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Case Report

A Case of Metastatic Fumarate Hydratase-Deficient–like Renal Cell Carcinoma Successfully Managed by Ipilimumab plus Nivolumab

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We report a 62-year-old male with metastatic fumarate hydratase-deficient renal cell carcinoma (FH-deficient RCC) without *fumarate hydratase* (*FH*) mutation (FH-deficient–like RCC). The International Metastatic RCC Database Consortium risk score was intermediate, and immunotherapy with nivolumab and ipilimumab (Ipi/Nivo) was initiated. Four cycles of Ipi/Nivo and 5 cycles of nivolumab resulted in a complete response of the metastases. Hypophysitis occurred as an immune-related adverse event after four cycles of Ipi/Nivo. The prognosis of patients with FH-deficient RCC is generally poor. Few reports of FH-deficient RCC successfully treated with Ipi/Nivo have been published. Ipi/Nivo can be effective for treating FH-deficient RCC.

Key words: fumarate hydratase, fumarate hydratase-deficient renal cell carcinoma, renal cell carcinoma, ipilimumab, nivolumab

Fumarate hydratase-deficient renal cell carcinoma (FH-deficient RCC) is a rare condition that is characterized by inactivating mutations in the *fumarate hydratase* (*FH*) gene [1]. It is known to be a cause of hereditary leiomyomatosis and renal cancer syndrome (HLRCC), an autosomal dominant disorder characterized by an inherited predisposition to early-onset uterine leiomyomas, multiple cutaneous leiomyomas, and renal cell carcinoma (RCC). FH-deficient RCC commonly presents as a locally advanced or metastatic disease and portends a poor prognosis. One report demonstrated that 71% of 32 patients with FH-deficient RCC presented with stage ≥ pT3a disease. After a median follow-up of 16 months (range, 1 to 118 months) in 26 patients, 19% showed no evidence of disease, 31% were alive with the disease, and 50% had died of the disease [2].

Immunotherapy with nivolumab, a programmed cell death protein 1 (PD-1) inhibitor and ipilimumab, a cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitor (Ipi/Nivo), has recently become a standard and important treatment regimen for metastatic RCC. Ipi/Nivo was approved as a first-line therapy for International Metastatic RCC Database Consortium (IMDC) intermediate- or poor-risk metastatic RCC by the U.S. Food and Drug Administration (FDA) in 2018. However, to our knowledge, only one case of metastatic FH-deficient RCC treated with Ipi/Nivo has been previously reported [3]. Herein we report a case of FH-deficient–like RCC (*i.e.*,

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a histologically compatible FH-deficient RCC without *FH* mutation). Thirteen months after robot-assisted partial nephrectomy was performed, lymph node and bone metastases occurred. A renal hilar lymph node metastasis was the target lesion and Ipi/Nivo resulted in a complete response (CR).

Case Report

The patient is a 62-year-old Japanese male with a good performance status. A renal mass was found incidentally in a routine ultrasound examination. His family history included renal cancer in his maternal uncle, aunt, and grandmother. Contrast-enhanced computed tomography (CT) revealed a cystic lesion with enhancing mural nodules in the left kidney (Fig. 1). The lesion was estimated to be 46×42 mm in size and the Bosniak classification was category IV. No metastatic lesions were detected. The tumor-node-metastasis clinical classification was T1bN0M0, stage I. He underwent robot-assisted partial nephrectomy.

The macroscopic appearance of the tumor was a well circumscribed lesion of 45×40 mm in size. The surgical margin was negative. Histologically, the tumor showed papillary, solid, and tubular proliferation. The tumor cells had eosinophilic cytoplasm and nuclei with prominent nucleoli surrounded by halos (Fig. 2A). Immunohistochemically, tumor cells were negative for FH, cytokeratin 7, cluster of differentiation 10 (CD10), and Wilms tumor 1 (WT-1) expression and positive for epithelial membrane antigen (EMA) and alpha-methy-

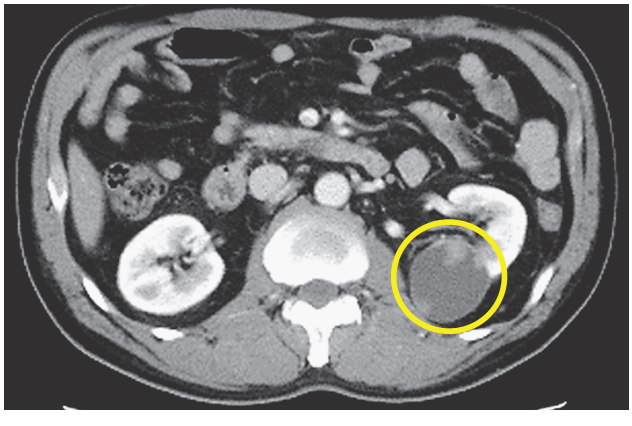

Fig. 1 CT with intravenous contrast medium showed a cystic lesion with enhancing mural nodules in the left kidney (yellow circle). The lesion was deemed 46×42 mm and the Bosniak classification was category IV.

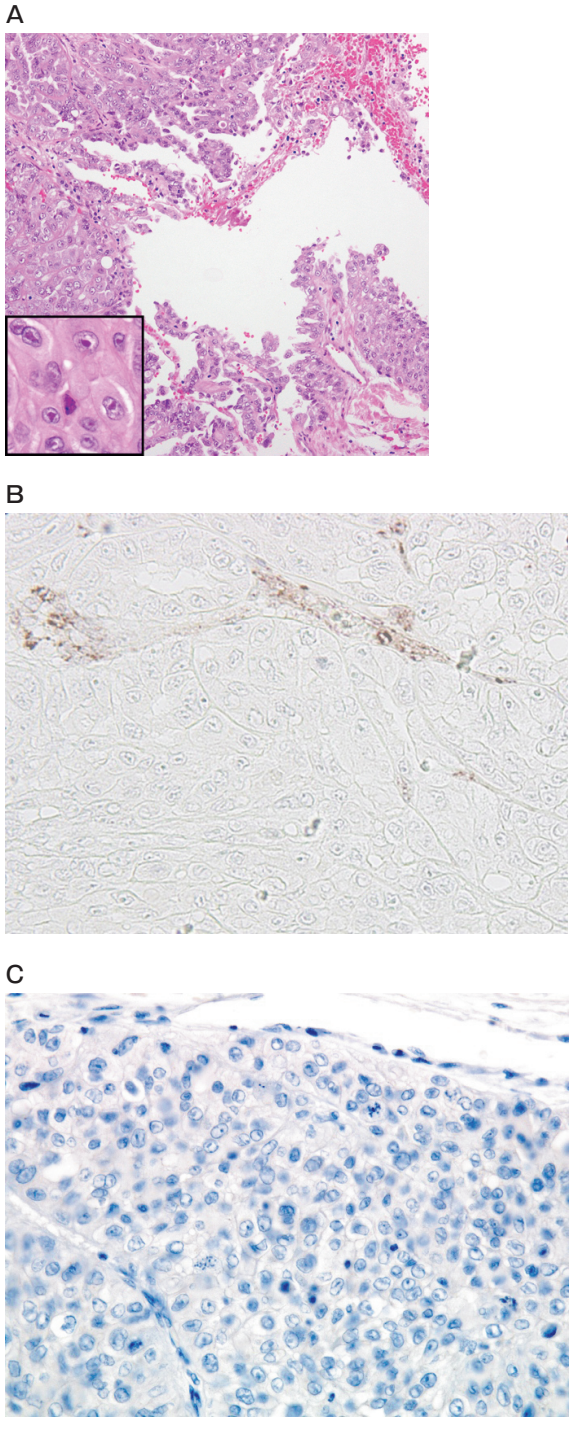

Fig. 2 A, Hematoxylin and eosin (HE) staining shows papillary proliferation. Inset. The tumor cells had eosinophilic cytoplasm and nuclei with prominent nucleoli surrounded by halos; B, Immunohistochemical staining showed no expression of fumarate hydratase (FH) in neoplastic cells, while capillary endothelial cells were positive for FH expression; C, Tumor cells were negatively stained for programmed death ligand 1 (PD-L1).

lacyl-CoA racemase (AMACR) expression (Fig. 2B). Tumor cells were negative for programmed death ligand 1 (PD-L1) expression (Fig. 2C). There were no obvious tumor-infiltrating lymphocytes (TILs). A histological diagnosis of FH-deficient RCC was made.

The patient's postoperative course was uneventful. No recurrences were observed in the first 13 months after surgery. Positron emission tomography and CT (PET-CT) at 13 months after surgery revealed left subclavicular, left renal hilar, and para-aortic lymph node metastases. PET-CT also demonstrated bone metastasis at the left fifth rib. The diameter of the hilar lymph node metastasis was 16 mm, which was the only target lesion eligible for response assessment according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria (Fig. 3A). The laboratory results were normal except for a diminished serum hemoglobin level of 13.3 g/dL (normal range, 13.7-16.8 g/dL), so the IMDC-risk score was intermediate based on a hemoglobin level below the lower limit of the normal range.

The patient was offered systemic immunotherapy consisting of intravenous nivolumab 240 mg and ipilimumab 1 mg/kg. These medications were administered every 3 weeks for 4 cycles, followed by nivolumab 240 mg alone every 2 weeks. Just after the administration of Ipi/Nivo was initiated, the patient experienced diarrhea (Grade 1 as per the Common Terminology Criteria for Adverse Events), which improved without any specific treatment within a few days. After 2 cycles of Ipi/Nivo, re-staging CT showed a partial response of the hilar lymph node metastasis, which was reduced to 10 mm (Fig. 3B). After 4 cycles of Ipi/Nivo, he complained of headache, nausea, and appetite loss for three days. Laboratory results showed decreased levels of sodium (122 mmol/L; normal range, 138-145 mmol/L), low cortisol (0.5 μg/dL; normal range, 4.0-18.3 μg/dL), and low adrenocorticotropic hormone (ACTH) (1.8 pg/mL; normal range, 7.2-63.3 pg/mL). Pituitary magnetic resonance imaging revealed no evidence of abnormalities. We suspected hypophysitis (Grade 3) as an immune-related adverse event (irAE). Treatment was initiated with corticosteroids consisting of intravenous hydrocortisone 100 mg/day for 4 days followed by oral hydrocortisone 20 mg/day. After the corticosteroid therapy, the patient's headache, nausea, and appetite loss improved, and he has continued on oral hydrocortisone 20 mg/day regularly since then. Due to hypophysitis, one cycle of nivolumab was withheld and rescheduled

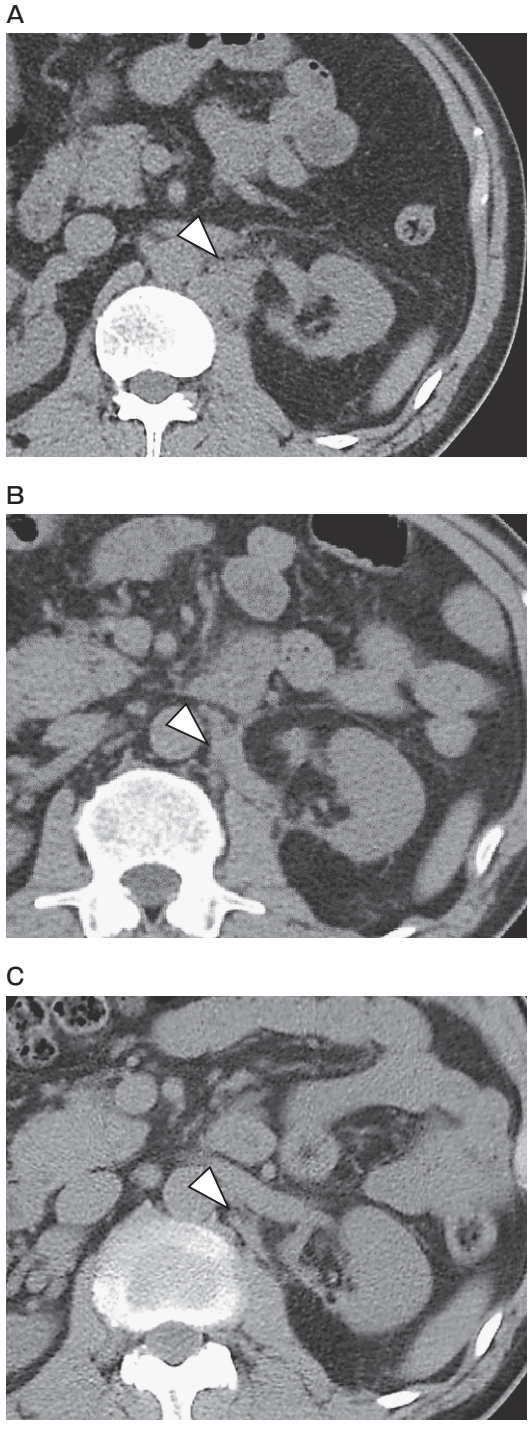

Fig. 3 **A**, A 16-mm renal hilar metastasis was detected on CT before the initiation of Ipi/Nivo; **B**, After two Ipi/Nivo treatment cycles, re-staging CT showed a partial response of the renal hilar metastasis, which was reduced to 10 mm; **C**, After four treatment cycles of Ipi/Nivo and five cycles of nivolumab, re-staging CT showed a complete response of the renal hilar metastasis, which was reduced to 6 mm.

after 2 weeks. After 4 cycles of Ipi/Nivo and one cycle of nivolumab, he experienced pruritus and redness on his lower extremities, which was considered to be asteatotic eczema. The skin lesions were resolved by treatment with topical emollients and low-potency steroids in five weeks. After four cycles of Ipi/Nivo and five cycles of nivolumab, re-staging CT showed a CR of the hilar lymph node metastasis, which was reduced to 6 mm in size (Fig. 3C). In addition, other metastatic lesions showed noticeable decreases in diameter. He has continued to receive nivolumab 240 mg monotherapy to date.

Twenty-eight months after the patient's original diagnosis, a gene panel test (FoundationOne CDx) was performed to evaluate his *FH* gene mutation status using primary tumor tissues. No genetic alterations were identified on DNA extracted from formalin-fixed, paraffin-embedded tumor samples. The patient and his family have not agreed to undergo genetic testing for germline mutations to date. The patient has been followed up and has shown no recurrence for 31 months.

Discussion

We have reported a case of metastatic FH-deficient RCC without *FH* gene mutation (FH-deficient–like RCC) that was successfully managed with Ipi/Nivo. The patient has been followed up with no recurrence for 31 months. To our knowledge, only one case of FH-deficient RCC treated with Ipi/Nivo, which resulted in a CR, has been reported [3].

FH-deficient RCC is a very rare tumor caused by mutations of the *FH* gene, which is located at 1q42.3-q43m and encodes an enzyme involved in the tricarboxylic acid cycle. This cycle hydrates fumarate to form malate [1]. FH-deficient RCC can occur sporadically, but it is also observed in syndromic and hereditary settings as part of HLRCC, an aggressive entity defined and recognized in the 2016 World Health Organization classification of renal cell tumors [4]. HLRCC is an autosomal dominant disorder that predisposes individuals to uterine and cutaneous leiomyomas and RCCs. The median age at diagnosis of patients with FH-deficient RCCs is 43 years (range, 18 to 69 years), with men more frequently affected than women (male/female ratio: 2.3: 1). Overall, 30% of patients have a family history of RCC [2]. The majority of FH-deficient RCC cases are metastatic at diagnosis or metastasize rapidly after diagnosis. The prognosis of most FH-deficient RCCs is poor, with a median survival of 18 months for patients with metastatic disease [5]. Histologically, FH-deficient RCCs show variable architectural patterns (*e.g.*, papillary, tubular, cystic, cribriform and solid). Most FH-deficient RCCs have a predominantly papillary pattern (52%), and commonly have mixed growth patterns (90% with at least 2 different patterns). Most cases show at least focal macronucleoli with perinucleolar clearing (halos) [2]. Immunohistochemistry (IHC) with anti-FH antibodies is useful for differentiating FH-deficient RCC and HLRCC from other renal tumors. FH-deficient RCC can be detected by negative IHC results using anti-FH antibodies, which are commercially available, and negative FH expression on IHC is highly specific for FH-deficient RCC. IHC with an anti-FH antibody was associated with a sensitivity of 86.0-87.5% and a specificity of 100% [6-7]. Accurate diagnosis of FH-deficient RCC can be made by performing *FH* mutation analysis [8]. In the current case, a gene panel test (FoundationOne CDx) was performed, and the tumor cells demonstrated a lack of *FH* mutations.

In the present case, some findings suggest FH-deficient RCC, *e.g.*, family history (such as renal cancer in his maternal uncle, aunt, and grandmother), certain histologic features (such as a predominantly papillary architecture mixed with other patterns within the same tumor, and eosinophilic inclusion-like macronucleoli with prominent perinucleolar halos), and negative FH expression on IHC. These findings contribute to make a histologically compatible diagnosis of FH-deficient RCC. The term "FH-deficient RCC" has also been used to describe RCCs with negative FH expression on IHC despite an unknown genetic status at pathological diagnosis [8], or RCCs with FH deficiency but lacking of evidence of *FH* germline mutation [9]. In one report, RCCs with negative FH expression on IHC and no detection of *FH* mutations were reported as unclassified RCCs or "FH-deficient–like RCCs" [7]. In the present case, no *FH* mutation was detected in a gene panel test, and this finding led us to use the term "FH-deficient–like RCC." In regard to the reason for the lack of *FH* gene mutation, we consider that the discrepancy between genetic alterations and the protein expression of FH could be explained by other mechanisms, including epigenetic alterations, which were not analyzed in the present case. Based on these findings, although it is controversial whether this case is truly a case of FH-deficient RCC, we have provided insights into the treat-

ment of FH-deficient RCCs, for which little evidence is available to date.

More recently, the efficacy of Ipi/Nivo as a treatment has shown it to be a clinically important regimen for metastatic RCC. Immunotherapy with checkpoint inhibitors, including Ipi/Nivo, is a standard and important treatment for metastatic RCC. The CheckMate 214 trial showed that the Ipi/Nivo combination has a higher overall survival rate and objective response rate than sunitinib among IMDC intermediate- and poor-risk patients with untreated clear-cell advanced RCC [10]. In 2018, Ipi/Nivo became an FDA-approved first-line treatment option for unresectable or metastatic RCC. However, few reports about the relationship between non-clear-cell RCC (nccRCC) and Ipi/Nivo have been published. The treatment of nccRCC is based on results from retrospective studies, whereas some prospective studies have recently become available [11].

In the current case, diarrhea (Grade 1), hypophysitis (Grade 3), and asteatotic eczema (Grade 1) were detected as irAEs after the initiation of Ipi/Nivo, and hypophysitis was of significant concern. Hypophysitis is not a rare irAE in patients receiving ipilimumab or checkpoint inhibitor combination therapy. Patients receiving a combination of ipilimumab and nivolumab or PD-L1 inhibitors are at a greater risk of developing hypophysitis than those on monotherapy (6.4% vs 3.4% with ipilimumab, 0.4% with nivolumab, and < 0.1% with PD-L1 inhibitors, respectively; $p = 0.0001$) [12]. Physicians should vigilantly monitor for irAEs while patients are undergoing treatment with immune checkpoint inhibitors. The development of autoimmune conditions has been correlated with a better response to ipilimumab monotherapy, particularly with respect to grade 3/4 irAEs. Immunotherapy can be postponed but should not be stopped due to hypophysitis [13].

Alaghehbandan *et al*. revealed that no association was found between PD-1/PD-L1 expression in tumor cells and TILs among 13 FH-deficient RCCs. PD-L1 expression in tumor cells was either weakly or strongly positive in 9 cases and negative in 4 cases [14]. Another study reported that 10 of 13 HRLCC-associated RCCs were positive for PD-L1 expression [15]. In the present case, tumor cells were negative for PD-L1 expression, and there were no obvious TILs. According to the classification of the tumor microenvironment based on tumor PD-L1/TIL status, this tumor can be classified as type II (a PD-L1–negative tumor with no TILs indicating immune ignorance) [16]. This finding may help to explain why single-agent checkpoint blockage is not sufficient to induce an anti-tumor response. Due to the lack of preexisting T-cell infiltrates, combinations of checkpoint inhibitors (such as Ipi/Nivo) recruit T-cells into tumors and induce T-cell responses, suggesting that Ipi/Nivo has potential efficacy for treating this type of tumor.

In conclusion, the present findings underscore the possibility that Ipi/Nivo could be an effective treatment for FH-deficient RCC. Going forward, additional studies are required to evaluate the combination of Ipi/Nivo for the treatment of patients with FH-deficient RCC.

References

1. Trpkov K, Hes O, Agaimy A, Bonert M, Martinek P, Magi-Galluzzi C, Kristiansen G, Lüders C, Nesi G, Compérat E, Sibony M, Berney DM, Mehra R, Brimo F, Hartmann A, Husain A, Frizzell N, Hills K, Maclean F, Srinivasan B and Gill AJ: Fumarate Hydratase-deficient Renal Cell Carcinoma Is Strongly Correlated With Fumarate Hydratase Mutation and Hereditary Leiomyomatosis and Renal Cell Carcinoma Syndrome. Am J Surg Pathol (2016) 40: 865–875.
2. Lau HD, Chan E, Fan AC, Kunder CA, Williamson SR, Zhou M, Idrees MT, Maclean FM, Gill AJ and Kao CS: A Clinicopathologic and Molecular Analysis of Fumarate Hydratase-deficient Renal Cell Carcinoma in 32 Patients. Am J Surg Pathol (2020) 44: 98–110.
3. Iribe Y, Furuya M, Shibata Y, Yasui M, Funahashi M, Ota J, Iwashita H, Nagashima Y, Hasumi H, Hayashi N, Makiyama K, Kondo K, Tanaka R, Yao M and Nakaigawa N: Complete response of hereditary leiomyomatosis and renal cell cancer (HLRCC)-associated renal cell carcinoma to nivolumab and ipilimumab combination immunotherapy by: a case report. Fam Cancer (2020).
4. Moch H, Cubilla AL, Humphrey PA, Reuter VE and Ulbright TM: The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs-Part A: Renal, Penile, and Testicular Tumours. Eur Urol (2016) 70: 93–105.
5. Muller M, Ferlicot S, Guillaud-Bataille M, Le Teuff G, Genestie C, Deveaux S, Slama A, Poulalhon N, Escudier B, Albiges L, Soufir N, Avril MF, Gardie B, Saldana C, Allory Y, Gimenez-Roqueplo AP, Bressac-de Paillerets B, Richard S and Benusiglio PR: Reassessing the clinical spectrum associated with hereditary leiomyomatosis and renal cell carcinoma syndrome in French FH mutation carriers. Clin Genet (2017) 92: 606–615.
6. Muller M, Guillaud-Bataille M, Salleron J, Genestie C, Deveaux S, Slama A, de Paillerets BB, Richard S, Benusiglio PR and Ferlicot S: Pattern multiplicity and fumarate hydratase (FH)/S-(2-succino)-cysteine (2SC) staining but not eosinophilic nucleoli with perinucleolar halos differentiate hereditary leiomyomatosis and renal cell carcinoma-associated renal cell carcinomas from kidney tumors without FH gene alteration. Mod Pathol (2018) 31: 974–983.
7. Pivovarčíková K, Martínek P, Trpkov K, Alaghehbandan R, Magi-Galluzzi C, Mundo EC, Berney D, Suster S, Gill A, Rychlý B, Michalová K, Pitra T, Hora M, Michal M and Hes O: Fumarate hydratase deficient renal cell carcinoma and fumarate hydratase deficient-like renal cell carcinoma: Morphologic comparative study of 23 genetically tested cases. Cesk Patol (2019) 55: 244–249.

8. Trpkov K and Hes O: New and emerging renal entities: a perspective post-WHO 2016 classification. Histopathology (2019) 74: 31–59.
9. Pan X, Zhang M, Yao J, Zeng H, Nie L, Gong J, Chen X, Xu M, Zhou Q and Chen N: Fumaratehydratase-deficient renal cell carcinoma: a clinicopathological and molecular study of 13 cases. J Clin Pathol (2019) 72: 748–754.
10. Motzer RJ, Tannir NM, McDermott DF, Arén Frontera O, Melichar B, Choueiri TK, Plimack ER, Barthélémy P, Porta C, George S, Powles T, Donskov F, Neiman V, Kollmannsberger CK, Salman P, Gurney H, Hawkins R, Ravaud A, Grimm MO, Bracarda S, Barrios CH, Tomita Y, Castellano D, Rini BI, Chen AC, Mekan S, McHenry MB, Wind-Rotolo M, Doan J, Sharma P, Hammers HJ, Escudier B and CheckMate 214 Investigators: Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. N Engl J Med (2018) 378: 1277–1290.
11. Gulati S, Philip E, Salgia S and Pal SK: Evolving treatment paradigm in metastatic non clear cell renal cell carcinoma. Cancer Treat Res Commun (2020) 23: 100172.
12. Tan MH, Iyengar R, Mizokami-Stout K, Yentz S, MacEachern MP, Shen LY, Redman B and Gianchandani R: Spectrum of immune checkpoint inhibitors-induced endocrinopathies in cancer patients: a scoping review of case reports. Clin Diabetes Endocrinol (2019) 5: 1.
13. Albarel F, Castinetti F and Brue T: MANAGEMENT OF ENDOCRINE DISEASE: Immune check point inhibitors-induced hypophysitis. Eur J Endocrinol (2019) 181: 107–118.
14. Alaghehbandan R, Stehlik J, Trpkov K, Magi-Galluzzi C, Condom Mundo E, Pane Foix M, Berney D, Sibony M, Suster S, Agaimy A, Montiel DP, Pivovarcikova K, Michalova K, Daum O, Ondic O, Rotterova P, Dusek M, Hora M, Michal M and Hes O: Programmed death-1 (PD-1) receptor/PD-1 ligand (PD-L1) expression in fumarate hydratase-deficient renal cell carcinoma. Ann Diagn Pathol (2017) 29: 17–22.
15. Furuya M, Iribe Y, Nagashima Y, Kambe N, Ohe C, Kinoshita H, Sato C, Kishida T, Okubo Y, Numakura K, Nanjo H, Nakaigawa N, Makiyama K, Hasumi H, Iwashita H, Ohta J, Kitamura H, Nakajima T, Yoshida T, Nakagawa M, Tanaka R and Yao M: Clinicopathological and molecular features of hereditary leiomyomatosis and renal cell cancer-associated renal cell carcinomas. J Clin Pathol (2020) 0: 1–7.
16. Teng MW, Ngiow SF, Ribas A and Smyth MJ: Classifying cancers based on T-cell infiltration and PD-L1. Cancer Res (2015) 75: 2139–2145.