

## Collision tumor of the kidney composed of clear cell carcinoma and collecting duct carcinoma treated with cabozantinib and nivolumab

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### ABSTRACT

Collision tumors (CT) refer to the phenomenon where two or more apparently different and unrelated tumors occur within the same location in an organ, forming the same lesion. We present the first case of renal CT with a mixed component of clear cell carcinoma and collecting duct carcinoma (CDC) with rhabdoid and sarcomatoid characteristics treated with the combination of cabozantinib and nivolumab. A 47-year-old man arrived at our clinic referring persistent dry cough, accompanied by a weight loss of 12 kg in the previous two months. Imaging studies revealed bilateral pulmonary lesions of metastatic appearance associated with a large tumor in the left kidney. After radical nephrectomy the histopathological report revealed a renal cell carcinoma (collecting duct carcinoma 85% and clear cell carcinoma 15%). The patient was included in a treatment protocol based on cabozantinib 40 mg QD plus nivolumab 240 mg every 15 days, obtaining a partial response after two months. This response was maintained for 12 months after initiation of systemic treatment. This is the first documented case of renal CT with a CDC component that obtained a partial response to combined treatment with immunotherapy and target therapy as first-line treatment; obtaining the longest overall survival reported in the setting of a metastatic renal CT with this histological combination. We need to expand the knowledge regarding the treatment of metastatic CDC, either as a single entity or as a component of a renal CT, in order to offer the best possible therapeutic outcome.

### 1. Introduction

Collision tumors (CT) refer to the phenomenon where two or more apparently different and unrelated tumors occur within the same location in an organ, forming the same lesion. To date, only a few cases of CT of renal origin have been published in the literature, involving different histological lines of renal cell carcinoma (Burch-Smith et al., 2014).

We present the first case of renal CT with a mixed component of clear cell carcinoma and collecting duct carcinoma (CDC) with rhabdoid and sarcomatoid characteristics treated with the combination of cabozantinib and nivolumab.

### 2. Clinical case

A 47-year-old man arrived at our clinic referring persistent dry cough, accompanied by a weight loss of 12 kg in the previous

two months. Imaging studies revealed bilateral pulmonary lesions of metastatic appearance associated with a large tumor in the left kidney. There was also evidence of bilateral adrenal involvement and regional adenopathy (Fig. 1A). After the initial approach, the patient underwent a left radical nephrectomy because he was considered at high risk for local complications.

The histopathological report revealed a renal cell carcinoma (collecting duct carcinoma 85% and clear cell carcinoma 15%) of 16 × 10.6 × 9.3 cm, with a sarcomatoid component and rhabdoid characteristics, nuclear grade 4, necrosis present in 30% of the sample, positive margins at the convexity, lymphovascular invasion present, and 1 out of 3 lymph nodes resected positive for metastasis (Fig. 2). PD-L1 was not evaluated in the initial pathological revision. After corroborating the pathological results, the case was evaluated by a multidisciplinary team. Our patient was included in a treatment protocol based on cabozantinib 40 mg QD plus nivolumab 240 mg every 15

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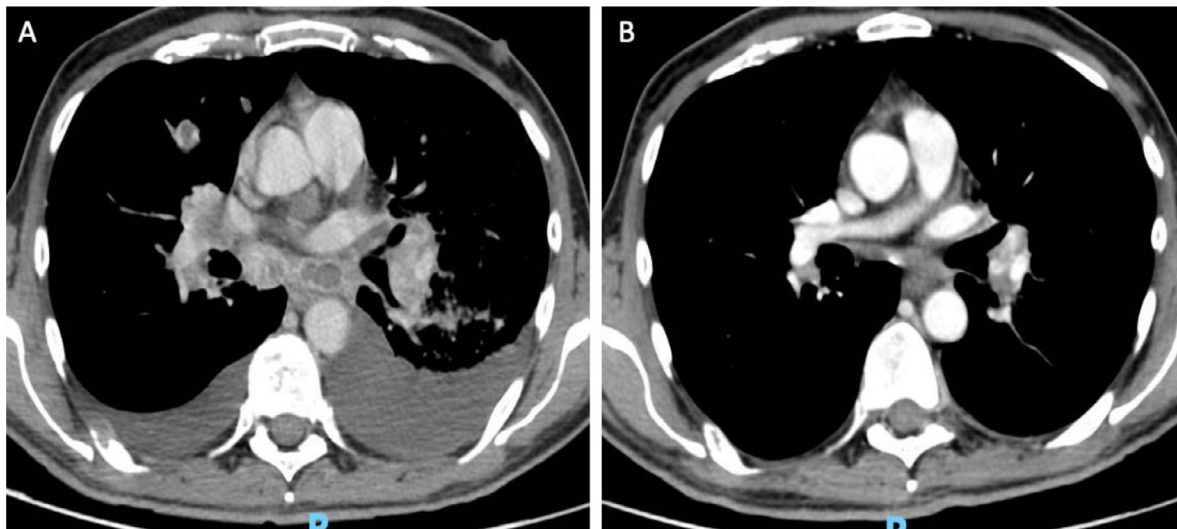
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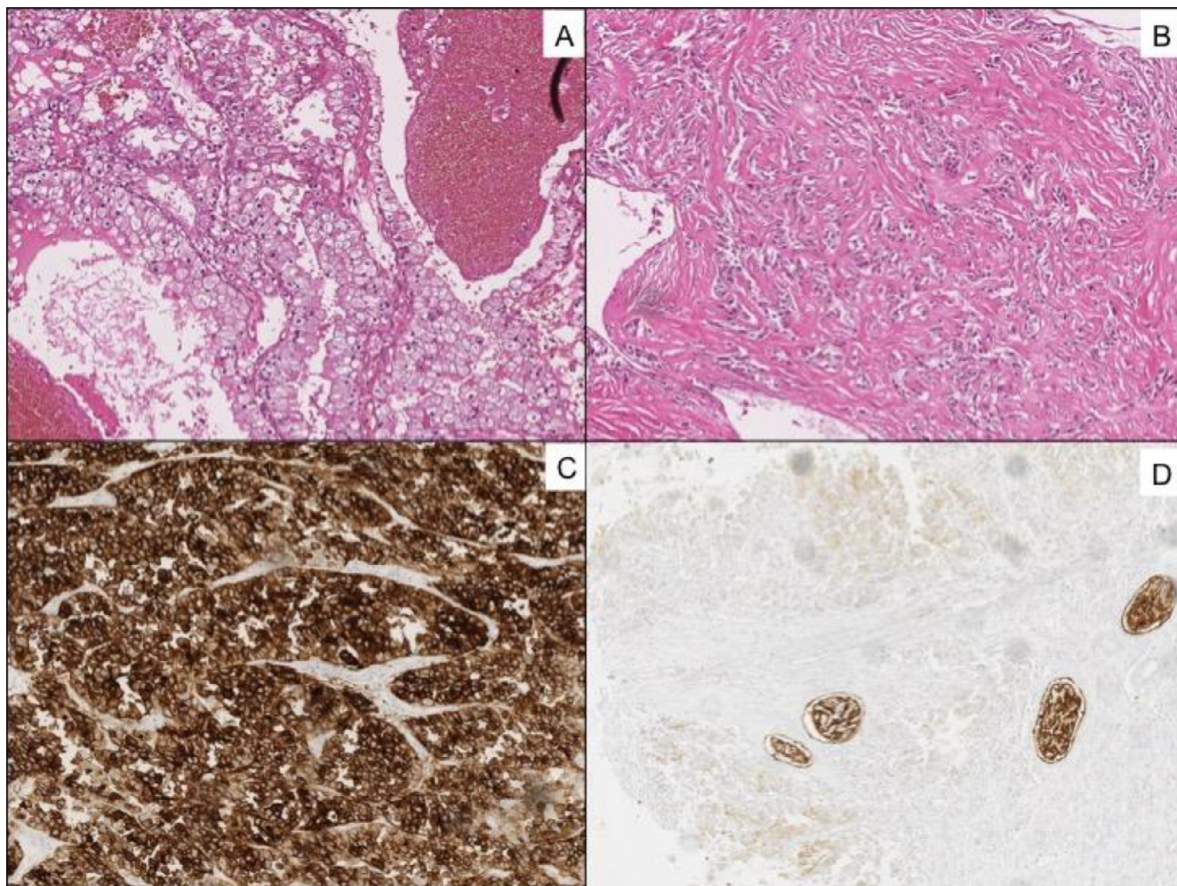
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**Fig. 1.** A. A CT scan that showed diffuse bilateral pulmonary metastatic lesions, the most representative at the level of the left hilum. B. Clinical response to treatment documented in the target lesions.



**Fig. 2.** Histological sections of the tumor: A. Clear cell carcinoma component; hematoxylin and eosin, 100x. B. Component of collecting duct carcinoma with an infiltrative type pattern; hematoxylin and eosin, 100x. C. Clear cell carcinoma intensively positive for CD10. D. Collecting duct carcinoma component negative for CD10, with a positive internal control at the level of adjacent glomeruli.

days, obtaining a partial response by RECIST 1.1 after two months (Fig. 1B).

Due to grade 3 stomatitis presented after 4 doses of cabozantinib, it was decided to decrease the dose to 20 mg QD, obtaining a partial improvement of symptoms. Despite dose reduction, the patient persisted

with a grade two stomatitis. Therefore, cabozantinib was permanently discontinued after 10 months of combined treatment, continuing only with nivolumab.

After 12 months of systemic treatment without evidence of progression and 15 months from its initial diagnosis, our patient was diagnosed

with an acute complicated bacterial pneumonia not related to treatment. Despite standard broad-spectrum antibiotic therapy and intensive care management, the patient died.

### 3. Discussion

Different postulates have been issued to try to explain the histogenetic basis of renal CT. In the review by Burch-Smith et al., three mechanisms that could explain the origin of these tumors were addressed: a simultaneous proliferation of two unrelated cell lines that give rise to two phenotypically different tumors; tumors from a single precursor cell that differentiated into two cell lines; or the incidental occurrence of two isolated tumors in a common anatomical site.

Despite the advances made in recent years in the management of renal cell carcinoma of clear cell variety, there is no standard treatment for CDC. CDC or Bellini's ductal carcinoma is characterized by being a rare and aggressive entity that usually presents in advanced stages, with a median survival of 11 months (Dason et al., 2013). None of the large randomized studies has specifically evaluated the response to treatments based on chemotherapy, immunotherapy or target therapy in this setting. Similarly, the benefit of cytoreductive nephrectomy in patients with metastatic CDC has not been established (Dason et al., 2013).

From a pathological point of view, there is some proximity between CDC and carcinomas of the upper urothelial tract, which has led to various trials extrapolating the treatment of these tumors. The results of a phase 2 study support the use of platinum-gemcitabine as a suitable option in this setting (Oudard et al., 2007); other authors have even evaluated adding bevacizumab or sorafenib to this combination, with a modest benefit (Pécuchet et al., 2013, Sheng et al., 2018).

There is little evidence supporting the use of tyrosine kinase inhibitors as the first line in metastatic CDC. To date, the best results came from a case series of patients treated with sunitinib (Pécuchet et al., 2013). In an Italian phase 2 study, eleven patients with metastatic CDC were treated with cabozantinib at a dose of 60 mg orally twice daily until disease progression. Of the total, only two achieved a partial response as the best response, while two achieved stable disease. No grade 3 or 4 toxicity was documented in this group (Procopio et al., 2019).

Regarding immunotherapy, the study by Choueiri et al. found a rate of PD-L1 positivity in CDC cells of 1 out of 5 cases evaluated, while all the cases were positive for PD-L1 expression in tumor-infiltrating mononuclear cells (TIMC) (Choueiri et al., 2014). To date, there are two case reports that documented a clinical response with nivolumab in patients with metastatic CTC with progression after chemotherapy and tyrosine kinase inhibitor therapy (Mizutani et al., 2017, Rimar et al., 2016).

In the context of a renal CT, the answer is even less clear. In the only case previously reported in the literature of a CT with the combination of clear cell carcinoma and CDC presented by Burch-Smith et al, systemic treatment for recurrent disease based on carboplatin and paclitaxel was started, obtaining a partial clinical response. Subsequently, the patient received gemcitabine-doxorubicin due to toxicity, resulting in a survival time from the diagnosis of localized disease of 14 months.

CDC is commonly categorized as an orphan disease due to the limited and unsatisfactory treatment options currently available, especially in the metastatic setting. The study of the genomics, biology, and molecu-

lar architecture of CDC is paramount to perform tailored biology-driven treatment choices (Pagani et al., 2019).

This report is relevant because it is the first documented case of renal CT with a CDC component that obtained a partial response to combined treatment with immunotherapy and target therapy as first-line treatment; obtaining a progression-free survival of 12 months and the longest overall survival reported in the setting of a metastatic renal CT with this histological combination.

### 4. Conclusion

The macroscopic revision of the surgical piece by the pathologist is vital to detect the presence of a renal CT, since the response to treatment, the behavior of the disease and the prognosis will be very different depending on the histologies involved. It is necessary to seek to expand the knowledge regarding the treatment of metastatic CDC, either as a single entity or as a component of a renal CT, in order to offer to this group of patients the best possible therapeutic outcome.

### Patient consent statement

The patient is sufficiently anonymized according to ICMJE guidelines.

### Declaration of Competing Interest

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

The authors declare that there is no conflict of interest regarding the publication of this paper.

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