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Illuminating and Instructive Clinical Case

Persistent Elevation of Alpha-fetoprotein in a Healthy Man Without Evidence of Malignancy: A Case Report and Focused Narrative Review

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Abstract

Alpha-fetoprotein (AFP) is widely used as a serum biomarker in the evaluation of hepatocellular carcinoma and nonseminomatous germ cell tumors, but persistent AFP elevation may occasionally occur without demonstrable malignancy or active liver disease. We report a 54-year-old asymptomatic man in whom routine health screening showed persistently elevated AFP values in the 200-400 ng/mL range. Liver biochemistry was normal; viral hepatitis and human immunodeficiency virus (HIV) testing were negative; AFP-L3, protein induced by vitamin K absence or antagonist II (PIVKA-II), carcinoembryonic antigen, and carbohydrate antigen 19-9 (CA 19-9) were not elevated; and targeted imaging, including abdominal ultrasonography, triple-phase contrast-enhanced computed tomography, testicular ultrasonography, and whole-body positron emission tomography/computed tomography, revealed no evidence of malignancy. Incidental simple hepatic cysts were identified, but they lacked suspicious imaging features; cyst-fluid cytology was negative, and cyst-fluid AFP was not elevated. Over 6 years of serial follow-up, AFP remained elevated. After exclusion of hepatocellular carcinoma, germ-cell tumor, active hepatic injury, and other occult malignancy, hereditary persistence of AFP or idiopathic persistent AFP elevation was considered the most plausible explanation. This case highlights the importance of confirming persistence, excluding common malignant and hepatic causes in a stepwise manner, and avoiding repeated invasive or high-burden investigations when the patient remains clinically stable.

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Introduction

Alpha-fetoprotein (AFP) is a fetal glycoprotein mainly produced by the yolk sac and fetal liver. Adult serum concentrations are usually low after postnatal repression of *AFP* gene expression. Clinically, AFP is most often interpreted in the context of hepatocellular carcinoma (HCC), germ-cell tumors, pregnancy, active hepatic inflammation or regeneration, and selected rare hereditary or metabolic disorders.[1,2] Current HCC guidance emphasizes that AFP alone is neither sufficiently sensitive nor specific for diagnosis; interpretation requires the clinical context and appropriate imaging.[3]

Persistent isolated AFP elevation in an otherwise healthy adult is uncommon and may create diagnostic uncertainty, repeated imaging, and patient anxiety. Hereditary persistence of AFP (HPAFP) is a rare benign condition, usually autosomal dominant, in which AFP remains elevated without clinical disease; sporadic or nonhereditary persistent AFP elevation has also been described.[4–8] We present a case of marked persistent AFP elevation in a healthy adult after exclusion of malignancy and active liver disease.

Case presentation

Clinical information was obtained from the patient's medical records, including medical history, serial serum AFP measurements, liver biochemistry, viral serology, additional tumor markers, imaging investigations, and hepatic cyst-fluid analysis. The diagnostic evaluation was directed primarily toward excluding hepatocellular carcinoma, germ-cell tumors, active liver disease, and other potential AFP-producing malignancies. Serial clinical, biochemical, and imaging findings from 2018 to 2024 were reviewed to characterize the longitudinal pattern of AFP elevation.

A 54-year-old man was referred after routine health screening detected a hepatic space-occupying lesion, subsequently characterized on ultrasonography as a simple hepatic cyst, and a concomitant marked elevation in serum AFP. He was asymptomatic and had no abdominal pain, weight loss, anorexia, fever, jaundice, testicular symptoms, or other constitutional symptoms. He reported no history of diabetes, hypertension, chronic liver disease, significant alcohol intake, viral hepatitis risk factors, or prior malignancy. There was no known family history of HCC or testicular cancer.

Liver function tests were within normal limits. Hepatitis B surface antigen, anti-hepatitis C virus antibody, and human immunodeficiency virus (HIV) testing were negative. Serum AFP was persistently elevated, with serial values rang-

Keywords: Alpha-fetoprotein; Hereditary persistence of alpha-fetoprotein; Hepatocellular carcinoma; Tumor marker; Case report; AFP-L3; PIVKA-II.

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Table 1. Summary of laboratory, imaging, and hepatic cyst fluid investigations

Test	Result	Reference range
Liver function tests	Within normal limits	—
Hepatitis B and C panel	Negative	Negative
HIV	Negative	Negative
AFP	258 ng/mL	<10–15 ng/mL
AFP-L3	<10%	<10%
CEA	Normal	<5 ng/mL
CA 19-9	Normal	<37 U/mL
PIVKA-II	Normal	<7.5 ng/mL

Modality	Findings
Abdominal ultrasonography	Normal liver architecture; few simple hepatic cysts; no focal hepatic lesion
Contrast-enhanced abdominal CT	A few simple hepatic cysts; no cirrhosis or lymphadenopathy
Testicular ultrasonography	Normal testes, no masses or microlithiasis
Whole-body PET/CT	No hypermetabolic lesion identified

Parameter	Result	Reference/interpretation
Volume	8.0 mL	—
Color	Pale yellow	—
Appearance	Clear	—
Clot/fibrin web	Absent	—
TLC	1 cell/mm^3	<500 cells/mm^3 (normal)
Total RBC count	100 cells/mm^3	Should be minimal
Neutrophils	100% (high)	Normally <25%
Lymphocytes, eosinophils, etc	0%	—
Mesothelial cells	0	—
Macrophages	0	—
Glucose	0.80 mg/dL	Reference not established
Total protein	0.10 g/dL	Reference not established
Chloride	126.10 mmol/L	Reference not established
AFP (cyst fluid)	0.97 ng/mL	Within normal limits
CEA (cyst fluid)	0.20 ng/mL	Reference not established
Cytology	Negative	No malignant cells seen

AFP, alpha-fetoprotein; AFP-L3, lectin-reactive alpha-fetoprotein fraction; CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; HIV, human immunodeficiency virus; PIVKA-II, protein induced by vitamin K absence or antagonist-II; CT, computed tomography; PET/CT, positron emission tomography/computed tomography; RBC, red blood cell; TLC, total leukocyte count.

ing approximately from 200 to 400 ng/mL during observation. The lectin-reactive AFP fraction (AFP-L3) was less than 10%. Protein induced by vitamin K absence or antagonist-II (PIVKA-II; des-γ-carboxy prothrombin), carcinoembryonic antigen, and carbohydrate antigen 19-9 (CA 19-9) were not elevated. Abdominal ultrasonography showed preserved liver architecture with simple hepatic cysts. Triple-phase contrast-enhanced computed tomography confirmed a few simple hepatic cysts and showed no cirrhosis, suspicious hepatic mass, arterial hyperenhancement with washout, lymphadenopathy, or metastatic disease. Testicular ultrasonography showed no mass or microlithiasis. Whole-body positron emission tomography (PET)/computed tomography (CT) showed no hypermetabolic lesion suggestive of malignancy. Brain and spine magnetic resonance imaging (MRI), performed during the earlier diagnostic work-up, showed no mass lesion. Laboratory investigations and imaging findings are summarized in Table 1.

Because the hepatic cysts were initially considered a possible confounder, cyst aspiration was performed before referral. Cyst fluid was clear and pale yellow; cytology was negative for malignant cells; cyst-fluid AFP was 0.97 ng/mL and cyst-fluid carcinoembryonic antigen was 0.20 ng/mL. These findings supported an incidental benign cyst rather than a source of AFP. The patient remained asymptomatic with stable AFP elevation before and after cyst aspiration,

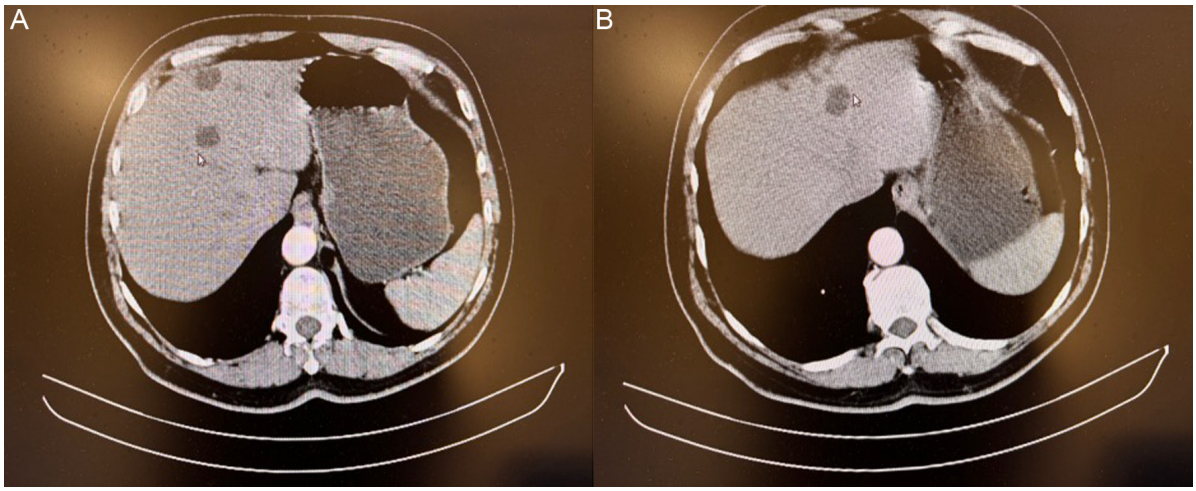


Fig. 1. Computed tomography images showing multiple well-defined, rounded, hypodense lesions of fluid attenuation within the liver parenchyma, with representative dimensions of 2.13 × 2.09 cm (A) and 1.64 × 1.5 cm (B). These lesions have imperceptibly thin walls and homogeneous fluid density, with no internal septations, solid components, calcifications, or venous-phase enhancement. The findings are consistent with benign simple hepatic cysts.

with no biochemical or imaging evidence of malignancy or liver disease. Genetic testing for *AFP* regulatory region variants and family AFP testing could not be performed because testing was unavailable and no first-degree relatives were available. The final clinical impression was probable HPAFP or idiopathic persistent AFP elevation after exclusion of malignant and inflammatory causes. Representative CT images are shown in Figure 1, and cyst-fluid findings are summarized in Table 1. The clinical timeline is presented in Table 2, and serial AFP values are shown in Figure 2.

Focused narrative review

A focused narrative review was undertaken to identify published reports of persistent AFP elevation without demonstrable malignancy or active liver disease. MEDLINE/PubMed,

Table 2. Clinical timeline

Date	Clinical event/investigation	Interpretation/action
May 5, 2018	Initial documented AFP elevation during health assessment	Marked elevation established; no serial trend yet
March 5, 2024	Abdominal ultrasonography	Avascular cystic lesions in the liver parenchyma measuring 2.13 × 2.09 cm and 1.64 × 1.54 cm
March 14, 2024	Repeat AFP	Persistent but lower than in 2018
April 17, 2024	Repeat AFP	Persistent fluctuation without a monotonic rise
April 23, 2024	Abdominal MRI	Hepatic cysts seen
May 20, 2024	Repeat AFP	Stable marked elevation
June 10, 2024	Repeat AFP	Stable marked elevation
June 23, 2024	Testicular ultrasonography: no mass or microlithiasis	Targeted germ cell tumor evaluation negative
August 29, 2024	Triple-phase liver CT	Multiple variably sized hepatic cysts in both liver lobes, the largest measuring 2 × 1.4 cm
August 30, 2024	Repeat AFP	Stable marked elevation
September 26, 2024	Whole-body PET/CT	No hypermetabolic lesion identified
October 11, 2024	Whole-body PET/CT repeated at a different center	No hypermetabolic lesion identified
October 15, 2024	Brain and spine MRI	Escalation testing negative
October 28, 2024	Repeat AFP	Lowest documented value; no progressive rise
November 20, 2024	Aspiration of simple hepatic cyst; cyst-fluid AFP 0.97 ng/mL, CEA 0.20 ng/mL, cytology negative	Cyst considered incidental; procedure retrospectively considered low yield
December 4, 2024	First serum AFP measured after cyst aspiration; latest documented AFP and clinical review	Approximately 6 years of marked but nonprogressive elevation

AFP, alpha-fetoprotein; CEA, carcinoembryonic antigen; CT, computed tomography; MRI, magnetic resonance imaging; PET/CT, positron emission tomography/computed tomography.

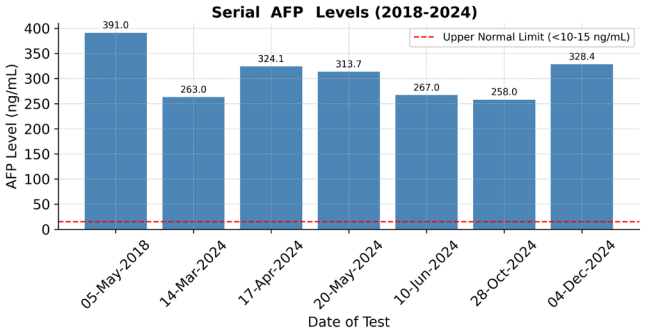


Fig. 2. Serial AFP levels at selected time points. AFP, alpha-fetoprotein.

Embase, and Google Scholar were searched from database inception through April 30, 2026. Search terms included "alpha-fetoprotein," "AFP," "persistent elevation," "healthy adult," "asymptomatic," "hereditary persistence of alpha-fetoprotein," "HPAFP," "idiopathic persistent AFP," and "without malignancy," combined using the Boolean operators AND and OR. Reference lists of relevant publications and reviews were additionally screened manually.

Eligible publications included case reports, case series, observational cohorts, and reviews describing persistent AFP elevation in the absence of an AFP-producing malignancy or active hepatic inflammation. Particular attention was given to AFP magnitude, duration of persistence, exclusion of hepatic and germ-cell malignancies, family AFP testing, and molecular analysis of *AFP* regulatory regions. Reports limited to transient AFP elevation, pregnancy-related elevation, established malignancy, or active hepatitis were excluded from the principal comparison.

A recent comprehensive literature search for HPAFP identified 25 publications describing 30 affected families, illustrating the rarity of the condition. Molecular confirmation was reported in only 9 of these 30 families, while the remainder were supported predominantly by pedigree and persistent AFP measurements.[4,6,8,10] The present search updated this evidence base through April 2026 and also included reports of sporadic or idiopathic persistent AFP elevation and clinically relevant reports illustrating diagnostic uncertainty during germ-cell tumor evaluation. Database-specific search terms, eligibility criteria, and the publications included in the comparative synthesis are provided in Supplementary Table 1. Key publications identified in the focused synthesis are summarized in Table 3.

Because the objective was a focused clinical synthesis rather than a systematic review or quantitative evidence synthesis, no meta-analysis or formal risk-of-bias assessment was performed.

Discussion

The main clinical challenge in this case was to distinguish a true tumor-marker signal from benign persistent AFP elevation. HCC and germ-cell tumors remain priority diagnoses to exclude when AFP is markedly elevated. However, this patient had normal liver biochemistry, negative viral markers, no cirrhosis or suspicious liver lesion on multiphasic imaging, normal testicular ultrasonography, normal AFP-L3 and PIVKA-II, and no PET-avid lesion. Although no single test completely excludes occult malignancy, the concordance of serial stability, negative multimodality assessment, and absence of clinical progression support a benign explanation.

Simple hepatic cysts are common benign imaging findings, and, in this case, there was no imaging complexity, mural nodule, enhancement, malignant cytology, or cyst-fluid AFP elevation. Therefore, the cysts are best interpreted as incidental rather than causative.

HPAFP is the most clinically relevant benign differential diagnosis. It has been described as an autosomal dominant trait and has been linked in some families to variants in the *AFP* promoter or enhancer regions, including hepatocyte nuclear factor binding sites.[4,6–12] Importantly, not all patients with persistent AFP elevation have an identifiable mutation in routinely studied regulatory regions, and nonhereditary stable AFP elevation in healthy adults has also been reported.[4,5] In the series by Jeon *et al.*, four healthy adults had persistent AFP elevation with negative malignancy workup; one family showed a hereditary pattern, but mutations were not found in the studied *AFP* promoter, enhancer, or silencer regions.[4] Similar benign familial persistence of AFP has also been reported in both adults and children.[13,14] In a larger observational cohort, Jang *et al.* reported stable AFP values and no development of cancer or liver disease during follow-up among asymptomatic adults with elevated AFP, suggesting that longitudinal follow-up may be reasonable after adequate initial exclusion of disease.[5]

Table 3. Key publications on persistent AFP elevation without evident malignancy or active liver disease

Publication	Design/population	AFP pattern	Diagnosis	Key relevance to present case
Schefer *et al.*[13]	Case report and literature review; healthy adult/familial context	Persistent low-to-moderate elevation	No malignancy identified	Early clinical description of benign persistent AFP elevation
Houwert *et al.*[6]	Literature review of HPAFP	Variable persistent elevation	Synthesized genetic and clinical features	Frames HPAFP as benign and often autosomal dominant
Jeon *et al.*[4]	Four healthy adults with persistent AFP elevation	Persistent AFP elevation; one hereditary pattern	*AFP* regulatory regions studied; no malignant disease	Shows persistent AFP elevation can remain unexplained even after regulatory-region testing
Jang *et al.*[5]	Retrospective cohort of 137 asymptomatic adults	Mostly mild, stable elevation	No cancer or liver disease during median follow-up	Supports longitudinal follow-up after adequate negative evaluation
Saracoglu *et al.*[8]	Case report of HPAFP	High persistent AFP	Imaging workup negative for HCC/germ cell tumor	Highlights avoidance of unnecessary procedures when HPAFP is likely

AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; HPAFP, hereditary persistence of alpha-fetoprotein.

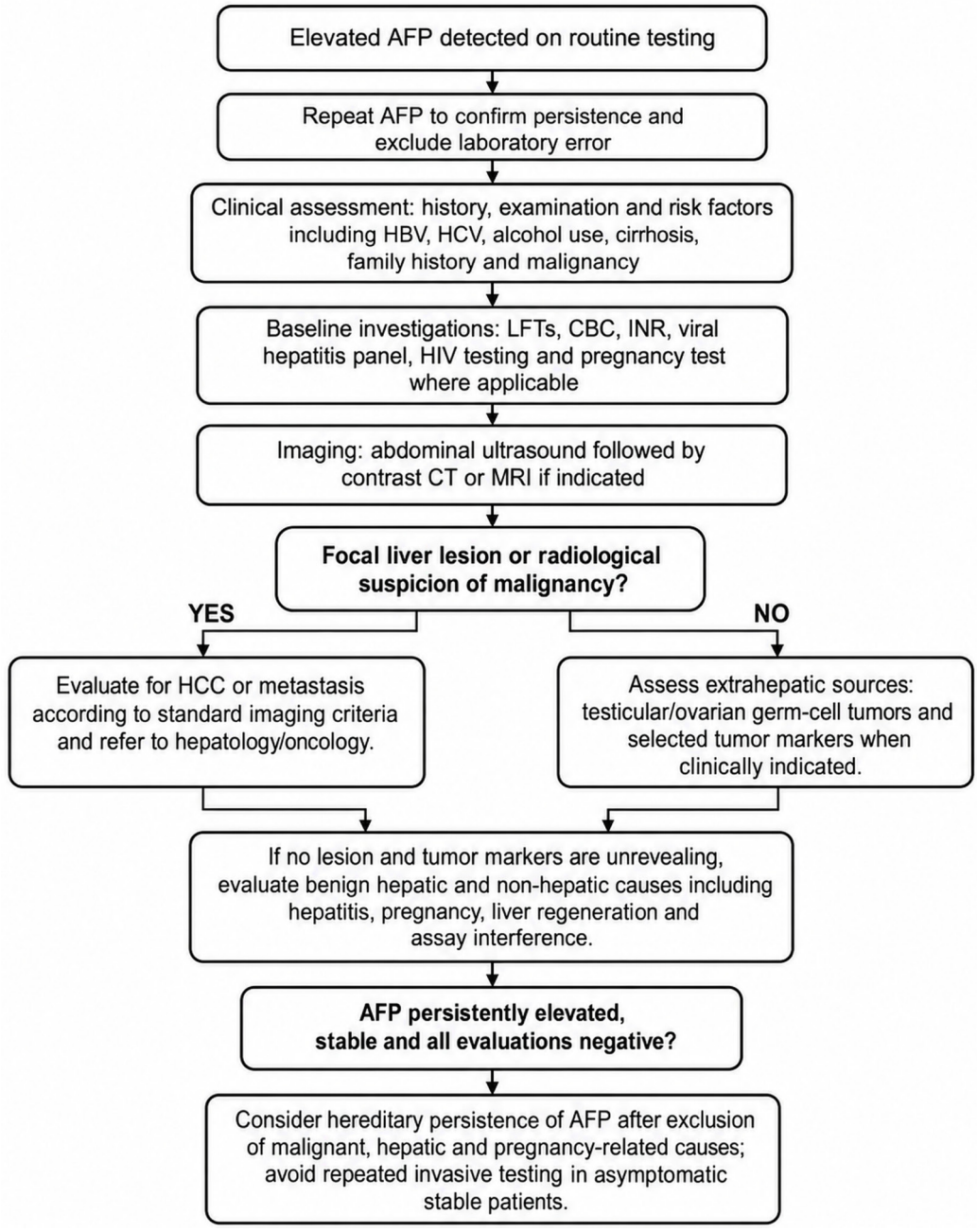


Fig. 3. Diagnostic algorithm for evaluating elevated AFP levels. This diagnostic algorithm represents a proposed clinical approach based on the available literature and expert interpretation and should not be considered a standardized or guideline-endorsed pathway. AFP, alpha-fetoprotein; CBC, complete blood count; CT, computed tomography; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INR, international normalized ratio; LFTs, liver function tests; MRI, magnetic resonance imaging.

The degree of AFP elevation in the present patient was higher than that in many asymptomatic adult cohorts but remains compatible with reported HPAFP cases. Saracoglu *et al.* described very high AFP concentrations in HPAFP and emphasized that the diagnosis should be considered when imaging evaluation for HCC and germ-cell tumor is negative.[8] Such cases are important because failure to recognize benign persistent AFP elevation may lead to repeated radiation exposure, invasive biopsies, unnecessary surgery, chemotherapy, or prolonged psychological distress.[7,8]

A practical stepwise approach may be useful. First, AFP should be repeated to confirm persistence and exclude analytical or transient causes. Second, history, examination, liver biochemistry, viral hepatitis testing, and targeted tumor-marker assessment should be performed. Third, evaluation should focus on the most probable AFP-producing malignancies, especially HCC and germ-cell tumors, using risk-appropriate imaging. Escalation to whole-body imaging may be considered when diagnostic uncertainty persists, AFP is markedly elevated or rising, symptoms or

abnormal examination findings are present, or results are discordant. When AFP is stable, AFP-L3 and PIVKA-II are not suggestive of HCC, imaging remains negative, and the patient is clinically well, HPAFP or idiopathic persistent AFP elevation may be considered, and long-term periodic surveillance may be more appropriate than repeated invasive testing. Common causes of elevated AFP are summarized in Supplementary Table 2, and a proposed diagnostic algorithm is shown in Figure 3.

The patient's imaging revealed multiple simple hepatic cysts, which are benign developmental lesions lined by cuboidal epithelium and filled with serous fluid. However, distinguishing among hepatic cyst types can be important, especially when AFP is elevated. Selected differential diagnoses for hepatic cysts are summarized in Supplementary Table 3.

Conclusions

Persistent AFP elevation in an otherwise healthy adult may rarely occur without malignancy or active liver disease. In this patient, the most plausible explanation after extensive negative evaluation was probable HPAFP or idiopathic persistent AFP elevation. Recognizing this possibility may help avoid unnecessary procedures while maintaining prudent longitudinal follow-up. Annual clinical review with AFP trend assessment and repeat imaging only if AFP rises substantially, symptoms develop, or liver tests become abnormal may be a reasonable individualized strategy.

Supporting information

Supplementary material for this article is available at https://doi.org/10.14218/JCTH.2026.00397.

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None to declare.

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

JP and VG contributed substantially to the conception, drafting, critical revision, and final approval of the manuscript. All authors agree to be accountable for the accuracy and integrity of the work.

Ethical statement

This manuscript describes a single anonymized clinical case report. Because no experimental intervention was performed and the report is based on routine clinical evaluation and follow-up, formal institutional ethics committee approval was not required for an anonymized case report. The authors confirm that the study was conducted in accordance with the ethical principles of the Declaration of Helsinki (as revised in 2024). Written informed consent was obtained from the patient for publication of this case report and its accompanying clinical details. All identifying information has been removed or anonymized to protect patient confidentiality.

Data sharing statement

All relevant clinical information supporting the conclusions of this case report is included within the article. Additional patient-level data are not publicly available in order to preserve patient confidentiality.

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