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Papillary renal cell carcinoma: what is missing in research? A case report and a review of literature

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Abstract

The incidence of renal cell carcinomas in adults ranges has been increasing over the past decades in both men and women. Once the incidence was 2.9%, now is reported to have increased to 3%–5% with male predominance according to the most recent reports of cancer statistics. The disease typically describes a group of different histopathological subtypes; the most common is clear cell carcinoma which accounts for 70%–80% of the diagnosed cases, while papillary renal cell carcinoma and chromophobe types represent 20% and 5%, respectively. In 1996, the renal cell carcinomas Heidelberg classification was introduced by Delahunt et al. It divides renal cell tumors into benign and malignant parenchymal neoplasms, excluding Wilm's tumor and secondary metastases and limiting each subcategory to the most commonly documented genetic abnormalities, if applicable. In this report, we discuss a case of metastatic type I papillary renal cell carcinoma treated with the anti-vascular endothelial growth factor receptor sunitinib and showing marked long-term clinical response. Through this case, we highlight the importance of re-classifying papillary renal cell carcinoma subtypes to prioritize the clinical management of these cases.

Keywords

Renal cell carcinoma, papillary renal cell carcinoma, metastatic, tyrosine kinase inhibitor, sunitinib, response

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Background

The incidence of renal cell carcinomas (RCC) in adults ranges has been increasing over the past decades in both men and women. Once the incidence was 2.9%, now is reported to have increased to 3%–5% with male predominance according to the most recent reports of cancer statistics.[1–4] The disease typically describes a group of different histopathological subtypes; the most common is clear cell carcinoma (CCC) which accounts for 70%–80% of the diagnosed cases, while papillary renal cell carcinoma (pRCC) and chromophobe types represent 20% and 5%, respectively.[5] The remaining are considered unclassified RCC, and this include a group of rare pathological presentation where the tumor histology does not show any of the distinct features of the major RCC subtypes or may have pure sarcomatoid/rhabdoid histology. These tumors are histologically heterogeneous, most commonly high grade.[6]

In 1996, the RCC Heidelberg classification was introduced by Delahunt et al. It divides renal cell tumors into benign and malignant parenchymal neoplasms, excluding Wilm's tumor and secondary metastases and limiting each subcategory to the most commonly documented genetic abnormalities, if applicable.[7] Focusing on pRCC, the disease was divided into two types: type I and type II pRCC. Type I is characterized by MET alterations, and type II, which is linked to familial pRCC.[8,9] And thus, Type II is in fact a group of tumors that are cause by the various hereditary cancer syndromes such as fumarate hydratase (FH) gene mutations that result in hereditary leiomyoma renal cell carcinoma (HLRCC).[10–12] The whole classification was based mainly on the histological morphology and genetic knowledge at the time,

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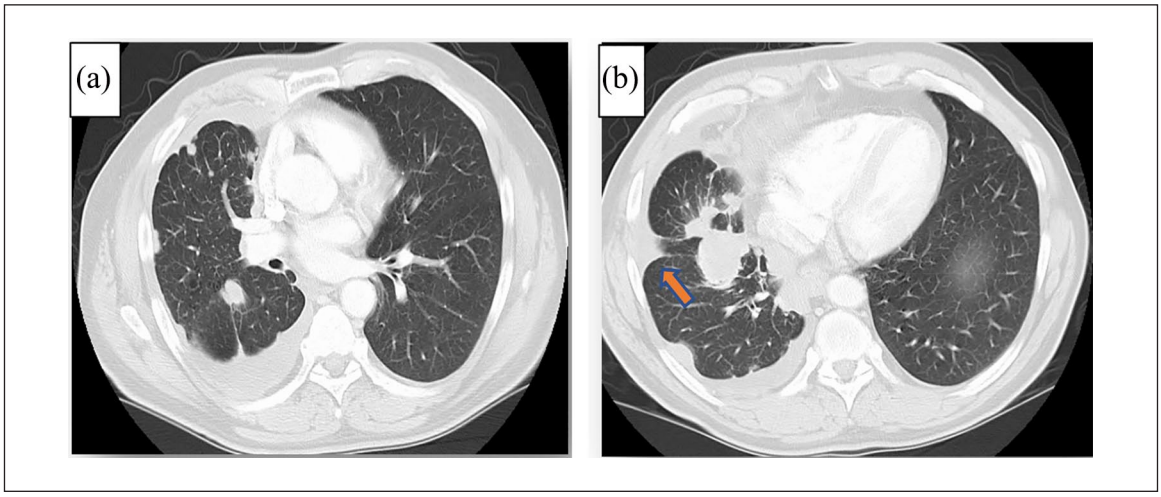

Figure 1. A CT chest of the patient for initial evaluation. a) and b) both cuts show a right hemithorax mass involving the pleura (red arrow in b).

and described by the authors as being clinically applicable,[7] but researchers nowadays consider that an introduction of classification updates is mandatory.[9] However, this opinion is focused on type II pRCC, which is known for its basic genetic heterogeneity even at the time of classification. This in today's advances in understanding the tumor genome and next generation sequencing (NGS) seems to be a humble plan, but can serve as an otherwise one of the possible first steps since proper molecular and genetic characterization typically requires an extended plan timewise in order to reach comprehensive clinical consensus, defining possible druggable pathways and/or addressing causes of the disease modest therapy responses.[5,13]

The interest in using vascular endothelial growth factor receptor (VEGFR) inhibitors in pRCC was explored by several researchers following reports that these tumors show VEGFR over-expression,[14,15] and after the significant activity these drugs have been shown in CCC clinical trials gaining the approval of Food and Drug Administration (FDA) in metastatic setting.[16] The CCC tumors were found to have mutations in the von Hippel–Lindau (VHL) gene with a defective gene product, VHL protein. This results in increased transcription of hypoxia-inducible genes such as VEGFR.[17] A similar concept was not thoroughly investigated in pRCC.[16] Instead, researchers depended on immunohistochemical reports for VEGFR expression on sporadic pRCC tumors. In fact, there has been recent studies published that still try to find the predictive significance of VEGFR and platelet-derived growth factor receptor (PDGFR) expression in pRCC.[18] The clinical trials that studied the outcome of anti-VEGFR, mainly sunitinib and sorafenib, in pRCC have used radiological response as a measure of response to treatment. They also included chromophobe and other non-CCC RCC in the experimental groups. Both points introduce weaknesses in the structure of the trial. Although there is a lack of molecular markers in those patients, the effect on those that have them should have been measured by biological markers such as circulating tumor DNA (ctDNA) for the value of information that could have been obtained especially for type II.[13,16,19] These studies reported modest outcome for anti-VEGFR therapy though was superior to other available treatment options. Even though clinical outcome is the most valid point in drug therapy approval, a proper understanding of the molecular characteristics of tumor cells is necessary to complement therapy decision in a chronic disease.[20–22]

Currently, therapy for pRCC is determined by staging. If the disease is localized, it is treated by surgery and radiotherapy, but once it is out of the confines of local treatment, its prognosis becomes worse and targeted therapy of anti-VEGFR have modest outcomes. Furthermore, this disease is the most likely RCC to be metastatic.[23] In this report, we follow a case of histologically diagnosed pRCC who received sunitinib according to National Cancer Comprehensive Network (NCCN) guidelines. The patient response to treatment and outcome was recorded.

Case presentation

A 59-year-old Caucasian male patient was referred to the university of Cincinnati Cancer Medical Center following a computed tomography (CT) scan revealing a most likely malignant metastatic nodule occupying the right hemi-thorax and involving the pleura (Figure 1: upper panel). The patient past history was significant for past heavy smoking, and chronic cough for 3 years. A CT scan of abdomen was obtained that showed a non-enhancing 1.5-cm low-density focus within the lateral mid-pole of the left kidney with no additional renal masses identified (Figure 2: lower panel). Histopathological analysis of a transthoracic biopsy revealed adenocarcinoma with an immune profile with positive reaction for: vimentin, AE1, CK7, AMACR, RCCM, PAX2, and

PAX8 and negative for: CD117, kidney-specific cadherin, and parvalbumin which is consistent with pRCC (Figure 3). The patient received sunitinib 50 mg daily on a 4-week-on and 2-week-off regimen with an initial good clinical response manifested in improvement of his respiratory symptoms followed by stable condition. A total of 3 years after initiation of therapy, his dose was reduced by 12.5 mg for the patient to receive a total of 37.5 mg daily following skin rash development. A new CT scan of the thorax, abdomen, and pelvis was obtained showing an unchanged primary lesion; however, the size and configuration of the thorax metastases regressed markedly, and there was no evidence of metastatic disease in the abdomen or pelvis (Figure 4).

The patient continued to receive reduced dose sunitinib with stable symptoms up to date.

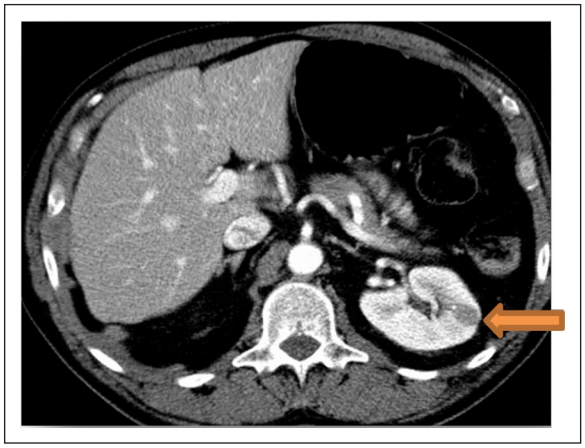

Figure 2. A CT abdomen done on 26 January 2011 showing non-enhancing 1.5-cm low-density focus within the lateral mid-pole of the left kidney (Yellow Arrow), no additional renal mass identified.

Discussion

In this report, we have reviewed a case of metastatic pRCC. The case had the advantage of representing the most frequent clinical picture seen in this group of patients while reflecting the defects in the available standard of care plans. A male patient, in his 50s, with type I pRCC and no family history indicating hereditary malignant syndromes. He presented with metastatic pRCC to the lung. He had a stunning 2-year history of respiratory symptoms, seeking medical advice when his dyspnea started to escalate rapidly. Although the extend of his lung lesions was in concordance with his respiratory symptoms, the primary lesion in the right kidney was only 1.5 cm. The patient had a very good response to the anti-VEGFR, sunitinib, at regular dose and good tolerance for 3 years before modulation of the treatment was required. He also maintained the good response on the reduced dose for another 2 years. As mentioned before, pRCC is the most common subtype of non-CCC RCC, accounting for 10%–15% of all RCCs.[24] The pRCC2 is significantly associated with higher stage and higher grade than the pRCC1. It was identified as a factor of significantly poorer prognosis associated with shorter survival.[25] In vitro reports have shown that inhibition of the PDGFR and VEGFR can affect tumor-dependent angiogenesis, encouraging the use of anti-VEGFR, sunitinib, which has previously shown efficacy in CCC, for pRCC.[26]

The presentation of a localized primary lesion with extensive lung metastases goes with the reports that some pRCC tumors have higher metastatic potential.[5,9] However, they also recognize metastasis as a strong prognostic and predictive factor which our case disease history denies. This particular point show that pRCC can have different subcategories that need to be better addressed. Vimentin expression in this case can be a clue. Previously, there has been data that suggest that vimentin expression in lung cancer is prognostic

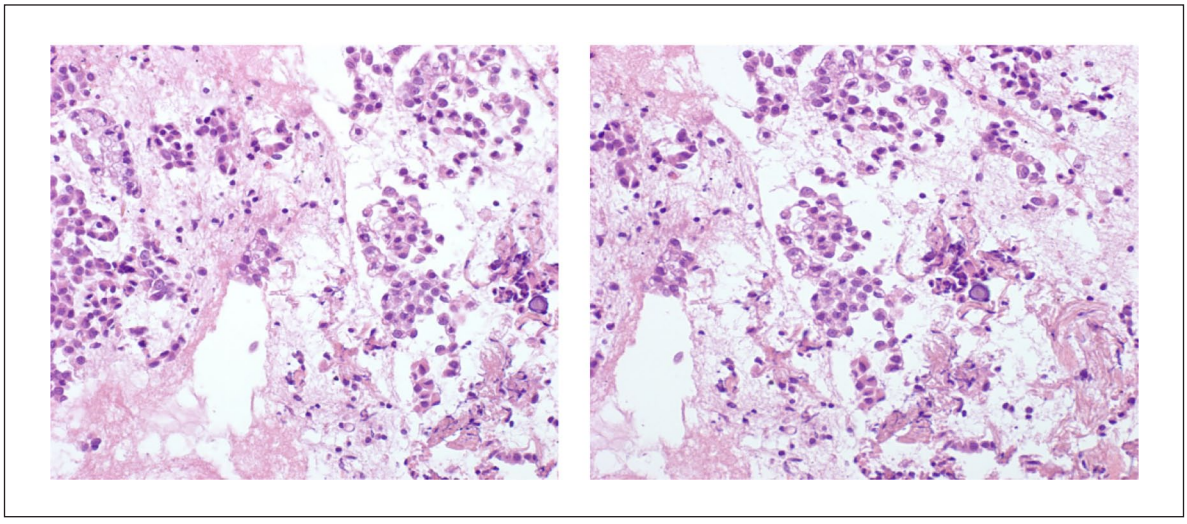

Figure 3. Showing the histological image from the patient's lung mass.

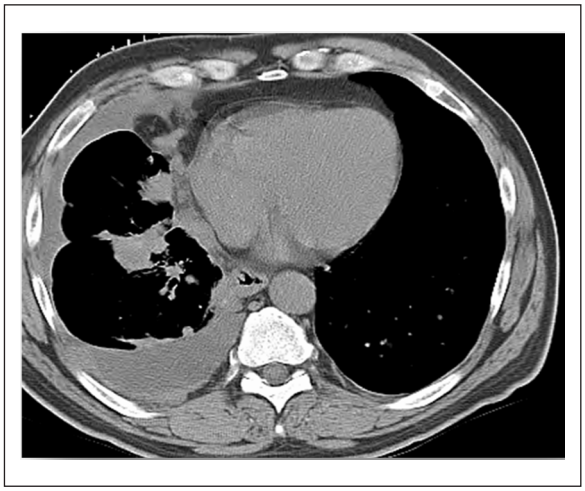

Figure 4. A CT scan of the abdomen and pelvis obtained 3 years after initiation of treatment. The image shows marked improvement of the lung lesion.

factor for distant metastasis.[27,28] Our case had strong positivity to vimentin; there is lack of data about the percentage of pRCC expression of this marker for both subtypes of the disease, although it has been reported to be expressed by this tumor.[29] Type I pRCC is known for MET gene alterations, which was correlated to vimentin expression in lung cancer as well.[30]

The initial response to sunitinib was previously documented in previous studies, even though it only occurs in 30% of the cases of non-CCC.[5,13] However, maintaining long-term stable disease for a 5-year period in a poor prognosis disease is not as common. This indicates that this subset of patients who we can consider as anti-VEGFR responders are worth a closer look to the tumor cell microenvironment to identify who can benefit more from this treatment.

Conclusion

Clinical outcomes of pRCC cases indicate that the tumor has far more than what the current classification has to offer. A new classification which is introduced should be built on studying the tumor biology, molecular characteristics, and prioritizing the clinical aspects. This is a poor prognosis disease, and histopathological diagnosis no more poses the challenge it used to before for the benefit of the patient.

Declaration of conflicting interests

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Ethical approval

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Informed consent

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