Giant Cavernous Hemangioma of the Liver in a Patient with Autosomal Dominant Polycystic Kidney Disease

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Male, 41-year-old
Final Diagnosis: Autosomal dominant polycystic kidney disease
Symptoms: Pain
Medication: —
Clinical Procedure: Computed tomography • ultrasonography
Specialty: Gastroenterology and Hepatology • Medicine, General and Internal • Nephrology

Objective: Congenital defects/diseases
Background: Autosomal dominant polycystic kidney disease (ADPKD) is frequently associated with liver cysts, but an association with giant cavernous liver hemangioma is not mentioned in the literature.
Case Report: We report the case of a 41-year-old man with ADPKD, secondary arterial hypertension, and stage 4 chronic kidney disease who presented with a 2-week history of persistent pain at the base of the right hemithorax and in the right hypochondrium. An ultrasound examination and a contrast-enhanced computed tomography scan revealed a giant cavernous liver hemangioma. Surgery was intially taken into account (however, twice delayed because of the COVID-19 pandemic) but later refused because it would have left the patient with dangerously few liver parenchyma.
Conclusions: To our knowledge, this is the first reported case of ADPKD associated with cavernous liver hemangioma. Vascular endothelial growth factor could be the pathophysiological link between the 2 conditions. Further research may unravel the molecular biology that underlies this possible association, pointing to new therapeutic avenues for ADPKD.

MeSH Keywords: Hemangioma, Cavernous • Polycystic Kidney, Autosomal Dominant • Vascular Endothelial Growth Factors

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Background

Autosomal dominant polycystic kidney disease (ADPKD) is a monogenic multisystem disease in which multiple cysts develop in the kidneys and in other organs, especially in the liver [1–3]. Cavernous hepatic hemangiomas are benign hypervascular tumors consisting of endothelial-lined, blood-filled cavernous spaces embedded in a thin fibrous stroma, from which fine fibrous septa arise that insinuate themselves between the vascular structures [4,5]. In the literature, we could not find an association between ADPKD and cavernous liver hemangioma, although there are theoretical justifications for it. We present a case of ADPKD associated with a giant cavernous liver hemangioma.

Case Report

A 41-year-old man with a history of ADPKD, secondary arterial hypertension, and stage 4 chronic kidney disease (CKD) presented to the hospital with a 2-week history of persistent pain at the base of his right hemithorax and in his right hypochondrium. He denied tobacco smoking, alcohol abuse, or use of illicit drugs. The patient was on daily furosemide (40 mg), perindopril (4 mg), amlodipine (10 mg), allopurinol (100 mg), and keto-analogs of essential amino acids at a dose based on his body weight.

Physical examination of the man revealed high blood pressure (150/80 mmHg), a regular heart rhythm at a rate of 68 bpm, normal breath sounds with no rales, a soft abdomen with tenderness in the right hypochondrium, an enlarged liver, bilaterally enlarged kidneys, normal urine output, and no edema. Blood testing revealed no abnormalities, apart from accumulation of nitrogenous waste products (serum creatinine 336 µM/L, corresponding to an estimated glomerular filtration rate of 19 mL/min/1.73 m^2, and blood urea nitrogen 18 mmol/L). Albumin and protein excretion in the urine was normal. There were no signs of liver dysfunction. Serum levels of aminotransferases (alanine aminotransferase 17 U/l, aspartate transaminase 16 U/l), alkaline phosphatase (69 U/L), total bilirubin (0.42 mg/dL), albumin (4.6 g/dL), and prothrombin time (11.8 s) were all normal. The patient's platelet count (175×10^9/L), coagulation parameters (activated partial thromboplastin time 28.5 s, international normalized ratio 1.04), and fibrinogen (306 mg/dL) and unconjugated bilirubin (0.37 mg/dL) levels were all normal, hence there was no evidence of consumptive thrombocytopenia (Kasabach-Merritt syndrome) [6], consumptive coagulopathy [7], disseminated intravascular coagulation [8], or microangiopathic hemolytic anemia [9], which in rare cases, are known to occur in association with giant hemangiomas.

Six years before, the patient had presented to another hospital with complaints of fever, nausea, and vomiting, which at the time were attributed to a bout of pyelonephritis. Ultrasound revealed enlarged kidneys containing multiple cysts (but no cysts in the liver, pancreas or spleen), and that finding, combined with the increased creatinine level (150 µM/L) and high blood pressure, led to a diagnosis of CKD due to ADPKD with secondary hypertension. The man's serum creatinine level remained stable for the next 3 years and then slowly increased: 230 (2018), 256 (April 2019), 271 (July 2019), 336 (March 2020), 423 (July 2020) (all values are in µM/L), along with a progressive increase in the size of his kidneys and the number and dimensions of the cysts.

Unfortunately, the patient could not provide any written ultrasound report or recorded images of his kidneys or liver. The attending physician who had performed follow-up on him for 6 years was contacted and stated that she had not noticed anything remarkable in his liver. No images of the man's kidneys were recorded during the follow-up period because the patient was considered to have ADPKD that was being followed in the usual course of the disease. It is difficult to establish whether, indeed, nothing happened to the man's liver during those 6 years or whatever happened was simply overlooked because the organ appeared to be disease-free at the time of his initial diagnosis. At no point in the patient's history was anemia documented. The timeline of known hemoglobin levels (in g/dL) is as follows: 14.1 (2014), 13.1 (2016), 13.6 (2017), 14.2 (2018), 12.3 (April 2019), 12.8 (March 2020) and 12.9 (July 2020).

The man's family history included unrelated diseases in his parents: an ovarian tumor in his mother and diabetes mellitus and hypertension in his father. There was no reliable information regarding his grandparents' medical history. The patient had a 38-year-old sister who was disease-free. In him, the diagnosis of ADPKD was based on the appearance of his kidney. He had grossly enlarged kidneys in which the normal architecture had been completely replaced by countless cysts of various dimensions (>10 cysts measuring >5 mm in both kidneys) [3]. Therefore, genetic testing to establish the diagnosis of ADPKD was considered unnecessary, even though the patient's family history was negative for this disease [3,10].
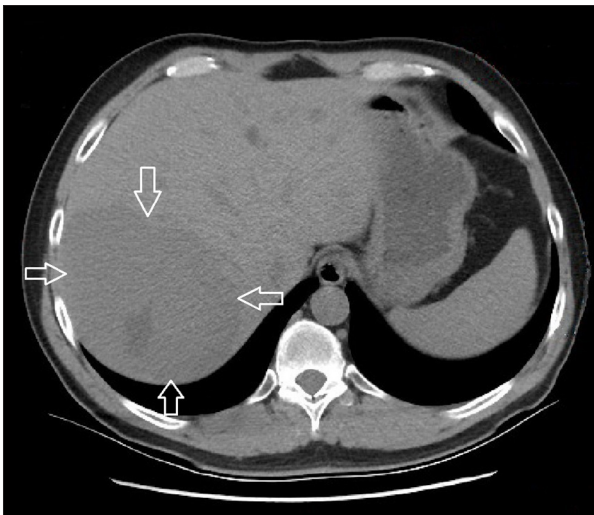
On abdominal ultrasound, a mass was detected in the right lobe of the man's liver that had a heterogeneous structure, net borders, and no Doppler signal, and seemed to compress surrounding vascular structures such as the inferior vena cava (Figure 1). Given the atypical appearance, a decision was made to perform contrast-enhanced abdominal computed tomography (CT), despite kidney dysfunction. The patient was given normal saline and bicarbonate infusion (to induce alkaline diuresis) [11] and intravenous (IV) acetylcysteine (for averting
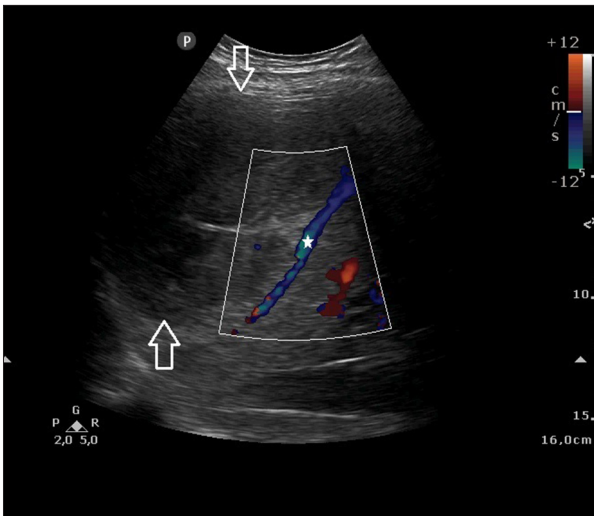
Figure 1. Abdominal ultrasound showing a mass in the right liver lobe with a heterogeneous structure and net borders (arrows), which is compressing surrounding structures such as the inferior vena cava (as revealed by the color Doppler signal filling its lumen) (white star).

Figure 2. Axial sections from contrast-enhanced computed tomography showing a cavernous hemangioma (arrows) in segments VI and VII.

Figure 3. Axial sections from contrast-enhanced computed tomography showing a cavernous hemangioma (arrows) with peripheral iodophilia in the arterial phase (black stars).


Figure 4. Axial sections from contrast-enhanced computed tomography showing a cavernous hemangioma with partial homogenization in the late phase (arrow) and a fibrotic area that is not opacified (black star).

oxidative stress injury) [12] before and after CT examination with the aim of preventing contrast nephropathy. The abdominal CT scan showed an enlarged liver (right lobe cranio-caudal diameter 197 mm) with diffusely distributed cysts, the largest of which, in segment IV, measured 19 mm. A hypodense mass was visible in segments VI and VII, which measured 112 mm. (The largest diameter is usually measured, followed by the diameter in a plane perpendicular to the plane in which the largest diameter was recorded. In this case, the 2 diameters happened to be the same.) (Figure 2). The contrast revealed peripheral iodophilia in the arterial phase (Figure 3) and

partial homogenization in the late phase (Figure 4), suggestive of cavernous hemangioma [4]. The common and intrahepatic bile ducts were normal size. The gallbladder was normal size, with thin (normal) walls, and no gallstones. The kidneys were enlarged, with numerous bilateral cysts (Figure 5), some with peripheral calcifications and others with a hematic appearance. The largest cyst, which measured 63 mm, was localized at the right upper pole. Contrast secretion and excretion by the kidneys were normal.
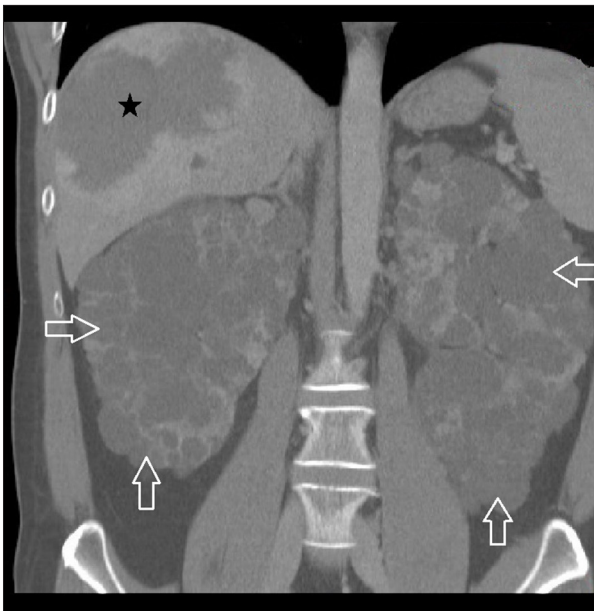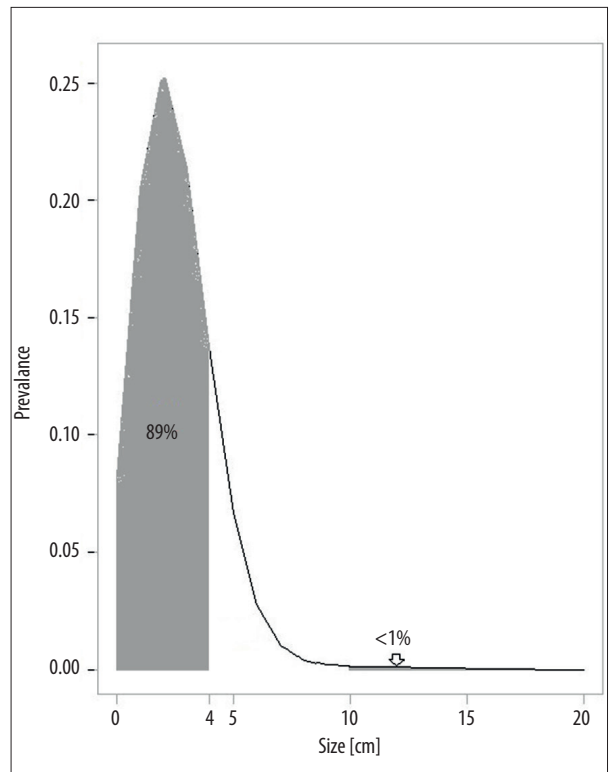
Figure 5. Reconstructed coronal contrast-enhanced computed tomography scan showing a giant cavernous liver hemangioma (black star) and numerous bilateral kidney cysts (arrows).

Figure 6. A normalized curve that models size distribution of hepatic hemangiomas, taking into account that the vast majority (89%) are <4 cm and some >10 cm (giant hepatic hemangiomas) and even >20 cm. The curve fitting these conditions suggests that only a tiny proportion of hepatic hemangiomas (<1%, denoted by the downward-pointing arrow) qualify as giant.

The patient was evaluated by a general surgeon, who decided to surgically resect the cavernous hemangioma. Because of the COVID-19 pandemic, however, the intervention was delayed twice. Another general surgeon to whom the patient was referred decided not to perform the resection, considering that too much of the liver parenchyma would have had to be resected in the process, leaving dangerously little of the organ. The patient continues to complain of persistent discomfort in his right hypochondrium, which is aggravated by motion and deep breathing. He will continue to be followed at 3-month intervals to determine whether other treatments, such as therapy for iron deficiency, anemia, or bone and mineral disorders, are necessary and when it would be appropriate to initiate renal replacement therapy. The patient also has been instructed to present to the Emergency Department immediately if he experiences symptoms such as fever, pain, or neurological signs that suggest complications of ADPKD.

Discussion

The estimated prevalence of hepatic hemangiomas ranges from 0.4% to 20%, with the highest estimates being from autopsy series, whereas imaging series suggest a more conservative 5% [13]. The only estimate of giant cavernous angioma prevalence we could find in the literature (10.9%) was based on a different threshold for the condition (4 cm) [14]. Mathematical modeling of the size distribution of liver hemangiomas needs to take into account that approximately 89% are <4 cm and diameters as high as 20 cm and even 40 cm

are possible [15,16]. Therefore, there should be a very right-skewed curve, with the bulk of the surface below 4 cm (the large gray area on the left in Figure 6). The area under such a curve for independent variable values ≥10 is approximately 0.0001 (if the curve is normalized, that is, with a total area under the curve of 1) (the tiny, skinny gray area on the right in Figure 6). Even an estimate that is 100 times greater (that is, 0.01) suggests that at most, 1% of liver hemangiomas measure >10 cm. That equates to a prevalence in the general population of giant (i.e. >10 cm) liver hemangiomas of no more than 5×1%, or 0.05%. The estimated prevalence of ADPKD also spans a large range, but is probably 5: 10 000 or less [17].

The liver cysts in ADPKD usually are asymptomatic, do not alter liver function, and are discovered incidentally during an imaging examination [18]. They may become symptomatic as a result of either the mass effect (abdominal pain, obstructive jaundice, early satiety) or a complication, such as infection, rupture, or bleeding [2,18]. Only regular follow-up, and not therapy, is required for liver cysts that produce no symptoms, which are the most common [19].

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Cavernous hepatic hemangiomas, too, are usually asymptomatic. Therefore, they are typically discovered accidentally. Their size varies, the adjective "giant" being applied to those >10 cm [4]. The large ones can elicit symptoms, including pain in the right hypochondrium and a sensation of early satiety [4]. Liver hemangiomas are generally considered vascular malformations. Their etiology is unknown and the only recognized risk factor seems to be estrogen exposure (as during pregnancy or exposure to hormone replacement therapy) [4].

The giant liver hemangioma in our case was discovered on ultrasound and confirmed with a CT scan that was precipitated by patient's complaints of pain at the base of his right hemithorax and in his right hypochondrium. We believe that this pain was a result of the large size of the hemangioma, because other causes were excluded on the ultrasound and CT images. None of the cysts associated with the man's ADPKD were complicated; his gallbladder was normal size, with walls of normal thickness, and free of stones; there was no anomaly, such as pneumonia or pleurisy, in his right lung and pleura/pleural space, and there was no apparent pathology in the man's colon.

Liver hemangiomas can be diagnosed using ultrasound, CT, or magnetic resonance imaging. On ultrasound, they are well demarcated, either homogeneously hyperechoic (the small ones) or heterogeneous (the large ones because of intervening areas of fibrosis, necrosis or hemorrhage) [5], and usually have a minimal Doppler signal [5]. On CT scan, small lesions are homogeneous and slightly less dense than the liver, whereas large lesions may be heterogeneous, sometimes with central hypodensity if contrast penetration is hindered by fibrosis, thrombosis, or degeneration [20]. Contrast uptake starts from the periphery as discontinuous, nodular enhancement during the early arterial phase, progresses toward the center during the venous phase, and is complete and persistent during the late phase [4]. These specific aspects were also observed in our patient during the CT examination.

Management of a liver hemangioma is based on the existence and severity of the symptoms elicited by the tumor, which are essentially related to its size. Persistently symptomatic giant liver hemangiomas call for definitive surgery or non-surgical therapy by an experienced team of healthcare providers [21]. Transarterial embolization sometimes is effective in controlling symptoms [22,23], but if it proves to be insufficient, surgery (enucleation or hepatic resection) can be performed. Alternatively, surgery can be considered in the first place [24]. Preoperative transcatheter arterial embolization can be used preoperatively to alleviate symptoms. It also can reduce tumor volume, making mobilization easier during surgery, which is especially useful when the hemangioma is located centrally or near important vascular structures [25]. In our case, surgery was the first choice because the patient had ADPKD with

stage 4 CKD, and administering IV contrast medium for transcatheter arterial embolization carried the risk of worsening his renal function.

To our knowledge, this is the first reported case of ADPKD associated with a cavernous liver hemangioma. We have found only 1 similar case in the literature: a symptomatic giant liver hemangioma associated with polycystic liver disease (but not with ADPKD). In that case, hepatic resection was performed, with a good long-term outcome [26]. Radiofrequency and microwave ablation are other nonsurgical therapies for liver hemangiomas. They are better suited to moderate-size liver hemangiomas and have been shown to be effective as definitive treatment in some cases [27,28]. Ablation is inadequate for large hemangiomas because it results in a high rate of complications. Radiation is an option for liver hemangiomas that cannot be resected [29]. Liver transplantation also can be considered in patients who have multiple giant hemangiomas, given the risk that the remaining liver tissue may be insufficient for optimal liver function [22]. The prognosis for patients with liver hemangiomas is generally good, and only rarely compromised by mechanical (spontaneous rupture) or infectious (abscess formation) complications [4,30].

The question arises whether the association between the giant liver hemangioma and ADPKD in our patient was pure chance or there was a pathophysiological connection between the 2 conditions. The scarcity of reported cases supports the pure chance hypothesis. However, there could be a pathophysiological link: vascular endothelial growth factor (VEGF). Shrinking of a giant liver hemangioma in the wake of treatment with bevacizumab (a VEGF inhibitor) for colorectal adenocarcinoma with liver metastases points to a key role for VEGF in the pathogenesis of these vascular liver tumors [31]. On the other hand, VEGF also seems to be involved in cyst growth in polycystin-2-defective mice [32]. The liver cysts in ADPKD are composed of immature cholangiocytes responsible for aberrant secretion of cytokines, chemokines, and growth factors [33]. VEGF and VEGF receptors are expressed in the cholangiocytes lining the liver cysts in ADPKD and promote ADPKD progression [32]. Therefore, abnormally regulated, VEGF-dependent pathways could be responsible for growth of both kidney and liver cysts and endothelial proliferation leading to (giant) liver hemangiomas.

In endothelial cells, VEGF has a mitogenic effect that is mediated by the Raf/MEK/ERK cascade [34]. The increased angiogenic activity it induces could lead to vascular tumors [35,36].

The genes identified so far as being responsible for ADPKD are PKD1 and PKD2. Polycystin-1 (PC1) and polycystin-2 (PC2) are the products of the 2 culprit genes, respectively. In the primary cilium of the tubular epithelial cells, PC1 interacts with PC2,
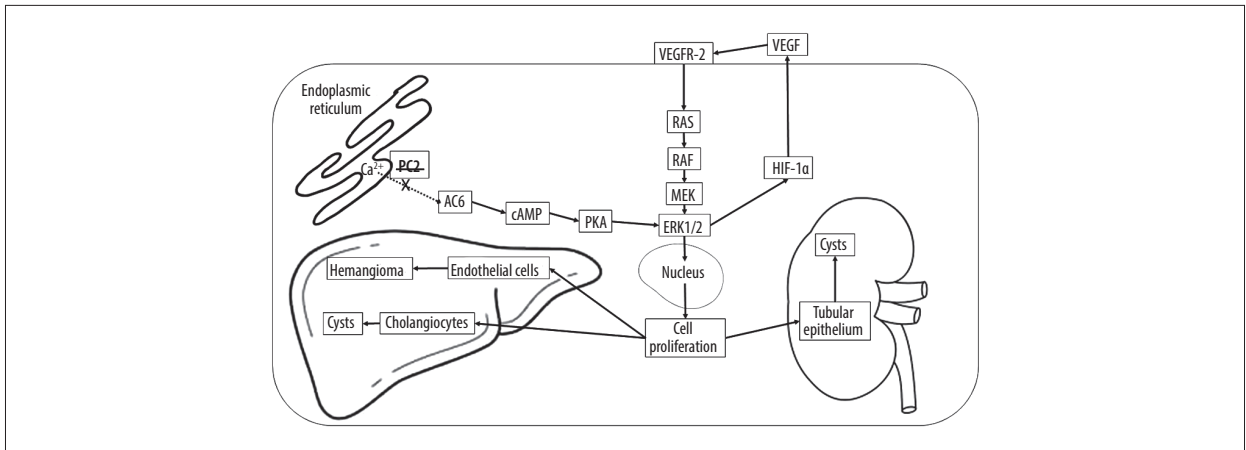
Figure 7. The working hypothesis regarding the putative pathophysiological link between cavernous liver hemangioma and autosomal dominant polycystic kidney disease. Blocking of calcium egress from the endoplasmic reticulum by defective polycystin-2 leads to ERK1/2 activation via the AC6-cyclic AMP/protein kinase A pathway, and by means of hypoxia-inducible-factor-1α mediation, to vascular endothelial growth factor (VEGF) secretion and autocrine and paracrine stimulation of VEGFR-2. VEGFR-2 activation results in activation of the RAS/RAF/MEK/ERK1/2 pathway, which induces proliferation of cells in the tubular epithelium, cholangiocytes, and endothelium. The result is generation of cysts in the kidney and cysts and hemangiomas in the liver.

a membrane-bound nonselective calcium channel [32,37]. PC2 is also present in the membrane of the endoplasmic reticulum (ER), thereby influencing intracellular calcium homeostasis. In normal individuals, functional PC2 mediates the exit of Ca^{2+} from the ER. Inactivation of calcium inhibitable adenyl cyclase 6 (AC6) lowers the level of 3',5'-cyclic adenosine monophosphate (cAMP), and hence, the activation of protein kinase A (PKA). The resulting decline in extracellular signal-regulated kinase (ERK)1/2 phosphorylation inhibits cell proliferation. In contrast, defective PC2 results in lower calcium cytosolic levels and decreased calcium-dependent inhibition of AC6. The net effect is AC6 activation, cAMP generation, PKA activation, and ERK1/2 phosphorylation [32]. Phosphorylated (activated) ERK1/2 downregulates hypoxia-inducible factor (HIF)-1α degradation, followed by HIF-1α entering the nucleus and binding to the hypoxia-responsive element on the VEGF promoter [38]. Consequently, increased autocrine and paracrine VEGF stimulation switches on the Raf-MAPK/ERK kinase (MEK)-ERK1/2 pathway, resulting in enhanced cell proliferation [32]. Hence, in the setting of a defective PC2, the involvement of VEGF in the genesis of liver cysts is mediated by the activation of the PKA-ERK1/2-HIF1α-VEGF signaling pathway in cholangiocytes [32].

The key element in the pathogenesis of cavernous hemangioma is the imbalance between angiogenesis-spurring and -hindering factors, the former including VEGF and matrix metalloproteinases [39,40]. The endothelial cells in a cavernous hemangioma have higher levels of VEGF compared with those in normal liver sinusoids [36]. Regional hypoxia increases the availability of HIF by blocking its degradation. HIF, in turn, activates several genes, particularly *VEGF* [41].

In summary, *VEGF* expression is controlled by the MEK-ERK1/2-HIF-1 pathway [32]. Cell proliferation induced by this pathway affects tubular epithelium (leading to cyst formation in the kidney and driving the progression of ADPKD), liver cholangiocytes (leading to cyst formation in the liver), and liver endothelial cells (leading to cavernous hepatic hemangiomas) (Figure 7) [31,32].

Nonetheless, the tentative conclusion that anti-VEGF therapy might improve the outcome of ADPKD seems to be contradicted by a study conducted in rats with cystic renal disease. Treatment with an anti-VEGF-A antibody was harmful by promoting proximal tubular epithelial cell proliferation, and hence, cyst growth associated with sagging VEGF and increasing HIF-1α levels in kidney parenchyma [42]. Other studies, however, have shown that VEGF-inhibitory agents may retard both the progression of ADPKD [43] and cyst growth in the liver in the context of ADPKD [32,44]. Moreover, VEGF-C ameliorates polycystic kidney disease by improving the organization pattern of pericystic vasculature, while simultaneously reducing pericystic macrophage infiltration and widening lymphatic vessels [45]. Therefore, it is not yet established whether modulation of the VEGF pathway favorably influences the course of ADPKD [46]. Further studies are needed to clarify this matter.

Of course, a single case does not prove that there is a pathophysiological association between ADPKD and giant cavernous liver hemangiomas. It should be noted, however, that among the causes of CKD, ADPKD is relatively uncommon, and consequently, there are relatively few cases of ADPKD in most nephrology centers. If the prevalence of giant cavernous hepatic

hemangiomas among patients with ADPKD is, say, 1% (which is far greater than the prevalence of giant cavernous hepatic hemangiomas in the general population, which we have estimated to be about 0.05%), many other nephrology centers might have 1 such case, which they have not considered worth reporting precisely because the association is deemed fortuitous. Reporting such a case might encourage many others to report their own similar cases, thereby bringing about the acknowledgement of a hitherto unrecognized association. A >1% prevalence of the posited association cannot be expected, as it already would have been noticed by other researchers.

Conclusions

What is distinctive in the present case is the association between a giant liver hemangioma and ADPKD. The association of ADPKD with liver cysts is well known, but the association with cavernous liver hemangioma had not been reported in the literature. *VEGF* could be the pathophysiological link explaining the association. Further research aimed at unraveling the molecular substrate of this possible association may lead to new therapeutic tools for ADPKD, whether or not it is associated with liver cysts and/or liver hemangiomas.

Department and institution where work was done

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Conflicts of interest

None.

References:

1. Tan YC, Blumenfeld J, Rennert H: Autosomal dominant polycystic kidney disease: Genetics, mutations and microRNAs. Biochim Biophys Acta, 2011; 1812(10): 1202–12

2. Halvorson CR, Bremmer MS, Jacobs SC: Polycystic kidney disease: Inheritance, pathophysiology, prognosis, and treatment. Int J Nephrol Renovasc Dis, 2010; 3: 69–83

3. Pei Y, Watnick T: Diagnosis and screening of autosomal dominant polycystic kidney disease. Adv Chronic Kidney Dis, 2010; 17(2): 140–52

4. Evans J, Willyard CE, Sabih DE: Cavernous hepatic hemangioma. StatPearls, 2020

5. Kim KW, Kim TK, Han JK et al: Hepatic hemangiomas: Spectrum of US appearances on Gray-scale, power Doppler, and contrast-enhanced US. Korean J Radiol, 2000; 1: 191–97

6. Aslan A, Meyer zu Vilsendorf A, Kleine M et al: Adult Kasabach-Merritt Syndrome due to hepatic giant hemangioma. Case Rep Gastroenterol, 2009; 3(3): 306–12

7. Suzuki H, Nimura Y, Kamiya J et al: Preoperative transcatheter arterial embolization for giant cavernous hemangioma of the liver with consumption coagulopathy. Am J Gastroenterol, 1997; 92(4): 688–91

8. Watanbe M, Yuasa S, Taketa K et al: A case of giant cavernous hemangioma of the liver complicated by intravascular coagulopathy. Acta Med Okayam, 1978; 32(1): 61–68

9. Shimizu M, Miura J, Itoh H, Saitoh Y: Hepatic giant cavernous hemangioma with microangiopathic hemolytic anemia and consumption coagulopathy. Am J Gastroenterol, 1990; 85(10): 1411–13

10. Harris PC, Rossetti S: Molecular diagnostics for autosomal dominant polycystic kidney disease. Nat Rev Nephrol, 2001; 6(14): 197–206

11. Burgess WP, Walker PJ: Mechanisms of contrast-induced nephropathy reduction for saline (NaCl) and sodium bicarbonate (NaHCO3). BioMed Res Int, 2014; 2014: 510385

12. Fishbane S: N-acetylcysteine in the prevention of contrast-induced nephropathy. Clin J Am Soc Nephrol, 2008; 3(1): 281–87

13. Colombo M, Forner A, Ijzermans J et al: EASL Clinical practice guidelines on the management of benign liver tumours. J Hepatol, 2016; 65: 386–98

14. Mocchegiani F, Vincenzi P, Coletta M et al: Prevalence and clinical outcome of hepatic haemangioma with specific reference to the risk of rupture: A large retrospective cross-sectional study. Dig Liver Dis, 2016; 48: 309–14

15. Bajenaru N, Balaban V, Săvulescu F et al: Hepatic hemangioma – review. J Med Life, 2015; 8(Spec Issue): 4–11

16. Koszka AJM, Ferreira FG, de Aquino CGG et al: Resection of a rapid-growing 40-cm giant liver hemangioma. World J Hepatol, 2010; 2: 292–94

17. Solazzo A, Testa F, Giovanella S et al: The prevalence of autosomal dominant polycystic kidney disease (ADPKD): A meta-analysis of European literature and prevalence evaluation in the Italian province of Modena suggest that ADPKD is a rare and underdiagnosed condition. PLoS One, 2018; 13: e0190430

18. de Miranda Henriques MS, de Morais Villar EJ: The liver and polycystic kidney disease. In: Polycystic Kidney Disease (Li X, Ed.) Codon Publications, 2015

19. Russell RT, Pinson CW: Surgical management of polycystic liver disease. World J. Gastroenterol, 2007; 13(38): 5052–59

20. Heiken JP: Distinguishing benign from malignant liver tumours. Cancer Imaging 2007; 7(Special issue A): S1–14

21. Marrero JA, Ahn J, Reddy RK: ACG Clinical Guideline: The Diagnosis and management of focal liver lesions. Am J Gastroenterol, 2014; 109: 1328–47

22. Ketchum WA, Lin-Hurtubise KM, Ochmanek E et al: Management of symptomatic hepatic "mega" hemangioma. Hawaii J Med Public Health, 2019; 78: 128–31

23. Sun JH, Nie CH, Zhang YL et al: Transcatheter arterial embolization alone for giant hepatic hemangioma. PLoS One, 2015; 10(8): e0135158

24. Liu Y, Wei X, Wang K et al: Enucleation versus anatomic resection for giant hepatic hemangioma: A meta-analysis. Gastrointest Tumors, 2016; 3: 153–62

25. Topaloğlu S, Oğuz Ş, Kalaycı O et al: Preoperative arterial embolization of large liver hemangiomas. Diagnostic Interv Radiol, 2015; 21: 222–28

26. Sandri GBL, Lai Q, Melandro F, Guglielmo N et al: Hepatic resection for giant haemangioma in a patient with a contemporaneous adult polycystic liver disease. Clin Ter, 2012; 163(5): 401–2

27. Gao J, Ke S, Ding XM et al: Radiofrequency ablation for large hepatic hemangiomas: Initial experience and lessons. Surg, 2013; 153: 78–85

28. Ziemlewicz TJ, Wells SA, Lubner MA et al: Microwave ablation of giant hepatic cavernous hemangiomas. Cardiovasc Intervent Radiol, 2014; 37: 1299–305

29. Gaspar L, Mascarenhas F, Sáda Costa M et al: Radiation therapy in the unresectable cavernous hemangioma of the liver. Radiother Oncol, 1993; 29: 45–50

30. Etemadi A, Golozar A, Ghassabian A et al: Cavernous hemangioma of the liver: Factors affecting disease progression in general hepatology practice. Eur J Gastroenterol Hepatol, 2011; 23: 354–58

31. Mahajan D, Miller C, Hirose K et al: Incidental reduction in the size of liver hemangioma following use of VEGF inhibitor bevacizumab. J Hepatol, 2008; 49: 867–70

32. Spirli C, Okolicsanyi S, Fiorotto R et al: ERK1/2-dependent vascular endothelial growth factor signaling sustains cyst growth in polycystin-2 defective mice. Gastroenterology, 2010; 138(1): 360–71.e7

33. Nichols MT, Gidey E, Matzakos T et al: Secretion of cytokines and growth factors into autosomal dominant polycystic kidney disease liver cyst fluid. Hepatology, 2004; 40: 836–46

34. Shibuya M: Differential roles of vascular endothelial growth factor receptor-1 and receptor-2 in angiogenesis. J Biochem Mol Biol, 2006; 39(5): 469–78

35. Ji Y, Chen S, Li K et al: Signaling pathways in the development of infantile hemangioma. J Hematol Oncol, 2014; 7: 13

36. Zhang WJ, Ye LY, Wu LQ et al: Morphologic, phenotypic and functional characteristics of endothelial cells derived from human hepatic cavernous hemangioma. J Vasc Res, 2006; 43: 522–32

37. Douguet D, Patel A, Honoré E: Structure and function of polycystins: Insights into polycystic kidney disease. Nat Rev Nephrol, 2019; 15(7): 412–22

38. Pugh CW, Ratcliffe PJ: Regulation of angiogenesis by hypoxia: Role of the HIF system. Nat Med, 2003; 9(6): 677–84

39. Chang J, Most D, Bresnick S et al: Proliferative hemangiomas: Analysis of cytokine gene expression and angiogenesis. Plast Reconstr Surg, 1999; 103: 1–10

40. Takahashi K, Mulliken JB, Kozakewich HPW et al: Cellular markers that distinguish the phases of hemangioma during infancy and childhood. J Clin Invest, 1994; 93: 2357–64

41. Bernhardt WM, Wiesener MS, Weidemann A et al: Involvement of hypoxia-inducible transcription factors in polycystic kidney disease. Am J Pathol, 2007; 170: 830–42

42. Raina S, Honer M, Krämer SD et al: Anti-VEGF antibody treatment accelerates polycystic kidney disease. Am J Physiol, 2011; 304(4): F778–83

43. Tao Y, Kim J, Yin Y et al: VEGF receptor inhibition slows the progression of polycystic kidney disease. Kidney Int, 2007; 72: 1358–66

44. Amura CR, Brodsky KS, Groff R et al: VEGF receptor inhibition blocks liver cyst growth in pkd2(WS25/-) mice. Am J Physiol Physiol, 2007; 293: C419–28

45. Huang JL, Woolf AS, Kolatsi-Joannou M et al: Vascular endothelial growth factor C for polycystic kidney diseases. J Am Soc Nephrol, 2016; 27: 69–77

46. Chade AR: Vascular endothelial growth factor therapy for the kidney: Are we there yet? J Am Soc Nephrol, 2016; 27(1): 1–3