

Case Report

Case Study: A Japanese patient with metastatic renal cell carcinoma who achieved long-term treatment-free survival with pembrolizumab and axitinib in the KEYNOTE-426 phase III trial of pembrolizumab and axitinib versus sunitinib

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Introduction: Our patient treated with pembrolizumab and axitinib is one of the longest survivors in Japan on KEYNOTE 426, despite adverse events, including delayed-onset hepatitis. We herein present a detailed clinical course and short discussion on the case.

Case presentation: This was a 49-year-old male with clear cell renal cell carcinoma and lung metastases. After cytoreductive nephrectomy, treatment with pembrolizumab plus axitinib was initiated and the patient demonstrated a radiographic partial response as best response. The main adverse event was pembrolizumab-induced delayed-onset hepatitis, which was successfully treated with prednisolone. Pembrolizumab was re-initiated and completed.

Conclusion: The survival benefit in the present case may be due to the initial potent anti-cancer effects of axitinib and durable immune effects of pembrolizumab, leading to long-term treatment-free survival.

Key words: axitinib, KEYNOTE426, metastatic renal cell carcinoma, pembrolizumab.

Keynote message

We report a case with long-term treatment-free survival in KEYNOTE-426. The case was a rare case that completed 35 pembrolizumab treatment. The patient developed delayed-onset immune-related hepatitis. Axitinib was withdrawn due to adverse events and Grade 3 hepatitis.

Introduction

In the KEYNOTE-426 trial, pembrolizumab plus axitinib significantly extended overall survival (OS) and progression-free survival in cases of advanced renal cell carcinoma.^{1,2} Our department registered four cases, one of which achieved long-term survival despite the development of adverse events. We herein present the case with a detailed clinical course and short discussion.

Case

This 49-year-old male was diagnosed 114 days before study entry (Day –114) after abnormal findings on a chest X ray were detected. Computed tomography (CT#1) showed lung masses (Figures 1, 2A-B) and a left renal mass. He was referred to our hospital for further evaluation. CT#2 using contrast medium identified the 106 mm renal mass as renal cell carcinoma (RCC; Figure 2C-D). He underwent cytoreductive nephrectomy (Day –65). The pathological diagnosis was clear cell RCC (pT3N0M1). He was enrolled in KEYNOTE-426 and received treatment with pembrolizumab (200mg) plus axitinib (10mg/day).^{1,2}

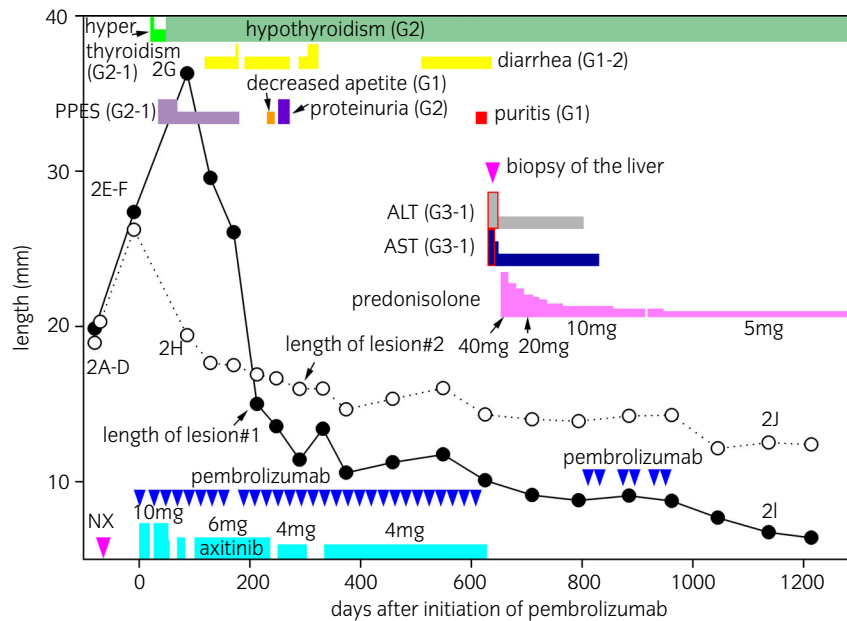


Fig. 1 Clinical course of the case. Black and white dots indicate the lengths of lesions #1 and 2, respectively. Adverse events are shown with colored columns (except for pink columns), the heights and widths of which indicate severity and duration, respectively. The adverse events shown are hyperthyroidism with abdominal pain (label: hyperthyroidism, color: green, Days #19-47), palmar-plantar erythrodysesthesia (PPES, light purple, Days #33-180), maculo-papular rash (rash, emerald green, Days #33-180), hypothyroidism (green, #Days 47-current), mucosal inflammation (peach, Days #54-180), diarrhea (yellow; Days #117-271, 287-323, 303-323, and 509-636), decreased appetite (orange, Days #231-245), proteinuria (purple, Days #251-272), pruritis (red, Days #608-628), high alanine aminotransferase (ALT, gray, Days #629-803), and high aspartate transaminase (AST, dark blue, Days #629-831). Pink columns indicate the dose and duration of prednisolone (initiation dose: 40mg). Blue arrowheads indicate the day of pembrolizumab administration. NX: cytoreductive nephrectomy. 2A-D, 2E-F, 2G, 2H, 2J, and 2I indicate images in Figure 2

Prior to receiving the treatment, the findings of a physical examination, including height (1.66m), body weight (63.4kg), and the Karnofsky Performance Status (score: 100), were normal. Laboratory findings, including serum levels of thyroid-stimulating hormone (TSH, 2.9 [0.35-4.94] μ IU/mL), triiodothyronine (2.66 [1.71-3.71]ng/mL), thyroxine (0.89 [0.70-1.48] μ g/dL), aspartate aminotransferase (AST, 19.0 [8-38]U/L), alanine aminotransferase (ALT, 15.0 [4-44] U/L) and calcium (9.9 [8.5-10.5]mg/dL), were normal. Hemoglobin concentration (16.3 [13.2-17.2]g/dL), neutrophil count (4692/ μ L) and platelet count ($246 \times 10^3/\mu$ L) were normal. He was judged to be in the intermediate risk category by the International Metastatic Renal Cell Carcinoma Database Consortium risk group classification.³ CT#3 continued to show lung metastases with an increase in the number of lesions compared to CT#1-2. We selected two metastases for radiological evaluation based on the Response Evaluation Criteria in Solid Tumours (version 1.1)⁴: lesions #1 (27.4mm, pink arrowhead in Figure 2E) and #2 (26.2mm, green arrowhead in Figure 2F).

On Day+19, the patient developed abdominal pain. On Days +20 and +27, low TSH (both 0.005 μ IU/mL), high thyroxine (4.52 and 1.88 μ g/dL, respectively) and high triiodothyronine (≥ 30 and 4.7ng/mL, respectively) were detected and suggested hyperthyroidism (maximum Grade 2 [G2]), which was presumably the cause of abdominal pain. From Day+33, the patient developed palmo-plantar erythrodysesthesia syndrome (PPES, G2, duration: 34 days) and a rash (Grade 1 [G1], 147 days). On Day+48, an increase

was observed in TSH (21.5 μ IU/mL) with decreases in thyroxine and triiodothyronine (<0.4 μ g/dL and 1.24ng/mL, respectively), leading to a diagnosis of hypothyroidism (G2). Treatment with synthetic thyroxine was initiated. From Day+54, the patient exhibited PPES (G1-2), rash, mucosal inflammation (stomatitis), diarrhea (G1-2), decreased appetite (G1), proteinuria (G2), and pruritis (G1). These adverse events were treated with intermittent suspension and dose reductions (to 5-6mg/day) of axitinib.

On Day 87, lesion #1 enlarged (36.3 mm, pink arrowhead in Figure 2G) and lesion #2 shrunk (19.4 mm, green arrowhead in Figure 2F). A non-target lesion (lesion #3), which appeared just before treatment (Figure 2A and E), disappeared (yellow-arrowhead in Figure 2G). Thereafter, lesion #1 decreased in size significantly and lesion #2 continued to decrease (Figures 1, 2I-J). Thus, each lesion showed heterogeneous response to the treatment.

On Day+630, AST and ALT levels increased to 443 and 427 U/L (Grade 3), respectively. Pembrolizumab and axitinib were both withdrawn. On Day+637, these levels remained elevated (404 and 348 U/L, respectively). He underwent liver biopsy, which showed following findings: (i) The inflammatory cells histologically infiltrated into the limiting plates (yellow-arrowheads in Figure 3A) between the portal tract and liver parenchyma, suggesting he had so-called 'interface hepatitis' which was mainly seen in the portal region. (ii) In the area of lymphocyte infiltration, many eosinophils (green-arrowheads in Figure 3B) and plasma cells (water-blue-arrowheads in Figure 3B) were also identified, as previously

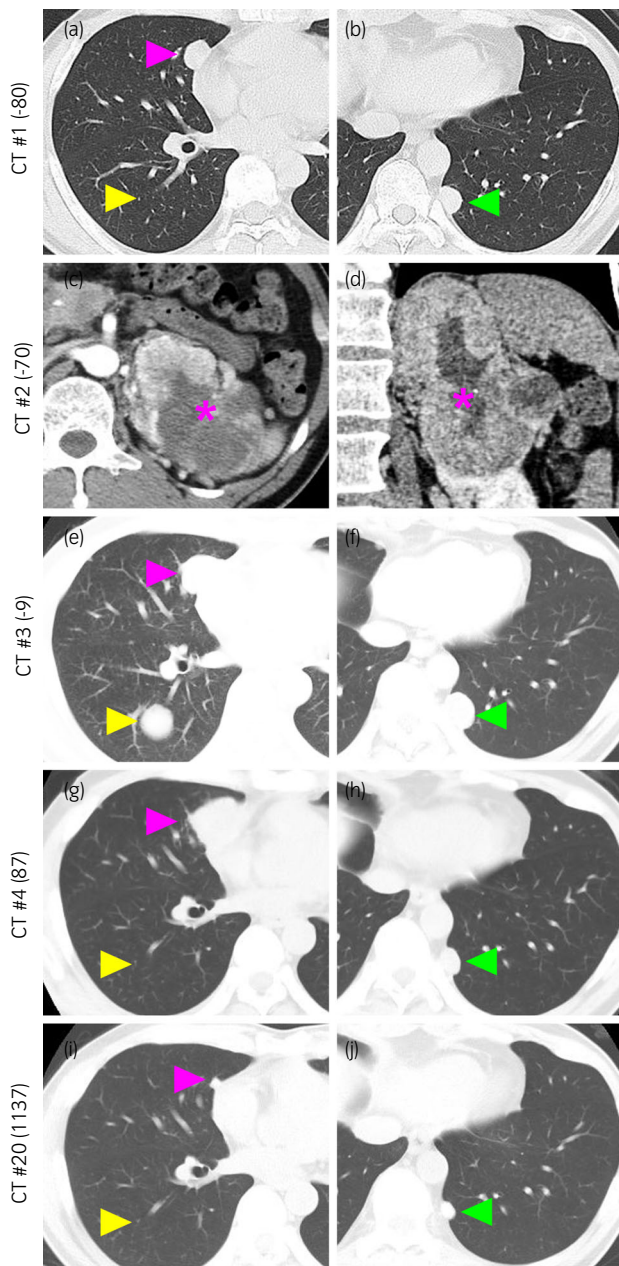


Fig. 2 Representative CT images of the present case. Pink and green arrowheads indicate lesions measured in the KEYNOTE-426 trial (lesions #1 and #2, respectively). Pink asterisks in panels C and B indicate a renal tumor in axial and coronal views of CT#2. CT#1, #2, #3, #4, and #20 were captured on Days #80 (80 days before the initiation of treatment with pembrolizumab plus axitinib), -70, -9, 87 (87 days after the initiation of treatment with pembrolizumab plus axitinib), and 1137. Panels A-J are indicated in Figure 1 as “2A-D”, “2E-F”, “2G”, “2H”, “2J”, and “2I”. Yellow arrowheads indicate lung metastasis that appeared after nephrectomy

reported.⁵ Many hepatocytes (* in Figure 3C-D) were encircled by CD8-positive lymphocytes (blue-arrowheads in Figure 3C-D), suggesting that hepatocytes were attacked by lymphocytes. These findings suggested that he had irAE-hepatitis and/or autoimmune hepatitis due to pembrolizumab. His serum levels of immunoglobulin G and anti-mitochondria antibody were negative, hence he was clinically diagnosed as

irAE hepatitis. He initiated 40mg-prednisolone, which carefully tapered based on AST/ALT levels. Pembrolizumab was re-initiated on Day+811 (cycle 30) and completed on Day+951 (cycle 35). As of Day+1,725, there has been no regrowth of lung metastases (#1: 5.5 mm, #2: 9.4 mm).

Discussion

An updated analysis from KEYNOTE-426 was recently published (median follow-up of 27 months² and 42 month⁵), and revealed ongoing superior OS, PFS and ORR benefit for pembrolizumab and axitinib over sunitinib with no new safety signals. Despite the good survival outcome in patients treated with pembrolizumab plus axitinib (42-month OS rate: 57.5%), only 129 (29.9%) completed the treatment.⁶ The good survival outcome was attributed to the durability of pembrolizumab over the inhibition of the vascular endothelial growth factor (VEGF) pathway. The present case was one of the cases that completed the 35 pembrolizumab infusions.

Adverse events occurred in the present case, as shown in Figure 1. Except for high ALT/AST serum levels, all events presumably to be caused by axitinib, which we frequently encounter in our clinical settings using axitinib monotherapy.⁶ Following the withdrawal of axitinib, there were no adverse events after the re-initiation of pembrolizumab. We measured 2 lung lesions. Lesion#1 quickly responded to the treatment, whereas lesion#2 did not. This differential response is likely related to the heterogeneity of tumor cell populations.⁷ This difference was possibly attributed to the VEGF pathway; lesion#1 responded to axitinib, whereas lesion#2 might not. The course of the present case possibly indicated that cells in lesion#1 destroyed by axitinib triggered the immune system via antigen presentation and PD-1/PD-L1 suppression by pembrolizumab.⁸ It is recently reported that median time to ALT elevation is 84.0 days (range: 7-840 days).⁹ Delayed-onset hepatitis (Day+629) appeared to support delayed immune activation. We previously experienced a case with metastatic RCC, who died of severe hepatotoxicity presumably due to nivolumab followed by pazopanib regardless of nivolumab withdrawal.¹⁰ irAE are generally characterized by an unexpected and sudden onset. Therefore, axitinib presumably played significant roles in initial tumor shrinkage and immune presentation.

In the KEYNOTE-426 trial, the permanent discontinuation of axitinib was planned for patients unable to tolerate 2mg twice daily; therefore, the present case discontinued the agent. Of 432 patients who received pembrolizumab plus axitinib, 129 patients (29.9%) completed 2 years of pembrolizumab plus axitinib treatment.⁶ Of the 129 patients, treatment-related adverse events and/or physician decision resulted in the discontinuation of axitinib in 28 (27.2%) patients. Long-term data from the trial may reveal whether responses are maintained when pembrolizumab and axitinib are both discontinued. However, data on the outcomes of patients who discontinued either or both pembrolizumab and axitinib, including those who received the protocol-defined maximum 35 doses of pembrolizumab, are not fully available for estimating the durability of benefits from this regimen after

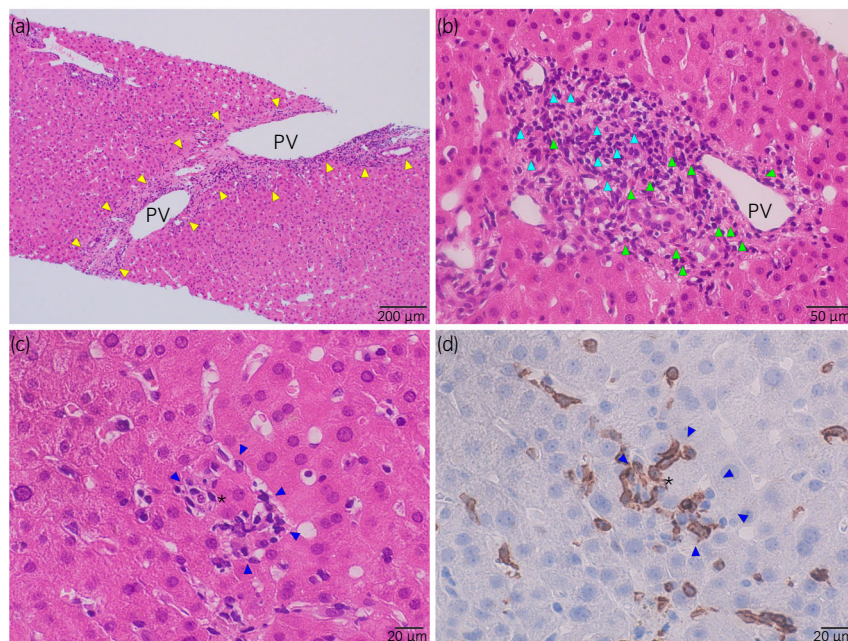


Fig. 3 Representative pathological findings of liver biopsy. (a) Hematoxylin and eosin staining of a biopsied section from liver tissue. Yellow arrowhead: limiting plates. (b) A representative portion of severe lymphocytes infiltration to the portal vein. Water-blue- and green-arrowheads indicate plasma cells and eosinophils, respectively. (c) A representative portion of a hepatocyte encircled by lymphocytes. (d) Immunohistochemistry for CD8 of the corresponding portion of (c). Asterisks in panels C and D indicate attacked hepatocyte. PV: portal vein

treatment cessation, as reported in the updated analysis.^{2,6} Therefore, further “real world” data, including case reports, are needed to estimate “treatment-free survival”¹¹ in cases treated with pembrolizumab plus axitinib.

Conflict of interest

The authors declare no conflict of interest.

Approval of the research protocol by an institutional reviewer board

Not applicable.

Informed consent

Not applicable.

Registry and the registration no. of the study/trial

Not applicable.

Author Contributions

Koshiro Nishimoto: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Software; Supervision; Visualization; Writing – original draft. Suguru Shirotake: Supervision; Writing – review & editing. Yu Miyama: Formal analysis; Investigation; Writing – review & editing. Go Kaneko: Writing – review & editing. Kent Kanao: Writing – review & editing. Daisuke Igarashi: Writing – review & editing. Takayuki Takahashi: Writing – review & editing. Yuta Umezawa: Writing – review & editing. Masanori Yasuda: Investigation; Writing – review &

editing. Masafumi Oyama: Supervision; Writing – review & editing.

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