Received: 11 July 2022 | Accepted: 1 September 2022

DOI: 10.1111/1759-7714.14660

CASE REPORT

WILEY

End-of-life impact of concurrent diabetes mellitus and adrenal insufficiency as immune-related adverse events in an advanced non-small cell lung cancer patient

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Abstract

A 49-year-old man diagnosed with metastatic non-small cell lung cancer was treated with immune checkpoint inhibitor (ICI) combination therapy (nivolumab + ipilimumab) as first-line therapy. During the treatment course, the patient developed ICI-associated diabetes mellitus and adrenal insufficiency, and insulin and hydrocortisone replacement therapy (10 mg/day) were initiated for endocrine toxicity. Despite systemic treatment, the disease progressed. Near the end of the patient's life, he was repeatedly hospitalized for diabetic ketoacidosis and adrenal crisis because he could not physically administer insulin subcutaneously or self-administer oral hydrocortisone due to the deterioration of his general condition as a result of disease progression. This case report demonstrates that it is necessary to evaluate not only the impact of immune-related adverse events on short-term quality of life during ICI treatment but also on the patient's end-of-life care.

KEYWORDS

case report, end of life, immune checkpoint inhibitors, immune-related adverse events, non-small cell lung cancer

INTRODUCTION

Immune checkpoint inhibitors (ICIs), such as programmed cell death receptor 1, programmed cell death ligand 1, and cytotoxic T lymphocyte-associated antigen 4 inhibitors, have become the standard of care for patients with metastatic non-small cell lung cancer (NSCLC).[1] Because ICIs enhance the host immune system, they can cause a unique spectrum of side effects termed immune-related adverse events (irAEs).[2] Common irAEs involve the skin, endocrine organs, lungs, liver, and gastrointestinal tract. Although most irAEs can be alleviated by treatment with immunosuppressive agents such as corticosteroids, tumor necrosis factor-alpha antagonists, and mycophenolate mofetil, the endocrine toxicity is permanent and requires lifelong hormone replacement therapy.[3] However, no reports have focused on how endocrine toxicity affects quality of life near the end of life. We encountered a case of ICI-associated diabetes mellitus (ICI-DM) and adrenal insufficiency caused by treatment with ICIs that were difficult to manage near the end of life.

CASE REPORT

A 49-year-old man diagnosed with metastatic NSCLC was treated with ICI combination therapy (nivolumab + ipilimumab) as first-line therapy. Five months after the initial ICI combination, weight loss, polyurea, polydipsia and marked hyperglycemia (blood glucose level: 600 mg/dl) developed. Antiglutamic acid decarboxylase was negative, but serum C-peptide levels were decreased, which showed complete depletion of insulin. The patient was diagnosed with ICI-DM following ICI combination therapy, and subcutaneous insulin medication for ICI-DM was initiated. After progression following first-line therapy, he received carboplatin, pemetrexed, and bevacizumab as second-line

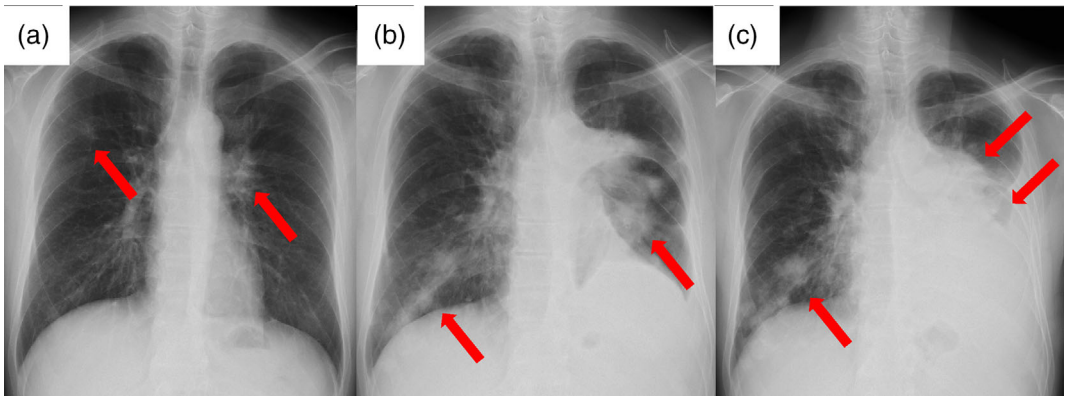

FIGURE 1 Chest radiography (tumor lesions: Red arrow) at the initiation of carboplatin, pemetrexed, and bevacizumab (a left), before docetaxel treatment (b middle), and at progression during docetaxel treatment (c right)

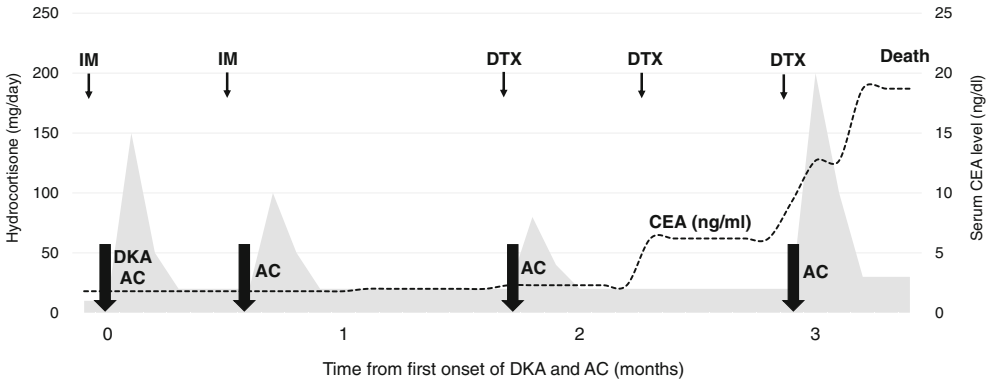

FIGURE 2 Patient's clinical course from first onset of adrenal crisis and diabetic ketoacidosis. Dotted line represents CEA value, and gray peaks represent hydrocortisone dose (mg/day). IM, immunomodulator; DTX, docetaxel; AC, adrenal crisis; DKA, diabetic ketoacidosis

therapy (Figure 1a). During second-line therapy, he presented with general malaise. His serum cortisol level was less than 0.2 μg/dl, and plasma ACTH level was 2.1 pg/ml in the early morning, while serum-free thyroxine level (FT4), and serum thyroid-stimulating hormone (TSH) were within the normal range. He was diagnosed with ICI-induced adrenal insufficiency. Hydrocortisone replacement therapy (10 mg/day) was initiated for the endocrine toxicity.

Despite systemic treatment, multiple distant metastases developed during treatment, and he began self-administering an unapproved immunomodulatory therapy which had not been prescribed (Figure 1b). After single-dose administration, fever and general malaise suddenly developed. He was hospitalized due to diabetic ketoacidosis (DKA) and adrenal crisis because he could not administer insulin subcutaneously or self-administered oral hydrocortisone due to the deterioration of his general condition. Laboratory tests revealed hyperglycemia (blood glucose level: 480 mg/dl), hyponatremia (123 mmol/l), metabolic acidosis (pH: 7.14, HCO_3: 12.5), presence of ketone bodies in the urine, and a low serum cortisol level (4.6 μg/dl).

Three weeks after recovery, adrenal crisis again developed after administration of the same immunomodulatory therapy, although he had been advised not to resume this therapy. He then started treatment with docetaxel as subsequent treatment. However, 7 days after the initiation of docetaxel, anorexia, fever, malaise and hypoglycemia were observed. As relative adrenal insufficiency was suspected, the hydrocortisone dosage was temporarily increased to 80 mg/day and the patient's symptoms promptly improved.

After three cycles of docetaxel, he was hospitalized as he could no longer receive hydrocortisone because of disease progression. Laboratory tests revealed hyponatremia (131 mmol/l) and low serum cortisol level (5.4 μg/dl). Additionally, hypotension developed, and he was again diagnosed with adrenal crisis (Figure 1c). Hormone replacement therapy (200 mg/day) temporarily improved the adrenal crisis, but his condition deteriorated rapidly, and he subsequently died (Figure 2).

DISCUSSION

Here, we encountered a case of adrenal insufficiency and ICI-DM caused by ICIs in which DKA and adrenal crisis recurred near the end of the patient's life. ICI-DM is similar to classic type 1 diabetes and is caused by destruction of pancreatic beta cells by the immune system.[3] Concurrent adrenal insufficiency and type 1 diabetes mellitus is rare, even in cases not associated with ICIs.[4] However, the number of concomitant endocrine disorders is expected to increase with the expansion of ICIs. Both adrenal insufficiency and type 1 diabetes mellitus are known to increase

the likelihood of DKA and adrenal crisis, which can be fatal.[3] Appropriate hormone replacement therapy with insulin and glucocorticoids, which have opposing effects on glucose metabolism, is needed in these patients.[5]

QOL and the clinical course of irAEs are assessed in clinical trials of ICIs during the treatment period.[1,6,7] However, it remains unclear how irAEs themselves, especially endocrine toxicities that require permanent, self-administered replacement therapy, affect QOL near the end of the patient's life. In general, medication management is a key component of palliative care that aims to improve quality of life. However, medication management at the end of life is challenging because self-administration such as subcutaneous insulin medication and hormone replacement therapy becomes physically difficult as the cancer progresses at end-of-life. Additionally, inappropriate medications for endocrine toxicity have a significant risk of fatal adverse events, such as DKA and adrenal crisis, which can lead to a decline in QOL near the end of life. Indeed, our patient was repeatedly hospitalized for treatment of DKA and adrenal insufficiency, because he did not administer replacement therapy appropriately due to the deterioration of his general condition caused by the cancer treatment and progression. Additionally, he received unapproved immunomodulatory therapy, which might have caused the development of his adrenal crisis and DKA, although it remains unknown how the immunomodulatory therapy affected the deterioration of his general condition. Therefore, in patients with advanced NSCLC receiving ICIs, it is necessary to evaluate not only the short-term impact of ICIs but also their impact on the patient's end-of-life care.

CONFLICT OF INTEREST

Dr Yoshida received grants and personal fees from AstraZeneca, Bristol-Myers Squibb, grants from Abbvie, MSD, Ono Pharmaceutical, Takeda Pharmaceutical, and personal fees from Chugai, Novartis. Dr Ohe received grants and personal fees from AstraZeneca, Bristol-Myers Squibb, Chugai, Eli Lilly, Janssen Pharma, Kyorin, MSD, Nippon Kayaku, Novartis, Ono Pharmaceutical, Pfizer, Taiho Pharmaceutical, Takeda Pharmaceutical, grants from Kissei, and personal fees from Boehringer Ingelheim, Celtrion. The remaining authors declare no competing interests.

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REFERENCES

1. Grant MJ, Herbst RS, Goldberg SB. Selecting the optimal immunotherapy regimen in driver-negative metastatic NSCLC. Nat Rev Clin Oncol. 2021;18(10):625–44. https://doi.org/10.1038/s41571-021-00520-1
2. Martins F, Sofiya L, Sykiotis GP, Lamine F, Maillard M, Fraga M, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. Nat Rev Clin Oncol. 2019;16(9):563–80. https://doi.org/10.1038/s41571-019-0218-0
3. Wright JJ, Powers AC, Johnson DB. Endocrine toxicities of immune checkpoint inhibitors. Nat Rev Endocrinol. 2021;17(7):389–99. https://doi.org/10.1038/s41574-021-00484-3
4. Chantzichristos D, Eliasson B, Johannsson G. MANAGEMENT OF ENDOCRINE DISEASE disease burden and treatment challenges in patients with both Addison's disease and type 1 diabetes mellitus. Eur J Endocrinol. 2020;183(1):R1–R11. https://doi.org/10.1530/EJE-20-0052
5. van Raalte DH, Ouwens DM, Diamant M. Novel insights into glucocorticoid-mediated diabetogenic effects: towards expansion of therapeutic options? Eur J Clin Invest. 2009;39(2):81–93. (In English). https://doi.org/10.1111/j.1365-2362.2008.02067.x
6. 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. https://doi.org/10.1056/NEJMoa1910231
7. Boutros A, Bruzzone M, Tanda ET, Croce E, Arecco L, Cecchi F, et al. Health-related quality of life in cancer patients treated with immune checkpoint inhibitors in randomised controlled trials: a systematic review and meta-analysis. Eur J Cancer. 2021;159:154–66. https://doi.org/10.1016/j.ejca.2021.10.005

How to cite this article: Nakamura T, Takeyasu Y, Yoshida T, Ohashi K, Ohe Y. End-of-life impact of concurrent diabetes mellitus and adrenal insufficiency as immune-related adverse events in an advanced non-small cell lung cancer patient. Thorac Cancer. 2022;13(21):3073–5. https://doi.org/10.1111/1759-7714.14660