Initial response of renal cell carcinoma to vemurafenib in a patient treated for metastatic melanoma

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Introduction

Vemurafenib is a selective inhibitor of overactive BRAF oncogene with a substitution of lysine for glutamic acid at residue 600 ($BRAF^{V600E}$), a mutation expressed in approximately 50% of all melanomas. We report a case of a patient with metastatic melanoma treated with vemurafenib, who subsequently presented with a biopsy-proven conventional renal cell carcinoma (RCC). We observed an initial complete regression of the mass while on vemurafenib. This was unexpected, given that vemurafenib is a specific inhibitor of $BRAF^{V600E}$ and most RCCs do not harbour this mutation.

Case report

A 55-year-old male was seen in consultation for an incidental finding of right renal mass. He had a history of B-Raf proto-oncogene, serine/threonine kinase (BRAF)-positive metastatic melanoma with unknown primary and metastasis to the inguinal fossa and right thigh diagnosed two years previously. The melanoma had been treated with a combination of surgical resection and radiotherapy. He was undergoing systemic chemotherapy with vemurafenib 720 mg twice daily. The patient had no evidence of disease for six months at the time of detection of the renal mass. He denied any flank pain, flank mass, or gross hematuria. Routine lab work, including creatinine, was normal. Abdominal computed tomography (CT) with contrast revealed a 2.9 cm complex enhancing mass in the right kidney with no evidence of lymphadenopathy or metastasis (Fig. 1). Due to the small size of the renal mass and the possibility that it may represent metastatic melanoma, the patient elected to undergo active surveillance with repeat abdominal CT in six months. The patient was continued on vemurafenib for treatment of his metastatic melanoma.

Followup imaging six months later showed interval size decrease of the mass to 1.9 cm. Repeat imaging four months later demonstrated complete resolution of the renal mass, suggesting that the mass was a metastatic melanoma deposit that responded to systemic therapy (Fig. 1). However, repeat CT at six and 12 months later showed recurrence and progression of the right renal mass to 2.6 and 3.7 cm, respectively. The patient underwent biopsy of the renal mass, which revealed conventional renal cell carcinoma (RCC). Repeat imaging three months later showed interval size increase of the mass to 4.2 cm with no signs of metastatic deposits. The patient underwent laparoscopic right radical nephrectomy without complication. Surgical pathology confirmed conventional RCC pT3AN0 disease with negative margins.

Discussion

Here we report a roughly 18-month clinical response to vemurafenib in a patient with conventional RCC. To the best of our knowledge, this is only the second case report of RCC showing response to a BRAF inhibitor.

BRAF is a signaling protein downstream of Ras that activates the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinases (ERK) pathway and is implicated in cell proliferation and differentiation.[1] BRAF is mutated in approximately 8% of all cancers and 50% of melanomas, with the most common mutation consisting of a substitution of lysine for glutamic acid at residue 600 ($BRAF^{V600E}$).[1] Vemurafenib is a small molecule inhibitor that binds the active form of BRAF and is highly selective for the constitutively active $BRAF^{V600E}$ mutant over wild-type BRAF.[2] Paradoxically, vemurafenib increases activity of wild-type BRAF and may stimulate cancers without the V600E mutation.[2] Although vemurafenib is believed to work primarily by inhibiting $BRAF^{V600E}$-induced oncogenic MAPK signaling, there is growing evidence that BRAF inhibitors may also act through sensitization of tumour cells to immune attack.[3,4]

Mutations in BRAF are not well-implicated in RCC. Molecular characterization of over 400 RCC tumour samples failed to reveal significant BRAF mutations.[5] Analysis of 50 RCC samples (20 papillary, 15 conventional, and 15 chromophobe) found no BRAF mutations.[6] Similarly, analysis of tissue from 99 patients with RCC (63 conventional,

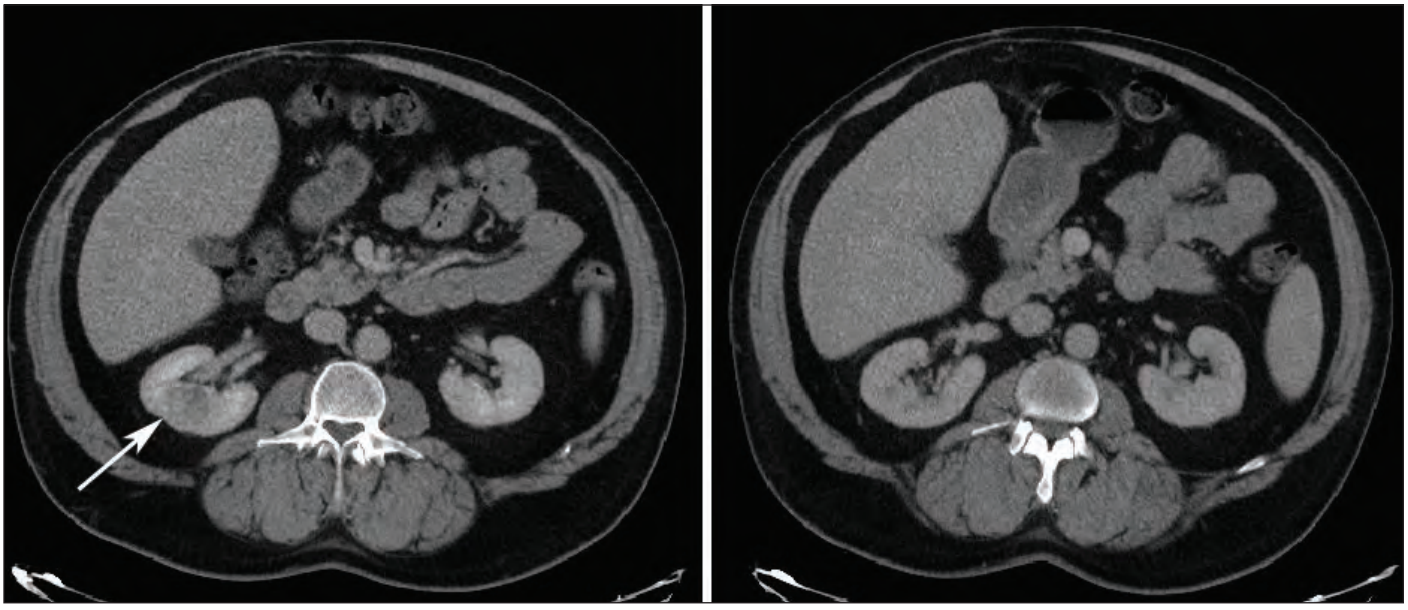

Fig. 1. Enhanced abdominal computed tomography scan showing a 2.9 cm complex enhancing lesion (left; arrow), and complete resolution of this lesion 10 months later (right).

22 papillary, and 14 chromophobe) failed to identify BRAF mutations.[7] However, the $BRAF^{V600E}$ mutation was identified in a papillary RCC.[8] Furthermore, a recent case report identified a patient with $BRAF^{V600E}$-positive metastatic papillary RCC who experienced a modest reduction in primary and metastatic lesions with vemurafenib.[9] Consequently, BRAF mutations do not seem to be a major oncological driver of most RCCs, but they are present in a subset of RCCs.

Given the lack of $BRAF^{V600E}$ mutations in RCC and the evidence that vemurafenib may stimulate cancers without the V600E mutation, we were surprised by the reduction in tumour size observed in the present case after treatment with vemurafenib. As there have been at least two reports of $BRAF^{V600E}$ -positive RCCs,[8,9] one possibility for the clinical response in our case is that our patient also harboured a $BRAF^{V600E}$ -positive RCC. Unfortunately, we were not able to perform genetic testing of the RCC specimen in the present case. Alternatively, the immunomodulatory effects of vemurafenib may have contributed to RCC tumour regression. Vemurafenib has been shown to increase tumour infiltration with CD8+ T-cells and decrease expression of immunosuppressive cytokines,[3] which could potentially induce tumour regression in the absence of a $BRAF^{V600E}$ mutation.

There is some evidence to indicate that patients with melanoma are at increased risk of developing secondary non-cutaneous malignancies, including RCC. In the largest prospective study to date, consisting of 4597 patients with histologically proven melanoma, the standardized incidence ratio for development of RCC was 2.5 (1.2–4.6).[10] Although common etiological factors for both RCC and melanoma are not well-established, there are several possible links between these cancers, including: 1) exposure to shared environmental risk factors, such as obesity;[11] 2) shared genetic abnormalities, such as a common missense mutation in microphthalmia-associated transcription factor,[12] alterations in the CDKN2A gene encoding p16INK4a,[13] and increased association of familial RCC and melanoma;[14] 3) alterations in the MAPK pathway;[15] 4) alterations in cell-mediated immunity;[16] and 5) increased medical surveillance leading to increased incidental detection of RCC.[16]

Conclusion

We report partial response of biopsy-proven conventional RCC to vemurafenib. This is unexpected, given that vemurafenib is a specific inhibitor of BRAF with a substitution of lysine for glutamic acid at residue 600 and most RCCs do not harbour this mutation. Further studies investigating the impact of vemurafenib on progression of RCC and the presence of BRAF mutations in RCC may be warranted, especially given the recent finding of a patient with $BRAF^{V600E}$-positive RCC that was similarly responsive to vemurafenib.

Competing interests: Dr. Roberts has served as a speaker for Mylan. The remaining authors report no competing personal or financial interests.

This paper has been peer-reviewed.

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