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Polycystic Liver Disease in a Patient With Metastatic Renal Cell Carcinoma: A Case Report

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Abstract. *We report a case of rapid evolution of polycystic liver disease in a 76-year-old patient with metastatic renal cell carcinoma who underwent treatment with numerous antineoplastic agents. The aim was to identify a causative etiology for these hepatic cysts of unclear origin. The cystic lesions of the patient were ultimately innumerable and developed rapidly, more than tripling the total liver volume from complete absence over the course of 24 months. The hepatic lesions continued to grow despite an otherwise moderate tumor response. Prior to patient death, the patient remained relatively asymptomatic from the cyst burden and was without signs of grossly metastatic disease. This rapid development of polycystic liver disease most likely represents a previously unseen medication side-effect of cabozantinib or pazopanib. It is important to identify adverse effects of novel antineoplastic agents in this time of oncological medical discovery.*

Renal cell carcinoma (RCC) is a malignancy originating from the renal epithelium. In the United States in 2019, there were 73,820 new cases diagnosed and 14,770 deaths resulting from renal cell carcinoma (1). The most common sites of metastasis include lung, liver, lymph nodes, and bone (2). Localized disease can be successfully treated with surgical removal, and metastatic disease can be managed with numerous kinase inhibitors, rapamycin complex 1 inhibitors (mTOR), vascular endothelial growth factor inhibitors, and immunotherapy (3-10). The treatment algorithm is based upon risk stratification, while subsequent therapy varies according to disease biology, response, and provider. With the growing abundance of novel therapeutic options, side-effect profiles are likely incompletely described, while it remains important to recognize unique side-effects to guide future management.

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Case Report

A 76-year-old male with a past medical history notable for hypertension, diverticulosis, bilateral knee replacement, benign prostate hyperplasia (BPH), and squamous cell carcinoma of the ear was diagnosed with high-grade clear cell RCC with biopsy confirmed retroperitoneal lymph node metastasis two years prior to case description after presenting with gross hematuria. Socially, he endorsed roughly 15-pack years of tobacco use and intermittent heavy alcohol consumption. Family history was not significant for oncologic, kidney or liver cystic disease. He was initially started on pazopanib and subsequently underwent renal mass embolization to control hematuria. The dose of pazopanib was reduced to 400 mg daily due to fatigue, mildly elevated LFTs (AST 48 U/l, normal range=5-34), elevated bilirubin (2.6 mg/dl, normal range=0.0-1.4 mg/dl), and thrombocytopenia (49 K/ul, normal range=160-370) which normalized with reduced dose. He continued to endorse mild fatigue. Three months into routine follow-up imaging, primary right renal tumor and lymphadenopathy were stable, but the patient was noted to have numerous arterial enhancing foci in the liver (Figure 1; timeline). Two months later, imaging showed decreased lymphadenopathy, stable primary tumor, and enlarging hepatic lesions that no longer enhanced during arterial phase and were felt to be cystic. After five months total of pazopanib treatment, pazopanib was discontinued due to nephrotic-range proteinuria. The patient was subsequently started on immunotherapy with single-agent nivolumab during which he enjoyed improved energy and appetite. Repeat scans three months after starting nivolumab, demonstrated a significant increase in the number and size of hepatic cysts, increased lymphadenopathy, and stable primary kidney tumor. Subsequently, the patient was taken off treatment with

nivolumab for disease progression and was enrolled in a phase 2 placebo-controlled clinical trial combining everolimus with experimental agent CB-839 (glutaminase inhibitor) *versus* placebo. This treatment was discontinued after two months due to a grade 3 maculopapular rash and drug-induced pneumonitis. Interestingly, scans at this time demonstrated decreased size of the primary tumor and decreased retroperitoneal, retrocrural, and thoracic lymphadenopathy; however, the number and the size of the liver cysts had increased. He was then started on cabozantinib at an initial dose of 60 mg daily which was later reduced twice, initially to 40 mg daily and then to 20 mg daily due to significant hand-foot syndrome and hypertension. Interval imaging demonstrated enlargement and increased number of hepatic lesions. His dose was subsequently increased back to 40 mg due to concerns for disease progression. The number and size of the aforementioned hepatic hypoattenuating cysts continued to increase, at this point 16 months since they were first identified (Figure 2). However, the primary renal mass was stable with decreased retroperitoneal and retrocrural lymphadenopathy, even after reducing the dose of cabozantinib twice. Due to unclear etiology and rapid growth of the hepatic lesions in the setting of otherwise moderate disease response, patient underwent targeted liver biopsy which showed normal liver parenchyma and no evidence of neoplasm in multiple step-sections (Figure 3). Three months later, the patient underwent a repeat MRI of the liver to better characterize the cysts which were again increased in size and number and did not enhance with gadolinium. Unexpectedly, the patient felt relatively well since developing these liver lesions and generally had no signs of rapidly progressive metastatic or liver disease. He specifically denied abdominal pain, decreased appetite, jaundice, ascites, weight loss, or fevers. He endorsed consistent mild fatigue that was felt to be associated with cabozantinib. On labs, the ALT, alkaline phosphatase, amylase, and bilirubin remained within normal range. There was as isolated mild elevation in AST (49 U/l, normal range=5-34) during treatment and alkaline phosphatase became elevated after treatment was discontinued. CT 3D reconstruction of the hepatic lesions was performed and yielded a total hepatic volume of 7,359 ml, 5,946 ml of which was made up of cysts (Figure 4).

Unfortunately, follow-up CT scans showed interval disease progression of the primary tumor, increased lymphadenopathy, as well as continued growth of the liver cysts. Treatment was changed to combination ipilimumab/nivolumab. He was subsequently hospitalized for acute kidney injury, abdominal pain, and significant fluid retention believed to be caused by compression of the IVC, possibly related to his massive hepatomegaly. After hospitalization, his condition continued to deteriorate with increased fluid retention, abdominal pain, and lack of appetite. The patient opted to discontinue ipilimumab/nivolumab after one cycle and transitioned to comfort care. The patient was provided and completed written consent to publish his case. He died few days after his enrollment with hospice.

Discussion

The etiology of sudden onset liver cysts in this patient remains unclear and is the subject of interest in writing this case report. Unfortunately, genetic testing and autopsy were not obtained to provide further diagnostic insight.

The initial consideration was metastatic disease from the patients known renal cell carcinoma. However, it would be atypical for a clear cell RCC to be hypoattentuating, non-enhancing (initially was enhancing but later non-enhancing) and cystic in appearance without septations or wall thickening. Other RCC subtypes were also considered including multilocular cystic renal neoplasm of low malignant potential, tubulocystic carcinoma, clear cell papillary RCC, and primary clear cell RCC with cystic degeneration. The initial pathology diagnosis from our patient was high-grade clear cell renal cell carcinoma with sarcomatoid differentiation. Multilocular cystic renal neoplasm of low malignant potential differs from our case in that it is defined by low Fuhrman grade and there are few, if any, reports of metastasis or sarcomatoid changes (11-13). Tubulocystic carcinoma is extremely rare having only been officially included in the Vancouver classification of renal cell cancer in 2012 (14). Additionally, tubulocystic carcinoma is similarly indolent and rarely metastasizes with only a few case reports describing metastasis (15). Clear cell papillary RCC is immunohistochemically and genetically distinct from clear cell RCC, but like these other alternative pathologies, it is also low grade and has not been reported to metastasize (16). It would be extremely unusual for a subclone high-grade RCC to revert to one of these rare low-grade pathologies. It would not be unreasonable to suspect that a renal cell carcinoma with focal sarcomatoid differentiation would potentially develop metastatic disease. Cystic hepatic metastases or degeneration have been described from a number of primary tumors but these cysts differ in that they are often less numerous and do not grow rapidly. More importantly, our patient was never confirmed to have metastatic lesions in the liver while these cysts appear to have developed within normal liver parenchyma (17, 18). Furthermore, no malignant tissue was identified on hepatic biopsy. It is possible that the biopsy failed to properly sample the tissue leading to a falsely negative result, but this seems unlikely given the significant cystic burden and that five core samples were obtained. Further suggesting against hepatic RCC metastasis, his primary tumor and lymphadenopathy responded to treatment while his liver cysts continued to grow. Finally, his normal liver function tests and overall lack of signs of progressive metastatic disease suggest against a malignant etiology.

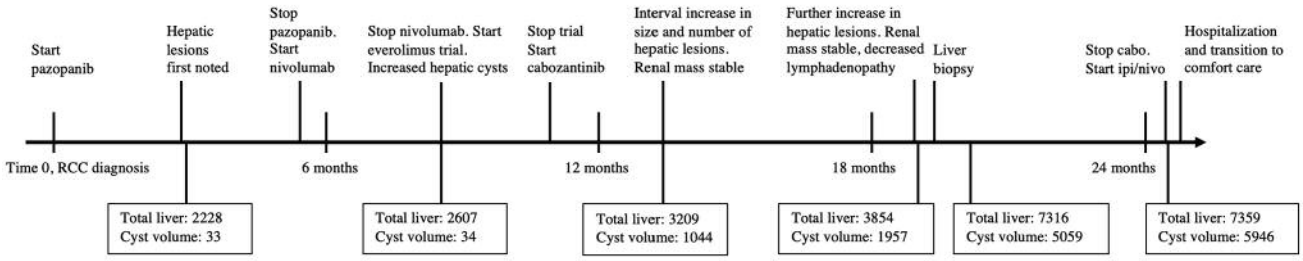

Figure 1. *Timeline of significant events and liver volumes after RCC diagnosis. Liver volumes obtained through CT 3D reconstruction.*

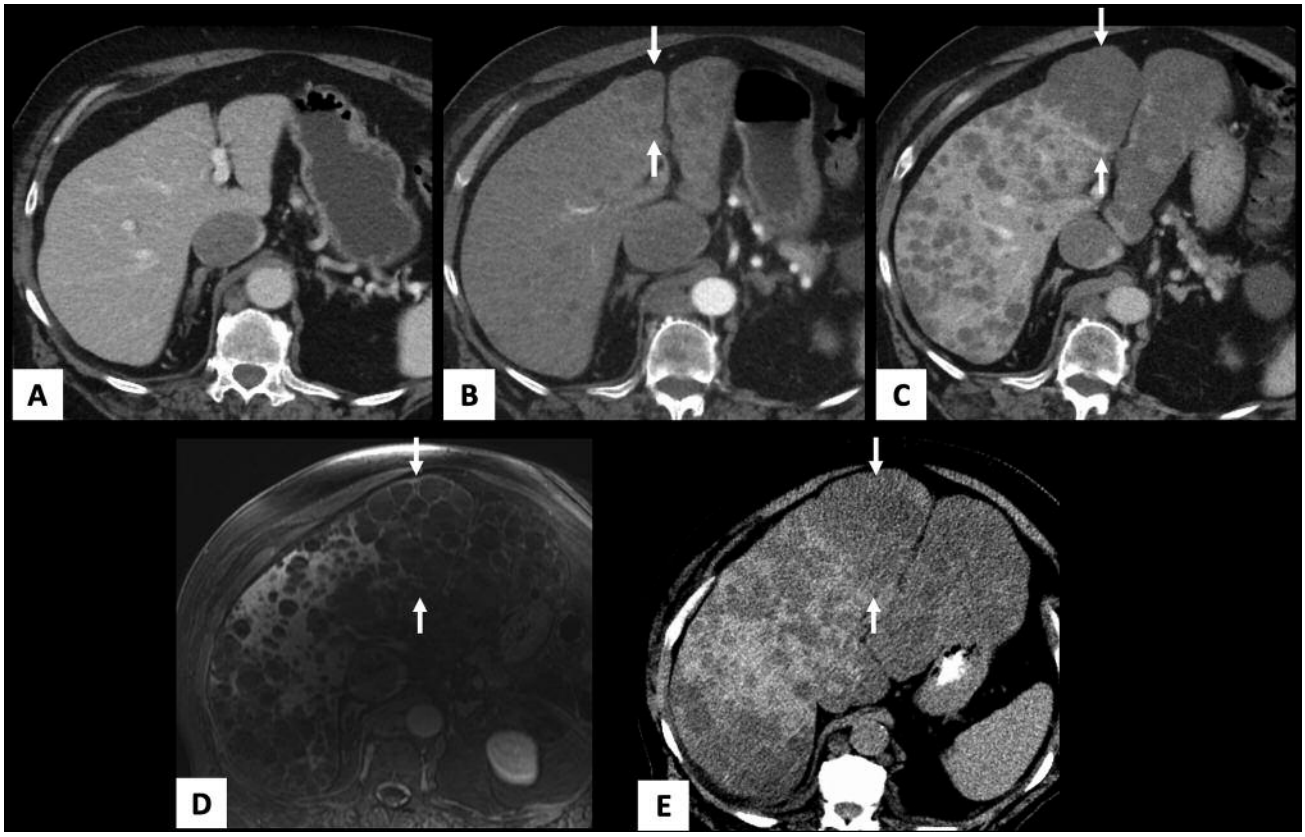

Figure 2. *Enlarging cluster of cysts in segment IV of the liver bracketed by arrows growing over time. (A) Contrast-enhanced CT (CECT) with normal liver three months after RCC diagnosis. (B) CECT with small cysts seen as hypodense (darker structures) between arrows, 10 months after diagnosis. (C) CECT with hypodense cysts replacing parenchyma and expanding segment IV of the liver 19 months from RCC diagnosis. (D) CE-MRI showing continued enlargement of the cysts 22 months after RCC diagnosis. (E) Non-contrast CT shows continued progression of cysts 24 months after RCC diagnosis.*

A unique acquired form of polycystic liver disease (PLD) remains high on the differential given the late onset of disease and rapid appearance of the cysts. An underlying genetic predisposition cannot be excluded. Genetically mediated PLD most commonly occurs as a manifestation of autosomal dominant polycystic kidney disease (ADPKD), a ciliopathy with a prevalence of 1:400-1:100. Less commonly, PLD may develop as a result of autosomal-dominant polycystic liver disease (ADPLD), a cholangiopathy with a prevalence of around 1:158,000 and a mean age of diagnosis of 52 years (19-21). Numerous genes integral to protein biosynthesis within the endoplasmic reticulum have been

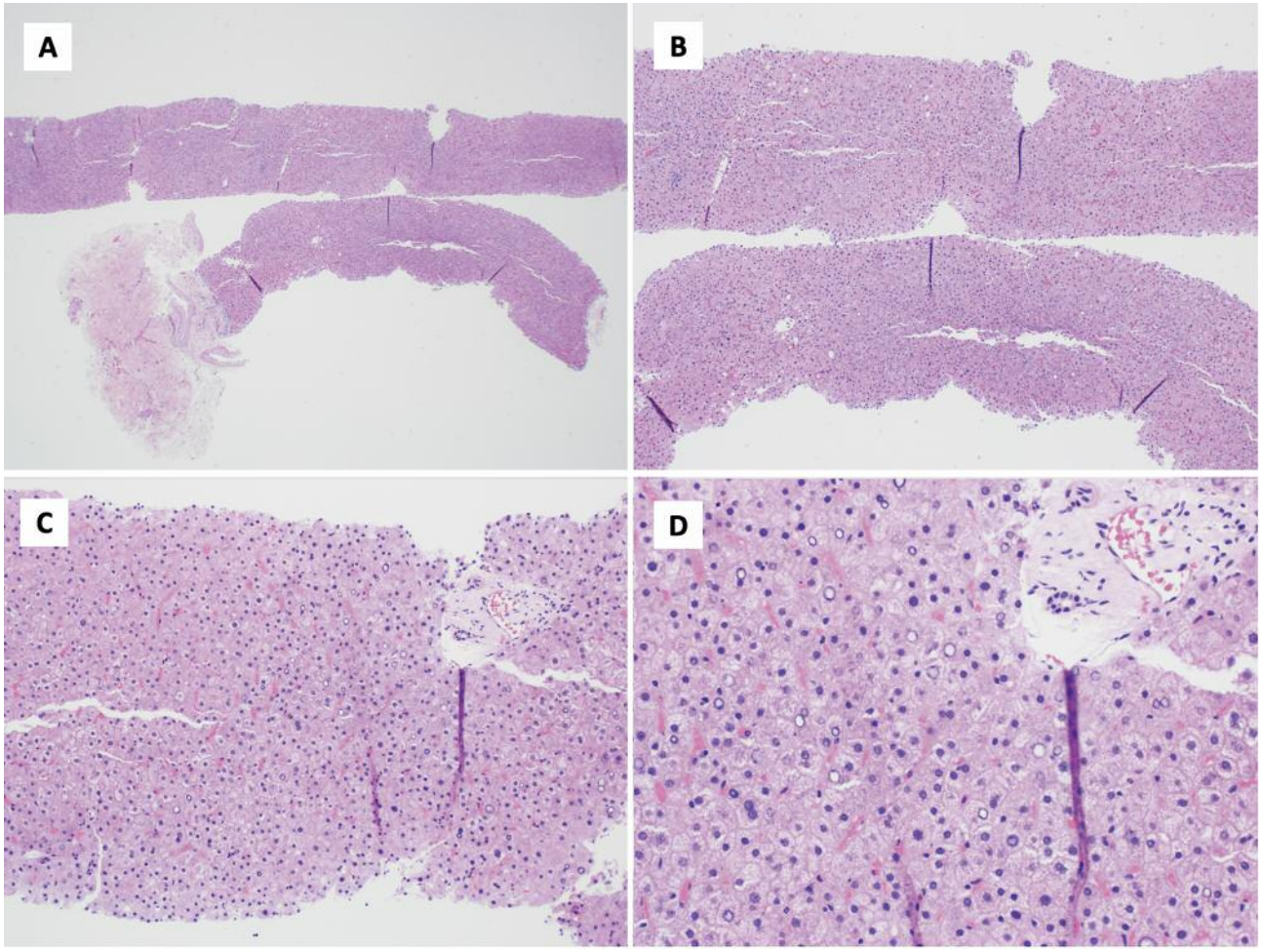

Figure 3. *Liver biopsy showing liver parenchyma within normal limits, negative for neoplasm in multiple step-sections. (Hematoxylin and eosin stain, A: 20×, B: 40×, C: 100×, D: 200×).*

implicated in ADPLD, with *PRKCSH* and *SEC63* being the most well described (22). ADPKD results from mutations in *PKD1* and *PKD2*, and more recently, mutations in *GANAB* have been implicated in ADPKD with a strong PLD phenotype (23). ADPLD and PLD in ADPKD are genetically distinct but have similar clinical course and pathogenic similarities. In both diseases, cyst generation is thought to occur after a 2nd hit to a heterozygous germline mutation leading to functional loss of the second allele (24). Estrogen exposure is a known risk factor, and female gender, estrogen replacement/oral contraceptives, and pregnancy increase the incidence and size of hepatic cysts (25-27). As such, symptomatic patients with PLD are primarily females (28).

PLD, in general, has a silent clinical course with normal liver function until the cyst burden and massive hepatomegaly results in compression of nearby structures leading to severe abdominal fullness and cardiac failure from IVC occlusion. Given the disease rarity, the clinical course and diagnostic criteria for isolated ADPLD are incompletely described, but are generally defined by a positive family history and having over 20 liver cysts whose phenotype is limited to the liver (29). Genetic testing for ADPLD is the only confirmatory test but is infrequently pursued clinically. Alternatively, diagnosis of ADPKD requires presence of multiple renal cysts.

For our patient, ADPLD is unlike given his gender, lack of family history, and age of presentation (our patient was 76 at time of diagnosis, mean age is 52). Rare cases of clinically silent ADPLD at age 70+ have been described, but the average rate of growth of polycystic liver is estimated at 0.9-1.6% in 6-12 months, and our patient far exceeded this rate (30-32). ADPKD with hepatic involvement is extremely unlikely as 94% of these patients present by age 46, and our patient lacked renal cysts (33).

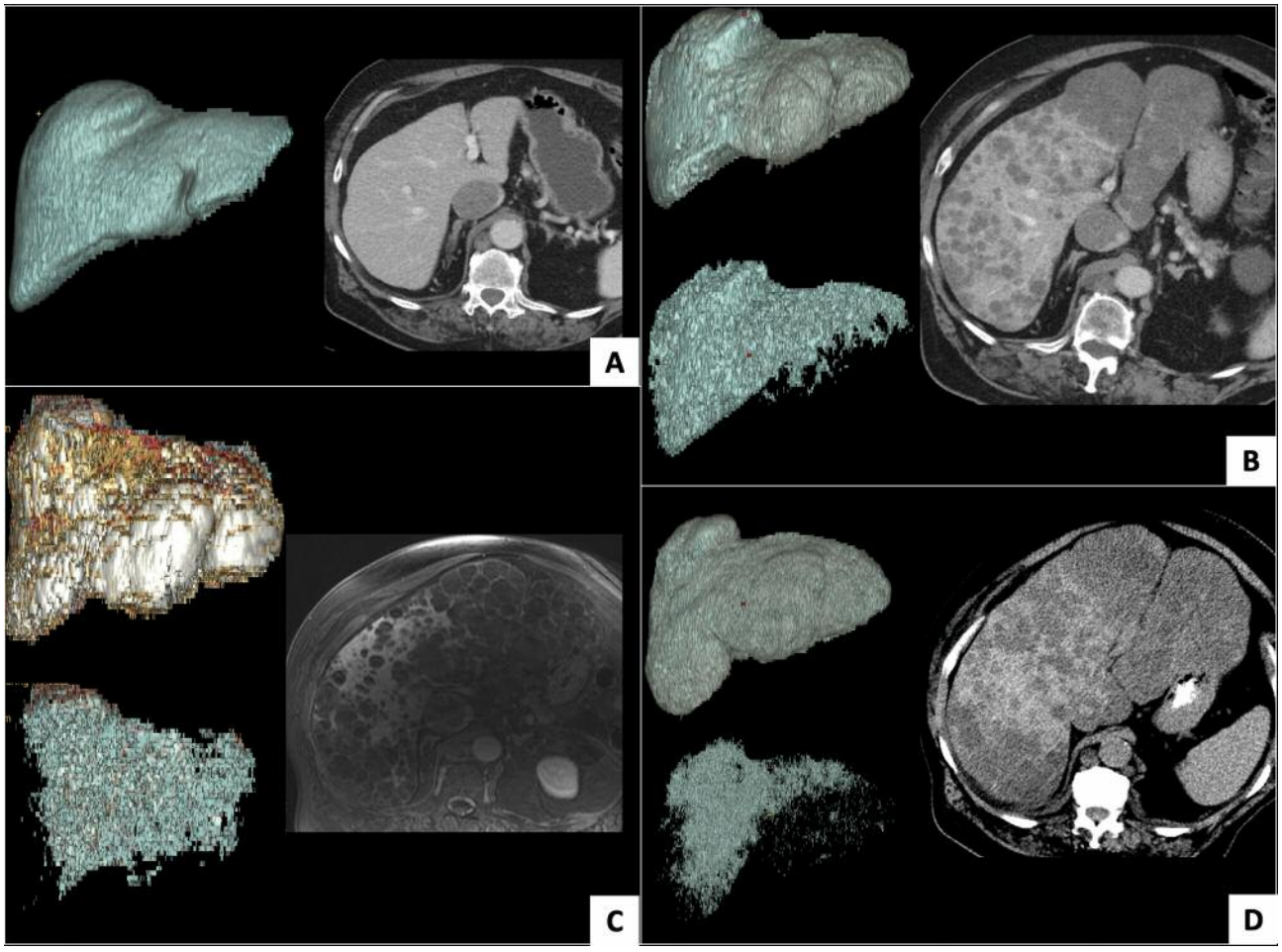

Figure 4. *Total liver and hepatic cyst volume assessment over time. (A) Three months from RCC diagnosis; Total liver volume: 2,228 ml. (B) Nineteen months from RCC diagnosis; Total liver volume: 3,854 ml (increased by 173%), cysts make up 51% of the total volume. (C) Twenty-two months from RCC diagnosis; Total liver volume: 7,316 ml (increased by 328%), cysts make up 69% of the total volume. (D) Twenty-four months from RCC diagnosis; Total liver volume: 7,359 ml (increased by 330%), cysts make up 81% of the total volume.*

A medication side-effect causing either *de novo* cholangiopathy or an unmasking/2nd hit of clinically silent germline heterozygous primary ADPLD, is the authors favored rationale for this late onset and rapidly progressive hepatic cyst development. Other than well studied antihypertensive medications, the patient was prescribed numerous anti-neoplastic agents as described. The temporality of cyst development and progression with therapeutic intervention specifically implicates pazopanib and cabozantinib as the most likely causal agents. The patient was taking pazopanib, a multikinase inhibitor of c-KIT, FGFR, FDGFR, and VEGFR, at the time his cysts were first identified. Notably, his dose was initially decreased due to known side-effects of elevated LFTs, hyperbilirubinemia, fatigue, and thrombocytopenia(34). He subsequently was treated with nivolumab, everolimus +/– a glutaminase inhibitor as part of clinical trial (patient remains blinded), and finally cabozantinib. Cabozantinib primarily targets VEGFR, AXL, and MET. To the author's knowledge and after thorough literature review, none of these medications have been described to cause PLD. Cystic renal lesions have been described as a toxicity from anaplastic lymphoma kinase (ALK) inhibitor crizotinib (35). Mechanistically speaking and as seen in other studies, it would instead be expected that the multikinase inhibitors and mTOR inhibitors would decrease cyst development and progression (36-41). Indeed, mTOR inhibitors have shown mixed efficacy in PLD with improvement in total liver volume in some studies but not in others (42-47). Polycystic liver disease as a drug reaction is therefore likely an idiosyncratic response. Lastly, it is possible that the patient is manifesting some sort of renal cell paraneoplastic syndrome leading to the cyst formation,

but this is unlikely given the lack of systemic symptoms, otherwise improving RCC, and normal labs.

Conclusion

A 76-year-old patient with metastatic renal cell carcinoma presented with numerous rapidly growing cystic liver lesions while receiving anti-neoplastic treatments. The etiology of these cysts remains unclear, but most likely this was an atypical and at least partially acquired form of PLD related to drug exposure to pazopanib/cabozantinib given the timing and rapidly progressive phenotype. There may have been underlying genetic predisposition but we cannot confirm or rule this out. Other less likely possibilities include radiographically benign and pathologically elusive metastatic RCC, uniquely late presenting ADPLD, or cystic sub-clone RCC metastasis.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

Authors' Contributions

Lucas Zarling: wrote manuscript, corresponded with authors to facilitate manuscript creation/revision/submission; Hamid Emamekhoo: provided direct patient care, oncologist expert opinion, manuscript revision; Gauri Bhutani: provided direct patient care, nephrologist and polycystic liver disease expert opinion, manuscript revision; Timothy Ziemlewicz: interpreted and provided CT/MRI images with 3D reconstruction, radiologist expert opinion, manuscript revision; Kristina A. Matkowskyj: interpreted and provided pathology/histology images, pathologist expert opinion, manuscript revision; Christos E. Kyriakopoulos: provided primary patient care, oncologist expert opinion, manuscript revision.

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