ISOLATED ADRENOCORTICOTROPIC HORMONE DEFICIENCY ASSOCIATED WITH PEMBROLIZUMAB THERAPY IN A PATIENT WITH ADVANCED URETER CANCER: A CASE REPORT AND LITERATURE REVIEW

TOSHIHIKO MASAGO*, TAKAHIRO HOSHINO, HIROSHI YAMAGUCHI AND TAKEHIRO SEJIMA
Division of Urology, Matsue City Hospital, Shimane, Japan

KENICHI TAKEDA
Division of Respiratory Medicine, Matsue City Hospital, Shimane, Japan

MOTOFUMI SASAKI
Division of Diabetes and Endocrinology, Matsue City Hospital, Shimane, Japan

Abstract：
Left lower ureter cancer, cT2N0M0, was identified in an 84-year-old woman, and she underwent a left radical uretero-nephrectomy at another hospital. The pathological stage was pT2, with a negative surgical margin. 6 months later, metastases of bilateral lungs were detected. Three cycles of gemcitabine and cisplatin were administered. However, the bilateral lung metastases became progressive, which prompted her introduction to our hospital. After five cycles of pembrolizumab were administered intravenously, the bilateral lung metastases diminished and were judged as complete response. After the 5th pembrolizumab administration, the patient experienced anorexia and paralysis of both arms and legs. Thus, pembrolizumab was stopped. A laboratory examination revealed a low serum cortisol level with an inappropriately low adrenocorticotropic hormone (ACTH) level. Corticotropin-releasing hormone testing demonstrated poor ACTH secretion responses and no cortisol response. We diagnosed her with isolated ACTH deficiency (IAD). Hydrocortisone was administered, and her general condition gradually improved. One year later, her cortisol level was so low that required hydrocortisone. No evidence of the progressive change was noted in the scar at the bilateral lung metastases without pembrolizumab administration. (Nishinihon J. Urol. **85**: 76-82, 2023)

Key words：isolated ACTH deficiency, pembrolizumab, ureter cancer

Introduction

Until recently, patients with locally advanced or metastatic urothelial carcinoma after progression on cisplatin-containing chemotherapy had limited options for systemic treatment, and such treatments provided no significant survival benefit and had poor tolerability. Platinum-based chemotherapy was introduced; however, no internationally accepted standard for care based on this approach has been established. Immune checkpoint inhibitors (ICIs) are anti-cancer medications, and ICIs include agents such as programmed cell death 1 (PD-1), PD-1 ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), which enhance the antitumor immune response by blocking negative regulators of T-cell function[1]. The ICI pembrolizumab is a secondary treatment for advanced urothelial carcinoma if the first chemotherapy with gemcitabine and platinum has failed. Although ICIs have improved the prognosis of several malignancies, new unfavorable immune-related adverse events

*Matsue City Hospital, 32-1 Noshira, Matsue, Shimane 690-8509, Japan.
Tel +81-852-60-8000, Fax +81-852-60-8005

(irAEs) have been observed in patients treated with ICIs, including pituitary dysfunction, thyroid dysfunction, type 1 diabetes mellitus, and adrenal dysfunction[2,3].

The clinical characteristics of patients with IAD—which is a form of primary pituitary dysfunction and secondary adrenal insufficiency that is specifically associated with pembrolizumab treatment—remain unknown because of the rarity of this adverse event. We herein present a case of IAD during single-agent pembrolizumab therapy for advanced ureter cancer.

Case report

At another hospital, a left lower ureter cancer was identified in an 84-year-old woman who was classified as cT2N0M0 **(Fig. 1)**. A left radical uretero-nephrectomy was performed. The pathological stage was pT2, with a negative surgical margin. Approximately 6 months later, bilateral lung metastases were detected **(Fig. 2A)**. Three cycles of gemcitabine and cisplatin were administered. However, the bilateral lung metastases became progressive. Then, the patient was introduced to our hospital. 5 cycles of pembrolizumab were administered intravenously. The lung metastases were completely scarred **(Fig. 2B)**. However, after the 5th pembrolizumab administration, the patient experienced anorexia and paralysis of both arms and legs. Laboratory tests demonstrated a low serum cortisol level with an inappropriately low ACTH level and hypoglycemia. Magnetic resonance imaging (MRI) revealed no evidence of eosinophilia or pituitary tumor. The patient's response to rapid ACTH testing was poor. On a corticotropin-releasing hormone test, there was no cortisol response but only a poor ACTH secretion response. The values of other anterior pituitary hormones on the challenge tests were all unre-

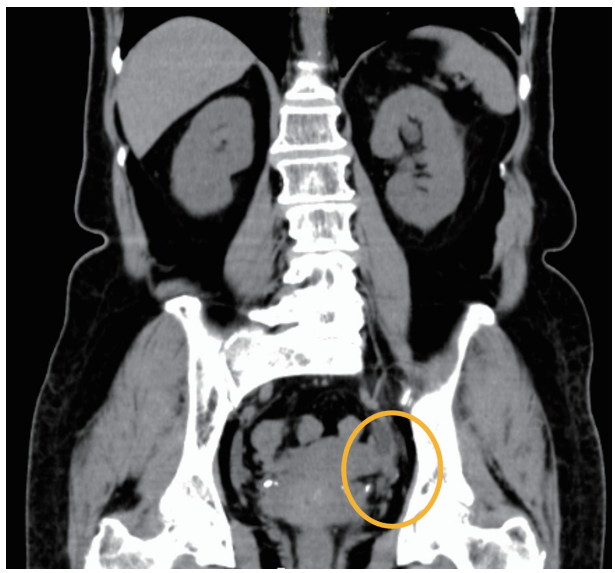
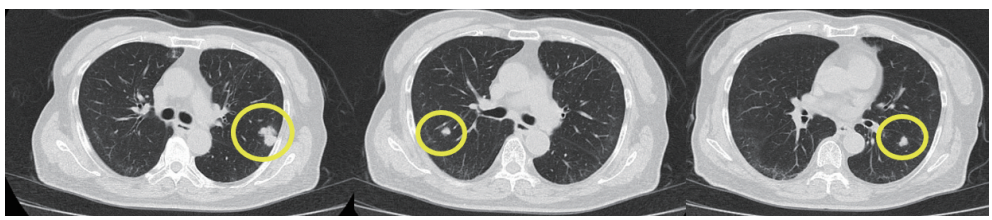
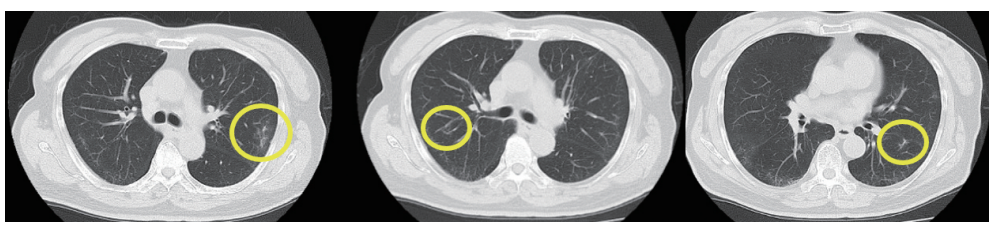


Fig. 1 Abdominal CT scan detected a solid mass at the left ureter (circle).



A



B

Fig. 2 **A** : Chest CT scan detected some metastases of the bilateral lungs (circle).
B : After 5 cycles of pembrolizumab were administered, the lung metastases were scarred (circle).

markable (**Fig. 3**). Abdominal computed tomography (CT) showed no change in the adrenal glands. Thus, we diagnosed this case as IAD. Hydrocortisone 15 mg/day was initiated, and the patient's general condition gradually improved. ACTH levels were not detectable on any occasion during the observation period.

One year, later without pembrolizumab administration, no changes in the scars at the patient's lung metastases were observable, whereas her cortisol levels ranged from 12.8 to 19.9 μg/dL.

Discussion

Immune checkpoint inhibition targeting PD-1 has shown substantial potential for the treatment of several malignancies including urothelial cancer. The PD-1 inhibitor pembrolizumab has demonstrated a beneficial effect against urothelial carcinoma in patients with chemotherapy failure[4]. However, some adverse autoimmunity-related events have been associated with pembrolizumab. To the best of our knowledge, 28 cases of IAD associated with the PD-1 inhibitors were reported. Even among them, the present case is the sixth report of IAD in a patient treated with pembrolizumab, and only the second case in a patient with ureter cancer (**Table 1**) [5-27].

The period from the initiation of PD-1 inhibitor therapy to IAD onset differed. The average periods of nivolumab and pembrolizumab were 4.7 and 6.8 months, respectively. Nearly all the cases indicated that continued administration with PD-1 inhibitors was difficult after IAD treatment. Currently, if the condition improved, PD-1 inhibitor could be administered continuously. We had to be aware of the patient's condition because the symptoms of IAD have been nonspecific, such as headache, chest pain, anorexia, fatigue, and others[28-31]. Regarding the efficacy of the PD-1 therapy, the number of no progression disease with nivolumab was fewer than that with pembrolizumab. In the current patient, the onset of anorexia and paralysis of the arms and legs occurred approximately 1 month after the initiation of pembrolizumab, and her complete response continued without pembrolizumab. In light of the outcome of the present case, some patients may not always need additional pembrolizumab—if a patient's favorable outcome continues as a durable response.

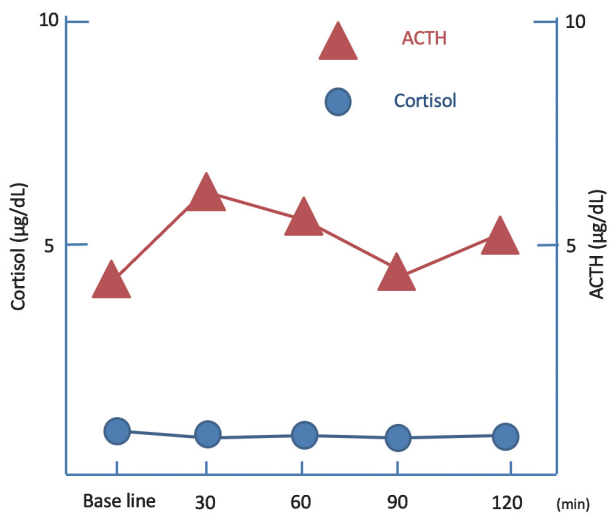


Fig. 3 Dynamic test for pituitary function revealed low ACTH and cortisol release after the administration of corticotropin-releasing hormone.

Adrenal insufficiency can be classified into primary and secondary types. When adrenal dysfunction due to a patient's ICI treatment is suspected, it is important to confirm the patient's serum cortisol, ACTH, aldosterone, and renin levels[32]. The levels of other hormones should be checked for an accurate diagnosis, for example, thyroid-stimulating hormone, free thyroxine, free tri-iodothyronine, gonadotrophins, and testosterone.

The mechanism responsible for the development of pembrolizumab-associated IAD remains unclear. ACTH-producing cells were reported to be vulnerable to anti-PD-1 therapy[33]. A study also reported that the condition of patients with pituitary-related pembrolizumab-associated IAD deteriorated; mild reductions of plasma ACTH and cortisol release that caused a decrease in adrenal functions were also described[34]. In the present case, the levels of hormones other than ACTH were unremarkable. CT and MRI did not reveal morphological changes in the pituitary gland. When IAD is suspected, it might be best to administer a dynamic test for the pituitary as soon as possible.

The treatment of adrenal insufficiency consists of systemic glucocorticoids. When an appropriate administration of ICIs was initiated, nearly all of the reported irAEs resolved themselves within weeks or months[35]. However, endocrine-related adverse

Table 1 Summary of reported cases of isolated adrenocorticotropic hormone deficiency associated with PD-1 inhibitors

No	Age	Gender	Target cancer	Period (months)	Major symptom	PD-1 inhibitors	Therapeutic effect	Authors	Year
1	50	M	Melanoma	3.5	Anorexia	Nivo	SD	Okano et al.[5]	2016
2	55	M	Melanoma	3	Anorexia	Nivo	N.D.	Ishikawa et al.[6]	2017
3	76	F	Melanoma	6	Fatigue	Nivo	SD	Cho et al.[7]	2017
4	54	M	Lung ca.	5	Fatigue	Nivo	SD	Cho et al.[7]	2017
5	64	M	Lung ca.	4.5	Fatigue	Nivo	SD	Cho et al.[7]	2017
6	57	M	Lung ca.	4.5	Appetite loss	Nivo	PD	Cho et al.[7]	2017
7	68	M	Melanoma	7	N.D.	Nivo	N.D.	Fujimura et al.[8]	2017
8	76	F	Melanoma	5	Anorexia	Nivo	N.D.	Narahira et al.[9]	2017
9	39	M	Melanoma	9	General malaise	Nivo	SD	Kitajima et al.[10]	2017
10	50	F	Melanoma	10	Fatigue	Nivo	PD	Kitajima et al.[10]	2017
11	75	M	Lung ca.	6	Appetite loss	Nivo	SD	Takaya et al.[11]	2017
12	74	M	Renal cell ca.	2.5	Appetite loss	Nivo	N.D.	Seki et al.[12]	2017
13	60	M	Lung ca.	5	Anorexia	Nivo	SD	Kastrisiou et al.[13]	2017
14	54	M	Renal cell ca.	6	Consciousness disturbance	Nivo	SD	Zeng et al.[14]	2017
15	55	M	Pulmonary pleomorphic ca.	8	Asthenia	Nivo	PR	Marchand et al.[15]	2017
16	63	F	Lung ca.	8	Anorexia	Nivo	PR	Ohara et al.[16]	2018
17	63	F	Melanoma	8	Fatigue	Nivo	SD	Ariyasu et al.[17]	2018
18	58	M	Melanoma	8	Appetite loss	Nivo	N.D.	Takebayashi et al.[18]	2018
19	55	F	Breast ductal ca.	14	Chest pain	Pembro	CR	Oristrell et al.[19]	2018
20	80	M	Melanoma	10.5	Headache	Pembro	SD	Lupi et al.[20]	2019
21	43	F	Melanoma	7	Asthenia	Nivo	PD	Lupi et al.[20]	2019
22	72	F	Melanoma	15	General malaise	Nivo	PD	Takeno et al.[21]	2019
23	71	M	Renal cell ca.	6	Appetite loss	Nivo	PD	Furubayashi et al.[22]	2019
24	69	F	Lung ca.	7	Anorexia	Nivo	PD	Ohara et al.[23]	2019
25	70	M	Urothelial ca.	4.5	Anorexia	Nivo	SD	Pierrard et al.[24]	2019
26	85	F	Lung ca.	5	Fatigue	Pembro	PR	Tanaka et al.[25]	2020
27	65	F	Cecal ca.	1.5	Fatigue	Pembro	SD	Bekki et al.[26]	2020
28	78	F	Urothelial ca.	4.5	Anorexia	Pembro	PR	Hinata et al.[27]	2021
29	84	F	Urothelial ca.	5	Anorexia	Pembro	CR	Present case	2021

M : male, F : female, CR : complete response, PR : partial response, SD : stable disease, PD : progression disease, N.D. : not determined, Nivo : nivolumab, Pembro : pembrolizumab

events would be irreversible ; thus, glucocorticoid therapy must be permanent in patients who have developed adrenal insufficiency. From this viewpoint, IAD might become more severe than other irAEs. All of the reported patients (including the current patient) who were treated with PD-1 agents needed steroid replacement therapy[36].

When IAD does not improve despite adequate steroid medications, immunosuppressive medicines such as anti-tumor necrosis factor-α, mycophenolate mofetil, and antithymocyte immunoglobulins would be necessary[37]. Careful observation of patients receiving ICIs is very important because longer-term glucocorticoid therapy may lead to additional complications such as diabetes, Cushing features, osteoporosis, opportunistic infections, and others[38].

In summary, IAD associated with pembrolizumab treatment for advanced ureter cancer is very rare. The onset of autoimmune manifestations during immunotherapy cannot be predicted at this time. More cases and further research are necessary to clarify the relationships between genetic and clinical parameters and IAD.

Conclusion

We describe a patient with advanced ureter carcinoma who developed IAD after the 5th pembrolizumab administration. The nonspecific clinical presentation can lead to a delayed diagnosis and demonstrates the need for systematic and regular hormonal evaluation, especially cortisol screening. Therefore, we should be aware of the unexpected ICI-related endocrinopathies, including IAD, while cooperating with different medical experts.

References

1) Sharma, P. et al.: Novel cancer immunotherapy agents with survival benefit: recent successes and next steps. Nat. Rev. Cancer. **11**: 805-812, 2011.
2) Barroso-Sousa, R. et al.: Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: a systematic review and meta-analysis. JAMA Oncol. **4**: 173-182, 2018.
3) Ohara, N. et al.: Isolated adrenocorticotropin deficiency due to nivolumab report and literature review. Intern. Med. **57**: 527-535, 2018.
4) Bellmunt, J. et al.: Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N. Engl. J. Med. **376**: 1015-1026, 2017.
5) Okano, Y. et al.: Nivoluma-induced hypophysitis in a patient with advanced malignant melanoma. Endocr J. **63**: 905-912, 2016.
6) Ishikawa, M. et al.: Case of hypophysitis caused by nivolumab. J Dermatol. **44**: 109-110, 2017.
7) Cho, KY. et al.: Hyponatremia can be a powerful predictor of the development of isolated ACTH deficiency associated with nivolumab treatment. Endocr J. **64**: 235-236, 2017.
8) Fujimura, T. et al.: Isolated adrenocorticotropic hormone deficiency possibly caused by nivolumab in a metastatic melanoma patient. J Dermatol. **44**: e13-14, 2017.
9) Narahira, A. et al.: Isolated adrenocorticotropic hormone deficiency associated with nivolumab therapy. J Dermatol. **44**: e70, 2017
10) Kitajima, K. et al.: Isolated ACTH deficiency probably induced by autoimmune-related mechanism evoked with nivolumab. Jpn J. Clin Oncol. **18**: 1-4, 2017.
11) Takaya, K. et al.: Isolated adrenocorticotropic hormone deficiency caused by nivolumab in a patient with metastatic lung cancer. Intern. Med. **56**: 2463-2469, 2017.
12) Seki, T. et al.: Secondary adrenal insufficiency following nivolumab therapy in a patient with metastatic renal cell carcinoma. Tokai J. Exp. Clin. Med. **42**: 115-120, 2017.
13) Kastrisiou, M. et al.: Nivolumab-induced hypothyroidism and selective pituitary insufficiency in a patient with lung adenocarcinoma: A case report and review of the literature. ESMO. Open. **2**: e000217, 2017.
14) Zeng, MF. Et al.: Primary hypothyroidism and isolated ACTH deficiency induced by nivolumab therapy: Case report and review. Medicine (Baltimore), **96**: e8426, 2017.
15) Marchand, L. et al.: Nivolumab-induced acute diabetes mellitus and hypophysitis in a patient with advanced pulmonary pleomorphic carcinoma with a prolonged tumor response. J. Thorac. Oncol. **12**: e182-184, 2017.
16) Ohara, N. et al.: Isolated adrenocorticotropin deficiency due to nivolumab-induced hypophysitis in a patient with advanced lung adenocarcinoma: A case report and literature review. Intern. Med. **57**: 527-535, 2018.
17) Ariyasu, H. et al.: Thyrotoxicosis and adrenocortical hormone deficiency during immune-checkpoint inhibitor treatment for malignant melanoma. In Vivo. **32**: 345-351, 2018.
18) Takebayashi, K. et al.: Isolated adrenocorticotropic hormone deficiency and severe hypercalcemia after Isolated adrenocorticotropic hormone deficiency and severe hypercalcemia after

destructive thyroiditis in a patient on nivolumab therapy with a malignant melanoma. J. Clin. Med. Res. **4**: 358–362, 2018.

19) Oristrell, G. et al.: Cardiac tamponade and adrenal insufficiency due to pembrolizumab: a case report. Eur. Heart J. Case Rep. **3**: 1–5, 2018.

20) Lupi, I. et al.: Clinical heterogeneity of hypophysitis secondary to PD-1/PD-L1 blockade: insights from four cases. Endocrinol. Diabetes Metab. Case Rep. DOI: 10.1530/EDM-19-0102, 2019.

21) Takeno, A. et al.: late-onset isolated adrenocorticotropic hormone deficiency caused by nicolumab: A case report. BMC. Endocr. Disord. **19**: 25, 2019.

22) Furubayashi, N. et al.: Isolated adrenocorticotropic hormone deficiency potentially induced by nivolumab following pseudo-progression in clear cell renal cell carcinoma: A case report. Mol. Clin. Oncol. **10**: 304–308, 2019.

23) Ohara, N. et al.: Isolated adrenocorticotropic hormone deficiency and thyroiditis associated with nivolumab therapy in a patient with advanced lung adenocarcinoma: A case report and review of the literature. J. Med. Case. Rep. **13**: 88, 2019

24) Pierrard, L. et al.: Isolated adrenocorticotropic hormone (ACTH) deficiency and Dullian-Barre-syndrome occurring in a patient treated with nivolumab. BMJ. Case. Rep. **12**: e230848, 2019.

25) Tanaka, S. et al.: Isolated ACTH deficiency during single-agent pembrolizumab for squamous cell lung carcinoma: case report. Clin. Diabetes Endocrinol. **6**: 1, 2020.

26) Bekki, T. et al.: A case of isolated adrenocorticotropic hormone deficiency caused by pembrolizumab. Case Rep. Oncol. **13**: 200–206, 2020. doi: 10.1159/000505687

27) Hinata, Y. et al.: Isolated adrenocorticotropic hormone deficiency associated with severe hyperkalemia during pembrolizumab therapy in a patient with ureteral cancer and an ileal conduit: a case report and literature review. Am. J. Case Rep. **15**: 22: e931639, 2021.

28) Robert, C. et al.: Pembrolizumab versus ipilimumab in advanced melanoma. N. Engl. J. Med. **372**: 2521–2532, 2015.

29) Garon, E. B. et al.: Pembrolizumab for the treatment of non-small cell lung cancer. N. Engl. J. Med. **372**: 2018–2028, 2015.

30) Borghaei, H. et al.: Nivolumab versus docetaxel in advanced non-squamous non-small cell lung cancer. N. Engl. J. Med. **373**: 1627–1639, 2015.

31) Robert, C. et al.: Nivolumab in previously untreated melanoma without BRAF mutation. N. Engl. J. Med. **372**: 320–330, 2015.

32) Hagg, E. et al.: Value of basal plasma cortisol assays in the assessment of pituitary adrenal insufficiency. Clin. Endocrinol. **26**: 2221–2226, 1987.

33) Faje, A. et al.: Hypophysitis secondary to nivolumab and pembrolizumab is a clinical entity distinct from ipilimumab associated hypophysitis. Eur. J. Endocrinol. **181**: 211–219, 2019.

34) Yamagata, S. et al.: Progression of hypopituitarism and hypothyroidism after treatment with pembrolizumab in a patient with adrenal metastasis from non-small cell lung cancer. Intern. Med. **58**: 3557–3562, 2019.

35) Champiat, S. et al.: Management of immune checkpoint blockade dysimmune toxicities: A collaborative position paper. Ann. Oncol. **27**: 559–574, 2015.

36) Weber, J. S. et al.: Management of adverse events following treatment with anti-programmed death-1 agents. Oncologist. **21**: 1230–1240, 2016.

37) Naidoo, J. et al.: Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. Ann. Oncol. **26**: 2375–2391, 2015.

38) Huscher, D. et al.: Dose-related patterns of glucocorticoid-induced side effects. Ann. Rheum. Dis. **68**: 1119–1124, 2009.

Pembrolizumab により ACTH 単独欠損症を呈した進行性尿管癌の一例

松江市立病院泌尿器科[1)]　松江市立病院呼吸器内科[2)]
松江市立病院糖尿病・内分泌内科[3)]
眞砂俊彦[1)]・星野貴洋[1)]・山口広司[1)]・武田賢一[2)]・佐々木基史[3)]
瀬島健裕[1)]

（受付日：2022 年 7 月 22 日，受理日：2023 年 1 月 10 日）

抄録：

症例は 84 歳，女性。他院にて左尿管癌で腎尿管全摘除術を実施した。病理組織学所見は，尿路上皮癌，pT2 および切除断端陰性であった。術後 6 カ月目に両側肺転移が出現し，GC 療法を 3 コース施行したが，転移巣は増大し，PD の判断にて，当科へ紹介となった。ペムブロリズマブを 5 コース施行したところ，転移巣は著明に縮小し，CR を呈したが，四肢の痺れと不穏症状及び Grade 3 の食思不振を認めたため休薬とした。ペムブロリズマブの休薬から 3 カ月が経過した際に，負荷試験で ACTH のみ無反応にて低値を示していたことから，ACTH 単独欠損症の診断にて，ヒドロコルチゾンを投与することで，状態は著明に改善した。ペムブロリズマブの休薬から 1 年が経過した現在も，転移巣は画像上 CR を維持した状態だが，ヒドロコルチゾンの内服を継続している。

（西日泌尿．**85**：76–82, 2023）

キーワード：ACTH 単独欠損症，ペムブロリズマブ，尿管癌