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Oncology

A complete response to Pembrolizumab for metastatic collecting duct carcinoma of the kidney

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A B S T R A C T

Collecting duct carcinoma, also known as Bellini duct cancer, is a rare subtype of renal cell carcinoma with a poor prognosis in the metastatic setting. There are limited data to suggest the efficacy of targeted therapy or immune checkpoint inhibitors for collecting duct carcinoma, except for small series and case reports. Herein, we present the case of a patient with collecting duct carcinoma who exhibited a complete response to pembrolizumab and long-term remission approximately 5 years after drug withdrawal.

1. Introduction

Collecting duct carcinoma (CDC) is a rare subtype of renal cell carcinoma (RCC). After diagnosis, the median survival time is 13 months, which is significantly lower than that of clear cell RCC (CCRCC). Over 70 % of patients with CDC are diagnosed with metastatic disease.[1] However, no appropriate treatment for CDC has been fully established. In recent years, patients with metastatic RCC (mRCC) have been treated with immune checkpoint inhibitors (ICIs) and molecular-targeted therapies, with numerous reports of positive outcomes. However, only a few cases of metastatic CDC (mCDC) treated with these medications exist; therefore, there is little evidence to support the efficacy of these targeted therapies, except for short-term results and case reports. Herein, we present a rare CDC case in which a complete response (CR) to pembrolizumab, a humanized anti-human programmed cell death protein 1 monoclonal antibody, and a durable response were achieved.

2. Case presentation

A 67-year-old female was assessed and treated for a left kidney tumor at our department. Contrast-enhanced computed tomography (CT) revealed a 9.0 × 7.0 cm hypovascular tumor near the lower pole of the left kidney (Fig. 1A) and some slightly enlarged para-aortic lymph nodes about 4-5 mm (Fig. 1B). The pathological results of the laparoscopic radical left nephrectomy and para-aortic lymph node dissection revealed CDC, infiltrating type, Fuhrman Grade G3, and pT3aN0 (Fig. 2A). Immunohistochemical staining revealed the presence of 34E12, CK7, 9 PAX8, p63, and vimentin, but not GATA3 (Fig. 2B). For postoperative adjuvant chemotherapy, two cycles of cisplatin plus gemcitabine (GC) therapy were administered following the NCCN (National Comprehensive Cancer Network) guidelines. However, a 5-month postoperative CT revealed liver metastases and peritoneal dissemination (Fig. 3A). Therefore, pembrolizumab (200 mg intravenously) was administered as second-line therapy every 3 weeks. CT showed an increased size of both liver metastases and peritoneal dissemination after two cycles of pembrolizumab (Fig. 3B); however, after three cycles, both shrunk (Fig. 3C). Subsequently, the metastatic lesion continued to shrink, and after seven cycles, CT showed that the metastatic lesion had completely disappeared, indicating CR (Fig. 3D). After eight cycles of pembrolizumab, skin rashes and periungual inflammation developed. Pembrolizumab was discontinued owing to the risk of immune related adverse events (AEs). Approximately 5 years after the last pembrolizumab cycle, the rashes and periungual inflammation disappeared without steroid use, and the patient remained in CR (Fig. 3E). Blood counts were retrospectively evaluated. The neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) were higher before pembrolizumab administration (6.68 and 334.8, respectively) than after pembrolizumab administration. NLR and PLR started declining after two cycles of pembrolizumab. At the time of CR, after seven cycles of pembrolizumab, NLR and PLR were 1.13 and 34.8, respectively. 5 years after pembrolizumab discontinuation, NLR and PLR remained low at 1.45 and 100.7, respectively (Fig. 4).

3. Discussion

CDC was defined in 1979 and considered a subtype of RCC. The incidence of CDC is low, accounting for 0.4 %–2.0 % of all RCC cases, and CDC is diagnosed as metastatic in approximately 70 % of cases.

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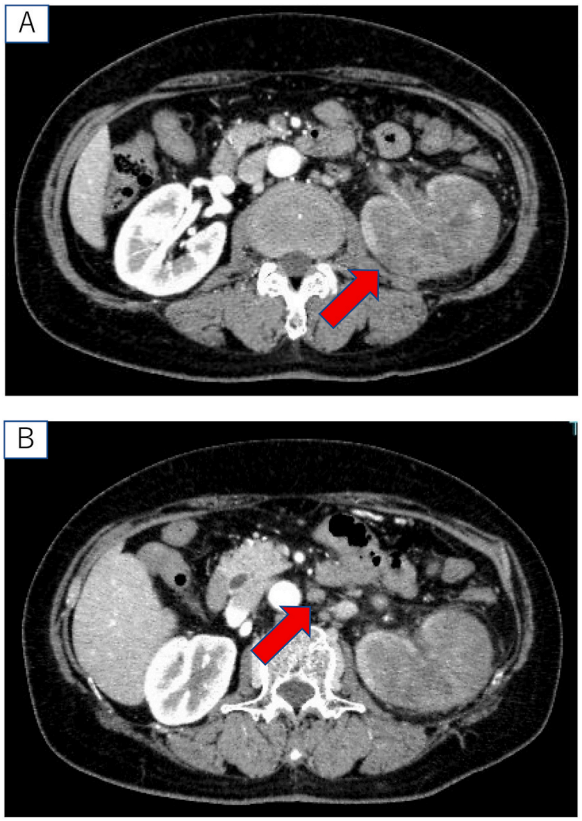

Fig. 1. The abdominal contrast-enhanced computed tomography (CECT) findings. (A) The CECT showed 9.0 × 7.0 cm hypovascular tumors near the lower pole of the left kidney. (B) The CECT showed enlarged para-aortic lymph nodes.

Compared with CCRCC, CDC is characterized by a higher grade and stage, positive lymph nodes, and metastatic disease. The median overall survival (OS) for CDC was 13.2 months compared with 122.5 months for CCRCC. Therefore, the prognosis is poor, partly because there are few effective treatments for advanced CDC. The prospective phase 2 BONSAI trial recently evaluated cabozantinib, with encouraging results as first-line treatment for mCDC, with an objective response rate (ORR) of 35 % and median progression-free survival (PFS) of 6.0 months.[2] However, CDC remains aggressive and manifests at an advanced stage, resulting in a poor prognosis. CDC exhibits biological features similar to those of urothelial carcinoma (UC); CDC might be distinct from conventional RCC and share biologic features with UC, with consequent implications in management. Due to their shared embryologic ancestry as progressive branching of the mesonephric duct, collecting duct and urothelial cells may be the source of this relationship between CDC and UC.[3] Therefore, advanced CDC treatment may be based on UC treatment strategy. The conventional chemotherapy regimen comprising gemcitabine and platinum preparations was examined prospectively in patients with mCDC.[4] One patient achieved CR, whereas five achieved partial response (PR), yielding an ORR of 26 %. The median PFS and OS were 7.1 and 10.5 months, respectively. To our knowledge, this was the first prospective multicenter phase II study to demonstrate that platinum preparation combination is an effective first-line treatment for mCDC. In the present case, two cycles of GC therapy were administered as adjuvant chemotherapy; however, peritoneal dissemination and liver metastasis appeared 5 months after the operation, and the disease progressed rapidly. Pembrolizumab was authorized as a second-line treatment for advanced or metastatic UC in Japan in 2017. The KEYNOTE-045 trial demonstrated the superiority of pembrolizumab as a second-line treatment for advanced or metastatic UC.[5] The KEYNOTE-427 trial assessed pembrolizumab's efficacy in patients with advanced non-CCRCC. The ORR was 26.7 %; 6.7 % of patients achieved CR, whereas 20 % achieved PR. This trial showed that pembrolizumab exhibited sustained anticancer efficacy in untreated patients with non-CCRCC.[6] In the present case, pembrolizumab was administered as a second-line therapy based on a UC treatment strategy. Recent research has demonstrated that NLR and PLR are valuable prognostic indicators in various carcinoma cases.[7,8] In RCC, NLR and PLR have also been associated with prognosis.[9] In the present case, NLR and PLR were higher before pembrolizumab administration than after pembrolizumab administration. Notably, CT showed exacerbation of liver metastases and peritoneal dissemination after two cycles of pembrolizumab; however, NLR and PLR had started declining. Therefore, the increased metastatic area on the images could be due to pseudo-progression, suggesting that NLR and PLR may be useful biomarkers of CDC treatment efficacy. Since the patient requested pembrolizumab discontinuation due to AEs, pembrolizumab was withdrawn after eight cycles. However, no relapse occurred 5 years after withdrawal, and a durable response was obtained. One limitation of this case is that it has been reported only once. Therefore, further accumulation of CDC cases is required.

4. Conclusion

CDC is associated with poor prognosis because chemotherapy is ineffective; however, ICIs, such as pembrolizumab, can be effective treatments. In the present case, CR and durable response to pembrolizumab were achieved. However, a further accumulation of cases is required to address this report's limitation.

CRediT authorship contribution statement

Satoki Abe: Writing – original draft. **Toru Inoue:** Supervision.

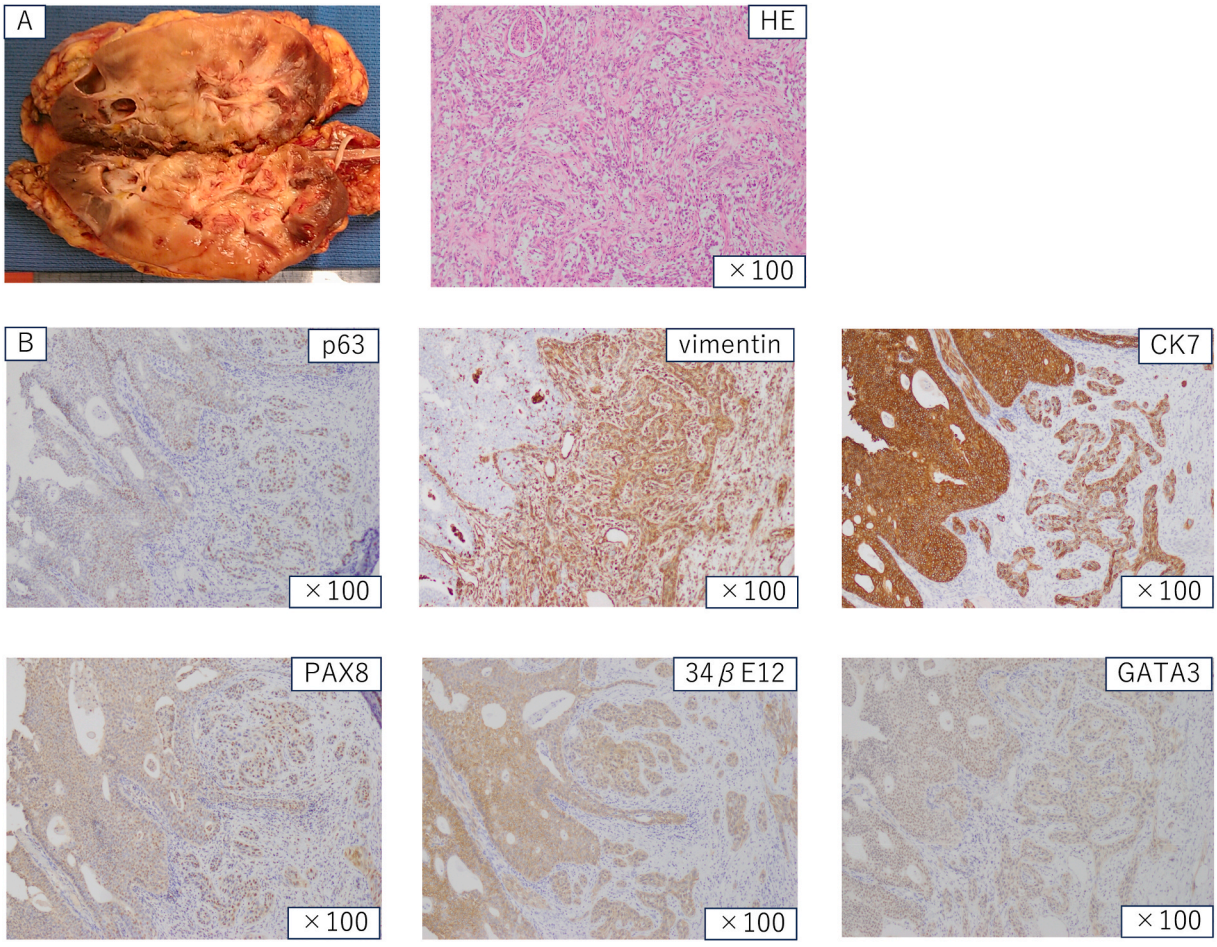

Fig. 2. Histological examination shows the irregular tubular pattern of the tumor growth and fibrosis of the interstitium (Hematoxylin and eosin staining, 100X). (A) Immunohistochemical staining revealed the presence of 34E12, CK7, PAX8, p63, and vimentin, but not GATA3. (B).

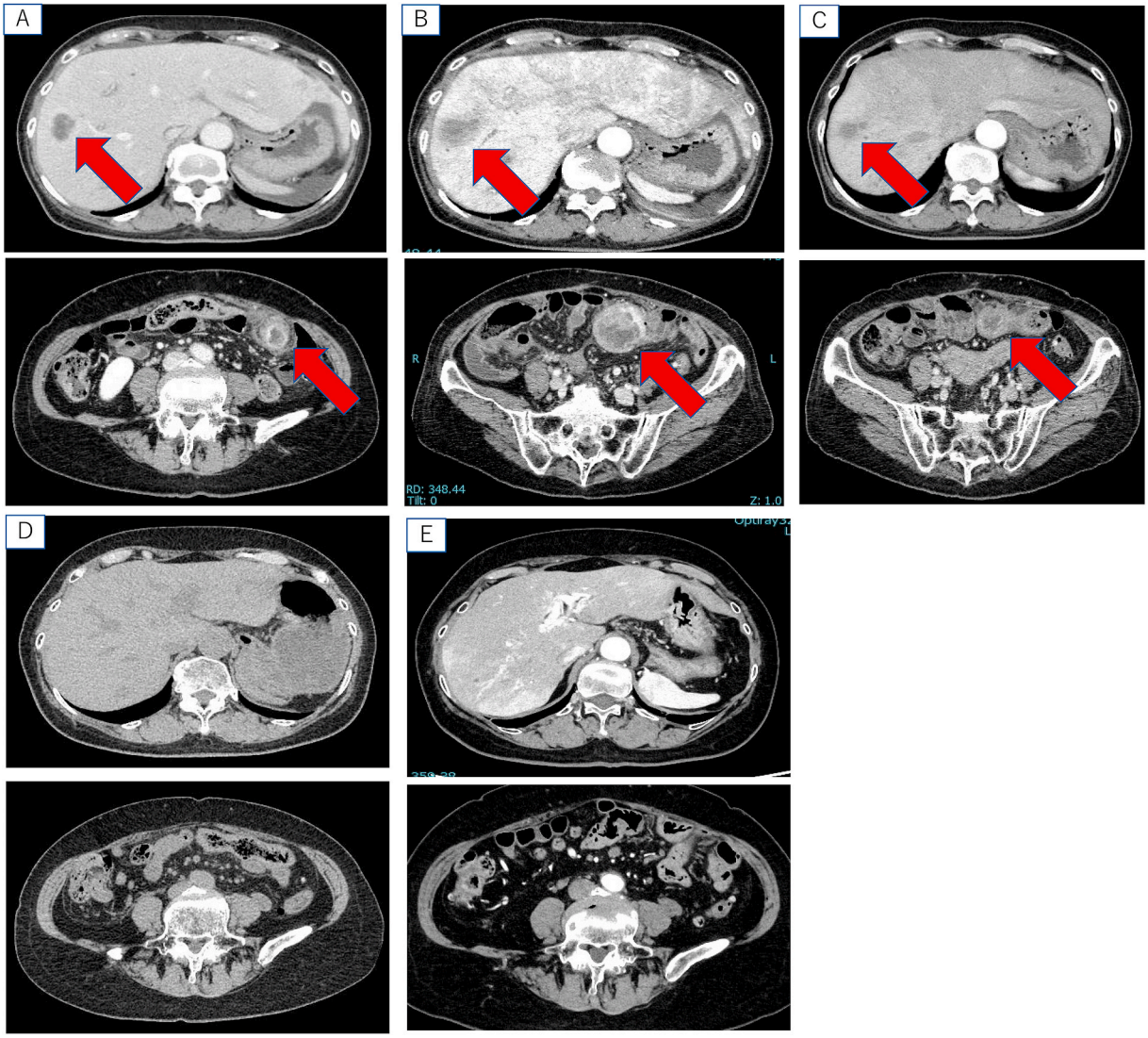

Fig. 3. CT shows a decrease in the size of liver metastases and peritoneal dissemination after pembrolizumab administration. (A) Before treatment with pembrolizumab. (B) After two cycles of pembrolizumab. (C) After three cycles of pembrolizumab. (D) After seven cycles of pembrolizumab. (E) Five years after the last pembrolizumab cycle.

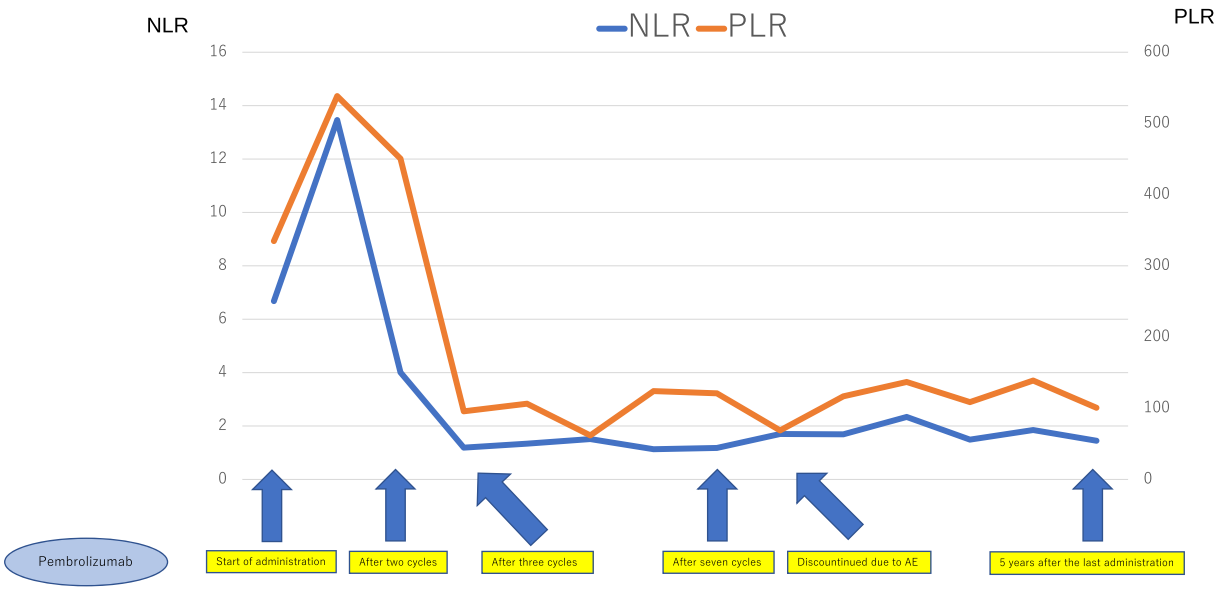

Fig. 4. The graph shows the transition of NLR and PLR after starting pembrolizumab treatment.

Shinro Hata: Writing – review & editing. **Tadamasa Shibuya:** Writing – review & editing. **Tadasuke Ando:** Writing – review & editing, Conceptualization. **Toshitaka Shin:** Writing – review & editing.

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Abbreviations

CDC: Collecting duct carcinoma
RCC: renal cell carcinoma
CCRCC: clear cell RCC
mRCC: metastatic RCC
ICIs: immune checkpoint inhibitors
mCDC: metastatic CDC
CR: complete response
CT: computed tomography
GC: cisplatin plus gemcitabine
AEs: adverse events
NLR: neutrophil-lymphocyte ratio
PLR: platelet-lymphocyte ratio
OS: overall survival
ORR: objective response rate
PFS: progression-free survival
UC: urothelial carcinoma
PR: partial response