Case Report

Delayed nivolumab-induced hepatotoxicity during pazopanib treatment for metastatic renal cell carcinoma: An autopsy case

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Abbreviations & Acronyms
ALT = alanine aminotransferase
Ao = aorta
AST = aspartate aminotransferase
CT = computed tomography
fT3 = free triiodothyronine
fT4 = free thyroxine
HE = hematoxylin-eosin
ICI = immune checkpoint inhibitor
irAE = immune-related adverse events
IVC = inferior vena cava
Kid = kidney
mRCC = metastatic renal cell carcinoma
Panc = pancreas
POD = postoperative day
RCC = renal cell carcinoma
TKI = tyrosine kinase inhibitor
TSH = thyroid-stimulating hormone
VB = vertebra

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Introduction: Pazopanib, a tyrosine kinase inhibitor, and nivolumab, an immune checkpoint inhibitor, are both considered to cause hepatotoxicity with different pathophysiology. We report a case in which a patient died of severe hepatotoxicity who was presumed to have been caused by the administration of nivolumab followed by pazopanib for metastatic renal cell carcinoma.

Case presentation: A 74-year-old male with metastatic renal cell carcinoma was treated with nivolumab as a third-line treatment. However, nivolumab was subsequently discontinued, as it caused severe thyroiditis. About 2 months after the final dose of nivolumab was administered, pazopanib was initiated as a fourth-line treatment. The patient suffered from lethal hepatic failure and died 18 days after the initiation of pazopanib treatment. An autopsy revealed that CD8-positive lymphocytes had infiltrated the thyroid gland and liver.

Conclusion: The patient was considered to have died of severe hepatic failure due to the aggravation of mild nivolumab-induced immune-related hepatitis by pazopanib.

Key words: hepatotoxicity, metastatic renal cell carcinoma, nivolumab, pazopanib.

Keynote message

We experienced a case in which a patient with mRCC died of severe hepatotoxicity who was suspected to have been caused by treatment with nivolumab followed by pazopanib. The autopsy suggested that nivolumab had induced CD8-positive T-cell accumulation in the liver, which might have persisted after the cessation of nivolumab treatment. We assumed that pazopanib caused lethal hepatotoxicity by enhancing the immunological reactions induced by nivolumab. Immunosuppressive treatment, for example, with glucocorticoids, should be considered when severe hepatotoxicity arises in a patient who has been treated with a TKI followed by an ICI.

Introduction

Nivolumab is a highly selective humanized antibody against programmed cell death protein 1, which acts as an ICI. It is commonly utilized to treat mRCC.[1,2] Nivolumab induces various persistent irAE, including thyroiditis and hepatitis of varying degrees.[2–4] The usage of a TKI followed by an ICI might aggravate mild persistent irAE. Here, we report an autopsy case of severe hepatic failure who may have been caused by mild nivolumab-induced hepatitis being lethally aggravated by the administration of pazopanib.

Case presentation

A 74-year-old Japanese male (SIMC-Uro #3044, a unique nonsequential patient control number used at SIMC-Uro) complained of gross hematuria and visited a nearby hospital. Right-sided RCC (length: 77.6 ± 1.2 mm [mean ± standard error], measured by three co-authors

[TH, TM and HK], as reported previously[5]) and an intra-aortocaval lymph node metastasis (15.6 ± 2.5 mm) were identified on abdominal contrast-enhanced CT (scan #1, Fig. 1a,b and Figures S1 and S2). He was referred to our institution to undergo further evaluation and treatment for the RCC. His physiological and laboratory data, including data regarding serum markers of the liver and thyroid function, were within normal limits (Fig. 2, Table S1). Based on further imaging studies, he was finally diagnosed with RCC combined with lymph node metastasis (cT2aN1M0).

He underwent right radical nephrectomy combined with right adrenalectomy and regional lymph node dissection. A pathological examination revealed that the tumor was a clear cell RCC (Fuhrman grade 2, pT1bN0). Two incidental papillary RCC (3 and 8 mm in length) were also detected during the pathological examination (labeled* in Figure S1; Fuhrman grade 1). A CT scan performed on POD #419 revealed an intra-aortocaval lymph node metastasis (CT scan #5, Fig. 1d). The enlarged intra-aortocaval lymph node that was detected on CT scan #1 was not removed during the above-mentioned surgical procedure.

Sunitinib treatment (25 mg/day, 4 weeks on and 2 weeks off) was initiated on POD #419, and the swollen lymph node had shrunk to 18.9 ± 2.5 mm by POD #566 (CT scan #6, Table S2). Its size did not change significantly thereafter, but a new left-sided adrenal metastasis was identified on POD #1745 (CT scan #18, 18.4 ± 0.8 mm). Axitinib (6 mg/day) was initiated as a second-line treatment on POD #1813, which was effective against both the lymph node metastasis (16.7 ± 2.5 mm, CT scan #20, Fig. 1) and the adrenal metastasis (9.4 ± 0.4 mm). Although the patient did not complain of any symptoms, he had to cease taking axitinib, as elevated serum levels of AST (311 U/L [normal range: 8–38 U/L]) and ALT (332 U/L [normal range: 4–44 U/L]) were detected on POD #1910 (grade 3, Fig. 2).

After the normalization of the patient's serum AST/ALT levels, bi-weekly nivolumab (3 mg/kg) was initiated as a third-line treatment on POD #1979. However, nivolumab was discontinued after the administration of the 13th dose because the patient's serum TSH level had increased to 23.3 μIU/mL (0.35–4.94) by POD #2176, and the adrenal mass had increased in size to 25.3 ± 0.9 mm by POD #2162 (CT scan #24, Fig. S2). The size of the metastatic lymph node had not changed (13.3 ± 2.1 mm). Pazopanib treatment (600 mg/day, fourth-line treatment) was initiated on POD #2221; however, the patient developed pyrexia after 10 days of pazopanib

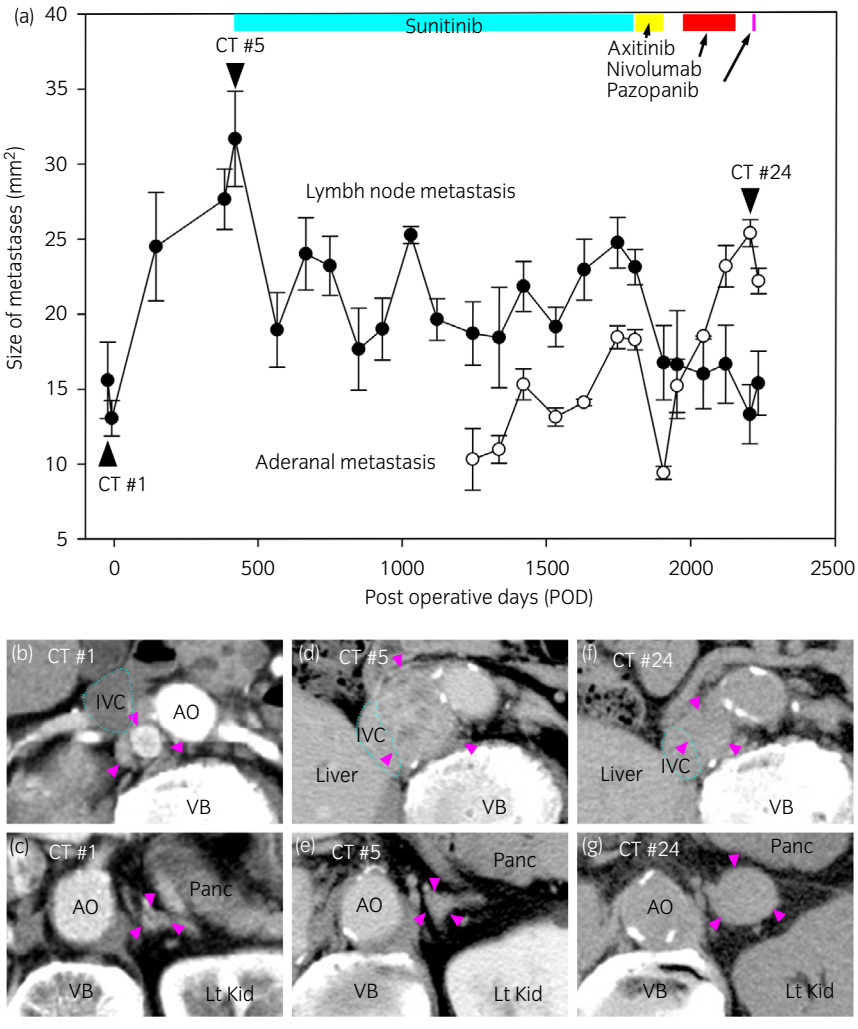

Fig. 1 Changes in the lymph node and adrenal metastases during the patient's clinical course. (a) The changes in the sizes of the metastases were measured by three investigators (the black and white dots with error bars indicate the sizes of the lymph node and adrenal metastases and standard error values, respectively); (b–g) CT images of the lymph node metastasis (b,d,f) and adrenal metastasis (c,e,g) are shown. The CT examinations are numbered, starting from the first visit. The pink arrowheads indicate the metastases (see also Table S2 and Figures S1, S2).

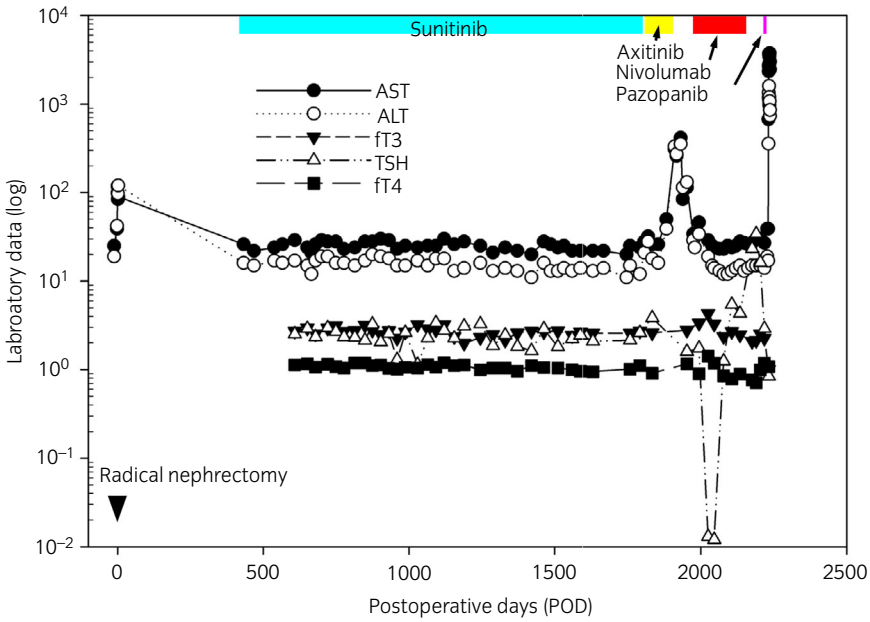

Fig. 2 Laboratory data obtained during the patient's clinical course. Data regarding ALT, AST, TSH, fT4, and fT3 levels are plotted.

treatment (POD #2231, body temperature: 38.8°C, serum AST level: 39 U/L, serum ALT level: 17 U/L). On POD #2232, the patient developed severe liver dysfunction involving high serum AST (674 U/L) and ALT (356 U/L) levels, which resulted in him being hospitalized at our institution, as well as the cessation of pazopanib treatment. Before the patient was hospitalized, febuxostat, levothyroxine sodium hydrate, amlodipine, and fexofenadine were regularly administered for hyperuricemia, hypothyroidism, hypertension, and pruritus, respectively, which, based on their pharmacological actions, presumably did not affect his liver function. Despite the cessation of pazopanib and the provision of intensive care, the patient's general condition worsened, and he died on POD #2238.

He underwent an autopsy after written informed consent was obtained from his family. His liver weighed 1030 g (normal range: 1200–1500 g), and the cut surface of the liver exhibited mild congestion (Fig. S4). Microscopically, hepatic cells were only observed in about 30% of the liver tissue (the eosinophilic portions of "liver, HE.tif" in Figure S3 and Figure 3a), which had been infiltrated by cytotoxic (CD8-positive) T cells (Fig. 3a,b). It should be noted that Figure 3a,b show non-serial sections. A left adrenal tumor (shown in CT scans #13–26) was macroscopically detected in the left adrenal gland, and it was microscopically diagnosed as a metastasis from RCC. It consisted of papillary cell carcinoma and clear cell carcinoma components (data not shown). No cancer cells were detected in the intra-aortocaval lymph node (Fig. 3c), which had been infiltrated by a moderate number of CD8-positive T cells (Fig. 3d). The thyroid gland had also been infiltrated by many CD8-positive T cells (Fig. 3e,f), which was consistent with the patient suffering from nivolumab-induced severe persistent thyroiditis (see TSH levels in Figure 2 and Table S1). Analyses of the blood sample taken after the patient's death did not detect the hepatitis virus (type A, B, C, or E); cytomegalovirus; Epstein-Barr virus; or autoimmune antibodies, including antimitochondrial and

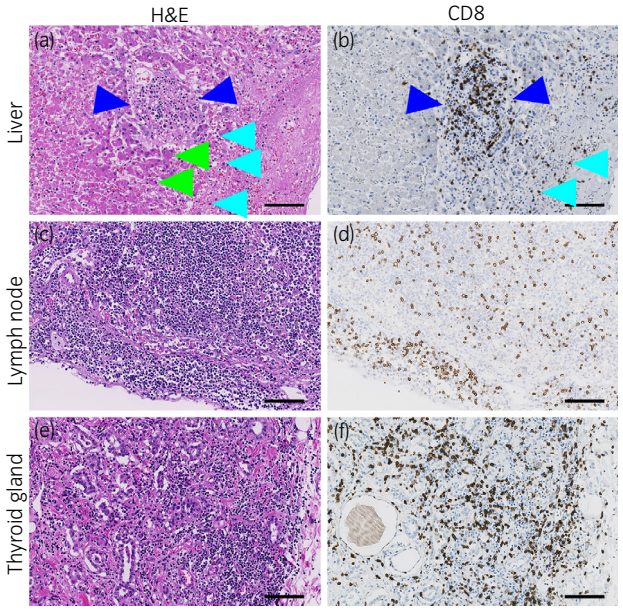

Fig. 3 The pathological findings obtained at autopsy. HE staining: (a) liver, (c) lymph nodes and (e) thyroid gland; CD8 immunostaining: (b) liver, (d) lymph nodes, and (f) thyroid gland; arrowheads: eosinophilic portions composed of residual normal hepatic cells (green), degenerated hepatic cells (blue), and CD8-positive cells (sky blue).

antinuclear antibodies. Considering the patient's clinical course and autopsy findings, we retrospectively assumed that he died of severe hepatic failure, possibly due to the lethal aggravation of mild nivolumab-induced hepatitis caused by the administration of pazopanib.

Discussion

We experienced a case of mRCC, in which the patient died of severe hepatotoxicity, possibly due to treatment with nivolumab followed by pazopanib. TKI, including pazopanib,

frequently cause hepatic disorders (any grade according to the Common Terminology Criteria for Adverse Events: 34.0–39.2%, >grade 3: 5.0–5.2%).[6] On the other hand, nivolumab only causes liver dysfunction in 8% of patients (elevated AST/ALT levels are seen in about 4% of patients), and severe liver dysfunction (>grade 3) occurs in 2.9% of patients.[7] It was reported that the median duration of the period from the initiation of treatment to the onset of liver dysfunction was >1 month for both pazopanib and nivolumab[7,8]; therefore, it is recommended that serum AST/ALT levels should be measured every 2–4 weeks for the first 8 weeks after the initiation of such treatment.[6,9] In the current case, severe hepatic dysfunction occurred within about a week after the initiation of pazopanib. Although the mechanisms underlying TKI-related hepatotoxicity have not yet been clarified, it has been suggested that pazopanib-induced hepatotoxicity might be associated with polymorphisms in the *HFE* gene (which encodes a homeostatic iron regulator).[10] However, in the current case, the pathological examination did not reveal any findings that were indicative of hepatic iron overload. The autopsy demonstrated that the liver and thyroid gland had been significantly infiltrated by CD8-positive lymphocytes. The patient's clinical course and autopsy findings suggested that the patient's liver had been affected by the persistent inflammatory effects of nivolumab[4] and that these effects were significantly enhanced by the administration of pazopanib.

Currently, many mRCC cases are sequentially treated with nivolumab followed by a TKI. Clinicians must take the persistent effects of ICI into consideration in patients who suffer from severe complications, including liver dysfunction, after such treatment.

Acknowledgments

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Conflict of interest

The authors declare no conflict of interest.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1. Whole-slice images obtained during the first CT scan showing a right renal tumor and the associated lymph node metastasis.
Figure S2. Serial images of the lymph node and adrenal metastases obtained during the first (POD #22) to 26th CT scans (POD #2233). The pink arrowheads indicate the adrenal (left) and lymph node (right) metastases.
Figure S3. The pathological findings of the liver, lymph nodes, and thyroid gland obtained at autopsy. The results of HE staining, CD4 immunostaining, and CD8 immunostaining are shown.
Figure S4. The macroscopic findings of the liver and thyroid gland obtained at autopsy.
Table S1. Laboratory data from the first visit to dead.
Table S2. Clinical course and tumor size of primary and metastatic sites during follow-up.