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CLINICAL VIGNETTE

Isolated Polycystic Liver Disease: A Rare Clinical Entity

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Introduction

A 49-year-old man with a past medical history of umbilical hernia presented to urgent care for evaluation of abdominal masses. He started noticing these masses about 6 months prior. He was not sure if these masses had been growing during this time span or if they had just become more prominent as he had recently lost weight as part of a diet and exercise plan. The masses were never painful. On further review of systems, he also reported discomfort around both testicles and intermittent hematochezia but denied melena, nausea, vomiting or fevers.

The patient was not taking any medications. He was born in Guatemala and immigrated to the US more than 30 years ago. He worked as a painter and had a 20 pack-year prior smoking history, having quit 15 years prior. He reported no alcohol or illicit drug use.

On exam, his temperature was 36.8° C, pulse was 92, blood pressure was 137/81 mmHg, respiratory rate was 16, and oxygen saturation was 98% on room air. The rest of the exam was significant for several firm nontender masses palpated in his right upper quadrant. There was a small umbilical hernia that was easily reducible. He had normal testes without any inguinal hernias or other palpable masses. Rectal exam was negative for blood.

Abdominal computed tomography with contrast revealed an enlarged liver, measuring approximately 28 cm in the mid-clavicular line, containing innumerable cysts. The pancreas, spleen, adrenal glands, and kidneys were normal. The gallbladder was not visualized. There was no free fluid or suspicious adenopathy. Representative images from the patient's CT scan are shown in Figures 1-3.

Upon further history, we learned that he had no family history of any known liver or kidney disease. The patient also reported previous animal contacts with dogs, cats, and cows growing up in Guatemala.

Laboratory studies were significant for normal liver chemistries, INR and platelets. Echinococcus IgG antibody was also negative.

The GI service was consulted regarding the patient's hepatic cysts. A preliminary diagnosis of isolated polycystic liver disease was made. Given that the patient was asymptomatic and had intact hepatic function, no intervention was recommended. The patient was counseled to avoid contact sports due to risk of cyst rupture. A scrotal ultrasound performed 1 month later revealed bilateral epidydimal head cysts and bilateral hydroceles. He was scheduled for outpatient colonoscopy to further evaluate his hematochezia. He has remained asymptomatic with regards to his hepatic cysts.

Hepatic Cysts – Differential Diagnosis

The potential etiology of hepatic cysts can be narrowed by whether the cysts are characterized as simple or complex. Complex hepatic cysts are fluid-filled lesions with one or more of the following: wall thickening or irregularity, multiple septations, internal nodularity, calcification, enhancement on imaging, and hemorrhagic or proteinaceous content.[1] Disorders causing complex cysts are typically infectious (e.g. abscesses, *Echinococcus*) or neoplastic in nature (e.g. hepatocellular carcinoma, cavernous hemangioma).[1]

In contrast, simple cysts lack the aforementioned features and instead are characterized by smooth, thin walls. Potential causes include benign developmental hepatic cysts, von Meyenburg complex (biliary hamartomas), Caroli disease (an autosomal recessive disorder with multifocal saccular dilation of the intrahepatic bile ducts) and polycystic liver disease.[1]

Polycystic Liver Disease

Polycystic liver disease is a clinical entity that can exist as a primary autosomal dominant disorder (PCLD) but more commonly is secondary to autosomal dominant polycystic kidney disease (ADPKD).[2]

Cyst formation is thought to be due to ductal plate malformation.[3] Several genes, *PRKCSH* and *SEC63*, have been implicated in PCLD but only account for about 20% of cases.[4] These two genes encode for the proteins hepatocystin and Sec63p respectively, which are involved in the translocation of glycoproteins across the endoplasmic reticulum.[2]

Patients with PCLD typically do not have any renal or other extra-hepatic cysts whereas hepatic cysts are the most common extra-renal manifestation in ADPKD.[4,5] Thus, while our patient was later discovered to have bilateral epididymal head cysts on scrotal ultrasound, this is likely unrelated to his PCLD. Interestingly, in ADPKD, non-renal extra-hepatic cysts have been described in the pancreas, seminal vesicles of the testes and CNS (arachnoid cysts).[2] Compared to ADPKD, PCLD

carries a more benign prognosis and is associated with significantly fewer serious hepatic complications based on one retrospective study, even though the cysts in PCLD tend to be larger.[6] While the prevalence of ADPKD is around 1/400 to 1/1000, PCLD is much rarer, estimated to affect only 1/100,000 to 1/1,000,000.[2]

Most patients with PCLD will be asymptomatic with normal liver chemistries, and intact liver function as in our patient.[4] Symptoms are mainly due to the cysts' mass effect, which include abdominal swelling, early satiety, nausea, vomiting, acid reflux and dyspnea.[4,7] Abdominal wall hernias found in PCLD patients, such as ours, may be due to chronic compression from high liver volumes.[2] If abdominal pain is reported by a patient with PCLD, the clinician should be vigilant in evaluating for possible complications such as cyst rupture, infection or torsion.[4] Other complications that have been previously tied to PCLD include compression of the important neighboring venous structures: the inferior vena cava, portal vein and hepatic vein.[8] In cases of severe PCLD, alkaline phosphatase and gamma-glutamyltransferase are the most common abnormal labs.[9] Elevated CA 19-9 levels correspond to increased polycystic liver volume as it is made by the cyst epithelia and could serve as a useful biomarker.[10]

In one population study of 137 patients with PCLD from the Netherlands, female patients and patients who carried the aforementioned mutations were more likely to be symptomatic.[9] Additional risk factors for the development of hepatic cysts include multiparity and prolonged estrogen exposure.[2,11]

PCLD should be considered whenever more than 20 hepatic cysts are present on imaging.[7] If there is family history of PCLD, then having just 4 or more cysts is considered sufficient.[3] Hepatic cysts will appear anechoic and well-circumscribed on ultrasound, hypodense and nonenhancing on CT and hypointense on T1-weighted imaging and hyperintense on T2-weighted imaging on MRI.[1] Malignancies that can rarely mimic PCLD, such as cystadenocarcinoma, must also be evaluated for by imaging.[12]

Management of PCLD largely depends on presence of symptoms. Asymptomatic patients, like ours, should be reassured of PCLD's generally benign prognosis.[12] If patients are taking exogenous estrogen, they should be counseled to stop due to estrogen exposure being a risk factor for cyst growth.[3] To our knowledge, there are no published guidelines that recommend serially following a patient's laboratory studies or cyst burden via imaging. As such, clinicians should order repeat testing primarily based on reported symptoms.

In symptomatic patients, there are two main categories of therapy: procedural (surgical, radiological) or medical.[3] Procedures include cyst aspiration-sclerotherapy, cyst fenestration, transcatheter arterial embolization, partial hepatic resection and liver transplantation.[3] Aspiration-sclerotherapy and fenestration can be helpful for clearly identified culprit cysts. However, for these two modalities, approximately 20-25% of patients ultimately experience recurrence of cysts.[4] Partial hepatic resection may be an option whenever there is at least 1 unaffected liver segment. Because of the relatively high morbidity and mortality rates, this is rarely performed.[3] For patients with otherwise untreatable complications from their PCLD, such as cirrhosis, liver transplantation is the only curative option.[3] As most cysts are supplied by hepatic arteries, transarterial embolization has also been explored to reduce hepatic cyst volume in patients who are not surgical candidates.[13]

Medical therapies include somatostatin analogues and mTOR inhibitors. Somatostatin inhibits fluid secretion in hepatic cysts by reducing intracellular levels of cAMP.[3] In one randomized placebo-controlled trial, lanreotide was found to be effective in reducing hepatic volume. This benefit was seen in both the PCLD and ADPKD groups.[14] mTOR inhibitors are also promising as they have been shown to delay renal cystogenesis in animal models.[4] In one retrospective study of ADPKD patients post-renal transplant, treatment with sirolimus was associated with a reduction in liver volume that was not seen in patients treated with tacrolimus.[15] However, further prospective studies will need to be done before mTOR inhibitors take on more of an established role in the treatment of PCLD patients.

Conclusion

Hepatic cysts present an interesting clinical conundrum. Polycystic liver disease is the most common extra-renal manifestation of ADPKD though it can also be its own separate entity. In general, the diagnosis is made by the presence of more than 20 simple hepatic cysts on abdominal imaging. The prognosis of isolated PCLD is generally favorable and most patients will be asymptomatic, have normal liver chemistries and intact liver synthetic function. Treatment is only indicated for symptomatic patients and includes both medical and procedural modalities. Patients should also be counseled to avoid contact sports due to risk for complications such as cyst rupture and to avoid estrogen exposure in order to minimize risk of cyst growth.

Figures

Figure 1. CT Abdomen (axial view) at initial presentation, demonstrating numerous simple hepatic cysts.

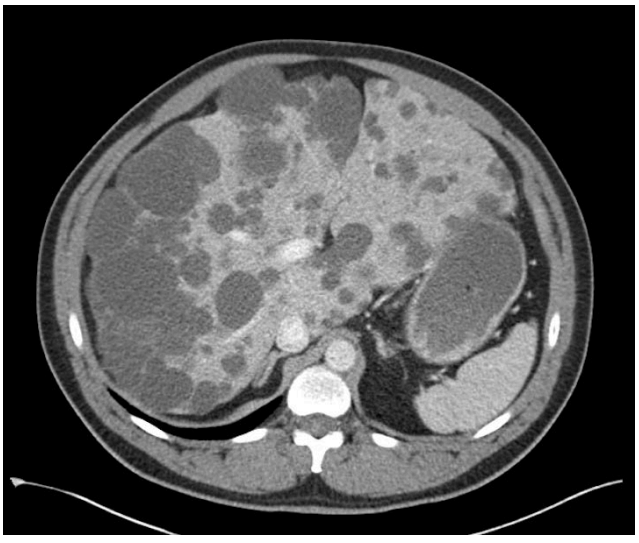


Figure 2. CT Abdomen (axial view) at initial presentation, demonstrating numerous simple hepatic cysts and normal appearing kidneys.

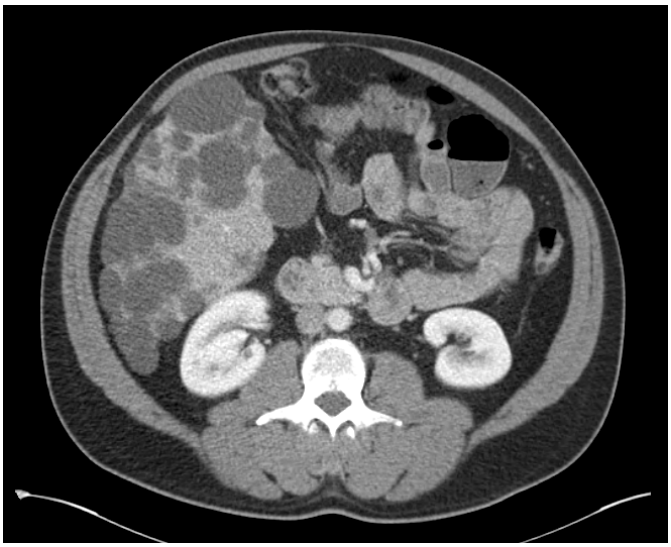
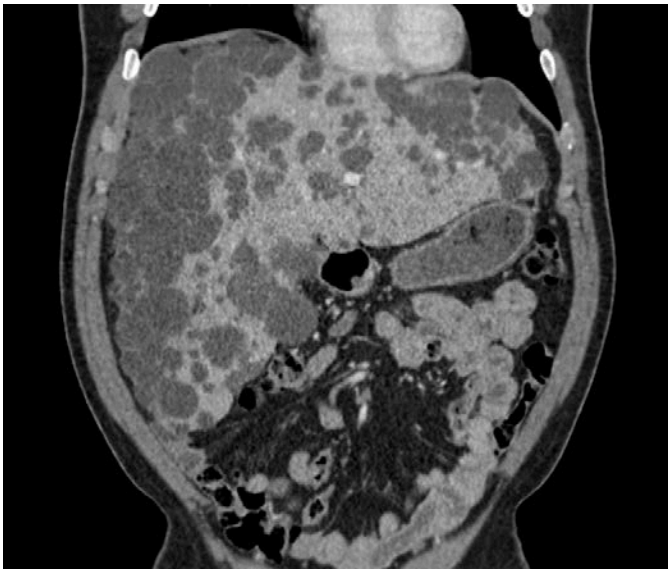


Figure 3. CT Abdomen (coronal view) at initial presentation, demonstrating numerous simple hepatic cysts.



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