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Undiagnosed Hypothyroidism as a Contributor to Cryptogenic Cirrhosis: A Case Report and Diagnostic Perspective

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Abstract

Cryptogenic cirrhosis presents a clinical challenge due to the absence of an identifiable underlying cause. Recent evidence suggests a bidirectional relationship between thyroid dysfunction—particularly hypothyroidism—and liver disease progression. This case study aims to explore the potential role of hypothyroidism as a contributing factor in cryptogenic cirrhosis. We report the case of a 48-year-old woman with chronic diarrhea, fatigue, cold intolerance, jaundice, and easy bruising, without a history of alcohol use, viral hepatitis, or known hepatic insults. Physical examination indicated bradycardia, psychomotor slowing, and signs of liver dysfunction. Laboratory tests revealed pancytopenia, elevated liver enzymes, hypoalbuminemia, and overt hypothyroidism, as indicated by low free T4 and elevated TSH levels. Imaging studies confirmed cirrhosis and the presence of benign thyroid nodules. The patient received levothyroxine therapy (100 mcg/day) along with supportive hepatic care. Within days, significant clinical and hematologic improvement was observed, including resolution of diarrhea and improved energy levels. This case underscores the importance of evaluating thyroid function in patients with unexplained liver disease. The findings support the hypothesis that hypothyroidism may not only coexist with but also contribute to the progression of liver dysfunction. Early detection and appropriate management of thyroid disorders in such patients could have meaningful therapeutic implications and potentially alter the clinical trajectory of cryptogenic cirrhosis.

Keywords: hypothyroid, cirrhosis, NAFLD, thyroid

INTRODUCTION

Cryptogenic cirrhosis represents a significant challenge in hepatology, characterized by cirrhosis with uncertain etiology that lacks definitive clinical and histological criteria for a specific disease (Mercado-Irizarry & Torres, 2016). *Cryptogenic cirrhosis* accounts for nearly 5% to 30% of cirrhosis cases. Chronic liver injury from various causes may progress to cirrhosis, making it essential to identify the underlying etiology due to its impact on patient management and long-term outcomes, including the need for liver transplantation. Hormonal disturbances in patients with chronic liver failure have been recognized for many years (Lonardo et al., 2019). While the hypothalamic-pituitary-gonadal axis is commonly affected, hepatic insufficiency also leads to alterations in other hormonal systems, including the thyroid and growth hormone axes (Arafa et al., 2012).

The liver plays a key role in producing hormone-binding proteins, including sex hormone-binding globulin (SHBG) and thyroid-binding globulin

(TBG), making the *thyroid* one of the primary hormonal systems to be affected (Quiroz-Aldave et al., 2024). Thyroid hormone concentrations and their associated binding proteins are frequently altered in patients with chronic liver disease. The low free T3 syndrome, commonly observed in individuals with cirrhosis, is characterized by elevated reverse T3 (rT3), reduced triiodothyronine (T3) levels, and a diminished T3 to T4 ratio (AK et al., 2016).

It has been shown that reduced serum thyroid hormone (TH) concentrations may contribute to the development of hyperlipidemia and obesity, thereby playing a role in the pathogenesis of non-alcoholic fatty liver disease (*NAFLD*) (Verma et al., 2017). Furthermore, studies have reported a negative correlation between free thyroxine (FT4) levels and the prevalence of *NAFLD*, suggesting that lower FT4 levels may facilitate the onset of this condition.

This case demonstrates the significance of evaluating liver function in patients presenting with clinical signs and symptoms of *hypothyroidism* and the indication for early therapy, aiming to ameliorate disease progression.

A critical analysis of previous studies highlights the well-recognized association between thyroid dysfunction and liver disease but also reveals key gaps when applied to *cryptogenic cirrhosis*. A meta-analysis by Zeng et al. (2021) found that both clinical and subclinical *hypothyroidism* are associated with increased risk and severity of *non-alcoholic fatty liver disease (NAFLD)*. However, most of the included studies were cross-sectional and limited by confounding factors such as obesity and dyslipidemia, making causal inference uncertain and therapeutic implications unclear. Similarly, Punekar et al. (2018) demonstrated consistent thyroid abnormalities—low FT3, elevated TSH, and a reduced FT3/FT4 ratio—in patients with advanced cirrhosis, correlating with disease severity scores. Yet, their single-center case-control design did not differentiate between non-thyroidal illness syndrome and primary *hypothyroidism*, nor did it assess outcomes following thyroid hormone therapy. The present study addresses this gap by reporting a clinically overt case of *hypothyroidism* coexisting with *cryptogenic cirrhosis* and documents significant early clinical improvement following levothyroxine administration. This adds a pathophysiologic rationale for routine thyroid function screening in patients with unexplained liver disease.

The objective of this study is to clarify the potential role of *hypothyroidism* as a modifiable contributor to *cryptogenic cirrhosis*, to provide clinical justification for early thyroid assessment in hepatology, and to encourage further interventional trials examining the therapeutic impact of thyroid hormone replacement on hepatic outcomes.

Case Report

A previously healthy 48 years old female came to the internal medicine outpatient department presenting with chronic diarrhea persisting for over three months, accompanied by bloating. The diarrhea was five to seven times

a day in frequency without mucus, blood or black stool. No fever or significant weight loss was reported. The patient's family has also observed a yellowish tint in the patient's skin and eyes for the past four months, with a progressive deepening of the yellow discoloration over time. Patients also noticed bruises observed in several parts of her body without a clear explanatory cause such as shinbone and knee pit. Since the onset of the illness, the patient reports persistent feelings of cold, even in warm environments. She experiences difficulty in attaining proper warmth despite wearing multiple layers of clothing and having blankets covering her body. No previews history of alcohol consumption, intravenous drug abuse, multiple sexual partners, previews chronic use of certain drugs, or family history of inherited diseases such as hemochromatosis, wilson's disease or a1-antitrypsin deficiency.

On admission the vitals were 95/51 mmHg for blood pressure, 55x/m for heart rate, 16x/m for respiratory rate, 36.6^{o}C for temperature and 100% for oxygen saturation using pulse oximeter. On physical examination found the patient was jaundice, had an icteric sclera, anemic eye conjunctiva and several ecchymosis on her lower extremities. The examiner also observed a significantly slow movement when the patient was asked to undress for the Electrocardiogram examination and observed that the patient's skin appeared markedly dry, scaly and there were several scratch marks suggestively caused by itchy skin. The signs of advanced liver disease including spider angioma, splenomegaly, caput medusae, edema, plantar erythema, ascites, and asterixis were not found. The abnormality of thyroid gland structure done by physical examination such as nodule, diffuse goiter or posttraumatic wound were not found.

The laboratory work using limited resource in our rural healthcare facility in this patient showed pancytopenia on admission suggestively caused by chronic liver disease, low fT4 and TSHS consistent with hypothyroid hormonal profile, elevated SGOT SGPT and low albumin indicating altered liver function and no hepatic viral infection as presented in table.1

Table 1. laboratory work results

Days/weeks from first admission	admission	2 weeks	2 weeks + 1 day	3 weeks
Hematology				
Hb (g/dL)	8.4	7.5	8.0	10.1
Ht (%)	24.4	22.2	23.7	30.0
Leu (cells/mm)	2700	2500	2800	11.500
Plt (cells)	54.000	54.000	59.000	315.000
Liver Function				
SGOT (IU/L)	74			
SGPT (IU/L)	43			
Total Protein (g/dL)	8.3			
Albumin (g/dL)	1.9			
Blood chemistry				
Total cholesterol (mg/dL)	144			

LDL (mg/dL)	66			
TG (mg/dL)	190			
Direct bilirubin (mg/dL)	2.14			
Total bilirubin (mg/dL)	2.78			
BG (mg/dL)	112	125		
Renal functions				
Ur (mg/dL)	28	28		
Cr (mg/dL)	1.13	1.15		
UA (mg/dL)	7.50			
Electrolytes				
K (mmol/L)	3.25		4.48	4.25
Ca (mmol/L)	1.22		1.10	1.18
Na (mmol/L)	137.4		136.6	138
Endocrines				
fT4 (ng/dL)		0.62		
TSHS (IU/ml)		11.53		
Immunoserology				
Anti-HIV		non -reactive		
HbsAg		non -reactive		
Anti-HCV		non -reactive		

Note: Hb: hemoglobin, Ht: hematocrite, Leu: leucocyte, Plt: platelet, SGOT: serum glutamic oxaloacetic transaminase, SGPT: serum glutamate pyruvate transaminase, LDL: low-density lipoproteins, TG:Triglyceride, BG: blodd glcucose, Ur:Ureum, Cr: Creatinine, UA: Uric Acid, K: Kalium, Ca: Calsium, Na: Natrium, fT4: free thyroxine, TSHS: thyroid stimulating hormone

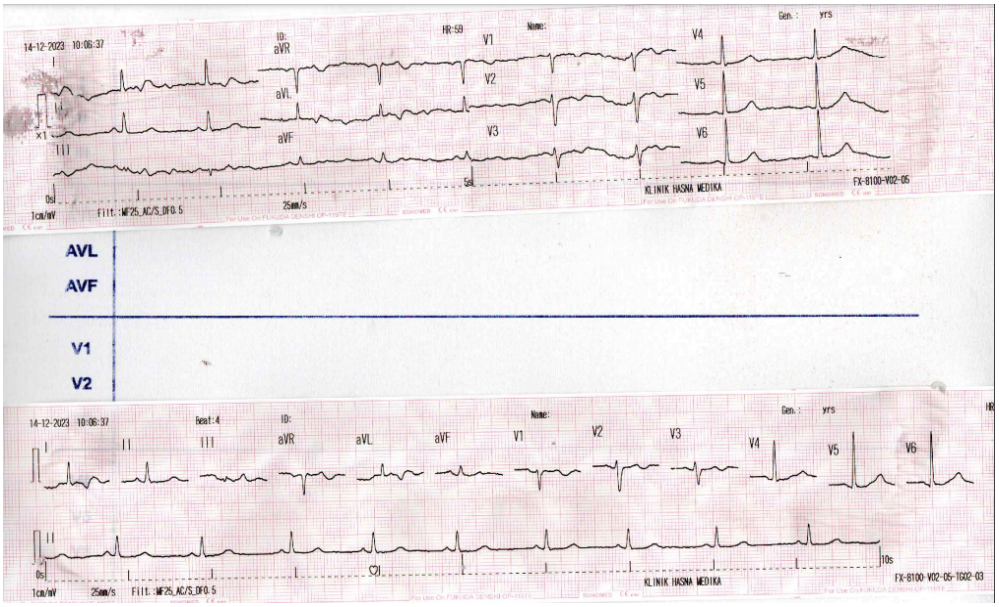

Figure 1. Electrocardiogram

The electrocardiogram revealed findings consistent with cardiovascular manifestations of hypothyroidism, including low voltage sinus bradycardia and subtle biphasic T-waves in leads V1-3, with the duration of the second peak of the T-wave less than 0.02 seconds, a normal finding. These observations correlate with the characteristic decrease in heart rate associated with hypothyroidism. Transthoracic echocardiogram was conducted in this patient, the result was significant for left ventricular concentric hypertrophy, tricuspid regurgitation with low probability of pulmonary hypertension without reduced ejection fraction.

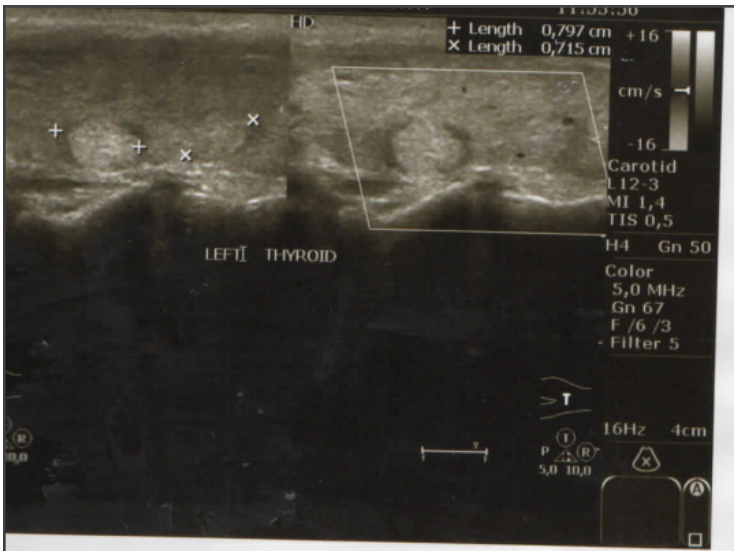

Figure 2. Thyroid Ultrasonography

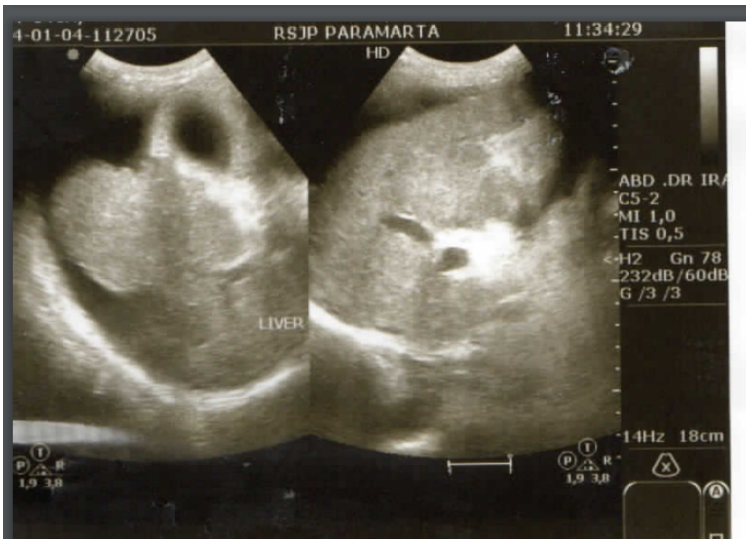

Figure 3. Abdominal Ultrasonography

The Thyroid ultrasonography conducted in this patient revealed multiple hypoechoic solid nodule at left thyroid lobe suggesting benign nodule.

Abdominal Ultrasonography also conducted in this patient for hepatic imaging revealed the size of the liver left lobe appears enlarged with a blunt edge. The surface was irregular and the parenchymal texture was coarse. No visible nodules or masses. The portal vein is dilated, while the hepatic veins are not dilated and there is evidence of fluid collection in the surrounding area consistent with hepatic cirrhosis with portal hypertension and ascites. Serum ceruloplasmin, a1-antitrypsin and ANA test were not conducted in this patient because of the limited sources in the area.

The patient received multidisciplinary care involving cardiology because of coronary artery disease diagnosed from ECG. Treatment included packed red blood cell transfusion and initiation of levothyroxine at a dosage of 100 mcg/day. The cardiologist also prescribed simvastatin and Acetylsalicylic acid. Oral albumin supplementation was administered due to limited resources precluding albumin transfusion. After three days of inpatient care, The diarrhea diminished, and the patient was discharged with furosemide 40 mg/day, bisoprolol 5 mg/day, spironolactone 100 mg/day, levothyroxine 50 mcg/day, oral albumin three times daily, Aspirin and simvastatin prescribed for home therapy. The patient is advised to continue attending follow-up appointments at the internist and cardiologist clinics to monitor clinical improvement and other workup examinations over time.

RESULT AND DISCUSSION

Hypothyroidism includes both subclinical and overt forms. Subclinical hypothyroidism is characterized by an elevated thyroid-stimulating hormone (TSH) level with normal serum free thyroxine (fT4) concentrations and no apparent clinical symptoms. In contrast, overt hypothyroidism is defined by an increased TSH level accompanied by reduced fT4 levels and is often associated with clear clinical manifestations (He et al., 2017). In recent years, an increasing number of studies have suggested a potential association between thyroid dysfunction and non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH) (Jahromi, 2014). In this case, it remains difficult to determine which condition preceded the other, making the causal relationship inconclusive.

Multiple studies have reported that the most frequent thyroid hormone abnormalities in patients with liver cirrhosis include reduced serum T3 levels, elevated reverse T3 (rT3), and normal thyroid-stimulating hormone (TSH) levels. Several mechanisms may contribute to these disturbances, such as changes in the concentration of thyroid-binding proteins in the plasma, impaired binding of T3 and T4 to these proteins, decreased hepatic clearance of rT3, elevated glucagon levels, and diminished peripheral conversion of T4 to T3 (Sharma et al., 2018). In our case, the presence of low free T4 levels accompanied by elevated TSH contrasts with the findings reported by Mobin et al. (2016), indicating that there is variability in the biochemical markers of hypothyroidism. One study proposed that the underlying mechanism of the

'low T4 syndrome' observed in critically ill patients is a reduced responsiveness of thyroid-stimulating hormone (TSH) to thyrotropin-releasing hormone (TRH) (Vincken et al., 2017).

It is important to note that the most consistently observed alteration in thyroid hormone levels among patients with decompensated cirrhosis is a reduction in serum T3 concentration. Serum T4 levels are typically within the normal range or mildly reduced, while TSH levels generally remain unchanged. Due to the reliability of these hormonal changes, some researchers have proposed using thyroid hormone levels as a sensitive indicator of liver function (Mobin et al., 2016).

In our case, the patient manifested diarrhea as one of the symptoms. Patients with hypothyroidism rarely present with diarrhea and more commonly report constipation. However, one study documented a case of a young woman with hypothyroidism who primarily presented with chronic diarrhea (Xu et al., 2024). Hypothyroidism presents with a wide range of clinical manifestations and non-specific symptoms, such as weight gain, fatigue, impaired concentration, depression, generalized myalgia, menstrual irregularities, and constipation. However, no single symptom is considered pathognomonic or reliably predictive of the condition (Chiovato et al., 2019). Therefore, our suspicion was raised when patients with cirrhosis presented with diarrhea and psychomotor slowing.

Given the presence of overt symptoms in this patient, we opted to initiate treatment for hypothyroidism. A review article supports this approach, suggesting that treating symptomatic hypothyroidism in patients with cirrhosis is reasonable. In our case, the patient demonstrated significant clinical improvement following therapy. However, the same study also highlights that liver cirrhosis can impair drug absorption, indicating that patients with advanced cirrhosis may require higher doses of levothyroxine. In such cases, switching to newer formulations—such as liquid preparations or softgel capsules—may help achieve better thyroid function control (Piantanida et al., 2020). Another study suggest that certain thyroid hormone metabolites may have therapeutic potential in the management of NAFLD; however, the risk of inducing hyperthyroidism remains a concern (Kizivat et al., 2020).

CONCLUSION

There is evidence of a bidirectional relationship between liver dysfunction and thyroid function, with liver cirrhosis known to impair thyroid activity and hypothyroidism shown to accelerate the progression of fatty liver disease and cirrhosis. Clinicians should therefore consider evaluating thyroid function in patients presenting with cirrhosis symptoms. Additionally, thyroid hormone replacement therapy has demonstrated potential in improving clinical outcomes in cirrhotic patients, as supported by our case experience. Future research should focus on larger, controlled trials to evaluate the therapeutic

benefits of hypothyroidism treatment in slowing or reversing liver disease progression.

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