Editorial

The search for a common denominator of gastrointestinal stromal tumors and renal cell carcinoma

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Comment on: Mendonca SJ, Sanchez A, Blum KA, *et al.* The association of renal cell carcinoma with gastrointestinal stromal tumors. J Surg Oncol 2018;117:1716-20.

Received: 04 November 2018; Accepted: 22 November 2018. Published: 23 November 2018.

doi: 10.21037/gist.2018.11.01

View this article at: http://dx.doi.org/10.21037/gist.2018.11.01

An association of gastrointestinal stromal tumors (GISTs) with other malignancies is not new (1-5). In 2006, Agaimy *et al.* (1) reported on secondary cancer diagnoses in 486 GIST patients, including cases from the literature. They found 228 GIST patients with gastrointestinal cancers (46.9%), of which 19.5% were of gastric origin and 22.4% were of colorectal origin. Esophageal carcinoma, gastric MALT lymphoma and small bowel adenocarcinoma were less common. Two hundred ninety GIST patients had secondary cancers outside the gastrointestinal tract. They included prostate cancer (8.8%), cancers of the lymphoreticular system (7.4%), breast cancer (7%), renal cell carcinoma (5.5%), lung cancer (5.3%), cancer of the female genital tract (5.1%), soft tissue and bone sarcoma (3.1%), carcinoid tumors (2.7%), malignant melanoma (2.5%), pancreas cancer (2.3%), urinary bladder cancer (2%), seminoma (1.2%), hepatocellular carcinoma (0.8%), thyroid cancer (0.8%), cancer of the gallbladder and biliary tract (0,8%), paraganglioma (0.6%), squamous cell carcinoma of the head and neck (0.4%), and others.

The current article of Mendonca *et al.* (6) entitled "*The association of renal cell carcinoma with gastrointestinal stromal tumors*" describes 9 patients with renal cell carcinoma in a collective of 405 patients with GIST (2.2%). In 2000, the same center (Memorial Sloan-Kettering Cancer Center) (2), reported in at the time 200 GIST patients: four patients with breast cancer (2%), two patients with prostate cancer (1%), and one patient (0.5%) each with skin, uterine, lung and renal cancer. In our own collective of 172 GIST patients, about 20% had a secondary malignancy, one of which had renal cell carcinoma (0.6%) (7).

Whilst micro-GIST of the stomach are frequent incidental findings in gastrointestinal or pancreaticobiliary tumor surgery (20–30/100) (8,9), the incidence of overt GIST is rare (0.2% of gastrointestinal tumors, 1–2/100,000) (10,11). The incidence of renal cancer varies from 1–10/100,000 within the different countries (12). The co-occurrence of GIST with other malignancies is not uncommon and seems to vary between 0.5% and 20%. As shown above, the likelihood of a patient presenting with GIST and another specific type of tumor however is small. Common environmental factors, such as smoking, obesity and hypertension (as in renal cancer) (13) do not seem to play a role, as these factors are not relevant in GIST (14). Nevertheless, there seems to be correlation with specific malignancies, such as prostate or renal cancer. It is possible to hypothesize that mechanisms involving protein tyrosine kinases are influenced by their cognate growth factors in the microenvironment (15). This would also explain, why the receptor tyrosine kinase cMET (whose ligand is hepatocyte growth factor) seems to be involved in renal cell cancer, however, association with hepatocellular cancer is extremely rare (16).

Both, renal cancer and GIST are highly vascularized tumors, and profit from anti-VEGFR treatment, such as sunitinib (17-19). Furthermore, in subgroups of GIST and renal cell cancer, the occurrence of germline mutations in succinate dehydrogenase (SDH) A, SDHC, and mutations of the Von-Hippel-Lindau (VHL) gene have been described (20-26). These mutations are involved in the energy

metabolism of tumors. SDH is an enzyme complex found in the inner mitochondrial membrane. It participates in both, the citric acid cycle and the electron transport chain (27). In wildtype (WT) GIST, loss of the subunit SDHB has been described (28). This leads to accumulation of succinate, the substrate of succinate dehydrogenase and stabilizes Hypoxia-inducible factor alpha (HIFα) which is being degraded under physiological conditions (29). The consequence is pseudo-hypoxia, which induces genes, which are involved in the survival of cells under hypoxic conditions such as angiogenesis, apoptosis resistance, and oxygen-independent ATP-synthesis, and lead to tumor progression (30).

The occurrence of XP11 translocation-associated renal carcinoma and GIST seems to be rare. The resulting gene fusions involve the transcription factor E3 (TFE3), which also is involved in mitochondrial energy balance and alterations which lead to abnormalities of glucose and lipid metabolism (31).

Is the development of RCC and GIST really associated or co-occurring? In the manuscript of Mendonca *et al.* (6), RCC and GIST were synchronous in 5/9 (55.6%) of the cases. Most RCC were pT1 8/9 (88.9%), half were clear cell RCC (4/9), half papillary RCC (4/9).

GISTs were not characterized according to their tumor stage. Their initial size was 7.6 cm with 4/9 (44.4%) being small bowel GIST, where the classification for risk of recurrence would at least be intermediate. 5/9 GIST (55.6%) were metastatic. Thus, GISTs were rather advanced compared to RCC. The authors argue that RCC diagnosis might be aided by serial imaging in the follow-up care of GIST. As RCC were detected early, operation could be curative with a mean follow-up of 9.2 (range 3.8–28.4) years. The question of concomitant treatment of RCC and GIST does thus not occur. Other articles however showed that not only tyrosine kinase inhibitor monotherapy, but also combination of i.e., sunitinib and cytotoxic chemotherapy (gemcitabine) are an active and well-tolerated combination in patients with aggressive RCC (32). This also conforms with our own experience of concomitant tyrosine kinase inhibitor treatment (imatinib) and systemic gemcitabine in GIST and urinary bladder cancer.

From the different available studies, it can be concluded that whilst we should generally be aware of other tumors in the follow-up care of GIST patients, some tumors co-occur more often than others, such as renal cancer. The association between these malignancies warrants further genetic testing to help identify specific mutations. Different pathways, such as tyrosine-kinase receptor pathways and an anti-inflammatory microenvironment (33) seem to be a common denominator. The current manuscript as a clinical report opens a glimpse into these complex mechanisms.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Gastrointestinal Stromal Tumor*. The article did not undergo external peer review.

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/gist.2018.11.01). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/gist.2018.11.01
Cite this article as: Cameron S. The search for a common denominator of gastrointestinal stromal tumors and renal cell carcinoma. Gastrointest Stromal Tumor 2018;1:3.