

# Isolated and Persistent Gamma-Glutamyl Transferase Elevation and Porto-Sinusoidal Vascular Disorder Diagnosis

## Gama-Glutamil Transferase Isolada e Persistentemente Elevada e Diagnóstico de Distúrbio Vascular Porto-Sinusoidal

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### Abstract:

Porto-sinusoidal vascular disorder (PSVD) is a distinct clinical entity often presenting with heterogeneous symptoms, from asymptomatic to complications of portal hypertension. This case report describes a 62-year-old male with a 30-year history of isolated elevated gamma-glutamyl transferase (GGT) without a clear cause after extensive evaluation. Despite the absence of liver disease stigmata or portal hypertension, persistent elevated GGT led to a liver biopsy, which confirmed the diagnosis of PSVD. This case underlines the importance of further investigation in patients with isolated and persistent elevated GGT, especially in males with low liver stiffness values (<10 kPa), as PSVD may be underdiagnosed. It emphasizes that isolated GGT elevation, typically overlooked without evidence of liver disease progression, should prompt additional diagnostic measures. Recognition of PSVD can lead to proper prognosis and monitoring, highlighting the requirement for liver biopsy to ensure accurate diagnosis.

**Keywords:** Biopsy; gamma-Glutamyltransferase; Porto-Sinusoidal Vascular Liver Disorder.

### Resumo:

O distúrbio vascular porto-sinusoidal (DVPS) é uma entidade única, com apresentação clínica variável, desde casos assintomáticos até complicações associadas à hipertensão portal. Este relato de caso descreve um homem de 62 anos, com gama-glutamil transferase (GGT) isoladamente elevada com 30 anos de evolução, sem causa evidente após avaliação acurada, culminando na realização de biópsia hepática, sendo confirmado o diagnóstico de DVPS.

Este caso salienta a importância da necessidade de uma investigação aprofundada em doentes com GGT isolada e persistentemente elevada, especialmente em indivíduos do género masculino com valores de elastografia baixos (<10 kPa). Destaca-se que a elevação isolada de GGT, tipicamente negligenciada na ausência de evidência de progressão da doença hepática, deve incitar medidas diagnósticas adicionais. O reconhecimento do DVPS pode levar a um prognóstico e monitorização adequados, sublinhando a necessidade de biópsia hepática para garantir um diagnóstico preciso.

**Palavras-chave:** Biópsia; Distúrbio Vascular Porto-Sinusoidal; gama-Glutamiltransferase.

### Learning Points

1. Isolated and persistent GGT should not be overlooked particularly in the absence of overt liver disease.
2. Liver biopsy shall be performed in patients with isolated and persistent GGT without a clear trigger, as it may be linked to PSVD diagnosis.
3. Liver biopsy remains a crucial diagnostic tool in cases of unexplained liver enzyme anomalies, especially when imaging and other non-invasive tests fail to reveal clear pathology.

### Introduction

Previously referred to as idiopathic portal hypertension, non-cirrhotic portal hypertension, or hepatoportal sclerosis, porto-sinusoidal vascular disorder (PSVD) is a unique clinical entity with various pathological features, rather than distinct clinicopathological entities.<sup>1</sup> The clinical presentation is highly heterogeneous, ranging from asymptomatic cases to portal hypertension and its complications, with up to 8.5% of the patients requiring liver transplantation.<sup>2</sup> Those requiring liver transplantation, have usually a good long-term prognosis, depending on the presence of previous clinical conditions (hyperbilirubinemia levels and renal function) and respective severity.<sup>3</sup> Portal vein thrombosis develops in 30% of patients with clinically significant portal hypertension.<sup>2</sup>

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Notably, the diagnosis still relies on liver histological findings, with the exclusion of cirrhosis being fundamental for diagnosis, and abnormalities typically found in portal venules and/or sinusoids.<sup>1</sup> In PSVD, mild liver enzyme anomalies are commonly detected in up to 80% of patients, particularly elevated alanine aminotransferase (ALT) or alkaline phosphatase (ALP) levels, though often at a lower range.<sup>1</sup>

Gamma-glutamyl transferase (GGT) is a key enzyme involved in the transport of amino acids across cell membranes, essential for peptide and protein synthesis. It also plays an important role in maintaining glutathione homeostasis.<sup>4</sup> Elevated GGT levels are usually associated with liver injury, particularly of the biliary ducts, and alcohol consumption. However, GGT is neither specific to liver disease nor to the liver itself, as elevated levels may also be related to cardiovascular, pulmonary, or renal disease.<sup>4</sup> Nevertheless, it is important to associate elevated GGT with a specific clinical entity, as this can guide diagnosis, treatment, or prognosis. This case illustrates the diagnostic approach to isolated GGT elevation over several decades, ultimately leading to the diagnosis of PSVD.

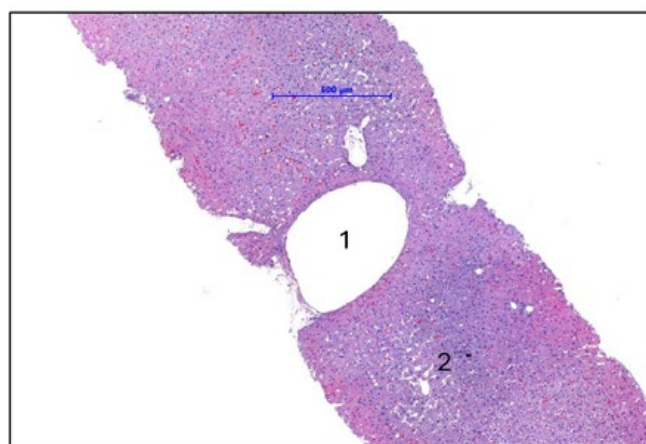
## Case Report

A 62-year-old man with cardiovascular risk factors [overweight (body mass index 28.6 kg/m<sup>2</sup>) and mixed dyslipidemia] known for 10 years, and a history of transient monocular blindness in 2023, treated with acetylsalicylic acid and atorvastatin by then, attended a hepatology consultation due to elevated GGT levels known for approximately 30 years. The patient was asymptomatic, with no history of alcohol consumption, other chronic medications, or nutritional supplements.

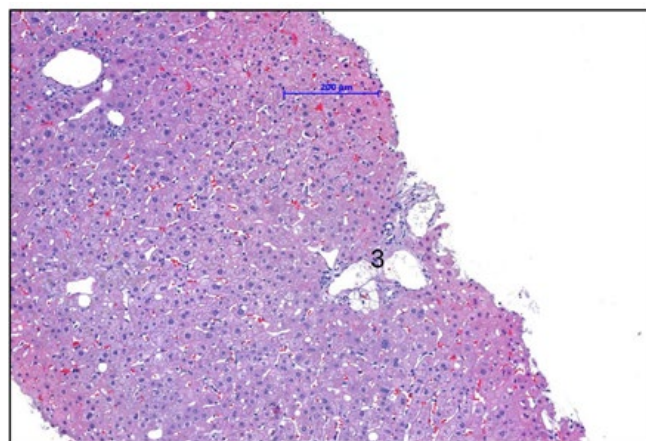
No stigmata of chronic liver disease and/or portal hypertension (no jaundice, malar telangiectasias, parotid hypertrophy, temporal atrophy, spider angiomas, or signs of collateral circulation) were observed. Laboratory tests revealed a normal blood count, with platelets at 208 000/ $\mu$ L, aspartate aminotransferase (AST) = 24 IU/L, ALT = 36 IU/L, GGT = 177 IU/L, ALP = 116 IU/L, and bile acids = 2.5  $\mu$ mol/L. There was no evidence of metabolic diseases (iron parameters, 24-hour urinary copper, alpha-1 antitrypsin, and angiotensin-converting enzyme levels were within normal ranges), autoimmune disorders (immunoglobulin profile, notably IgG4, as well as antinuclear, antimitochondrial, sp100, and gp210 antibodies, were all negative), or viral infections (hepatitis B or C). An abdominal Doppler ultrasound revealed a morphologically normal liver, an ultrasound fatty liver index of 2, a normal spleen, hepatopetal flow in the portal vein with normal velocity, and no signs of portal hypertension. The liver stiffness value (Fibroscan<sup>®</sup>) was 7.4 kPa, and the controlled attenuation parameter (CAP) was 275 dB/m.

Given the absence of a clear etiology for the analytical alteration and 30 years of persistent GGT elevation (which

occurred before the metabolic manifestations of overweight and dyslipidemia), a percutaneous ultrasound-guided liver biopsy was performed. The biopsy fragment was 2.1 cm in length, with 11 portal spaces represented. Histology revealed dilated centrilobular veins without inflammatory or structural changes (Fig. 1), dilation of portal veins, herniation of portal vein branches at the periphery of some portal structures, and multifocal sinusoidal dilation (Fig. 2). No biliary duct lesions were observed, and mild, scattered medium-sized vesicular steatosis was found intralobularly. The features of the portal venules and sinusoids were compatible with a definitive diagnosis of PSVD, without signs of portal hypertension.



**Figure 1:** Liver biopsy (haematoxylin and eosin stain) showing a dilated centrilobular vein(1) and sinusoids(2) in the adjacent areas.



**Figure 2:** Liver biopsy (haematoxylin and eosin stain) showing a portal space with dilated veins and herniation(3) of portal vein branches in adjacent parenchyma.

It was only recently that the possible link between isolated, persistent, and elevated GGT and PSVD was suggested. In a retrospective cohort of 29 patients with isolated GGT elevation where a liver biopsy was performed following a thorough investigation, Pugliese *et al* found PSVD histological criteria in 45%

of cases.<sup>5</sup> Interestingly, in the context of PSVD, isolated elevated GGT is more commonly seen in patients without portal hypertension.<sup>6</sup> These findings were confirmed in a larger and more robust Italian multicentric cohort study involving 144 patients from five centers.<sup>7</sup> Ninety-six (66.7%) of 144 patients had histological abnormalities related to PSVD diagnosis, including nodular regenerative hyperplasia. Most patients diagnosed with PSVD were male (59%), with a mean age of 50.3 years. Only 7% had portal hypertension, and the median elastography value was 4.8 kPa. The likelihood of a PSVD diagnosis was increased in male patients with unexplained and persistent GGT levels under 200 U/L and liver stiffness below 10 kPa.<sup>7</sup>

Gamma-glutamyl transferase is a non-specific liver enzyme, and its lack of specificity for liver disease explains why isolated increases in GGT are often neglected. Reports suggest that, in the absence of evidence of severe liver disease or its progression, elevated GGT is not a cause for concern.<sup>8</sup> GGT is commonly elevated in cholestatic liver diseases, alcohol and drug use, and metabolic-associated steatotic liver disease, but in these contexts, GGT elevation usually occurs alongside other liver enzyme abnormalities.<sup>4</sup>

Even though there is not, to date, a formal recommendation that mandates the performance of a liver biopsy in the context of the investigation of an isolated GGT, this case report demonstrates that isolated GGT elevation over several years should not be neglected, as a final diagnosis of PSVD was established, allowing for appropriate prognosis and monitoring. Our case report clearly mirrors the criteria mentioned by Pugliese N *et al*, reinforcing that these criteria may serve as a starting point for systematically performing a liver biopsy in this context, even though more data will be needed in the future. The absence of cardiovascular risk factors, alcohol abuse, or drug use before the onset of liver function test abnormalities, coupled with normal analytical (for viral, autoimmune, cholestatic, iron, and sarcoidosis-related liver diseases) and imaging results, led to a liver biopsy, which provided the final diagnosis. Porto-sinusoidal vascular disorder allows for concomitant liver diseases. The patient also presents, together with vascular abnormalities, and mild steatosis, confirmed by the value identified in the US fatty liver index, the CAP, as well as the liver biopsy findings, reflecting the role of the dysmetabolic changes that appeared in the last decade of life.

This case report supports the recent findings and highlights the need for increased awareness that patients with persistently and isolated elevated GGT, without an obvious cause after clinical interview, physical examination, and appropriate analytical and imaging studies, should undergo further investigation, particularly if male and with low liver elastography (<10 kPa). This may be particularly important when portal hypertension has been ruled out. Since the investigation of isolated elevated GGT typically does not lead to liver biopsy, the incidence of cases with PSVD may be underestimated. Being PSVD a rare vascular liver disorder, increasing diagnostic performance

may potentially increase the number of diagnosed patients, particularly those without complications of portal hypertension, providing us with more data regarding the natural history of this disease. While there are no specific treatments for PSVD so far, recognizing the disease in a less severe stage may lead to active measures that could slow the progression of the disease. For example, this could involve treating or avoiding recognized precipitants of PSVD or implementing lifestyle interventions to prevent concomitant liver diseases, such as metabolic steatotic liver disease, as seen in our patient. ■

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FN – Draft of the article, critical revision of the manuscript for important intellectual content, revision and approval of the final version.

MTG, FC – Critical revision of the manuscript for important intellectual content and revision and approval of the final version.

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**REFERÊNCIAS**

1. De Gottardi A, Rautou PE, Schouten J, Rubbia-Brandt L, Leebeek F, Trebicka J, et al. Porto-sinusoidal vascular disease: proposal and description of a novel entity. *Lancet Gastroenterol Hepatol.* 2019;4:399-411. doi: 10.1016/S2468-1253(19)30047-0.
2. Magaz M, Giudicelli-Lett H, J GA, Nicoara-Farcau O, Turon F, Rajoriya N, et al. Porto-sinusoidal vascular liver disorder with portal hypertension: Natural History and Long-Term Outcome. *J Hepatol.* 2025;82:72-83. doi: 10.1016/j.jhep.2024.07.035.
3. Magaz M, Giudicelli-Lett H, Nicoara-Farcau O, Rajoriya N, Goel A, Raymenants K, et al. Liver Transplantation for Porto-sinusoidal Vascular Liver Disorder: Long-term Outcome. *Transplantation.* 2023;107:1330-40. doi: 10.1097/TP.0000000000004444.
4. Brennan PN, Dillon JF, Tapper EB. Gamma-Glutamyl Transferase (gamma-GT) - an old dog with new tricks? *Liver Int.* 2022;42:9-15. doi: 10.1111/liv.15099.
5. Pugliese N, di Tommaso L, Lleo A, Alfarone L, Mastrococco E, Terrin M, et al. High prevalence of porto-sinusoidal vascular disease in patients with constantly elevated gamma-glutamyl transferase levels. *Liver Int.* 2022;42:1692-5. doi: 10.1111/liv.15257.
6. Zhang Y, Xiong Q, Zhong Y, Liu D, Liu H, Wang L, et al. Clinical characteristics and natural history of porto-sinusoidal vascular disease: A cohort study of 234 patients in China. *Liver Int.* 2024;44:2329-40. doi: 10.1111/liv.16002.
7. Pugliese N, Ponziani FR, Cerini F, di Tommaso L, Turati F, Maggioni M, et al. Link between persistent, unexplained gamma-glutamyltransferase elevation and porto-sinusoidal vascular disorder. *JHEP Rep.* 2024;6:101150. doi: 10.1016/j.jhepr.2024.101150.
8. Carey WD. How should a patient with an isolated GGT elevation be evaluated? *Cleve Clin J Med.* 2000;67:315-6. doi: 10.3949/ccjm.67.5.315.