin secretion ceased completely within 2 weeks. After the blood glucose level was brought under control, nivolumab was resumed and continued without other major adverse events. Human leukocyte antigen (HLA) analysis revealed that the patient carried the HLA-B*4002 haplotype, a susceptibility allele for this type of diabetes mellitus. This case suggests that fulminant type I diabetes mellitus may be triggered by nivolumab in patients with a genetic background associated with the condition, warranting careful future consideration of this particular adverse event.

Keywords Fulminant type I diabetes mellitus · Anti-PD-1 antibody · Immune-related adverse events · Nivolumab

Introduction

Recent clinical trials have revealed that anti-programmed cell death-1 (PD-1) antibodies are highly effective against relapsed or refractory classical Hodgkin lymphoma (cHL) [1] and several types of solid tumors [2–4]. Anti-PD-1 antibodies augment the host's immunological reaction against tumor cells and, hence, exhibit anti-tumor activities. On the other hand, immune-related adverse events due to blocking of the PD-1 molecule occur as a consequence of impaired self-tolerance associated with the loss of T-cell inhibition. The main immune-related adverse events of anti-PD-1 antibody therapy include pneumonitis, colitis, hepatitis, and thyroiditis [5]. These conditions are generally manageable via the prompt administration of corticosteroids or hormone replacement therapy. Here, we report a case in which a patient with relapsed cHL developed fulminant type I diabetes mellitus as a severe adverse event of anti-PD-1 antibody treatment, specifically with nivolumab.

Case report

A 72-year-old Japanese male with mixed cellularity cHL was enrolled in a Japanese phase II study of nivolumab (ONO-4538-15) [6] and began to receive nivolumab at a dose of 3 mg per kilogram every 2 weeks until disease progression, in accordance with the protocol. He had undergone six cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), and the most recently employed regimen was brentuximab vedotin monotherapy as the second-line treatment, but his disease was progressed. He did not have a history of diabetes mellitus. After the administration of four cycles of nivolumab, a whole-body

✉ Wataru Munakata
wmunakat@ncc.go.jp

¹ Department of Hematology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan

² Department of General Internal Medicine, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan

Fig. 1 The time-dependent changes in the patient's urinary C-peptide excretion values (green), blood glucose levels (blue), and lipase levels (orange). Endogenous insulin secretion ceased completely within 2 weeks

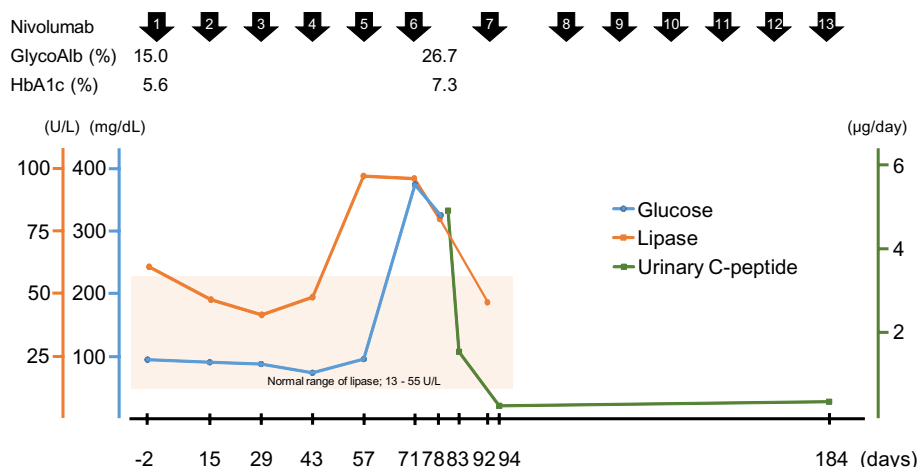
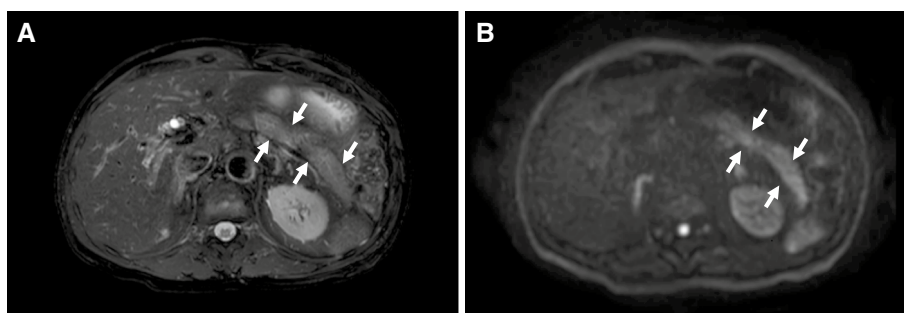


Fig. 2 MRI findings. The pancreas was diffusely enlarged on a T2-weighted image (a) and exhibited high signal intensity on a diffusion-weighted image (b)



computed tomography (CT) scan demonstrated moderate tumor shrinkage without any adverse events. However, on the first day of the sixth cycle, the patient's blood glucose level was markedly elevated (375 mg/dL; normal range 73–109 mg/dL). As he did not display any symptoms of hyperglycemia and had no history of diabetes mellitus, the sixth cycle of nivolumab was administered as scheduled. However, since it was considered possible that the patient was suffering from nivolumab-induced hyperglycemia, it was recommended that he have his blood glucose level reassessed by his family doctor. On day 3 of the sixth cycle, he had begun to experience slight thirst, polyuria, and general fatigue. On day 6, his blood glucose level was over 400 mg/dL, requiring immediate initiation of intensive insulin therapy. On day 9 of the sixth cycle, he was hospitalized for further evaluation and possible treatment of his hyperglycemia. Laboratory tests performed at the time of his hospitalization revealed the following results: blood glucose level, 326 mg/dL; HbA1c, 7.3 % (normal range 4.6–6.2 %); and glycoalbumin, 26.7 % (normal range 11.0–16.0 %). The patient's renal function, liver function, and electrolyte levels were within normal limits, but his serum lipase level was elevated (80.0 U/L; normal range 13–55 U/L). No ketoacidosis was detected. Tests for serum anti-glutamic acid decarboxylase antibody (≤ 1.3 U/mL),

anti-islet-cell antibody (<1.25 U), and anti-zinc transporter 8 antibody (<10.0 U/mL) were negative. The patient exhibited urinary C-peptide excretion of 5.0 $\mu\text{g/day}$ (normal range 22.8–155.2 $\mu\text{g/day}$). The time-dependent changes in the patients' urinary C-peptide excretion values after his hospitalization are shown in Fig. 1. His endogenous insulin secretion ceased completely within 2 weeks. Magnetic resonance imaging (MRI) revealed that his pancreas was diffusely enlarged (Fig. 2a) with high signal intensity on diffusion-weighted imaging (Fig. 2b). These MRI findings were indicative of diffuse pancreatic inflammation.

Even though neither ketoacidosis nor ketonuria was detected, the markedly acute onset of the patient's hyperglycemia was consistent with the typical clinical course of fulminant type I diabetes mellitus, and this diagnosis was supported by clinical data, including laboratory data and MRI findings. He was treated with intensive insulin replacement therapy. As the patient's endogenous insulin secretion had ceased, a long-term insulin replacement therapy was necessary. After his blood glucose level was brought under control, nivolumab was re-administered, and this did not lead to further hyperglycemia. Approximately 4 months after the onset of the patient's condition, his endogenous insulin secretion had not recovered.

Discussion

Nivolumab is a fully human IgG4 anti-PD-1 antibody that selectively blocks the interaction of the PD-1 receptor with its two known ligands, PD-L1 and PD-L2; this blockade disrupts the negative signaling that regulates T-cell activation and proliferation. The augmented immune response induced by nivolumab leads to anti-tumor activity. However, augmented immune responses involving T-cell reactivation can also induce autoimmune-related inflammation in normal tissues [5]. Such reactions mainly occur in the lungs, gastrointestinal tract, skin, and endocrine organs, including the thyroid gland, and cause adverse events. Pneumonitis, enterocolitis, diarrhea, hepatitis, skin rashes, thyroid dysfunction, renal injuries, and neurological disorders have been frequently reported as nivolumab-induced immune-related adverse events. Furthermore, previous studies identified hyperglycemia due to new-onset type I diabetes mellitus as one of the immune-related adverse events induced by anti-PD-1 antibodies, including nivolumab, in patients with solid tumors [7–12]. Some cases in these reports were consistent with the clinical course of fulminant type I diabetes mellitus, but precise data were not fully described. At this time, the evidence remains limited and the exact clinical course and frequency of this condition is unknown.

Fulminant type I diabetes mellitus is characterized by an extremely acute onset of hyperglycemia combined with ketoacidosis, and the absence of islet-related autoantibodies [13]. If prompt insulin replacement therapy is not administered, the associated severe ketoacidosis can be fatal. In our case, as prompt insulin therapy was initiated, it was possible to avoid ketoacidosis. In order to diagnose and manage fulminant type I diabetes mellitus without delay, it is important that clinicians keep this potential but fatal complication of nivolumab therapy in mind. However, there are no specific markers that can aid in the early diagnosis of this condition. In our case, the patient's serum lipase level was elevated before he developed hyperglycemia. Indeed, it was reported that an elevated serum pancreatic enzyme level is one of the clinical characteristics of fulminant type I diabetes mellitus [13]. It is considered that elevated serum pancreatic enzyme levels are indicative of inflammation of the exocrine pancreas. Thus, elevated serum lipase levels might be a valuable marker for facilitating the early diagnosis of fulminant type I diabetes mellitus.

The etiology of fulminant type I diabetes mellitus remains to be fully elucidated. However, genetic and environmental factors might contribute to its development. Regarding genetic factors, it was reported that the human leukocyte antigen (HLA)-DRB1*0405-DQB1*0401,

HLA-DRB1*0901-DQB1*0303, and HLA-B*4002 haplotypes and the cytotoxic T-lymphocyte-associated protein (CTLA)-4 CT60 polymorphism were associated with the onset of fulminant type I diabetes mellitus [14, 15]. As for environmental factors, viral infection might contribute to the development of this type of diabetes [16]. Some patients with fulminant diabetes mellitus display flu-like symptoms before the onset of their condition, and these are observed more frequently in fulminant type I diabetes mellitus (71.7 %) than in other types of type I diabetes mellitus (26.9 %) [16]. In our case, the patient did not exhibit any symptoms that were suggestive of a viral infection, but HLA analysis revealed that he carried the HLA-B*4002 haplotype, a susceptibility allele for this type of diabetes. Thus, we hypothesized that fulminant type I diabetes mellitus was triggered by nivolumab in a patient with a genetic background that is associated with the onset of the condition. This type of diabetes mellitus accounts for approximately 20 % of cases of type I diabetes mellitus in Japan [16] and 7 % of such cases in Korea [17]. On the other hand, the incidence of fulminant type I diabetes was reported to be lower in Western countries than East Asia [18]. These findings suggest that fulminant type I diabetes mellitus is an important subtype of diabetes, especially in East Asia. It is possible that nivolumab-induced fulminant type I diabetes mellitus is more common in East Asia, including Japan, than in other areas. Further careful investigations are warranted.

Conclusion

To the best of our knowledge, this is the first report to describe the precise clinical course of nivolumab-associated fulminant type I diabetes mellitus in patients with cHL. The results of the HLA analysis are interesting. As this is a single case report, further investigation is warranted to identify the risk factors for and incidence rate of fulminant type I diabetes mellitus induced by nivolumab and other immune checkpoint inhibitors. This case report should prompt oncologists and hematologists who are unfamiliar with fulminant type I diabetes mellitus to carefully monitor the blood glucose levels of patients that are treated with anti-PD-1 antibodies.

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Compliance with ethical standards

Conflict of interest K. Tobinai: Research funding from Ono Pharmaceutical Co., Ltd.

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