Sunitinib-induced Complete Response in Metastatic Renal Cancer Expressing Neuroendocrine Markers: A New Predictive Factor?

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Abstract. *Background: To date, no predictive factors are recognized and applied in the therapeutic choice for metastatic renal cell carcinoma. Due to significant side-effects and costs, which are relevant issues in this setting, optimization of treatments has become a priority. Case Report: We herein report a case of complete remission of metastatic renal cell carcinoma after 1 year of treatment with sunitinib. Since pancreatic metastases were detected by a 68Ga-DOTA-NOC positron emission tomography, it was decided to perform a histological revision of the specimens, with immunohistochemical staining for neuroendocrine markers on the primary tumor. Conclusion: On the basis of the detection of neuroendocrine markers on the primary neoplasm, together with pancreatic metastases positive on a 68Ga-DOTA-NOC positron emission tomography (PET), we hypothesize and discuss about a potential role of specific neuroendocrine markers as predictive indicators of response to sunitinib (and allegedly to other target therapies) in the treatment of this neoplasm.*

During the past years, treatment and prognosis of patients with metastatic renal cell carcinoma (mRCC) have been significantly improved by the development of targeted-therapeutics such as tyrosine kinase inhibitors (TKI) and mammalian target of rapamycin (mTOR) inhibitors. To date, several drugs are available, establishing a complex scenario in which the choice of the optimal agent for each patient is not always straight-forward.

The expression of neuroendocrine markers, like chromogranin A and neuron-specific enolase (NSE), was described many years ago in both tumor tissue and serum of patients with RCC but without significant clinical relevance and/or prognostic value (1-3). These analyses were then overwhelmed by studies focusing on angiogenesis mediators, like receptors of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), as well as mTOR, targets of the new drugs eventually effective in the treatment of mRCC.

Unfortunately about 9 to 21% of patients treated with VEGF-targeted therapy are primary refractory, and no predictive biomarkers have been recognized in order to maximize clinical benefit and spare unnecessary toxicities and significant costs (4).

We herein describe a case of mRCC showing a complete response to the TKI sunitinib after 1 year of therapy. We discuss whether the neuroendocrine markers noted (intense and significantly extensive expression of NSE in the primitive lesion, as well as pancreatic metastases positive on 68Ga-DOTA-NOC positron emission tomography (PET)) might have played a role in this response as potential predictive factors.

Case Report

A 60-year old man underwent radical nephrectomy for a clear cell carcinoma, grade 2 Fuhrman, pT2NxM1 for an ipsilateral adrenal metastasis. In his personal history we underline: thrombophilia (resistance to activated protein

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C - APC resistance - in factor V Leiden mutation - Q506) in anticoagulant therapy with warfarin; and arterial hypertension, treated with diuretics. About 9 months later, a computed tomography (CT) scan showed the appearance of some pancreatic lesions. The patient underwent further diagnostic exams in order to differentiate between pancreatic neuroendocrine tumor and metastasis from RCC. The pancreatic lesions, revealed in CT and nuclear magnetic resonance (NMR), were detected by a 68Ga-DOTA-NOC PET (Figure 1), thus a pancreatic endoscopic ultrasound (EUS)-guided fine-needle aspiration was performed (unfortunately not diagnostic).

A histological revision of the specimens, with immunohistochemical staining for neuroendocrine markers on the primary tumor, was performed. NSE protein expression was identifiable in about 40% of neoplastic cells with moderate-to-intense cytoplasmic granular pattern (Figure 2), while immunostaining for both synaptophysin and chromogranin A was negative, thus excluding the neuroendocrin origin of the tumor.

We considered the very high likelihood of metastasis from RCC (temporal correlation with primary cancer; evidence that lesions throughout the pancreatic gland are more frequently detected in patients with RCC than in those with other primary tumors, often as the only metastatic site (5); expression of neuroendocrine marker in the primary tumor), and then we started sunitinib, one of the drugs of choice in first line therapy for mRCC, prudentially with a reduced dose of 37.5 mg/day, scheduled 2/1+ 2/1 in order to verify tolerance in a patient co-treated with an anti-coagulant drug. Ten days from sunitinib initiation the patient was admitted to hospital for fever and severe abdominal pain. Blood sampling showed piastrinopenia G3, thus both sunitinib and anticoagulant administration were stopped. An NMR of the abdomen, performed after a negative ultrasound study, showed-after just 10 days of therapy-a mild reduction of the contrast enhancement in almost all the pancreatic lesions, in comparison with the previous control. All cultural analyses were negative for infections, a leukocyte and neutrophil count decrease was observed (down to 2,870 and 870/mm^3 respectively), then signs and symptoms gradually remitted.

Once platelet count was normalized, the patient restarted the anti-coagulant therapy and after about 1 month, when leucocytes normalized as well, sunitinib was restarted at 25 mg/day 2/1 + 2/1, with a titration up to 37.5 mg/day, without any clinically relevant blood cell count alteration. Follow-up at 3, 6 and 9 months showed progressive partial remission and a complete remission (NMR normal) after about 12 months.

Further toxicities occurred, such as dysgeusia and hand-foot syndrome G2. The patient also experienced a severe scrotal dermatitis, which was the principal dose-limiting toxicity, leading to a new dose reduction at 25 mg/day.

To date, the patient is still taking sunitinib, 25 mg/day, maintaining a complete response (CR).

Discussion

The case reported is unusual for two reasons: a complete remission after 1 year of therapy with sunitinib was achieved; and the expression of neuroendocrine markers in a clear renal cell carcinoma.

CR is a rare event in metastatic kidney tumors. The percentage of patients reaching a CR in registered studies for sunitinib, sorafenib, pazopanib and bevacizumab is less than 3% and, in other series and case reports published, CRs have often been achieved by integrating medical treatments with surgery, radiotherapy or both (6).

The second point is the expression of neuroendocrine markers in RCCs. Neuroendocrine (NE) cells are important for regulating cell growth and differentiation. In addition to specific NE tumors, NE activity can be detected in other types of tumors, such as breast (7) or prostate carcinomas (8). The expression of neuroendocrine markers has previously been studied in RCCs. In order to evaluate their prognostic potential, but without any conclusive results.

NSE seems the most expressed among NE markers in RCC, sometimes with a great heterogeneity (3). Ronkainen *et al.*, in a relatively recent paper about NE markers expression in 152 primary RCCs, described the expression of NSE in 48% of the cases (more common in clear cell RCCs than in other subtypes), while 8% of RCCs were positive for serotonin, 18% for CD56, only 1% for synaptophysin, none for chromogranin A and without a prognostic potential (1).

In our case, primary RCC showed a significant expression of NSE, while pancreatic metastases were identified by a ^{68}Ga scan. ^{68}Ga-DOTANOC has high affinity for somatostatin receptor subtypes 2, 3, and 5, and has shown good results in patients with neuroendocrine tumors, with a higher lesion detection rate than that achieved with ^{18}F-fluorodi-hydroxyphenyl-l-alanine PET, somatostatin receptor single photon emission TC (SPECT), CT, or NMR imaging (9).

In the normal human kidney SS receptors are expressed in the vasa recta, tubuli and glomeruli. Moreover, because renal irradiation is the dose-limiting factor in peptide receptor radionuclide therapy using radiolabelled SS analogues, it is not clear to what extent these receptors contribute to the total kidney radioactivity uptake (10).

In human RCCs, Reubi and Kvols first reported in 1992 the presence of specific SS receptors with autoradiographic techniques performed on surgically removed kidneys, although it was unknown whether these SS receptors were functional and, if so, what function of SS they might mediate (11). One year later, Flamen *et al.* demonstrated a pathological tracer accumulation by means of ^{111}In-labelled

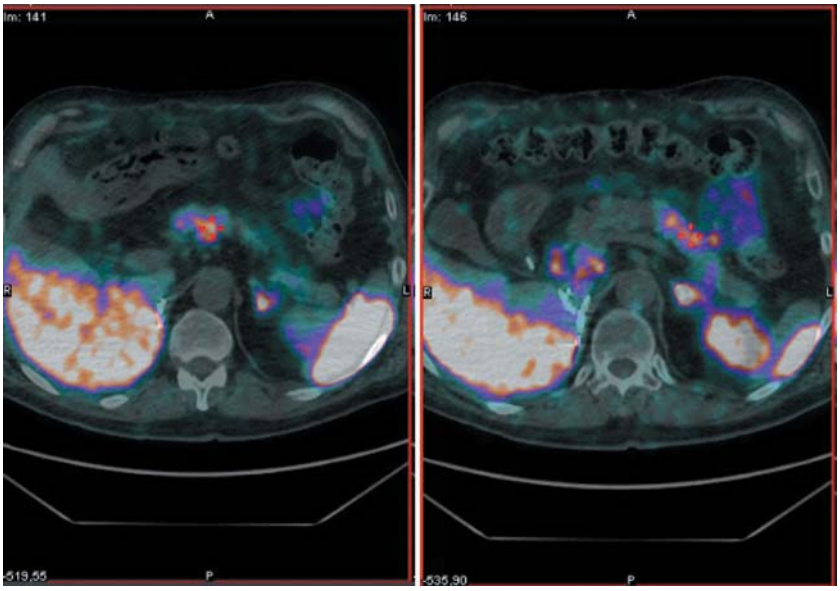

Figure 1. *Pancreatic metastases are detected by a ^{68}Ga-DOTA-NOC PET study.*

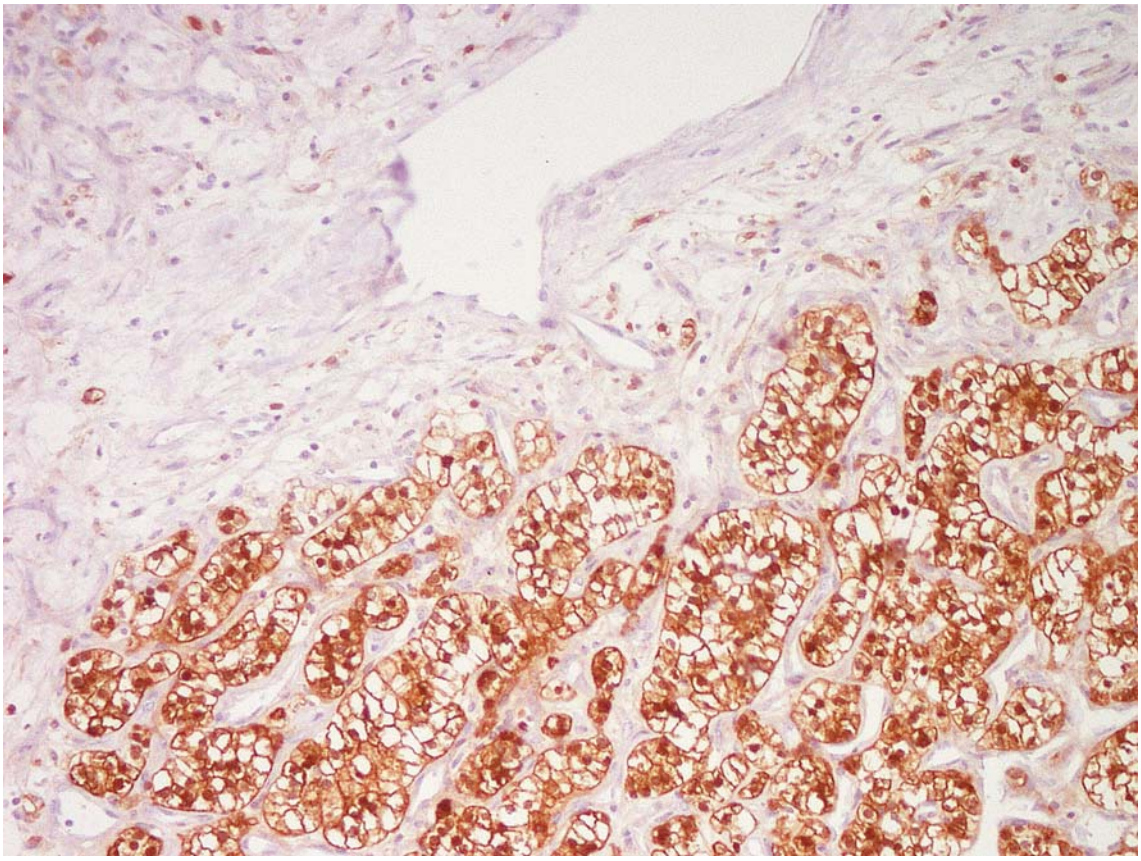

Figure 2. *NSE protein expression in primary RCC was identifiable in about 40% of neoplastic cells, with moderate-to-intense cytoplasmic granular pattern. Immunohistochemistry for NSE (polyclonal) was performed using an automated staining system (BenchMark ULTRA, Ventana, Roche, Tucson, AZ, USA).*

octreotide scintigraphy in three of seven patients (43%) with mRCC. In these patients, 20 out of 23 known tumor localizations were clearly visualized and tracer uptake could be inhibited by prior administration of cold octreotide (12). In 1999 Edgren *et al*. described SS receptors in all patients investigated (9 patients), in which 40 of 68 known lesions could be visualized with octreoscan scintigraphy. The authors suggested an intriguing future therapeutic possibility with an SS analogue bound to a β-emitting, targeted to tumors with a high density of SS binding sites (13).

Conversely, Montravers *et al*. reported a study in which scintigraphy with ^{111}In-pentreotide appeared to have little value for the detection of metastases in patients with renal cell carcinoma, as some metastases (especially those of the lungs) were missed; thus, the absence of ^{111}In-pentreotide uptake by large primary tumors suggested the inaccessibility of these very large tumors to drugs (14).

Reubi and co-workers described a very interesting link between SS receptor expression and tumor angiogenesis. They reported that since the vessels of normal non-neoplastic human tissues have few SS receptors, the increased SS receptor expression in peritumoral vessels observed might be linked to the neoplastic process itself. They concluded that SS and SS receptors may play a regulatory role for hemodynamic tumor-host interactions, possibly involving tumor stroma generation, tumor environment, angiogenesis and, particularly, vascular drainage of poorly differentiated neoplasms (15).

Treatment of mRCC with an SS analogue was described by Flamen and co-workers. They reported the presence of somatostatin receptors in a patient with a 12-year history of disseminated disease, who received octreotide therapy. The result was a successful palliation of painful bone metastasis but no remission of the neoplastic disease was noted (12).

Studies about neuroendocrine markers and SS receptors were then overwhelmed by various analyses focusing on angiogenesis mediators, such as receptors of VEGF, PDGF, as well as mTOR, targets of the new drugs eventually effective in the treatment of both metastatic renal cancer and neuroendocrine tumors.

After the CR observed in our patient, we proposed a link between response/efficacy of therapy and NE marker expression, for the following two reasons: (i) TKI and mTOR inhibitors are active and thus suitable also for the treatment of pancreatic neuroendocrine tumors-p-NET (16, 17); (ii) Sites of metastases (adrenal and pancreatic in our patient, frequent in mRCC) recall the "seed and soil" theory (18) and are concordant with an alleged relation with neuroendocrine expression and tumor behaviour.

Our hypothesis is that the expression of neuroendocrine markers could represent a predictive factor of response to the new drugs (TKI and mTOR inhibitors); to our knowledge, this is the first report describing such an action. This consideration could be the rational basis for a possible role for octreoscan (or other somatostatin receptor imaging) in the decision-making of therapeutic processes (*i.e*. in selecting patients suitable for such therapies or in monitoring therapeutic effects), as well as for a role of SS analogues, alone (with lesser toxicities and lesser costs) or in association with TKI/mTOR inhibitors.

Further studies about expression/activity of NE markers in mRCC and eventually the cut off values of these markers' concentration might be useful to confirm this hypothesis.

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