Radiology Case Reports 19 (2024) 2735–2740

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Case Report

Cryptogenic cirrhosis: Decoding diagnostic challenges through radiological insights ☆,☆☆

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ARTICLE INFO

Article history:
Received 22 January 2024
Revised 17 March 2024
Accepted 25 March 2024

Keywords:
Cryptogenic cirrhosis
Medical imaging
Spontaneous bacterial peritonitis
Radiological findings
Ascites
Portal hypertension

ABSTRACT

This case report delves into the intricate diagnostic journey of a 42-year-old male presenting with jaundice, abdominal distension, and ascites, where medical imaging, including CT scans and ultrasound, played a central role. Noteworthy radiological findings, such as irregular nodular margins and caudate lobe hypertrophy, illuminated the distinctive pathophysiology of cryptogenic cirrhosis. The study underscores the pivotal role of medical imaging in elucidating complex liver pathologies, emphasizing the relevance of radiological approaches in diagnosing cryptogenic cirrhosis and guiding comprehensive management strategies.

Introduction

Cryptogenic cirrhosis is a diagnosis made with reluctance after thorough investigation and exclusion of all other potential etiologies of cirrhosis. The utilization of this term has experienced a significant decline [1], attributed to the acknowledgment of nonalcoholic steatohepatitis (NASH), which is now known as metabolic dysfunction-associated steatohepatitis (MASH) [2], as a plausible cause and advancements in investigative methods [3]. However, cases like ours, where patients exhibit cirrhosis without meeting MASHcriteria or presenting any known cause, continue to emerge, challenging the notion of rendering cryptogenic cirrhosis an obsolete term.

☆ Acknowledgments: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

☆☆ Competing Interests: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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https://doi.org/10.1016/j.radcr.2024.03.069

Case presentation

A 42-year-old previously healthy male presented with a week-long history of jaundice, abdominal distention, and waxing and waning course of fatigue. The patient, with no significant medical history, reported a gradual onset of jaundice and abdominal distention. Notably, he denied abdominal pain, body pruritus, hematemesis, high-grade fever, pale-colored stool, or any relevant family history.

Upon examination, the patient displayed deep jaundice with yellowish skin and sclera, along with grade 2 pedal edema. Abdominal distention was observed, with an inverted and centrally located umbilicus. Positive fluid thrill and shifting dullness were noted, but there were no visible veins, scars, pulsations, or tenderness. Vitals were stable, including a blood pressure of 125/80 mmHg, heart rate of 80 beats per minute, temperature of 98°F, respiratory rate of 16 breaths per minute, weight of 75 kg, and oxygen saturation of 98% on room air.

The patient's clinical presentation prompted a meticulous consideration of various differential diagnoses, including MASH, toxic liver injury, hemochromatosis, viral hepatitis, cholestasis, hepatocellular carcinoma (HCC), thromboembolism, and autoimmune hepatitis (AIH). Notably, the absence of obesity, metabolic syndrome, or loss of appetite or weight, ruled out MASH, while the patient's history of avoiding homeopathic or allopathic medications and health supplements negated toxic liver injury. Furthermore, the patient denied needle stick injuries and use of IV drugs, and had no history of blood transfusions, which meant that hepatitis C was unlikely.

A comprehensive diagnostic work-up involved a thorough investigation with a focus on intricate imaging studies. Laboratory investigations revealed normal electrolytes and lipid profile, the results of which are outlined in Table 1. Serum iron and ferritin levels were within normal ranges, ruling out hemochromatosis. Viral hepatitis (B, C, and HIV) was excluded by negative immunochromatographic screening (ICT) and enzyme-linked immunosorbent assay (ELISA) tests. Cholestasis was ruled out based on elevated direct bilirubin (Table 1) and normal gamma-glutamyl transferase (GGT).

To explore autoimmune causes, an array of antibodies, including antinuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA), anti-liver-kidney microsomal antibodies (anti-LKM), and antimitochondrial antibodies (AMA), were tested, and returned negative results. This ruled out subclinical autoimmune hepatitis (AIH).

The diagnostic journey took a significant turn with detailed imaging studies. Ultrasound of the abdomen unveiled pleural effusion alongside maintaining a normal sized liver with mild coarse parenchymal appearance., Normal calibers of the portal vein and of the common bile duct were reported. No organomegaly was observed.

Subsequently, CT abdomen and pelvis with and without contrast was performed. The precontrast image (Fig. 1A) revealed irregular nodular margins and caudate lobe hypertrophy, indicative of cirrhotic changes. It also showed presence of ascites which indicated portal hypertension. The arterial phase did not reveal any enhancing focal lesions in the liver, which meant that HCC was unlikely. Imaging for the portal/venous phase (Fig. 1C) showcased heterogeneous liver parenchyma, caudate lobe hypertrophy, and ascites, further emphasizing the cirrhotic nature of the liver with additional findings of perigastric and perisplenic collaterals as markers of portal hypertension. Portal vein and its branches were observed to be patent in the portal/venous phase (Fig. 1D), which ruled out acute portal thrombosis. Other etiologies of liver cirrhosis were ruled out, including HCC due to the absence of abnormal growth and thromboembolism due to the absence of obstruction to venous blood flow.

Oesophagogastroduodenoscopy (OGD) added valuable information by revealing grade 2 esophageal varices and no obstruction to venous blood flow, further solidifying the presence of portal hypertension. This finding was crucial in guiding subsequent management decisions. The diagnostic ascitic tap, another pivotal component of the workup, not only confirmed the presence of liver pathology with a serum-ascites albumin gradient (SAAG) of 2.1 g/dL but also identified spontaneous bacterial peritonitis (SBP) through the revelation of elevated neutrophil counts (639 cells out of which 80% comprised neutrophils) and culture which yielded *Escherichia coli*, emphasizing the urgency of addressing the underlying infection. The ascitic fluid protein level was measured at 0.9 g/dL. The exhaustive exclusion of potential etiologies led to a suspected diagnosis of cryptogenic liver cirrhosis with SBP. The cirrhosis was categorized as Class C based on Child-Pugh classification.

In the pursuit of ameliorating the patient's condition, a comprehensive treatment plan was initiated. This included intravenous (IV) furosemide, oral spironolactone, carvedilol targeting liver cirrhosis, and IV cefotaxime to address SBP. The therapeutic approach yielded a salutary effect on the patient, as evidenced by the gradual reduction of abdominal swelling. After a week of hospitalization, there was a remarkable improvement in laboratory parameters, with bilirubin levels decreasing to a total of 19 mg/dL, direct bilirubin at 14 mg/dL, and indirect bilirubin at 5 mg/dL. Simultaneously, serum albumin levels rose to 3.1 g/dL.

Subsequent follow-up assessments further demonstrated the effectiveness of the treatment. Normal liver function tests were observed, bacterial growth in ascitic fluid was reduced, and the neutrophil count normalized, as indicated by a normal total leukocyte count. Upon physical examination during follow-up, the patient displayed no abdominal swelling, and the skin and sclera revealed a routine complexion, showcasing improvement from the jaundice observed earlier. The patient reported that the symptoms of fatigue also disappeared. This marked improvement translated into a significant enhancement in the patient's overall quality of life. These positive outcomes suggest a favorable trajectory for the patient's continued recovery.

Discussion

This case study illuminates the intricate diagnostic journey of a 42-year-old male patient who presented with jaundice, abdominal distension, and ascites, notable for the absence of abdominal pain or pruritus. A series of laboratory, radiological, and pathological assessments were conducted in a

Table 1 – Results of initial investigations performed.

Investigations	Results	Normal values
Aspartate aminotransferase	35 U/L	5–35 U/L
Alanine aminotransferase	58.3 U/L	10–50 U/L
Gamma-glutamyl transferase	30 U/L	5–35 U/L
Alkaline phosphatase	268 U/L	40–129 U/L
Serum bilirubin	31.6 mg/dL	0.1–1 mg/dL
Direct bilirubin	22.9 mg/dL	0–0.25 mg/dL
Indirect bilirubin	7.2 mg/dL	0–0.84 mg/dL
Albumin	2.69 g/dL	3.5–5.5 g/dL
Prothrombin time	16 seconds	10–13 seconds
Alpha-fetoprotein	4.16 IU/mL	<14.4 IU/mL
Alpha-1 antitrypsin	1.6 g/L	0.90–2.0 g/L
Immunoglobulin A	1.92 g/L	0.63–4.84 g/L
Immunoglobulin M	12.87 g/L	5.40–18.22 g/L
Immunoglobulin G	1.32 g/L	0.22–2.40 g/L
Serum ceruloplasmin	31.5 mg/dL	15–30 mg/dL
Urine copper	0.76 μmol/L	<0.9 μmol/L
Creatinine	2.17 mg/dL	0.64–1.2 mg/dL
Blood urea	40.9 mg/dL	18–45 mg/dL
Serum ferritin	53 ng/mL	12–300 ng/mL
Serum iron	72 μg/dL	60–180 μg/dL
Antinuclear antibody	Negative	Negative
Anti-mitochondrial antibody	Negative	Negative
Anti-smooth muscle antibody	Negative	Negative
Anti-liver kidney microsomal antibody	Negative	Negative
HIV serology, HBsAg, Anti-HCV	Negative	Negative
Rapid plasma reagent	Negative	Negative

concerted effort to pinpoint the underlying cause, yet all results remained inconclusive. Cryptogenic cirrhosis, also referred to as idiopathic cirrhosis, emerges as a perplexing puzzle in the realm of hepatology. The prevalence of employing this term for diagnosis is reported to have diminished from 5% to 30% of all cirrhosis cases to 5%, attributed to advancements in investigative techniques [4]. It is underscored that a comprehensive exploration of various etiologies is imperative before conclusively diagnosing cryptogenic cirrhosis. As it is a diagnosis of exclusion, it must be noted that cryptogenic cirrhosis is not an imaging diagnosis, rather a clinical one.

In the study conducted by Mohammed et al. [5], it was observed that men had a higher likelihood of being diagnosed with cryptogenic cirrhosis. The research also indicated no significant differences in survival rates across Child-Pugh classes A-C. However, a noteworthy contrast emerged when comparing cryptogenic cirrhosis to hepatitis-C-related liver cirrhosis, revealing a higher death rate in patients with cryptogenic liver cirrhosis [6]. Moreover, this cohort study concluded an association between cryptogenic cirrhosis and an increased incidence of complications, particularly liver decompensation. Additionally, the study reported several comorbidities associated with cryptogenic cirrhosis, such as diabetes mellitus, hypertension, and ischemic heart disease—all of which were notably absent in our patient.

The causes of cirrhosis encompass various etiologies, including persistent viral hepatitis, alcohol-induced liver disease, MASH, and hemochromatosis [7]. When the etiology of cirrhosis is unknown, the term "cryptogenic cirrhosis" is employed, representing a diagnosis achieved through exclusion. Cryptogenic cirrhosis is frequently linked with MASH due to similarities in clinical presentations [8]. However, MASH is associated with type 2 diabetes mellitus (T2DM), and obesity [9], none of which were present in the reported patient's case.

Contrary to the correlation previously reported, a study determined notable distinctions in the clinical characteristics between cryptogenic cirrhosis and MASH [10], providing valuable insights for distinguishing between these 2 diagnoses. Although metabolic changes linked to cirrhosis have been documented [11], no evidence of metabolic dysfunction was observed in our patient.

Patients experiencing toxic liver injury, such as those resulting from the use of homeopathic medication, typically manifest acute hepatitis and exhibit jaundice [12]. However, given the absence of any history of using homeopathic medication or health supplements in this patient, the likelihood of a toxic insult to the liver appeared diminished.

Another potential consideration is hemochromatosis, as the liver is the primary organ impacted by iron overload, leading to damage to hepatocytes [13]. Despite normal iron markers steering away from this possibility, it was crucial to highlight the lack of other systemic signs and symptoms of hemochromatosis in this case. These include comorbidities such as diabetes and hypothyroidism [13].

Viral hepatitis, including hepatitis B and C, is a significant factor in liver cirrhosis [14]. A thorough workup in our case excluded viral hepatitis as the cause of the liver pathology, with negative results in both ICT and ELISA for hepatitis B and C. The absence of active hepatitis B infection was confirmed by the lack of positive results in HBsAg and anti-HBc tests. Similarly, hepatitis C was ruled out with negative screening tests for HCV antibodies. Excluding viral hepatitis is crucial for a tar-

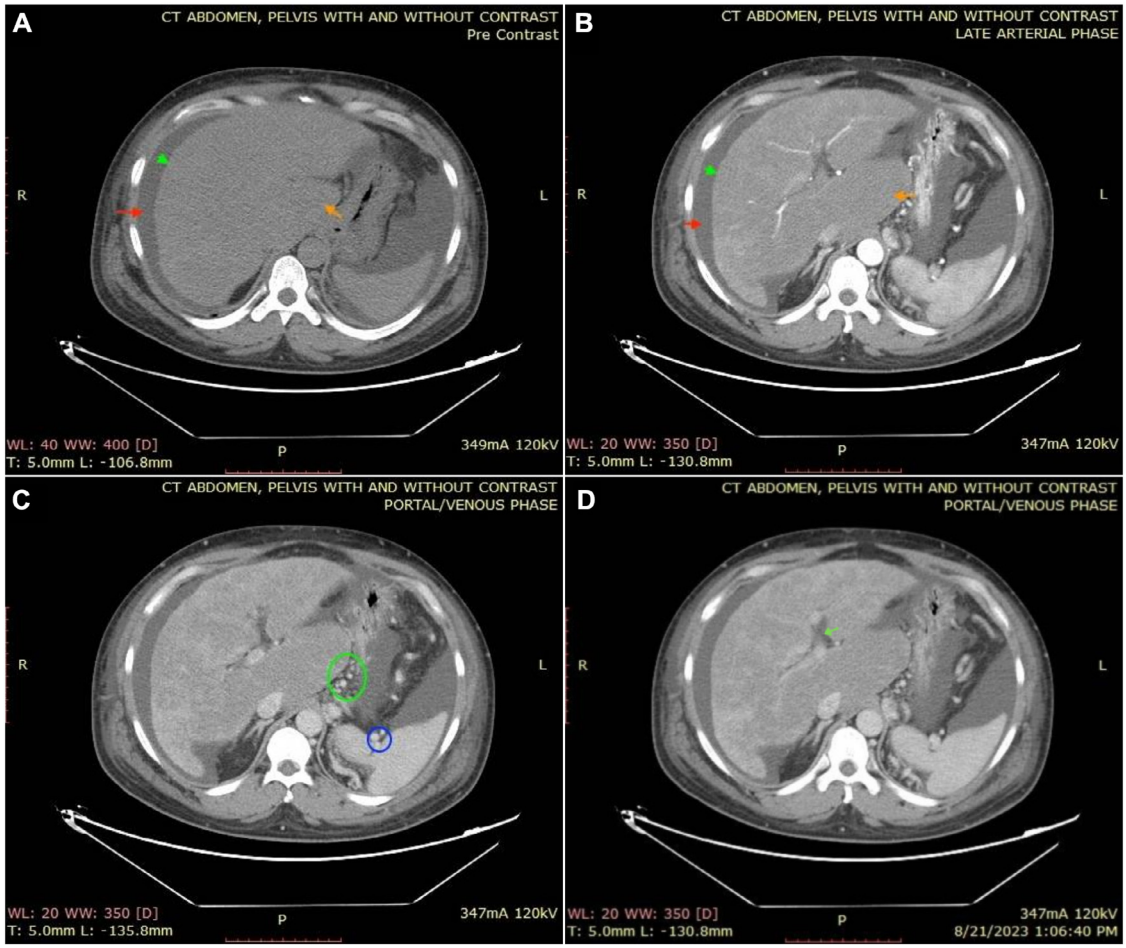

Fig. 1 – Pre-contrast (A) CT scan of the abdomen and pelvis revealing an irregular nodular margin of the liver (green arrowhead), caudate lobe hypertrophy (orange arrow), and the presence of ascites (red arrow). Arterial phase (B) CT scan of the abdomen and pelvis reveals no enhancing focal lesions in the liver; nevertheless, irregular nodular margins (green arrowhead), caudate lobe hypertrophy (orange arrow), and ascites are evident (red arrow). Portal/venous phase (C) CT scan of the abdomen and pelvis depicting heterogeneous liver parenchyma without apparent washout. Features indicative of a cirrhotic liver include caudate lobe hypertrophy, perigastric (green circle) and perisplenic (blue circle) collaterals, along with the presence of ascites. Portal/venous phase (D) CT scan of the abdomen and pelvis demonstrates a patent portal vein (green arrow) and its branches with no evidence of thrombosis or obstruction. Additionally, no enhancing focal lesions are observed in the liver.

geted approach in managing and treating the specific cause of liver cirrhosis, guiding the diagnostic focus toward other potential etiologies.

Our diagnostic path shifted when the suspicion of obstructive jaundice arose. Normal iron markers suggested that hematological abnormalities were unlikely, ruling out hemolytic jaundice. This prompted consideration of obstruction. Elevated GGT levels typically indicate cholestasis, as an obstruction to bile flow leads to increased synthesis and release of GGT in response to higher bile acid concentrations [15]. However, normal serum GGT levels in this patient ruled out the likelihood of obstructive jaundice.

Autoimmune hepatitis (AIH) has been considered a potential etiological factor for cryptogenic cirrhosis [1]. The accurate detection of AIH involves assessing autoantibodies [16]. In our case, AIH was effectively ruled out based on the absence of detectable autoantibodies.

Another potential cause of liver cirrhosis is carcinoma. It's worth noting that CT scans may sometimes overlook tumors, and a biopsy is typically essential to confirm the absence of cancerous growth. However, in the context of hepatocellular carcinoma, CT scans have demonstrated high sensitivity and specificity [17]. Despite the absence of histological confirmation due to the patient's refusal to undergo a liver biopsy, ruling out carcinoma was possible with the CT scan alone, as it revealed no abnormal growth.

The imaging findings in our case, including irregular nodular margins, caudate lobe hypertrophy, and varices of the spleen, offer valuable insights into the distinctive pathophysiology of cryptogenic cirrhosis [18]. The irregular nodular margins detected in the CT scan signify architectural distortion within the liver parenchyma, revealing the presence of regenerative nodules encased in fibrous tissue. Despite the elusive etiology of cryptogenic cirrhosis, these irregularities exem-

plify the chronic liver injury, inflammation, and fibrosis characterizing cirrhotic liver architecture.

Caudate lobe hypertrophy, a prominent imaging feature [19], highlights the caudate lobe's sensitivity to hemodynamic alterations in the context of cirrhosis. Increased resistance to blood flow in the portal vein leads to portal hypertension, and the hypertrophy of the caudate lobe serves as an adaptive response to maintain hepatic perfusion amidst altered blood flow patterns [19].

The identification of varices in the spleen is intricately linked to the hallmark of cryptogenic cirrhosis—portal hypertension [20]. This vascular condition arises due to heightened resistance within the liver vasculature, resulting from fibrosis and architectural distortion. As blood seeks alternative routes, the development of portosystemic collaterals, including splenic varices, becomes evident. Splenic varices, specifically observed in cirrhotic patients with cryptogenic cirrhosis, underscores the impact of portal hypertension on the splenic vasculature [21].

Despite the absence of a known etiology, cryptogenic cirrhosis shares commonalities in terms of chronic liver injury and fibrotic changes leading to cirrhosis [1]. The irregular nodular margins, caudate lobe hypertrophy, and splenic varices in imaging studies are characteristic of progressive liver damage. These findings support the diagnostic process, guide management decisions, and aid in targeted treatment of portal hypertension, preventing complications like spontaneous bacterial peritonitis (SBP).

All investigations and findings confirmed the suspected diagnosis of exclusion of cryptogenic liver cirrhosis with spontaneous bacterial peritonitis. Exclusion criteria included the absence of T2DM and obesity ruling out MASH, no homeopathic medication or health supplements indicating no toxic liver injury, normal serum ferritin and iron levels eliminating hemochromatosis, negative ICT, and ELISA results for hepatitis B and C excluding viral hepatitis, normal serum GGT levels ruling out cholestasis, and the CT scan excluding carcinoma and thromboembolism. Negative autoantibodies for AIH also ruled out that condition.

The 3-tiered strategy for treating cryptogenic cirrhosis involves slowing disease progression, preventing decompensation, and managing portal hypertension. Diuretics, such as furosemide and spironolactone, are utilized for ascites treatment, with spironolactone serving as the primary choice for ascites in liver cirrhosis [22]. Carvedilol, a non-selective beta-blocker, is linked to improved long-term survival in patients with concurrent liver cirrhosis and ascites [23]. This comprehensive treatment approach significantly ameliorated the patient's condition, resolving abdominal distension, and normalizing liver function tests. Additionally, IV cefotaxime was administered for the treatment of spontaneous bacterial peritonitis, with any third-generation cephalosporin being a viable option due to uncertain differences in outcomes [24].

Conclusion

The diagnostic journey of cryptogenic cirrhosis emphasizes the pivotal role of medical imaging. Radiological studies, including CT scans, unveil distinctive features such as irregular nodular margins, caudate lobe hypertrophy, and splenic varices, offering insights into the complex pathophysiology. Despite advancements, the term "cryptogenic cirrhosis" remains pertinent, emphasizing the challenges in diagnosis. Healthcare professionals should leverage imaging's specificity to guide tailored management. Vigilant follow-up, lifestyle modifications, and a nuanced understanding of liver cirrhosis without a clear cause ensure comprehensive care and better patient outcomes in the evolving landscape of medical imaging.

Patient consent

Written informed consent was obtained from the patient for their anonymized information to be published in this article (case report).

Authorship

All authors had access to the data and a role in writing this manuscript.

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