Hypopituitarism induced by pembrolizumab plus axitinib in the treatment of metastatic renal cell carcinoma: A case report

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Abstract. Immune checkpoint inhibitor (ICI) therapies have broadened the armamentarium for metastatic renal cell carcinoma (mRCC). As the ICI therapy spreads in the clinical settings, immune-related adverse events are more of a concern for clinicians. The present study reports three cases of mRCC treated with pembrolizumab plus axitinib and diagnosed hypopituitarism based on clinical symptoms and hormonal profile. Acute methylprednisolone infusion therapy was necessary in one case because of severe adrenal hypofunction; however, the clinical symptoms of the other two cases were controlled with oral corticosteroid therapy. To the best of our knowledge, there is no report of pembrolizumab plus axitinib related hypopituitarism in the treatment of mRCC. The present cases suggests that hypopituitarism after pembrolizumab plus axitinib treatment for mRCC can be handled with steroid therapy even after the development of hypopituitarism.

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Abbreviations: ACTH, adrenocorticotropic hormone; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; CTLA-4, cytotoxic T-lymphocyte associated antigen-4; ECOG, Eastern Cooperative Oncology Group; HDC, hydrocortisone; IAD, Isolated ACTH deficiency; ICI, immune checkpoint inhibitors; irAE, immune-related adverse events; KPS, Karnofsky Performance status; PSL, prednisolone; mPSL, methylprednisolone; mRCC, metastatic renal cell carcinoma; MRI, magnetic resonance imaging; PD-1, programmed cell death protein 1; PS, Performance status; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor

Key words: metastatic renal carcinoma, anti-programmed cell death 1-specific monoclonal antibody, tyrosine kinase inhibitor, hypopituitarism, pembrolizumab, axitinib

Introduction

The treatment of mRCC has undergone a paradigm shift from conventional immunotherapy such as interferon and interleukin, through molecular targeted drug therapy such as TKI and mTOR inhibitors, to treatment using ICI such as anti-PD-1 and anti-CTLA-4 antibodies. Currently, combination therapies such as ICI plus ICI and ICI plus TKI have shown efficacy against mRCC (1,2). Pembrolizumab, an anti-PD-1 monoclonal antibody, and axitinib, a vascular endothelial growth factor receptor TKI, demonstrated antitumor activity in patients with untreated advanced RCC in the KEYNOTE-426 clinical trial (3).

ICI reactivates immune responses that are suppressed by cancer cells, and results in the promotion of T cell attacking cancer tissue (4,5). On the other hand, it has been noted that activation of the immune response can cause immune related adverse events. In pembrolizumab plus axitinib therapy, irAEs (hypothyroidism, gastrointestinal disorders, and hepatitis) were frequently reported in more than 50% of all patients in the KEYNOTE-426 clinical trials (3). Endocrine-related irAEs are common, and endocrine disorders such as hypopituitarism, primary hypophysitis, thyroid dysfunction, hypoparathyroidism, and type 1 diabetes mellitus can be severe, and guideline-based treatment is recommended (6,7). Hypopituitarism is irAE that should be taken care, because adrenal crisis may develop and long-term hormone replacement may be required. To our knowledge, there have been no prior literature of hypopituitarism in patients with mRCC treated with pembrolizumab plus axitinib. We report three cases of pembrolizumab plus axitinib treated mRCC that resulted in clinically diagnosed hypopituitarism which required constant steroid replacement therapy.

Case report

Case 1. A 73-year-old male had previously undergone laparoscopic left nephrectomy and diagnosed clear cell carcinoma pT1b. Lung and bone metastases were discovered 11 months after surgery. The patient was diagnosed with mRCC and identified as favorable risk according to the International mRCC Database Consortium criteria. ECOG PS was 0, KPS was 100%. Pembrolizumab 400 mg every 6 weeks plus

axitinib 5 mg twice daily was started. The lung metastasis had shrunken after 2 courses of pembrolizumab, however, the patient claimed general fatigue and appetite loss. The laboratory data showed liver dysfunction (aspartate aminotransferase 288 U/l, alanine aminotransferase 638 U/l) CTCAE ver 5.0 grade 3, so pembrolizumab plus axitinib was discontinued and intravenous methylprednisolone succinate 125 mg daily was initiated. The patient has been checked viral infection such as HAV, HBV, HCV, HIV, however they were all negative. EBV was negative by checking viral capsid antigen (VCA) IgA, Epstein-Barr nuclear antigen (EBNA1) IgA. Cytomegalovirus was also negative by checking CMV IgG, IgM. With the decrease of liver enzymes, the dose of prednisolone was gradually reduced over 2 months from 60 to 2.5 mg. When prednisolone was tapered off to 0.5 mg, fatigue and decrease in appetite were observed. Laboratory data showed a decrease in ACTH (3.5 pg/ml) and cortisol (1.3 μg/dl) but no decrease in other hormone levels. Pituitary MRI to differentiate from lymphocytic hypopituitarism or pituitary tumor was not performed. The patient was diagnosed with hypopituitarism and CTCAE ver 5.0 grade 3 based on clinical symptoms and regular laboratory tests and was treated with steroid replacement. ACTH remained low (3.5 to 8.6 pg/ml) after steroid replacement, and daily oral prednisolone 1 mg was required to maintain clinical well-being of the patient (Fig. 1). Regarding the course of treatment, after discontinuation of pembrolizumab plus axitinib, the patient was followed up with no treatment. However, the disease has not progressed during the 20 months since the start of treatment.

Case 2. A 77-year-old male had undergone laparoscopic left nephrectomy and diagnosed clear cell carcinoma pT1b. Follow up CT revealed a single metastatic site in the left lung 17 years after nephrectomy. Lung metastasectomy was performed by thoracic surgery unit. Nine months after the metastasectomy, sub bronchial lymph node metastasis appeared. The patient was clinically diagnosed mRCC identified as favorable risk. ECOG PS was 0, KPS was 100%. Pembrolizumab 400 mg every 6 weeks plus axitinib 5 mg twice daily was started and the size of the sub bronchial lymph node decreased. During the third course of pembrolizumab plus axitinib, liver dysfunction CTCAE ver 5.0 grade 3 was observed. Pembrolizumab plus axitinib were stopped and oral daily prednisolone 50 mg/day was started. The dose was gradually reduced 10 mg weekly to 10 mg/day, and liver enzymes peaked out. As the dose was tapered off, the patient complained general fatigue. Laboratory data showed a decrease in ACTH and cortisol but no decrease in other hormone levels. ACTH was below detection sensitivity and cortisol ranged from l 1.0 to 2.4 pg/ml. Pituitary MRI was not performed in this case either. The patient was diagnosed with hypopituitarism CTCAE ver 5.0 grade 2 based on clinical symptoms and regular laboratory tests. The patient was consulted to an endocrinologist, and treatment was changed from prednisolone to hydrocortisone. The dose of hydrocortisone had to be kept 10 mg daily as replacement therapy (Fig. 2). After stopping pembrolizumab and axitinib, the patient was followed up without treatment, and the disease had not progressed for about 12 months since the start of treatment. Then axitinib was started as a second line therapy after the increase of sub bronchial lymph node metastasis was observed.

Case 3. A 67-year-old male had previously undergone laparoscopic right nephrectomy and diagnosed clear cell carcinoma pT3b. The patient's left lung metastatic lesion was discovered 15 years after the primary surgery and metastasectomy was performed. Multiple pancreatic metastases appeared 9 months after lung metastasectomy. The patient was diagnosed mRCC identified as favorable risk. ECOG PS was 0, KPS was 100%. Pembrolizumab 400 mg every 6 weeks plus axitinib 5 mg twice daily were started. The sizes of the pancreatic metastases decreased after the first course. The dose of pembrolizumab plus axitinib were decreased according to symptoms of adverse events such gastrointestinal disorder and general fatigue. Blood tests and pituitary MRI were used to diagnose hypopituitarism. Blood tests showed a decrease in ACTH to 17.4 pg/ml and cortisol to below detection sensitivity, and no decrease in other hormone levels. Based on clinical symptoms and various test findings, a clinically diagnosis of hypopituitarism CTCAE ver 5.0 grade 3 was made. The patient started hydrocortisone 50 mg daily administered orally. When hydrocortisone was tapered off to 10 mg daily, the patient's symptoms showed remission and worsening. The dose of hydrocortisone was then increased to 20 mg daily due to a decrease of ACTH to 3.93 pg/ml. The patient continued hydrocortisone 20 mg daily with no general fatigue (Fig. 3). Regarding the course of treatment, after 4 courses of treatment, metastases in the pancreas and liver became increased, and metastases in the left lung appeared. However, pembrolizumab plus axitinib were continued for about 17 months with volume adjustment according to the degree of adverse events, despite the increase of pancreatic and liver metastases. Meanwhile, there was no apparent worsening of hypopituitarism. After that, the patient was started on pazopanib as second line. Contrast-enhanced pituitary MRI was performed in the present case at the diagnosis of hypopituitarism (Fig. 4). MRI showed no abnormalities in the size or shape and no nodular structures.

Discussion

ICI has been demonstrated to be effective in the treatment of advanced cancers of various types and improved the treatment for malignant tumors. Some prior literatures have reported that hypopituitarism associated with anti-CTLA-4 antibodies is 1.5 to 17%, whereas that associated with anti-PD-1 antibodies is less frequent, less than 1.5% (6,8,9). In the KEYNOTE-426 study, hypopituitarism and hypophysitis induced by pembrolizumab plus axitinib occurred in only 2 (0.5%) and 13 (3.0%) of 429 patients, respectively (3,10). The frequency of hypopituitarism is reported to be very rare, however, we have experienced in 3 out of 5 patients treated with pembrolizumab plus axitinib in our hospital. This may have been associated with multiple factors such as clinical course, patient background, environmental factors, or genetic predisposition. There might be chances that the patients' status is different from that in the clinical trials which diverge from actual clinical practice. In terms of patient background, all patients were male, their medical history was unremarkable except for hypertension and hyperuricemia, which were already treated. What was uncommon in the clinical course was the steroid treatment for liver dysfunction which were prescribed in two of the three patients before the onset of hypopituitarism.

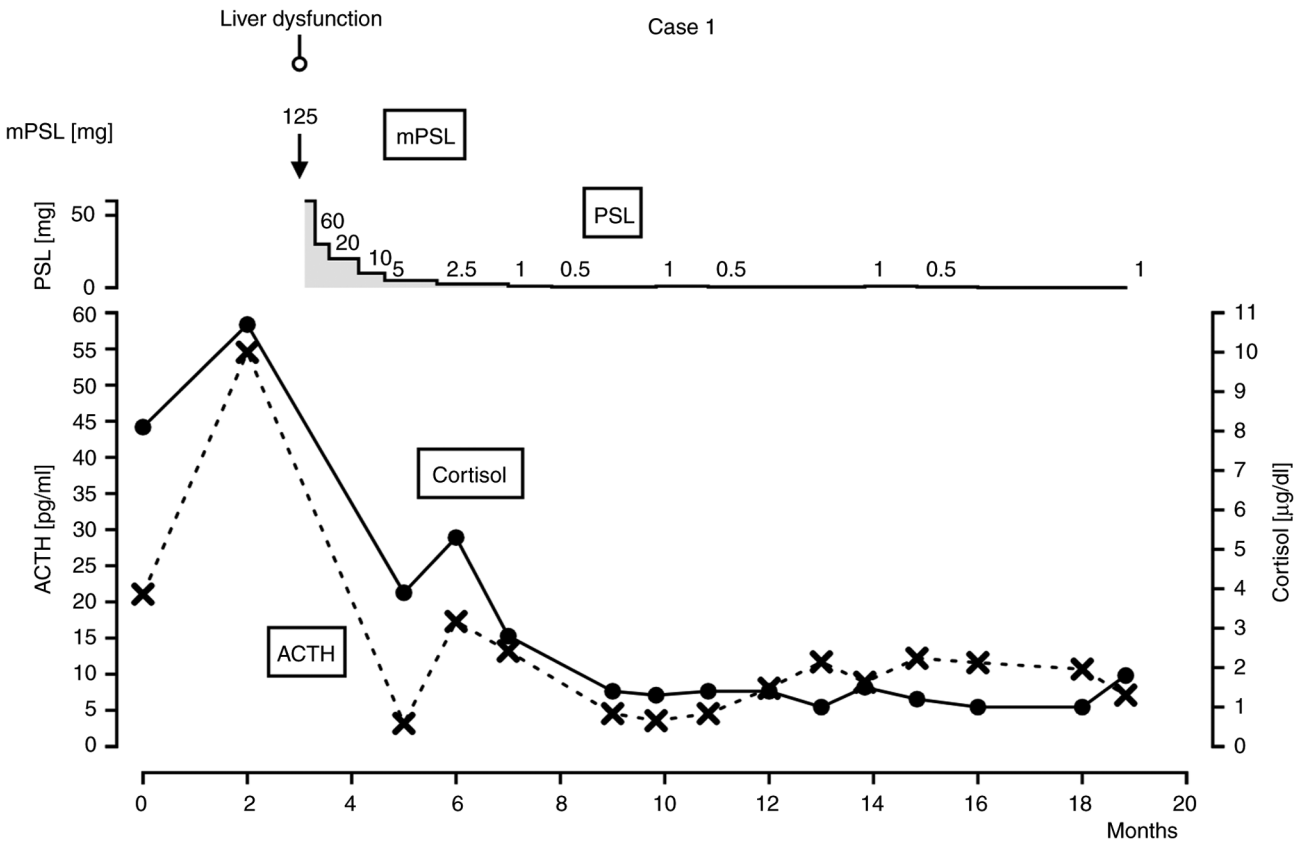

Figure 1. Clinical course of case 1. After administration of pembrolizumab plus axitinib, the time course of ACTH (pg/ml), cortisol (μg/dl) and prednisolone dosage. ACTH, adrenocorticotropic hormone; PSL, prednisolone; mPSL methylprednisolone.

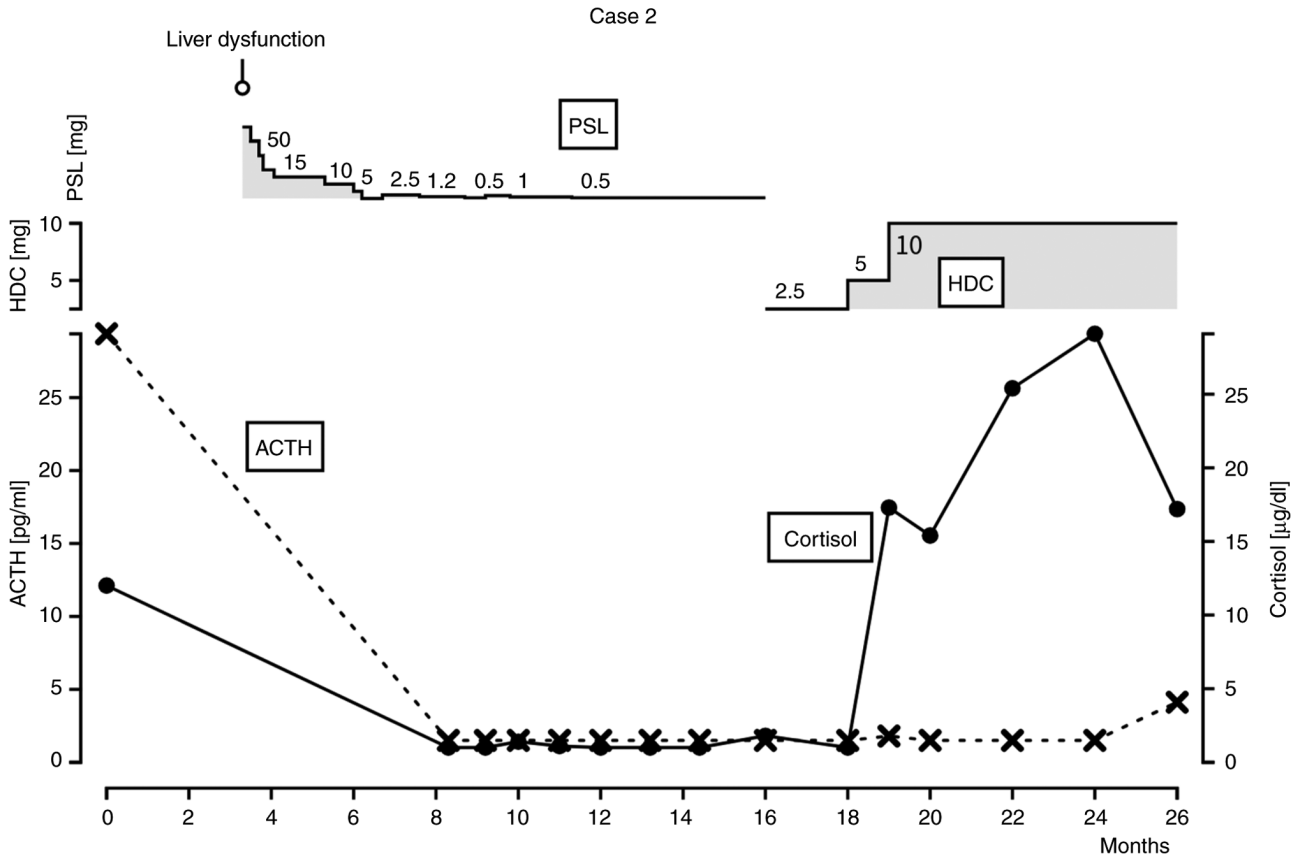

Figure 2. Clinical course of case 2. After administration of pembrolizumab plus axitinib, the time course of ACTH (pg/ml), cortisol (μg/dl) and prednisolone dosage. ACTH, adrenocorticotropic hormone; PSL, prednisolone; HDC, hydrocortisone.

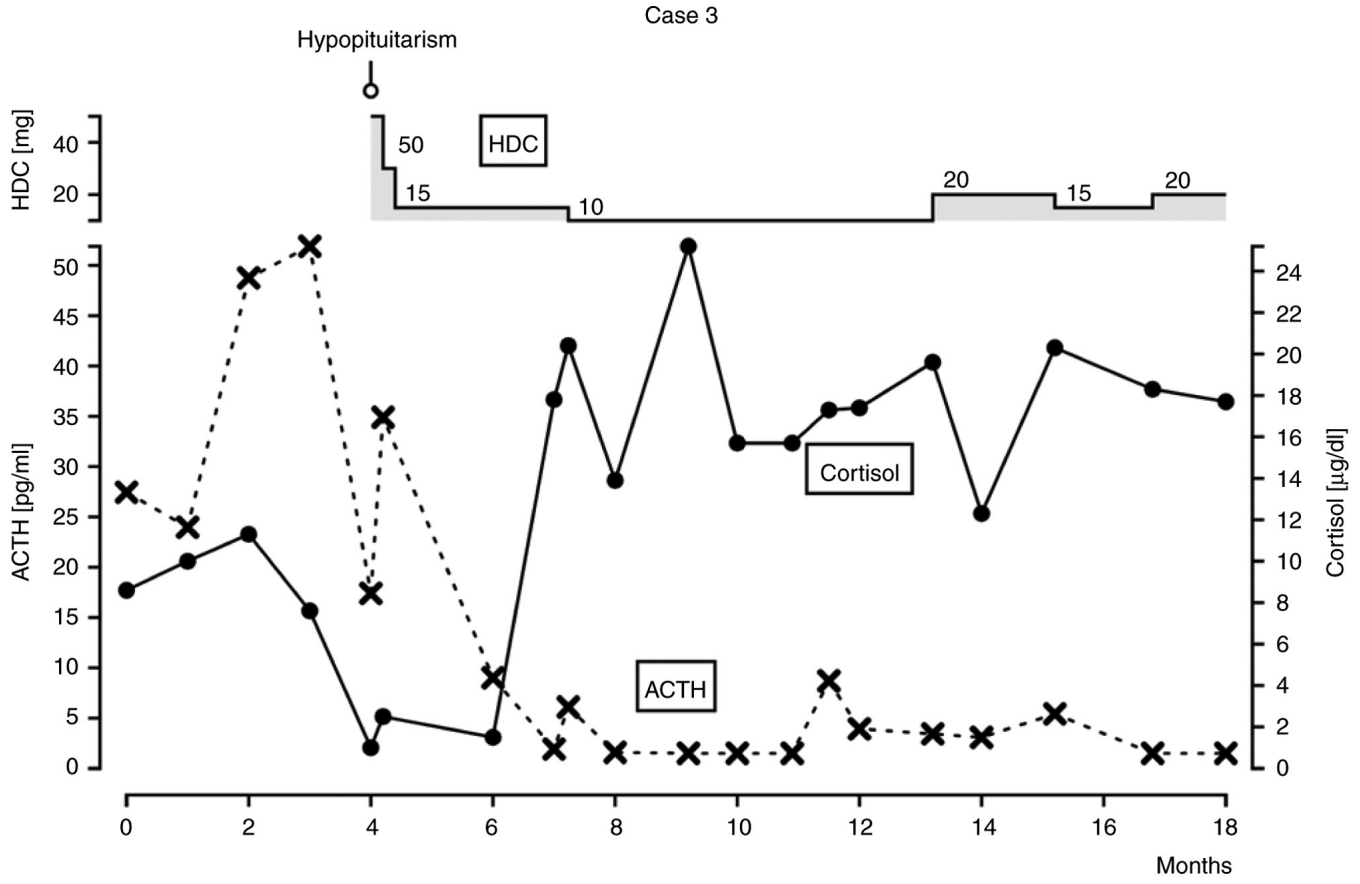

Figure 3. Clinical course of case 3. After administration of pembrolizumab plus axitinib, the time course of ACTH (pg/ml), cortisol (μg/dl) and prednisolone dosage. ACTH, adrenocorticotropic hormone; HDC, hydrocortisone.

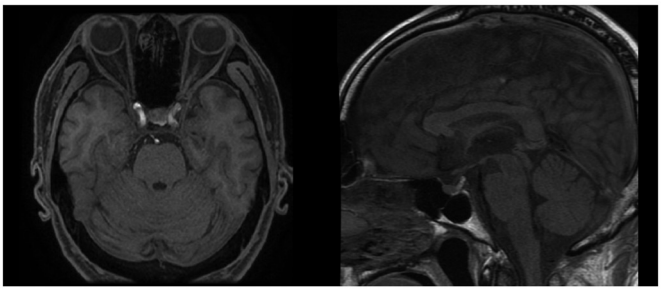

Figure 4. T1-weighted sagittal pituitary magnetic resonance imaging showed no abnormalities in the size or shape and no nodular structure.

Hypopituitarism induced different hormone type defects, depending on the type of ICI used. CTLA-4 inhibitor therapy often results in impaired secretion of thyroid-stimulating hormone (TSH), luteinizing hormone (LH)/follicle-stimulating hormone (FSH), as well as impaired ACTH secretion (11,12). On the other hand, anti-PD-1 antibodies induce IAD more commonly (13-15). In fact, in a report including 16 cases of hypopituitarism caused by anti-PD-1 antibodies alone, 14 cases induced IAD (13). The detailed mechanism of hypopituitarism is unknown, but previous studies have hypothesized that ICI itself directly attacks secretory cells in the pituitary gland, or that ICI activates autoimmunity and induces autoantibodies (11,13).

It is also thought that anti-CTLA-4 antibodies and anti-PD-1 antibodies may have different mechanisms (13). A study on the mechanism of hypopituitarism induced by anti-CTLA-4 antibodies reported that one of the causes is that anti-CTLA-4 antibodies induce a direct interaction with CTLA-4 ectopically expressed on secretory cells in the pituitary gland, inducing complement-dependent cell damage to the pituitary gland (11). On the other hand, PD-1 has not been reported to be ectopically expressed on secretory cells in the pituitary gland, making it unlikely that anti-PD-1 antibodies act directly on the pituitary gland to cause hypopituitarism. Kanie *et al* (13) hypothesized that ectopic ACTH expression in tumors can evoke autoreactive T-cell activation and ICI administration can enhance the autoimmunity, ultimately resulting in the specific injury of corticotrophs and ACTH deficiency. This hypothesis is consistent with reports of a higher frequency of IAD in hypopituitarism caused by anti-PD-1 antibodies (15,16) and with this report. To evaluate the three cases in this report for ectopic expression of ACTH from tumor cells, immunostaining for ACTH was performed on specimens of the primary renal tumor in Case 1 and on specimens of lung metastases in Cases 2 and 3, however, no ectopic expression of ACTH was found in either case. In Case 2 and 3, the expression in the primary tumor could not be evaluated because the kidney specimens were not available due to the time since the surgery of the primary tumor. Kanie *et al* (13) also reported that some cases of hypopituitarism did not show ectopic expression of ACTH, and it is possible that the ectopic expression was transient and difficult to detect.

The irAE in our cases were treated the appropriate medication volume (16), and it is unlikely that the suppression of the hypothalamic-pituitary-adrenal axis due to long-term high-dose steroid administration is the primary cause of hypopituitarism. Considering previous studies, it is likely that there is some relationship, such as the pituitary gland receiving negative feedback from steroid therapy was more prone to hypopituitarism due to the involvement of autoimmunity induced by anti-PD-1 antibodies. When comparing the incidence of irAE in our hospital with the general incidence, we can hypothesize that hypopituitarism may occur more frequently after the treatment of irAE by steroid. A retrospective study of 22 patients with mRCC treated with ipilimumab plus Nivolumab combination therapy reported hypopituitarism in 41% of all patients (17). The incidence of hypophysitis and hypopituitarism, which may be included in hypopituitarism in the checkmate 214 study, is 5 and 3%, respectively, indicating that some racial difference might be related (18). Another concern is that most patients with hypopituitarism has previously experienced irAEs in Takagi's report when compared with Checkmate 214 study. Although there is no description of therapies of irAE in Takagi's report (17). It can be suggested that steroid therapy might be used to treat irAEs in this report. Limitation of this report include the number of patients in this report is small and does not include statistical analysis and pituitary MRI was not performed in two of three cases. The two cases had no symptom of headache, visual disturbance and no hormonal disruption other than ACTH, therefore we have not considered hypophysitis and MRI were not taken. MRI was taken only in case 3 and showed no sign of hypophysitis. The reason of not performing MRI is that the patients did not show pituitary tumor related symptoms such as headache or visual disturbances. A prospective study of the relationship between steroid therapy and hypopituitarism for irAE is ideal, but it is unrealistic to conduct such studies with the addition of MRI findings and anti-pituitary antibodies.

In conclusion, the present study reports three cases of hypopituitarism in combination therapy with pembrolizumab plus axitinib for mRCC. All patients developed IAD, and two patients developed hypopituitarism after steroid therapy for irAE. Hypopituitarism is more likely to develop in patients previously prescribed steroids for irAE due to pembrolizumab plus axitinib.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

KH, NS, SK and TM conceived and designed the study. JA, YO, YK, KM, HS and TM made substantial contributions to acquisition of data, and analysis and interpretation of data. KH and NS confirm the authenticity of all the raw data and drafted the manuscript. HS, SK, and TM critically revised the manuscript. All authors agreed to the journal to which the article was submitted and agreed to take all the responsibility of the article. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of University of Yamanashi Hospital (approval no. 2616; Yamanashi, Japan).

Patient consent for publication

The patients provided written informed consent for the publication regarding their related data.

Competing interests

The authors declare that they have no competing interests.

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