

## CAS CLINIQUE/CASE REPORT

# A TWO-FRONT WAR: TARGETING SYNCHRONOUS METASTATIC PANCREATIC AND RENAL CELL CARCINOMAS WITH THE COMBINATION OF GEMCITABINE AND SUNITINIB

<http://www.lebanesemedicaljournal.org/articles/65-4/case5.pdf>

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Assi T, El Rassy E, Moussa T, Kattan J. A two-front war: Targeting synchronous metastatic pancreatic and renal cell carcinomas with the combination of gemcitabine and sunitinib. *J Med Liban* 2017; 65 (4): 234-236.

**ABSTRACT** • The occurrence of multiple synchronous primary tumors is extremely rare. The management plan of synchronous cancers has long been debatable and difficult mainly in tumors with different molecular characteristics. In this report, we present the second case in literature of a concomitant diagnosis of a metastatic pancreatic adenocarcinoma and a locally advanced renal cell carcinoma. We also elaborate on our management combining chemo-therapy and targeted therapy through an extensive review of literature.

Keywords: synchronous; double primary; pancreatic; renal cell cancer

## INTRODUCTION

In view of the advances in the therapeutic fields, the overall survival of cancer patients is increasing. Thus, the occurrence of multiple primary tumors (MPT) during the lifetime of a patient is not rare and the diagnosis of synchronous primary malignant tumors is becoming more common [1,2]. The management plan of such tumors is often debatable especially when it requires a combination of cytotoxic chemotherapy and targeted agents. One preliminary protocol combining gemcitabine and sunitinib has shown synergistic effect in several clinical trials [3,4]. In the following case, we made an attempt to assess their synergistic effect in targeting two synchronous primary tumors.

## CASE PRESENTATION

A 73-year-old man presented to our clinic early 2015 for a one month history of asthenia, weight loss and abdominal discomfort. Initial abdominal CT scan revealed two hepatic hypoechogenic lesions, a huge solid mass of the left kidney, and a fungating mass arising from the tail of the pancreas. The laboratory tests showed normal levels of carcinoembryonic antigen (CEA) and Ca19-9. The guided biopsies of the liver lesions and kidney mass demonstrated the presence of clear cell carcinoma Furhman II in the kidney (immunohistochemistry positive for pancytokera-

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Assi T, El Rassy E, Moussa T, Kattan J. Une guerre sur deux fronts: Le ciblage d'une tumeur rénale à cellules claires et d'un adénocarcinome pancréatique par l'association de gemcitabine et sunitinib. *J Med Liban* 2017; 65 (4): 234-236.

**RÉSUMÉ** • Le diagnostic de tumeurs malignes synchrones est extrêmement rare et pose des difficultés de traitement surtout en cas de tumeurs avec des caractéristiques moléculaires différentes. Dans cet article, nous présentons le second cas rapporté dans la littérature d'un patient porteur de deux tumeurs synchrones: un adénocarcinome pancréatique métastatique et un carcinome rénal à cellules claires localement avancé. La prise en charge thérapeutique de notre patient a été élaborée à la lumière d'une revue extensive de la littérature.

Mots-clés: synchrone; double primitive; pancréatique; carcinome rénal à cellules claires

line AE1-AE3, vimentine and CD10; negative for CK7) and pancreatic adenocarcinoma in the liver (immunohistochemistry positive for CK7 and partially for CDX2; negative for CK20 and TTF1).

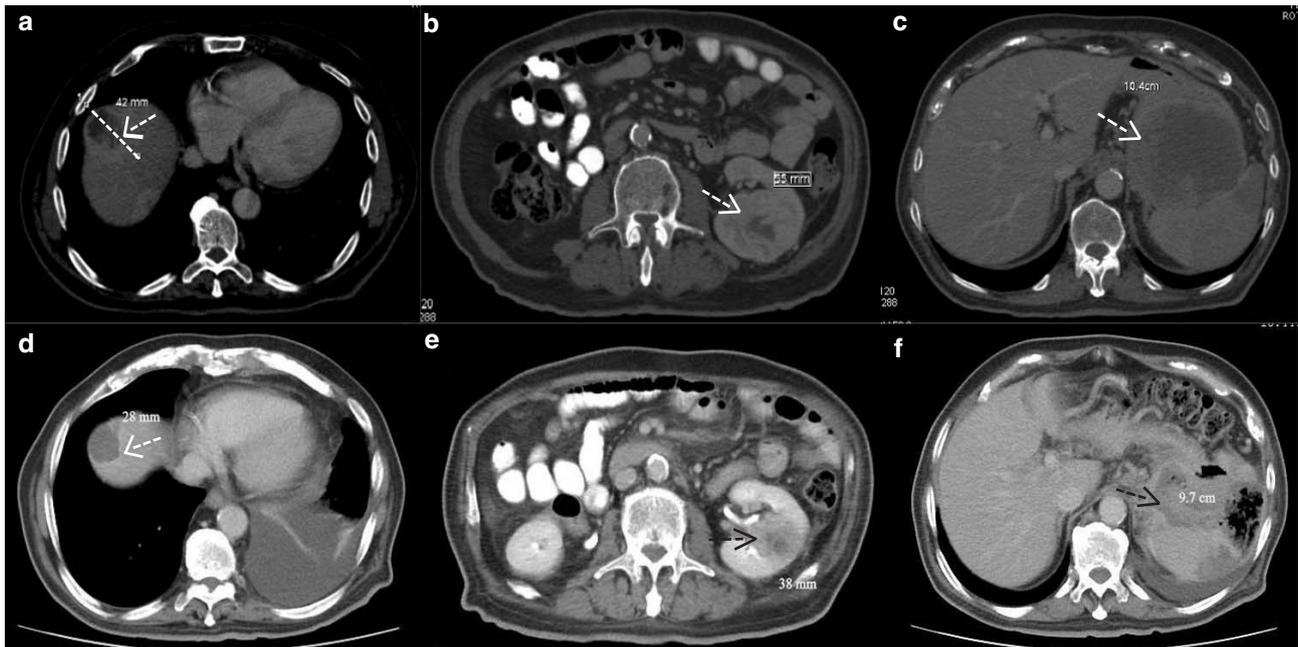
The patient was unfit for any surgical procedure (ECOG 3). The possible treatment options were discussed with the patient who approved the combination of gemcitabine (800 mg IV on day 1 and 8 repeated on a 3-week cycle) and sunitinib (50 mg/day PO for 2 weeks of a 3-week cycle).

The follow-up CT scan two months later showed an overall partial response by RECIST (*Response Evaluation Criteria In Solid Tumors*). This regimen was well tolerated without notable adverse effects. At eight months of therapy, the patient remains in partial remission (Figure 1).

## DISCUSSION

Although pancreatic and kidney cancers are known to be independent, a crucial step in the diagnosis process of synchronous MPT is to eliminate a possible connection between the two different tumors [5]. Interesting genetic analysis of patients with concomitant pancreatic and renal cancers demonstrated microsatellite instability and mutations of codon 12 of k-ras gene [6,7]. Overall, the management plan of synchronous tumors is dictated by the staging of each primary tumor. The therapeutic plan of patients with early stage MPT necessitates complete surgical resection whilst that of patients with metastatic disease requires medical treatment [8]. In the later scenario, the pharmacodynamics and pharmacokinetics of the drugs are assessed for potential synergistic effect to obtain a maximal effect on both tumors [9].

Our patient received a nucleoside analogue (gemcitabine) concomitantly with a tyrosine kinase inhibitor (suni-



**FIGURE 1.** Contrast-enhanced CT scan of the abdomen at the diagnosis [a, b, c] and after 4 months of chemo-targeted therapy [d, e, f] showing: • Heterogeneous hypodense hepatic dome lesion with annular enhancement (42 mm) [a] decreasing in size to 28 mm with complete necrosis [d] • Heterogeneous hypodense left cortical renal mass (55 mm) [b] decreasing in size to 38 mm [e] • Caudal fungating pancreatic mass (104 mm) [c] decreasing in size to 97 mm with further necrosis [f].

tinib). Our biological rationale intended a blockage of the tumor growth and progression via sunitinib. Moreover, gemcitabine has been shown to overcome tumor resistance to sunitinib [10]. In metastatic pancreatic cancer, the combination of gemcitabine (1000 mg/m<sup>2</sup> on day 1, 8 and 15 repeated on a 28-day cycle) and sunitinib (50 mg/day for 2 weeks of a 3-week cycle) showed a progression free survival of 11.6 weeks and overall survival of 30.4 weeks. Toxicities included grade 3-4 neutropenia 48.1% but were tolerable with dose adjustment [11]. In patients with metastatic renal carcinoma, the association of gemcitabine (1000 mg/m<sup>2</sup> on on day 1 and 8 repeated on a 21-day cycle) and sunitinib (50 mg/day PO for 2 weeks of a 3-week cycle) showed a progression free survival of 5 months and overall survival of 15 months. Grade 3 or higher toxicities included neutropenia 51.3%, anemia 25.6% and fatigue 17.9% [12].

Published literature of synchronous pancreatic and renal cell carcinomas shows localized primary tumors that were managed surgically except for one patient (Table I). The latter is a 43-year-old man who was diagnosed with a metastatic pancreatic cancer and localized renal cell carcinoma. He was treated with a combination of gemcitabine (750 mg/m<sup>2</sup> intravenously days 1, 8 and 15 repeated on a 28-day cycle) with sunitinib (37.5 mg PO for 4 weeks every 6 weeks) requiring multiple dose reductions and interruptions due to multiple comorbidities. Toxicities included grade 3 neutropenia and grade 2 hypertension. The patient had an overall survival of 8 months after achieving partial response with this innovative combination [13,14]. Similarly, our patient was not surgically fit and a medical management had to be ensued. A recent paper showed that

high levels of vascular endothelial growth factor receptors (VEGF) were expressed on both pancreatic and renal cancerous cells [11,15].

Therefore, in line with literature, we combined sunitinib (VEGF inhibitor approved in renal cell carcinoma) to gemcitabine (cytotoxic agent approved in pancreatic cancer). The regimen was tolerated perfectly and did not require any dose adjustment.

#### CONCLUSION

This case report demonstrates a rational strategy in treating multiple primary tumors and highlights the importance of understanding cancer pathogenesis and molecular biology.

CONFLICT OF INTEREST: None to declare

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**TABLE I** CHARACTERISTICS OF PUBLISHED REPORTS WITH SYNCHRONOUS PANCREATIC AND RENAL CANCER

| Authors               | Age (years) | Sexe | Staging   | Treatment                              | Response | Overall Survival |
|-----------------------|-------------|------|---|--|----------|------------------|
| Toshiyuki et al. [16] | 54          | M    | Localized pancreatic and renal cancer                 | Surgery*                               | N/A      | 6 months         |
| Rabbani et al. [17]   | N/A         | N/A  | N/A   | N/A                                    | N/A      | N/A              |
| Alexakis et al. [18]  | N/A         | M    | Localized pancreatic and renal cancer                 | Surgery*                               | N/A      | N/A              |
| Olgay et al. [19]     | 82          | M    | Localized pancreatic and renal cancer                 | Surgery* and Chemotherapy              | CR       | Alive            |
| Bharthuar et al. [13] | 43          | M    | Metastatic pancreatic cancer and localized renal cell | Chemotherapy (Gemcitabine + Sunitinib) | PR       | 8 months         |
| Ismail et al. [6]     | 62          | M    | Localized pancreatic and renal cancer                 | Nephrectomy and Gemcitabine            | N/A      | N/A              |
| Muller et al. [7]     | 70          | M    | Localized pancreatic and renal cancer                 | Surgery*                               | CR       | Alive            |
| Muller et al. [7]     | 70          | M    | Localized pancreatic and renal cancer                 | Surgery*                               | N/A      | 5.25 months      |
| Muller et al. [7]     | 71          | M    | Localized pancreatic and renal cancer                 | Surgery*                               | N/A      | 3.25 months      |
| Barkin et al. [5]     | 65          | M    | Localized pancreatic and renal cancer                 | Surgery*                               | CR       | N/A              |
| Ghothim et al. [20]   | N/A         | M    | Localized pancreatic and renal cancer                 | Surgery* and Gemcitabine               | N/A      | 19 months        |
| <b>Our patient</b>    | 73          | M    | Metastatic pancreatic cancer and localized renal cell | Chemotherapy (Gemcitabine + Sunitinib) | PR       | Alive            |

\*: Complete nephrectomy with Whipple procedure CR: complete remission F: female M: male N/A: not available PR: partial remission

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