Chromophobe Renal Cell Carcinoma With Sarcomatoid Dedifferentiation Treated With Pazopanib: A Case Report

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Clinical Practice Points

- Pazopanib is a multi-targeted tyrosine kinase inhibitor that blocks vascular endothelial growth factor receptors, a tyrosine protein kinase (c-Kit), and platelet-derived growth factor receptor-β and is FDA-approved for the treatment of advanced renal cell carcinoma (RCC).
- Chromophobe renal cell carcinoma (ChRCC) is a rare type of RCC, which when metastatic is associated with a more indolent course than clear-cell RCC and papillary RCC.
- Sarcomatoid dedifferentiation represents transformation to higher grade malignancy and is an independent prognosticator of aggressive outcome in any type of RCC, including ChRCC.
- There are no robust data regarding the clinical efficacy of targeted agents in advanced ChRCC or any type of RCC with sarcomatoid dedifferentiation.
- Our case report suggests that pazopanib might have efficacy in both clinical settings, and was very well tolerated in an elderly patient.
- Until additional data are available, clinicians might consider treating ChRCC and RCC with sarcomatoid dedifferentiation with pazopanib.

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Introduction

Chromophobe renal cell carcinoma (ChRCC) is a subtype of non-clear cell renal cell carcinoma (RCC) that is associated with a good prognosis. ChRCC is believed to be derived from the intercalated cells of the distal nephron and shows histologic overlap with renal oncocytoma.[1] Sarcomatoid dedifferentiation might occur with any type of RCC and is characterized by development of high-grade spindle cell areas in juxtaposition with more conventional epithelial areas of the tumor. Responses of ChRCC to targeted therapies have been published, but to date there are no reports of treatment with pazopanib.

Case Report

An 82-year-old female underwent a left radical nephrectomy, distal pancreatectomy, splenectomy, and retroperitoneal lymph node dissection for a locally-advanced renal mass. Pathology revealed a fleshy tan-brown tumor with focal firm fleshy areas intermixed with golden yellow tan soft areas and focal areas of hemorrhage and necrosis. Histologically, the tumor was consistent with ChRCC Fuhrman nuclear Grade 4 with 60% sarcomatoid dedifferentiation, invading into perinephric adipose tissue. The ChRCC areas of the tumor was made up of cells arranged in sheets, which demonstrated perinuclear clearing. The nuclei demonstrated wrinkling of the nuclear membrane resulting in a "raisinoid" appearance as well as frequent binucleation typical of chromophobe RCC (Figure 1). Higher-grade sarcomatoid areas within the tumor demonstrated prominent spindling of the tumor cells with frequent mitotic activity (Figure 2). A 5 × 4 × 3 cm tumor was noted in the distal pancreas. Surgical margins and 8 paraaortic lymph nodes were negative.

Six months postoperatively, she developed lung metastases. Biopsy was consistent with metastasis from the original ChRCC. Pazopanib 800 mg daily was commenced. Two months later, the largest nodule decreased from 1.3 × 1.4 cm to 1 cm × 0.9 cm. Four months later, it decreased to 0.7 × 0.6 cm (Figures 3 and 4). The patient received pazopanib at full dose for 8 months, until she developed progressive disease (PD). She then received sorafenib for 2 months with PD. She is currently receiving MK-2206, an investigational AKT inhibitor.

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Figure 1 Hematoxylin and Eosin Stained Section of the Tumor Demonstrating Chromophobe Renal Cell Carcinoma. Tumor Cells are Arranged in Sheets and Demonstrate Perinuclear Clearing. Inset: The Nuclei Demonstrated Wrinkling of the Nuclear Membrane Resulting in a "Raisinoid" Appearance as Well as Frequent Binucleation; Typical of Chromophobe Renal Cell Carcinoma

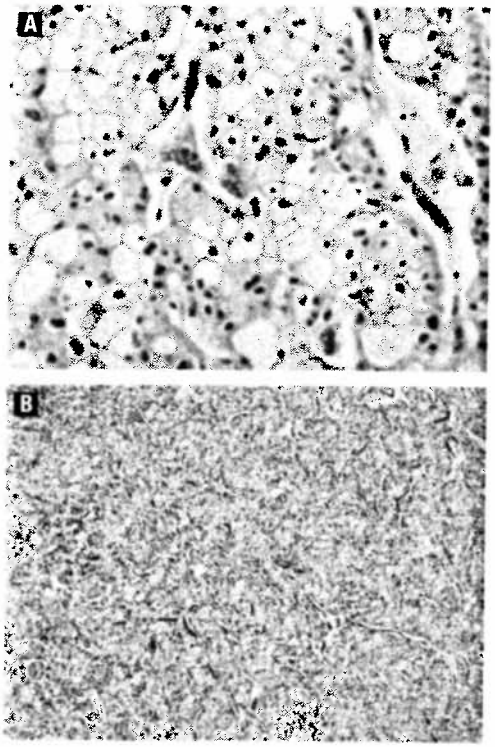


Figure 2 Higher-Grade Sarcomatoid Areas Within the Tumor Which Demonstrate Prominent Spindling of the Tumor Cells. Inset: The Tumor Cells in These Areas Were of High Nuclear Grade With Frequent Mitotic Activity, Consistent With Sarcomatoid Transformation

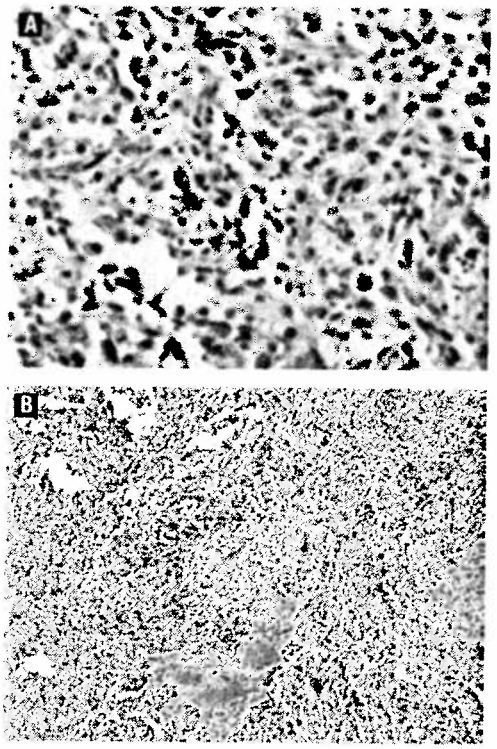


Figure 3 CT at Baseline

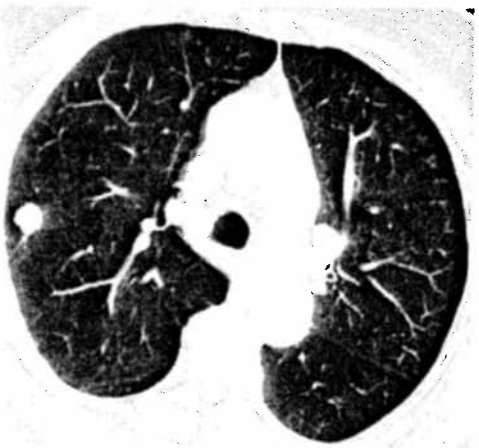
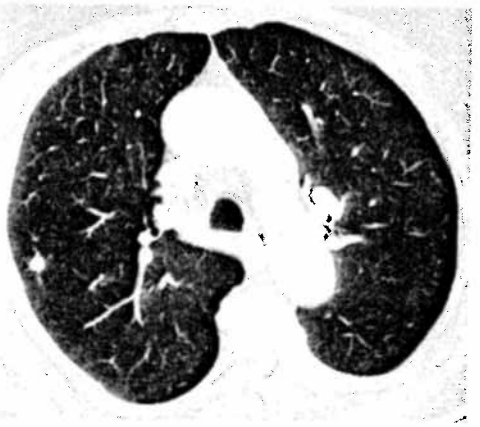


Figure 4 CT After Six Months of Treatment



Discussion

ChRCC tends to recur and metastasize at a lower rate than clear-cell RCC. Sarcomatoid change represents transformation to higher grade malignancy and is an independent prognosticator of aggressive outcome in ChRCC.[2] There are a few reports of improved outcomes in advanced ChRCC using targeted therapies. Paule and Brion published a case of ChRCC with response to temsirolimus.[3] Choueiri et al reported on the efficacy of sunitinib and sorafanib in 12 ChRCC patients. Two out of 5 patients receiving sorafenib and 1 of 12 receiving sunitinib achieved partial response (PR).[4] Twenty patients with ChRCC were treated with sorafenib in the Advanced RCC Sorafenib Expanded Access Program, with a disease control rate of 90%. Larkin et al described a patient with ChRCC who achieved PR with sequential sunitinib followed by everolimus.[5]

Evidence is sparse regarding treatment of RCC with sarcomatoid dedifferentiation with targeted agents. In a retrospective study of 43 patients treated with vascular endothelial growth factor-targeted agents; 19% achieved PR, and 49% had stable disease.[6] Staehler et al noted prolongation of progression-free survival in 5 of 9 patients treated with gemcitabine and doxorubicin followed by sorafenib.[7]

Pazopanib is an approved multi-targeted tyrosine kinase inhibitor that blocks downstream signaling of growth factors including vascular endothelial growth factor receptors (VEGFR), a tyrosine protein kinase (c-Kit), and Platelet-derived growth factor receptor-β. To our knowledge, we present the first case of ChRCC and the first case of any RCC type with significant sarcomatoid dedifferentiation, with demonstrated response to pazopanib. c-Kit and VEGFR are often overexpressed in these tumors, partly explaining the efficacy of pazopanib in this setting. Until additional data are available, clinicians might consider treating ChRCC and RCC with sarcomatoid dedifferentiation with pazopanib.

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