International Cancer Conference Journal (2020) 9:32–35
https://doi.org/10.1007/s13691-019-00389-z

CASE REPORT

Complete response to combination therapy with nivolumab and ipilimumab for metastatic collecting duct carcinoma of the kidney

Kyohei Watanabe[1] · Takayuki Sugiyama[1] · Atsushi Otsuka[1] · Hideaki Miyake[1]

Received: 30 July 2019 / Accepted: 17 September 2019 / Published online: 28 September 2019

Abstract

Collecting duct carcinoma (CDC) of the kidney is a rare subtype of renal cell carcinoma (RCC) arising from the distal collecting tubules, characterized by an aggressive phenotype, unfavorable response to several types of systemic agent and a poor prognosis. Recently, treatments with immune checkpoint inhibitors have been widely performed for patients with metastatic RCC; however, no data are available regarding the impact of first-line combination therapy with nivolumab and ipilimumab on metastatic CDC. Here, we report a CDC patient with multiple lymph node metastases who underwent cytoreductive open nephrectomy and subsequently, received nivolumab and ipilimumab therapy. Following four courses of this combined therapy, all nodal metastases had shrunk to < 1 cm in diameter, and thus this patient was judged to show a complete response (CR). To our knowledge, this is the first reported case of a patient with metastatic CDC achieving a CR to combined treatment with nivolumab and ipilimumab, which could be a promising first-line therapy against metastatic CDC.

Keywords Metastatic collecting duct carcinoma · Nivolumab · Ipilimumab · Complete response

Introduction

Collecting duct carcinoma (CDC) of the kidney, also known as Bellini duct carcinoma, is a variant subtype of renal cell carcinoma (RCC), that originates in the distal collecting ducts and is estimated to comprise < 2% of all cases of RCC [1]. Clinically, CDC is characterized by a markedly aggressive phenotype, with metastatic disease spread in > 70% at diagnosis; thus, the prognosis of CDC patients is extremely poor with a median overall survival (OS) of approximately 1 year [2]. Furthermore, CDC has been reported to show an unfavorable response to several types of systemic therapy, including chemotherapeutic and molecular-targeted agents [1, 2].

The recent introduction of immune checkpoint inhibitors (ICIs), targeting major molecules mediating immune checkpoint pathways, such as programmed death-1, PD-ligand 1 and cytotoxic T-lymphocyte antigen 4, has revolutionized the therapeutic strategy for patients with advanced clear cell RCC (CCRCC) [3]. In particular, ICI-based combination therapies have become a new standard of care for patients with treatment-naïve advanced CCRCC [4–7]. For example, the combination of two ICIs, nivolumab and ipilimumab, was demonstrated to significantly prolong OS compared with sunitinib in a pivotal phase 3 trial targeting intermediate and poor-risk CCRCC patients without a previous history of treatment with systemic agents [5]. To date, however, limited information exists with respect to the efficacy of ICIs for patients with non-CCRCC, including CDC.

In this report, we describe the clinical course of a patient with CDC involving multiple lymph nodes who showed a complete response (CR) to combined treatment with nivolumab and ipilimumab introduced as a first-line therapy after cytoreductive nephrectomy.

Case report

A 44-year-old man with an 8.3 cm left renal mass and metastases involving the paraaortic and bilateral external iliac lymph nodes was referred to our institution. At the first visit, his Karnofsky performance status was 90, and there were no abnormal findings on the laboratory study, except for thrombocytosis (platelet count = $59 \times 10^4/\mu L$). The left renal tumor lacked evident enhancement in the

✉ Hideaki Miyake
hideakimiyake@hotmail.com

[1] Department of Urology, Hamamatsu University School of Medicine, Hamamatsu, Japan

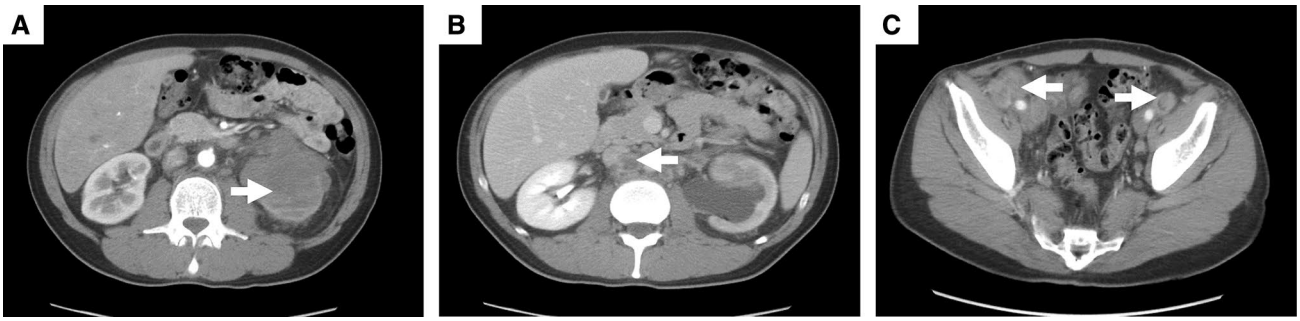

Fig. 1 Primary (**a**) and metastatic lesions (**b**, **c**) at diagnosis

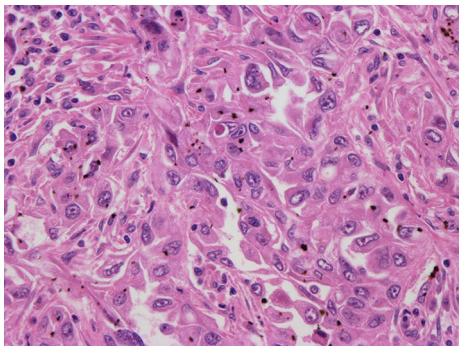

Fig. 2 Hematoxylin and eosin staining of tissue sections from the nephrectomy specimens (original magnification ×400)

arterial phase on dynamic contrast-enhanced computed tomography (CT) (Fig. 1). Under a clinical diagnosis of metastatic non-CCRCC classified into the intermediate risk group based on the International Renal Cell Carcinoma Database Consortium (IMDC) system [8], cytoreductive open left nephrectomy was performed; however, lymphadenectomy was not simultaneously conducted due to a wide range of nodal involvement. Pathological examination showed that the resected tumor was CDC (Fig. 2), pT3a and Fuhrman grade 4, with the following findings on immunehistochemical studies: strongly positive for epithelial membrane antigen and CAM5.2, weakly positive for AE1/AE3, and negative for CD10 and vimentin.

Following cytoreductive nephrectomy, combined treatment with nivolumab and ipilimumab was introduced as first-line systemic therapy. In this case, ipilimumab and nivolumab were intravenously administered at a dose of 3 mg/kg and 240 mg/body, respectively, every 3 weeks and continued for 4 courses. Thereafter, nivolumab was continuously administered every 2 weeks. After the completion of four courses of the combined treatment, CT was performed, and all metastatic lymph nodes had shrunk to < 1 cm in diameter (Fig. 3). Six months after the initiation of this combination therapy, there were no significant changes in any of the metastatic lymph nodes, and no adverse events associated with the use of ICIs were observed. Collectively, this patient was judged to show a CR to the combined therapy with nivolumab and ipilimumab.

Discussion

Collecting duct carcinoma is an uncommon and highly aggressive subtype of RCC. Although radical nephrectomy has been the mainstay for patients with localized CDC, effective systemic therapy for those with advanced diseases has not been established even after the introduction of multiple effective agents with different mechanisms of

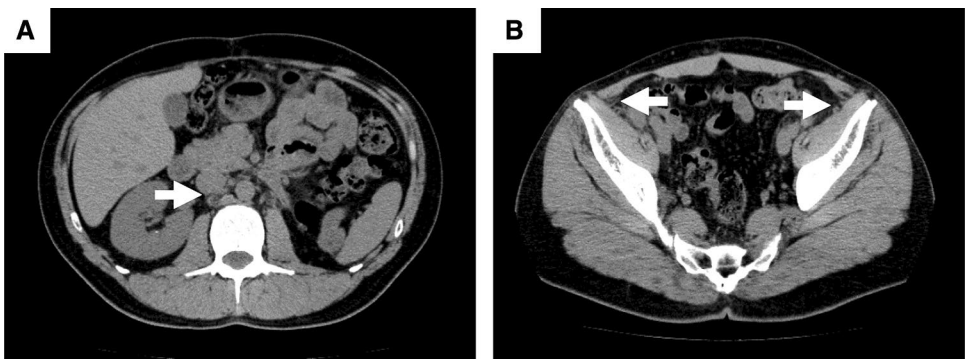

Fig. 3 Metastatic lesions after the completion of 4 cycles of combined treatment with nivolumab and ipilimumab

action against CCRCC [1, 2]. Accordingly, the prognosis of patients with CDC is still extremely poor. In fact, the majority of CDC patients have been reported to die within 3 years of the initial diagnosis [2]. Considering these findings, it is very important to explore whether novel systemic therapies, such as ICIs, could effectively control the progression of CDC and subsequently improve the prognosis of patients with this disease.

Recently conducted randomized clinical trials demonstrated that treatment of advanced RCC patients with ICIs could significantly improve the OS compared with conventional targeted agents in several therapeutic settings [4–7, 9]; thus, ICI-based systemic therapies are currently regarded as standards of care for the wide range of patients with advanced RCC. Of these, the combination of nivolumab and ipilimumab for untreated advanced RCC patients classified into either an intermediate or a poor prognosis group by the IMDC system was shown to have a better efficacy than sunitinib [5]. In particular, this combined therapy achieved a CR in 9% of included patients and was more effective for younger patients. Considering these findings, despite the absence of data on CDC, the combined treatment with nivolumab and ipilimumab was introduced for this patient. After the completion of 4 cycles of nivolumab plus ipilimumab therapy, all metastatic nodes had shrunk to < 1 cm in diameter, and the maintenance of this status was confirmed 6 months after the initiation of this combined treatment. To our knowledge, therefore, this may be an initial case with metastatic CDC who achieved a CR to the combination of nivolumab plus ipilimumab.

To date, some reports have described patients with metastatic CDC showing a response to ICIs [10–13]. For example, Rimar et al presented a patient with metastatic CDC showing a partial response to nivolumab after being refractory to chemotherapy and pazopanib [10], while Mizutani et al reported the clinical course of a patient with metastatic CDC who favorably responded to nivolumab after the failure of systemic treatment with chemotherapy and temsirolimus [11]. Based on these findings, it is of interest to investigate theoretical backgrounds associated with therapeutic impacts on CDCs. Malouf et al. recently reported a high enrichment of the immune signature in CDC tissues, including the infiltration of CD3 and CD8 cells, indicating the feasibility of treatment with ICIs for advanced CDCs [14].

Another point of interest is the significance of multidisciplinary therapy against advanced CDC. In a recently conducted retrospective study including 577 CDC patients, Sui et al reported data suggesting a survival benefit of multidisciplinary therapy with surgery plus chemotherapy and/or radiotherapy over single mode therapy on multivariate analysis [2]. In the era of ICIs, this might be specifically true considering the unique features of radiotherapy that occasionally exerts local as well as systemic immune-mediated antitumor activities [15]. In fact, radiotherapy, particularly that combined with ICIs, has been shown to induce tumor shrinkage in lesions distant from the primary site of radiation, which is recognized as the abscopal effect [16]. We also encountered two cases with metastatic CCRCC showing a markedly favorable response to combined treatment with nivolumab and radiation [17].

In this report, we presented a CDC patient with multiple lymph node metastases who underwent cytoreductive nephrectomy and subsequently received combined therapy with nivolumab and ipilimumab that induced the shrinking of all nodal lesions to < 1 cm in diameter; therefore, this may be the first case of CDC who showed a CR to the combination of nivolumab and ipilimumab. To date, treatment with either cytotoxic chemotherapeutic agents or tyrosine kinase inhibitors has been performed as first-line therapy against advanced CDC at our institution; however, based on this case, in addition to previously accumulated findings on CDC, such as the biological characteristics and prognostic benefit of multidisciplinary therapy [1, 2, 10–14], it might be strongly recommended to perform systemic treatment with ICIs, particularly that with the combination of nivolumab plus ipilimumab, for patients with advanced CDC.

Compliance with ethical standards

Conflict of interest K Watanabe, T. Sugiyama, A. Otsuka and H. Miyake have declared no conflict of interest.

References

1. Srigley JR, Eble JN (1998) Collecting duct carcinoma of kidney. Semin Diagn Pathol 15:54–67
2. Sui W, Matulay JT, Robins DJ et al (2017) Collecting duct carcinoma of the kidney: disease characteristics and treatment outcomes from the National Cancer Database. Urol Oncol 35:540.e13–540.e18
3. Atkins MB, Clark JI, Quinn DI (2017) Immune checkpoint inhibitors in advanced renal cell carcinoma: experience to date and future directions. Ann Oncol 28:1484–1494
4. Escudier B (2019) Combination therapy as first-line treatment in metastatic renal-cell carcinoma. N Engl J Med 380:1176–1178
5. Motzer RJ, Tannir NM, McDermott DF (2018) Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med 378:1277–1290
6. Motzer RJ, Penkov K, Haanen J et al (2019) Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 380:1103–1115
7. Rini BI, Plimack ER, Stus V et al (2019) Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 380:1116–1127
8. Heng DY, Xie W, Regan MM et al (2009) Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol 27:5794–5799

9. Motzer RJ, Escudier B, McDermott DF et al (2015) Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 373:1803–1813
10. Rimar KJ, Meeks JJ, Kuzel TM (2016) Anti-programmed death receptor 1 blockade induces clinical response in a patient with metastatic collecting duct carcinoma. Clin Genitourin Cancer 14:e431–e434
11. Mizutani K, Horie K, Nagai S et al (2017) Response to nivolumab in metastatic collecting duct carcinoma expressing PD-L1: a case report. Mol Clin Oncol 7:988–990
12. Yasuoka S, Hamasaki T, Kuribayashi E et al (2018) Nivolumab therapy for metastatic collecting duct carcinoma after nephrectomy: a case report. Medicine (Baltimore) 97:e13173
13. Koshkin VS, Barata PC, Zhang T et al (2018) Clinical activity of nivolumab in patients with non-clear cell renal cell carcinoma. J Immunother Cancer 6:9
14. Malouf GG, Compérat E, Yao H et al (2016) Unique transcriptomic profile of collecting duct carcinomas relative to upper tract urothelial carcinomas and other kidney carcinomas. Sci Rep 6:30988
15. Chajon E, Castelli J, Marsiglia H et al (2017) The synergistic effect of radiotherapy and immunotherapy: a promising but not simple partnership. Crit Rev Oncol Hematol 111:124–132
16. Ko EC, Formenti SC (2018) Radiotherapy and checkpoint inhibitors: a winning new combination? Ther Adv Med Oncol 10:1758835918768240
17. Matsushita Y, Nakamura K, Furuse H et al (2018) Marked response to nivolumab combined with external radiation therapy for metastatic renal cell carcinoma: report of two cases. Int Cancer Conf J 8:29–32