Case Report

Durable response to pembrolizumab in microsatellite instability-high advanced adrenocortical carcinoma

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Abbreviations & Acronyms
ACC = adrenocortical carcinoma
AEs = adverse events
CT = computed tomography
EDP-M = mitotane with etoposide, doxorubicin, and cisplatin
MMR-D = mismatch repair - deficiency
MRI = magnetic resonance imaging
MSI-H = microsatellite - instability-high
PD-1/PD-L1 = programmed death-1/programmed death - ligand 1
PEM-M = pembrolizumab and mitotane

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Introduction: Advanced adrenocortical carcinoma has a poor prognosis and is treated with chemotherapy that includes mitotane with etoposide, doxorubicin, and cisplatin as first-line therapy. However, second-line therapy has not been determined yet. Pembrolizumab has been approved for high microsatellite instability for which standard treatments have failed.

Case presentation: Here, we present a patient with advanced adrenocortical carcinoma treated with complete surgical resection. 21 months later, he had local and metastatic recurrences. After four cycles of first-line therapy, we switched to pembrolizumab because microsatellite instability-high was detected in his tumor. He has received mitotane and pembrolizumab for 15 months, and this has exerted a radiographical response without severe adverse events.

Conclusion: We presented a patient with microsatellite instability-high advanced adrenocortical carcinoma treated with pembrolizumab and mitotane.

Key words: adrenocortical carcinoma, microsatellite instability, mitotane, pembrolizumab, tumor-agnostic treatment.

Keynote message

All patients with advanced ACC should be investigated for MSI-H/MMR-D to explore the possibility of treatment with pembrolizumab. Pembrolizumab may be effective for advanced ACC regardless of MSI status, and it may also be more effective for advanced ACC with MSI-H. The efficacy and safety of PEM-M remain unclear. A further clinical trial is needed.

Introduction

ACC is a rare malignant tumor with an estimated incidence of 0.7–2.0 cases per 1 million population per year and a poor prognosis, with a 5-year survival rate of 15–44%.[1,2] Complete surgical resection is needed to give a good prognosis for patients with localized ACC and even recurrent or metastatic ACC.[3] A randomized control trial demonstrated the efficacy and safety of mitotane (4 g/day) in combination with etoposide (100 mg/m^2 on Days 5 to 7), doxorubicin (20 mg/m^2 on Days 1 and 8), and cisplatin (40 mg/m^2 on Days 2 and 9) every 4 weeks.[4] EDP-M therapy is considered a first-line treatment for unresectable ACC. However, median progression-free survival and overall survival were only 5.6 and 14.8 months, respectively, and the rate of serious AEs was 58%. Second-line therapy has not been determined yet.

A large-scale study showed clinical benefits for all MSI-H/MMR-D solid tumors that had progressed during prior treatment.[5] Pembrolizumab is the first tumor-agnostic treatment to be based on cancer's genetic and molecular features regardless of the cancer type or the primary location of the cancer in the body. Tumor-agnostic treatment would be expected to result in a change in management for advanced ACC. Here we report a case of metastatic ACC with MSI-H, treated with PEM-M following EDP-M therapy.

Case presentation

A 38-year-old man presented to our hospital with a complaint of left abdominal pain. A CT scan and MRI revealed an 11 × 10 × 8 cm tumor of the left adrenal gland with tumor thrombosis to the inferior vena cava but with no evidence of metastasis (Fig. 1a,b). I-123 metaiodobenzylguanidine scintigraphy revealed no accumulation in the tumor. An endocrine evaluation did not reveal any remarkable findings. He was diagnosed with ACC with T4N0M0 (stage III) by The European Network for the Study of Adrenal Tumors classification. He underwent open left adrenalectomy, nephrectomy, and thrombectomy. The pathology report revealed a full score for the Weiss criteria, Ki-67 of 11%, and complete resection (Fig. 1c).[6] Adjuvant therapy was not administered. 21 months later, he had local and metastatic recurrences at the wall of the inferior vena cava, lung, and liver (Fig. 2a–c). He received EDP-M every 4 weeks. When we examined an archived sample of his tumor tissue for MSI during treatment with EDP-M, MSI-H was identified. As his grandfather had a history of stomach cancer, the possibility of Lynch syndrome was considered, and we recommended germline genetic panel testing, but he declined. Although the patient received four cycles of EDP-M, he experienced severe AEs, including grade 3 fatigue, grade 3 diarrhea, grade 3 nausea and vomiting, and grade 4 neutropenia. A CT scan was performed after two and four cycles of EDP-M and revealed stable disease according to the response evaluation criteria in Solid Tumors (version 1.1) (Fig. 2d–f). Given that he had severe AEs and the result of MSI-H despite no evidence of radiographical progression, we decided to switch to PEM-M (mitotane; 4 g/day, pembrolizumab; 200 mg every 3 weeks). He has not experienced any severe AEs. He has received PEM-M for more than 15 months, and a CT scan showed a long-lasting radiographical response (Fig. 2g–i).

Discussion

MSI-H was detected in 4.4% of ACC.[7] Genomes of MMR-D tumors have MSI-H and harbor somatic mutations that encode neoantigens that can trigger a human immune response.[8] Pembrolizumab, an anti-PD-1 monoclonal antibody, can enhance this human immune response by reducing PD-1-mediated immune downregulation. Inhibitors of immune checkpoints such as an anti-PD-1 (nivolumab, pembrolizumab), an anti-PD-L1 (avelumab), and a cytotoxic T-lymphocyte-associated antigen 4 (ipilimumab) have been studied for advanced ACC after first-line treatment, and exerted objective response rates of 6% to 23%.[9–13] The efficacy and safety of pembrolizumab alone for advanced ACC were proven, regardless of MSI, the PD-L1 status, and the tumor mutation burden. Median progression-free survival and median overall survival were 2.1 and 24.9 months, respectively, as second-line or later therapy.[9] Grade 3 or higher AEs were observed in 20% of patients, which is lower than the rate of 58% in EDP-M therapy.[14] An objective response of SD or more was observed in 4 (67%) of 6 patients with MSI-H, compared with 11 (34%) of 32 patients without MSI-H, which suggests that MSI-H is a useful biomarker to determine the use of immune checkpoint inhibitors for ACC.[9]

When switching EDP-M to pembrolizumab in the present case, we decided to continue mitotane, although the efficacy and safety of PEM-M remain unclear. Given the proven benefit of mitotane monotherapy for ACC and the fact that AEs were the primary reason for discontinuation of EDP-M, we considered the possibility that the antitumor effect of mitotane was maintained.[15] Head *et al*. reported a case treated with PEM-M in which all six patients with metastatic ACC survived for at least 16 months after initiating combined therapy.[16] A radiographical complete response after four cycles of PEM-M was reported in a patient with metastatic ACC.[17] This, as well as the pembrolizumab monotherapy discussed above, might be expected to provide a durable response. However, it was shown that patients receiving concomitant mitotane had a higher rate of grade 3 or higher AEs than those receiving pembrolizumab alone, particularly elevation in liver enzymes.[14] Although our patient had no severe AEs, it is necessary to make a careful decision concerning the use of concomitant mitotane. Further research through clinical trials is necessary to assess the efficacy and safety of this combination therapy.

Cancer therapy is progressing toward tumor-agnostic treatment with the goal of achieving precision medicine. In

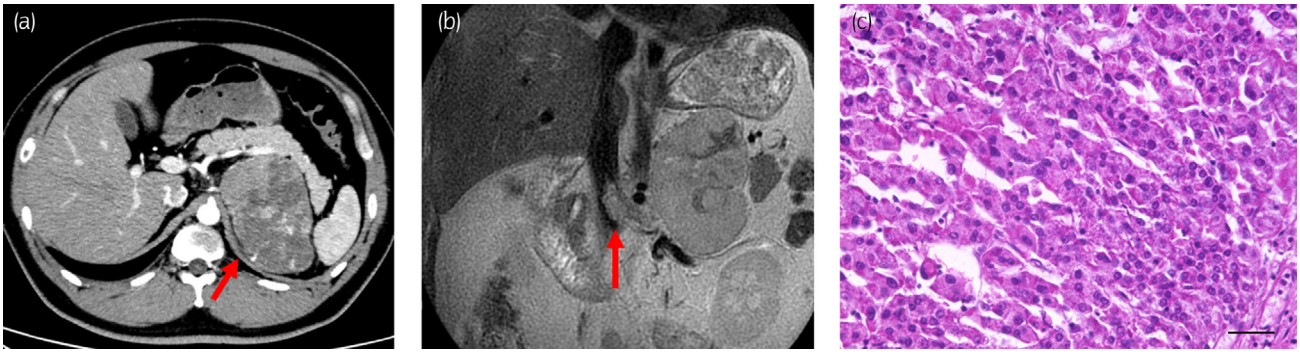

Fig. 1 Axial image of abdominal CT indicating an 11 × 10 × 8 cm mass on the left adrenal gland (a). Coronal image of T2-weighted abdominal MRI showing a tumor thrombosis of the left adrenal vein to the inferior vena cava (b). Hematoxylin–eosin histology shows a high nuclear grade, mitotic rate > 5/50 high-power fields, atypical mitoses, clear cells composing 25% or less of the tumor, diffuse architecture, necrosis, venous invasion, sinusoidal invasion, and capsular invasion, which led to a full score for the 9 Weiss criteria (scale bar = 50 μm) (c).

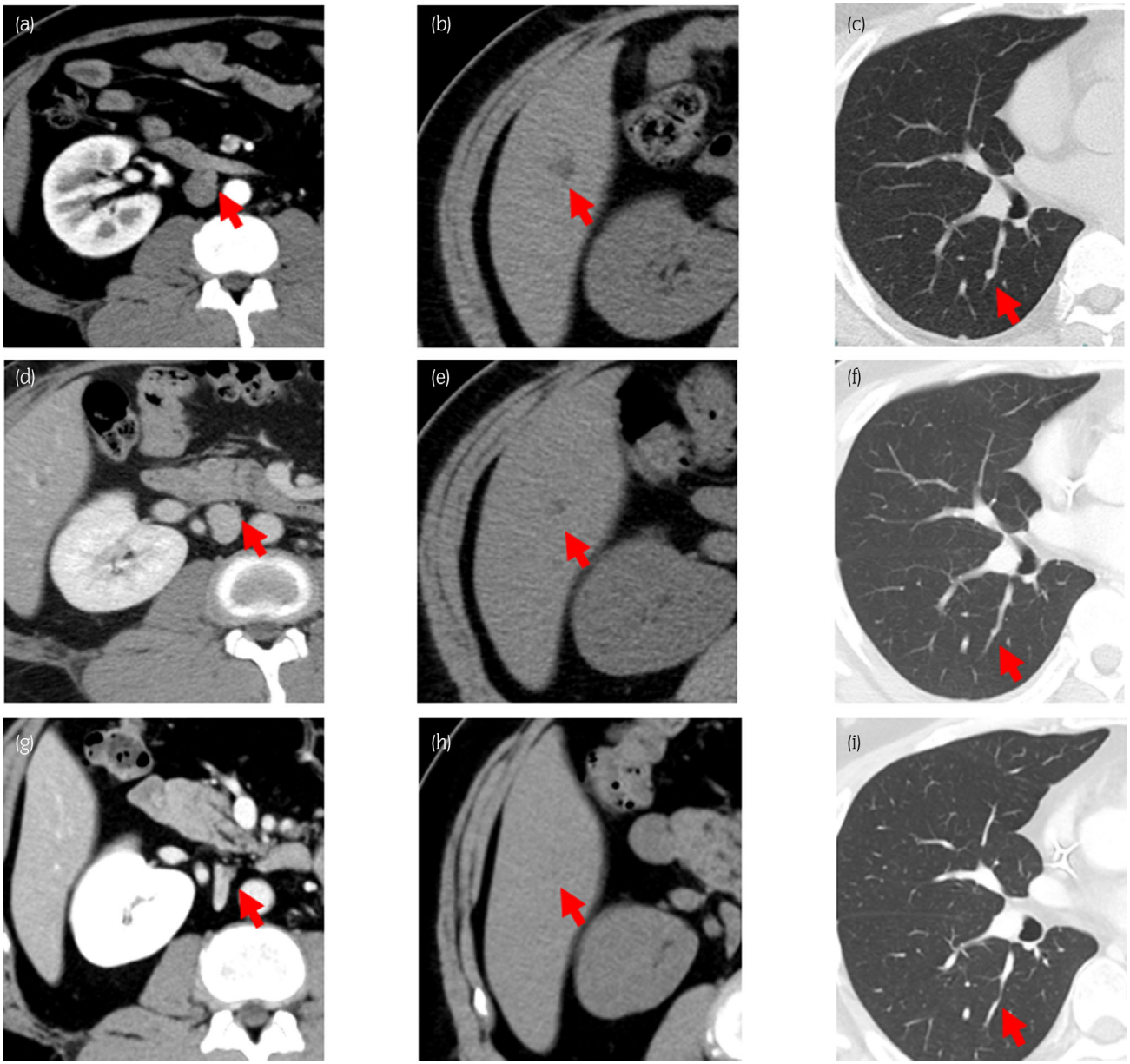

Fig. 2 Before EDP-M (a–c), after four cycles of EDP-M (d–f), and after 15 months of PEM-M (g–i). Axial image of abdominal and chest CT indicating a 10 mm mass of the inferior vena cava (a), a 13 mm mass at segment six of the liver (b), and a 6 mm mass at segment six of the lung (c) before EDP-M. Axial image of abdominal and chest CT indicating a 4 mm mass of the inferior vena cava (d), a 7 mm mass at segment six of the liver (e), and a 4 mm mass at segment six of the lung (f) after four cycles of EDP-M, which were in a stable disease state. Axial image of abdominal and chest CT indicating a 7 mm mass of the inferior vena cava (g), disappearance of the mass of segment six of the liver (h), and disappearance of the mass of segment six of the lung (i) after 15 months of PEM-M, indicating a partial response.

advanced ACC, as in this case, it may be useful to evaluate genomic variants and determine an appropriate time to discontinue EDP-M therapy.

Conclusion

We reported a case treated with PEM-M therapy for metastatic ACC with MSI-H. All patients with advanced ACC should be investigated for MSI-H/MMR-D to explore the possibility of treatment with pembrolizumab.

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Author contributions

Masaya Senda: Conceptualization; visualization; writing – original draft. Kohei Hashimoto: Conceptualization; investigation; supervision; visualization; writing – original draft.

Tetsuya Shindo: Conceptualization; supervision. Ko Kobayashi: Conceptualization; supervision. Toshiaki Tanaka: Conceptualization; supervision. Naoya Masumori: Conceptualization; supervision; writing – review and editing.

Conflict of interest

The authors declare no conflict of interest.

Approval of the research protocol by an Institutional Reviewer Board

Not applicable.

Informed consent

Informed consent was obtained from the patient for the publication of this case report.

Registry and the Registration No. of the study/trial

Not applicable.

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