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Case Report Open Access

A Case of Metastatic Papillary Renal Cell Carcinoma Responsive to Bevacizumab and Erlotinib

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Abstract

Papillary renal cell carcinoma is an uncommon non-clear-cell subtype of renal cell carcinoma, representing about 15% of all renal cell carcinomas. There is relatively little data on treatment of papillary renal cell carcinoma. Historically, this subtype has a poor response to most commonly used systemic agents. However, the altered cellular metabolism in papillary renal cell carcinoma presents a weakness that can be exploited by targeted agents. We present a case of a young patient with metastatic papillary renal cell carcinoma who, having progressed on three prior therapies, has an excellent and durable response to bevacizumab and erlotinib. Our case illustrates the importance of recognizing papillary renal cell carcinoma and mutational testing since there are targeted agents that, while not typically considered in renal cell carcinoma, have efficacy and profound impact on patient care.

Keywords: Renal cell carcinoma; Papillary; Fumarate hydratase; Bevacizumab; Erlotinib

Introduction

Kidney cancer is the twelfth most common cancer in the world. In the United States, an estimated 62,700 people will be diagnosed with renal cancer and 14,240 will die of the disease in 2016 [1].

Histologically, subtypes of renal cell carcinoma include clear cell (80.5%), papillary (types 1 and 2), (14.3%), and chromophobe (5.2%) [2]. Type 1 and 2 papillary renal cell carcinoma refer to distinct microscopic patterns: type 1 tumors have thin basophilic papillae with clear cytoplasm; while type 2 tumors have heterogeneous, thicker papillae with eosinophilic cytoplasm [3].

Systemic therapy is indicated for patients with metastatic renal cell carcinoma. Given the relative rarity of metastatic papillary renal cell carcinoma, most trials have included only patients with the clear-cell subtype of renal cell carcinoma. In fact, at time of this publication, there are no completed phase 3 trials of patients specifically with metastatic papillary renal cell carcinoma.

Papillary renal cell carcinoma does not respond well to cytokine therapy [4] or cytotoxic chemotherapy [5]. Targeted agents are effective for patients with non-clear-cell renal cell carcinoma; however, patients with non-clear-cell renal cell carcinoma have inferior response rates to these agents and worse overall survival when compared to patients with clear-cell renal cell carcinoma [6].

Approved combination therapies for the treatment of metastatic renal cell carcinoma include bevacizumab/interferon-α [7] and lenvatinib/everolimus [8]. However, these combinations are recommended only for patients with predominantly clear-cell renal cell carcinoma.

Although less common, the diagnosis of papillary renal cell carcinoma is important to not miss, as patients with this histologic subtype generally have poor response to common systemic therapies and shorter overall survival. We present a case of metastatic papillary renal cell carcinoma and review pathophysiology and new treatment considerations.

Case

A 35-year-old female presented with complaints of hematuria, flank pain, and a right abdominal mass. A computed tomography (CT) scan revealed 6 × 5 × 5 cm right renal mass, mildly enlarged retrocaval lymph nodes, and multiple sub-centimeter bilateral pulmonary nodules (Figure 1). A right cytoreductive nephrectomy was performed, and pathology revealed a type-2 papillary renal cell carcinoma. She was classified as intermediate risk by the IMDC prognostic scoring system.

Several weeks later, she began adjuvant treatment with pazopanib. After three months, CT imaging revealed an increase in the size of the bilateral pulmonary nodules; and her treatment was switched to axitinib. Within five months, her clinical condition deteriorated significantly; she was confined to a wheel chair.

Her disease progressed, and her therapy was changed to temsirolimus. Within two months, her health continued to decline, and she was enrolled in hospice. However, her tumor had been sent for genetic testing; a deficiency in fumarate hydratase was discovered. She presented to our clinic for a second opinion.

We took her out of hospice and started bevacizumab and erlotinib. Her response to therapy was rapid, and her clinical condition improved significantly. Within one month, she no longer required supplemental oxygen or a wheel chair; her ECOG performance status had improved from ECOG 4 to ECOG 0. Follow-up imaging revealed a partial response, with a decrease in size of pulmonary nodules and a decrease in size of a left pleural effusion. Her most recent CT scan revealed stable disease (Figure 2). One year later, she is doing well with

continued stable disease and an excellent tolerance to bevacizumab and erlotinib.

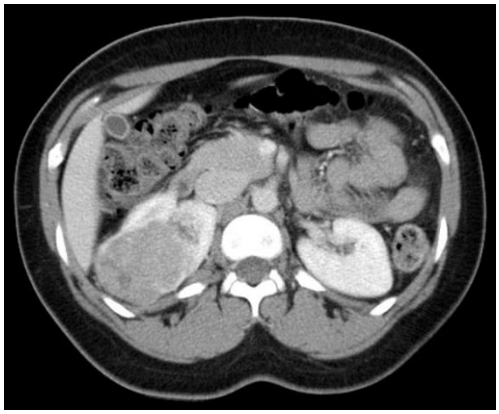

Figure 1: A large, right renal mass on computed tomography, transverse view.

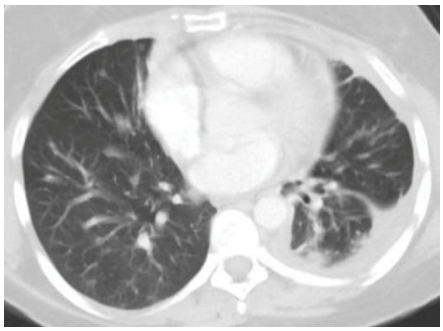

Figure 2: Bilateral pulmonary nodules and a rind of pleural thickening around the left lung on computed tomography, transverse view.

Discussion

Fumarate-hydratase-deficient papillary renal cell carcinoma undergoes a shift to aerobic glycolysis [9]. There is an increased need for vascularity and glucose transport in order to facilitate aerobic glycolysis. Increased fumarate inhibits prolyl hydroxylase, resulting in stabilization of hypoxia-inducible factor 1α (HIF-1α), leading to increased transcription of vascular endothelial growth factor and glucose transporter 1 (Figure 3). Bevacizumab, a VEGF inhibitor, and erlotinib, an EGFR tyrosine kinase inhibitor that can down-regulate MYC-regulated genes such as GLUT1, would theoretically be an ideal combination to target this increased glycolytic demand.

Bevacizumab has activity in metastatic renal cell carcinoma. The combination of bevacizumab and erlotinib had been previously shown not to provide an additional clinical benefit compared with bevacizumab alone [10]. However, patients in that study had predominant clear-cell histology, not the papillary type associated with deficiency in fumarate hydratase and subsequently increased levels of VEGF and GLUT1.

Figure 3: Deficiency in fumarate hydratase (FH) leads to increased fumarate, which inhibits prolyl hydroxylase (PHD). PHD inhibition stabilizes hypoxia-inducible factor 1α (HIF-1α), which increases transcription of vascular endothelial growth factor (VEGF) and glucose transporter 1 (GLUT1).

Finding from a recent phase II clinical trial present strong evidence for tailoring therapy in advanced renal cell cancer depending on histologic subtype [11]. In this trial of 41 patients with advanced papillary renal cell carcinoma (including both hereditary and sporadic subtypes), the overall response rates were 65% and 29% for hereditary and sporadic papillary renal cell carcinoma, respectively. In the hereditary leiomyomatosis and renal cell cancer cohort, the median progression-free survival was an impressive 24.2 months. With most commonly used regimens today, the median progression-free survival in this cohort is less than 6 months.

In conclusion, advanced papillary renal cell carcinoma is an aggressive disease that typically responds poorly to systemic regimens used for clear-cell renal cell carcinoma. This case shows that the combination of bevacizumab and erlotinib is well-tolerated and can produce durable responses in papillary renal cell carcinoma, even in the case of a heavily pretreated patient.

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