VIA MEDICA

CASE REPORT

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Long-term survival and remarkably durable treatment response in a case of inoperable fibrolamellar carcinoma of the liver — a comprehensive analysis of an 8-year chemotherapeutic journey

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ABSTRACT

Hepatocellular carcinoma is the most common primary malignancy of the liver. The fibrolamellar subtype of hepatocellular carcinoma (FLHCC) is a rare liver malignancy constituting ~0.5% of liver cancers. FLHCC can be distinguished by its lack of specific risk factors and unique molecular profile. This case study aims to present an 8-year medical history of a 32-year-old patient with unresectable FLHCC and his outstanding response to systemic therapy. The patient was referred to the liver surgery center due to suspicion of liver cancer based on radiological findings. The tumor turned out to be inoperable and a surgical biopsy was performed. Histopathology confirmed fibrolamellar carcinoma. Six transarterial chemoembolization procedures with doxorubicin-eluting microspheres were performed, which resulted in disease control. Subsequently, from April 2013 to December 2021, the patient received 11 lines of systemic treatment. Sorafenib resulted in disease control lasting 28 months. Cisplatin did not trigger any response. Systemic doxorubicin provided 6 months of stabilization. The patient did not respond to subsequent lines of capecitabin plus temozolomide, vinorelbine, cyclophosphamide, or 5-fluorouracil plus interferon α2b. The reintroduction of sorafenib resulted in 7 months of disease stabilization, and subsequent regorafenib, used as the 9th line of treatment, led to an objective response lasting 26 months. Later, two more lines of treatment consisting of cabozantinib and paclitaxel were administered and they were not effective. The patient died in December 2021 due to liver failure and hemorrhage.

FLHCC treatment needs an individual approach. One can hope that in the future, more data on FLHCC management will be available.

Keywords: fibrolamellar hepatocellular carcinoma, FLHCC, transarterial chemoemblization, chemotherapy, sorafenib, regorafenib, *DNAJB1-PRKACA* fusion gene, rechallenge

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Introduction

Malignancies of the liver are still one of the leading causes of cancer mortality worldwide [1]. According to 2020 cancer statistics, 905 677 cases of liver malignancies were reported, and more than 830 180 deaths from the disease [1]. These numbers represent 4.7% of all cancer cases and 8.3% of all cancer deaths, respectively [1]. According to experts, the majority (75–90%) of primary liver cancer cases are hepatocellular carcinoma although

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precise data on the epidemiology of different liver cancer histologies are scarce [2, 3].

The fibrolamellar subtype of hepatocellular carcinoma (FLHCC) is a unique hepatic malignancy described by Edmondson in 1956 and confirmed by Craig et al. in 1980 [4, 5]. Previously, it was stated that FLHCC is a subtype of hepatocellular carcinoma (HCC), which is why it is called fibrolamellar HCC. However, this hepatic malignancy differs significantly from classic HCC as it is not associated with typical risk factors for HCC; it also has a distinct molecular profile. Therefore, some authors now consider it a distinct type of liver cancer [6–8], even though the last WHO Classification of Tumors (5th Edition, 2019) still classifies this malignancy in the HCC cancer group. The percentage of FLHCC cases among all HCC cases is around 0.5% [9]. Unlike HCC, the fibrolamellar subtype (carcinoma) usually occurs in younger individuals without underlying liver conditions [4–6]. Recent data show that most patients are under 40 years of age with a mean age of 33 (± 20) at the time of diagnosis [10]. Another peak in incidence is observed in the seventh decade of life [11].

The pathogenesis of the disease is not yet fully understood, as specific carcinogens and risk factors have not been identified yet. However, a specific large deletion resulting in a fusion of *DNAJB1-PRKACA* genes has been described as a crucial factor in pathogenesis [12]. α-fetoprotein level in FLHCC is usually not elevated and does not correlate with disease stage [10]. Previously, fibrolamellar carcinoma was believed to have a better prognosis than traditional HCC, but the results of the latest studies are ambiguous, and this subject needs further prospective analysis [13, 14].

The rarity of this malignancy results in limited data on its management. Due to this fact, FLHCC treatment follows HCC protocols, as no specific guidelines exist. Complete or partial hepatectomy and liver transplantation are the first lines of treatment in early disease stages. Several studies described locoregional therapies, such as transarterial chemoembolization (TACE) and transarterial radioembolization (TARE), as viable options in disease treatment, but these recommendations are based on low-grade evidence [15–17]. Liver transplant ought to be considered in patients with unresectable tumors and without extrahepatic disease [18]. Systemic treatment with HCC regimens is considered a viable option for advanced disease [18]. There are few data on the routine use of radiation therapy in FLHCC. There are reports on the effectiveness of radiotherapy in the management of FLHCC metastases [19]. A study focusing on the inhibition of the DNAJB1-PRKACA fusion protein in FLHCC provided some hopeful results that may be used to design future therapies [20].

Fibrolamellar carcinoma requires a substantial amount of research as this hepatic malignancy is still poorly understood. Every case of the disease brings to light new information that changes the perception of this cancer. This case report aims to present an 8-year medical history of a male patient with inoperable metastatic fibrolamellar carcinoma and his response to different regimens of systemic therapy.

Case presentation

A 32-year-old male presented with a strong suspicion of hepatocellular carcinoma, based on radiological findings. The core needle biopsy of the lesion showed a tumor built of cells with abundant eosinophilic cytoplasm and with large eosinophilic nuclei, lying in groups. A yellow substance, bile, was visible in some neoplastic cells. Abundant thick collagen bands that divide tumor cells into irregular areas were visible throughout tumor tissue. The image corresponded with fibrolamellar hepatocellular cancer (Fig. 1).

The tumor turned out to be inoperable during exploratory surgery; therefore, only a surgical biopsy and a cholecystectomy were performed. The histopathological diagnosis was again the fibrolamellar subtype of hepatocellular carcinoma. Gallbladder showed no signs of cancer spread.

Postoperative magnetic resonance imaging (MRI) showed a tuberous mass (110 × 91 × 100 mm located in the right and left lobes of the liver, mostly in segments IV, V, and VIII (Fig. 2). The mass was heterogeneous with arterial enhancing, necrosis areas, and calcifications. In addition, a tubular lesion infiltrating the right branch of the portal vein was identified. The lesion growing in the vein was strongly enhanced in the arterial phase of the scan. Intrahepatic bile ducts were slightly distended, but the liver did not show signs of intrahepatic cholestasis. Imaging of the chest revealed singular nodules of ambiguous morphology, up to 6 mm in diameter, located in both lungs.

In April 2013, the patient was redirected to the liver surgery reference center for another attempt at tumor resection. Unfortunately, during the procedure, the tumor was once again determined as inoperable. Transarterial chemoembolization with doxorubicin-eluting microspheres was administered instead. A total of six procedures were performed with good tolerance and effect.

Due to definite unresectability, sorafenib was started at a typical continuous dose of 800 mg per day. Owing to poor hematological tolerance, the dosage of sorafenib was modified — the patient received a reduced dose of the drug (400 mg) because he suffered from severe leukocytopenia. The dose was repeatedly increased to 800 mg after an improvement in leukocyte count. The patient was treated for twenty months until the

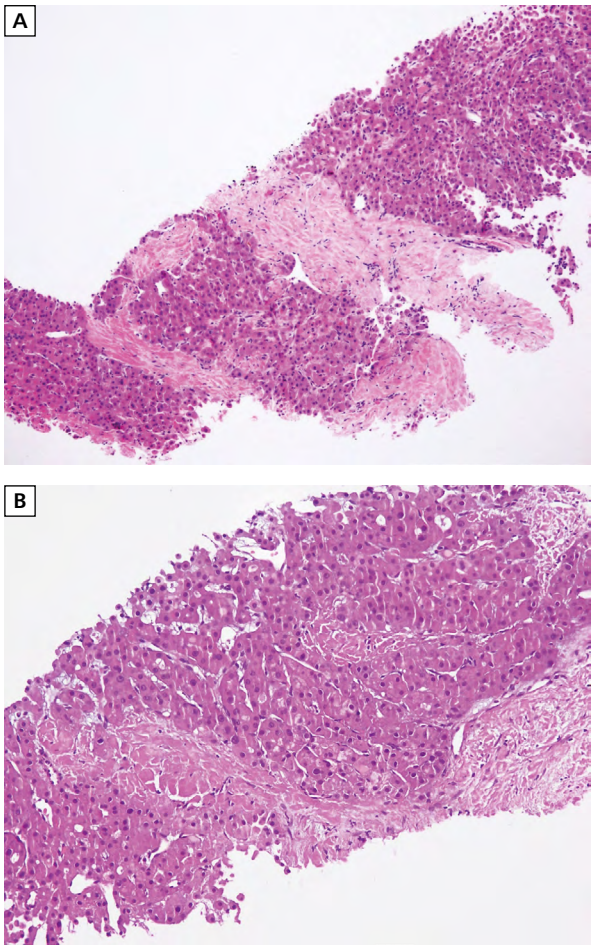

Figure 1. Histopathological view of the tumour. Neoplastic hepatocytes divided by fibrous bands of tissue. Sample from core needle biopsy; **A.** H&E, ×20; **B.** H&E, ×40

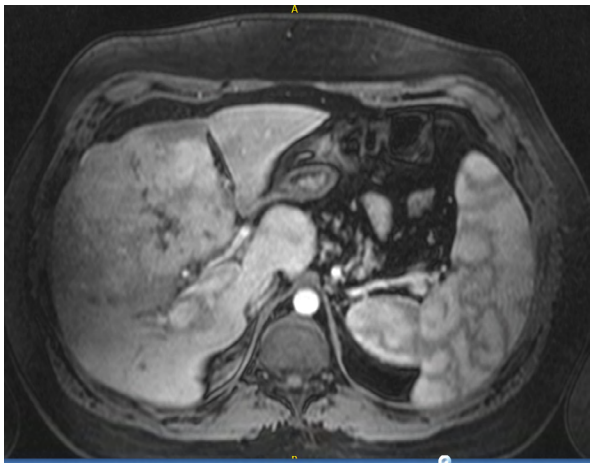

Figure 2. Magnetic resonance imagining (MRI), T1 sequence with fat saturation, without contrast, axial view. Tuberous mass visualized in right and left lobes of the liver

computed tomography (CT) scan performed in August 2015 revealed disease progression in the liver and mesenteric lymph nodes. At this point, the patient exhausted the standard treatment options available at the time. No clinical trials were found where he could be enrolled (search for trials was repeated before every subsequent line of therapy).

The next line of chemotherapy consisted of cisplatin 25 mg/m^2 and gemcitabine 1000 mg/m^2 administered on days 1 and 8, every 3 weeks. It started in October 2015. During the course of the treatment patient once again presented hematological adverse effects such as anemia and neutropenia, which were managed routinely. A CT scan 3 months into chemotherapy showed progression in the liver and lungs and a good response in the mesenteric lymph nodes.

Later, the patient was receiving 60 mg/m^2 of doxorubicin every 3 weeks, beginning in January 2016. Due to the risk of febrile neutropenia, prophylactic treatment with filgrastim was administered. A CT scan 3 months into treatment showed stabilization of the disease. After 6 cycles, doxorubicin was discontinued. Progression in the lungs and liver, including new lesions, was detected on the next CT.

Another line of systemic therapy with capecitabine 1200 mg/m^2 (days 1–14), and temozolomide 150 mg/m^2 (days 10–14) was started in October 2016. Three months later, progression in the lungs and liver was evaluated by CT.

The patient was again qualified for another line of metronomic vinorelbine treatment at a fixed dose of 40 mg administered 3 times a week. After three cycles of vinorelbine, progression was discovered on imaging. The patient was placed on metronomic therapy with cyclophosphamide 50 mg daily, which was also discontinued due to persistent progression.

Another line of treatment administered was 200 mg/m^2/day of fluorouracil in a continuous 21-day infusion, combined with subcutaneous injections of 4 MIU/m^2 of interferon α-2b administered three times a week. The whole regimen was repeated every 4 weeks. The choice of this treatment was based on the results of a phase II clinical trial that showed very promising response rates [21]. In this case, this line of treatment turned out to be ineffective as progression was still present on imaging.

After a series of ineffective treatment lines, the patient received rechallenge with sorafenib in March 2018. A follow-up CT done 3 months into therapy showed a minor response, thanks to which the disease was qualified as stable according to the RECIST criteria. Another CT 3 months later showed slow progression. Due to this fact, in October 2018, the therapy was switched to regorafenib 160 mg/day for 3 weeks repeated

every 4 weeks. Again, hematological adverse effects were observed during treatment, which was interrupted accordingly due to severe toxicity. Furthermore, CT revealed signs of partial response in the liver and lungs since the liver lesion previously identified on CT was not present and nodules in the lungs shrank substantially (3 mm *vs*. 6.5 mm and 4.5 mm *vs*. 10 mm). The response to regorafenib lasted more than two years.

Although the previous imaging study indicated partial remission, the next one indicated low-grade progression in the liver and lungs. The patient and the physician decided to continue with regorafenib therapy due to the lack of better options. Further progression, especially in the liver hilum, caused the introduction of another line of treatment with cabozatinib 40 mg/day in January 2021.

After two cycles of cabozatinib, the patient developed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia and was hospitalized. Treatment with cabozatinib was entirely stopped during the infection.

As another progression was discovered in the images, the treatment was changed to paclitaxel in monotherapy, 80 mg/m^2 weekly. After one cycle, the patient was admitted to the emergency room (ER) with febrile neutropenia. He was hospitalized, treated with antibiotics, filgrastim, and hepatoprotective drugs, and discharged after improvement. After this episode, it was deemed unfeasible to continue the systemic treatment.

In the next weeks, the patient developed severe anemia and leukopenia, prominent progression was evaluated on imaging. Additionally, signs of progressing liver failure occurred. The patient also presented intermittent signs of bleeding from the upper gastrointestinal tract. This set of symptoms frequently reappeared, which led the patient to visit the ER several times in three months. On each occasion, symptomatic treatment would briefly improve the patient's condition. However, his general condition deteriorated rapidly, symptoms exacerbated, and primary disease progression appeared to become more and more pronounced. In December 2021, the patient died from a hemorrhage in the gastrointestinal tract and severe impairment of liver function. The patient survived for 106 months since the diagnosis of inoperable FLHCC (Fig. 3).

Discussion

The concept of FLHCC as a separate entity with unique pathogenesis has been established in recent years. The molecular profile of this malignancy shows that this cancer cannot be considered a subtype of HCC [7]. The disparity between those malignancies calls for development of treatments specific to FLHCC. The rarity of FLHCC has resulted in lack of specific treatment guidelines, which is especially important since most HCC trials exclude FLHCC patients. In recent years, several clinical trials focused on FLHCC therapy have published their results and some are still ongoing [22]. Table 1 [21, 23–34] presents current clinical trials that focus on FLHCC treatment.

Patt et al. [21] investigated the use of 5-FU combined with recombinant interferon α-2b in HCC. They reported the remarkable efficacy of this treatment in the FLHCC population [21]. Nivolumab in conjunction with 5-FU and interferon α-2b generated several objective responses (OR) and disease stabilization in a similar study [28]. Additionally, the results of a phase II/III trial investigating cisplatin and combination chemotherapy are currently pending in the United States and Australia [31].

Aromatase expression and activation of the mTOR pathway are also observed in FLHCC [35]. Therefore, a study investigating treatment with estrogen deprivation therapy (leuprolide and letrozole) and everolimus was conducted in patients with unresectable FLHCC, regardless of previous treatment lines. However, the efficacy of this therapy was underwhelming, with 0% of objective responses, 35% of patients having stable disease at first assessment, 0% of patients reaching the primary endpoint of 6 months of progression progression-free survival (PFS), median PFS of 2.7 months, and median overall survival (OS) of 12.4 months [23].

The use of next-generation sequencing revealed that FLHCC has a stable genome with a low tumor mutational burden (TMB) [8]. Additionally, the presence of the *DNAJB1-PRKACA* fusion gene in tumor cells is widely observed in FLHCC [12, 36]. The fusion is caused by ~400 kb somatic deletion on chromosome 19 [12]. *DNAJB1-PRKACA* encodes the catalytic domain of protein kinase A and causes the overexpression of Aurora kinase A (AURKA). The abnormal activity of PKA and AURKA presumably drives FLHCC tumorigenesis. Therefore, therapies targeting *DNAJB1-PRKACA* seem a promising treatment option. A study conducted to assess the efficacy of the anti-AURKA drug ENMD-2076 in FLHCC was performed [24]. The drug demonstrated moderate efficacy with one patient reaching an objective response, 57% of patients with stable disease (SD), median PFS of 3.9 months, and median OS of 19 months. The authors concluded that the treatment strategy is not worthy of further research [24]. Currently, another study investigating the use of the DNAJB1-PRKACA vaccine with the addition of nivolumab and ipilimumab is underway. The goal is to assess the safety of treatment and the response of T cells to tumor cells [26]. Treatment targeting this oncogenic pathway in FLHCC needs further research to demonstrate its value.

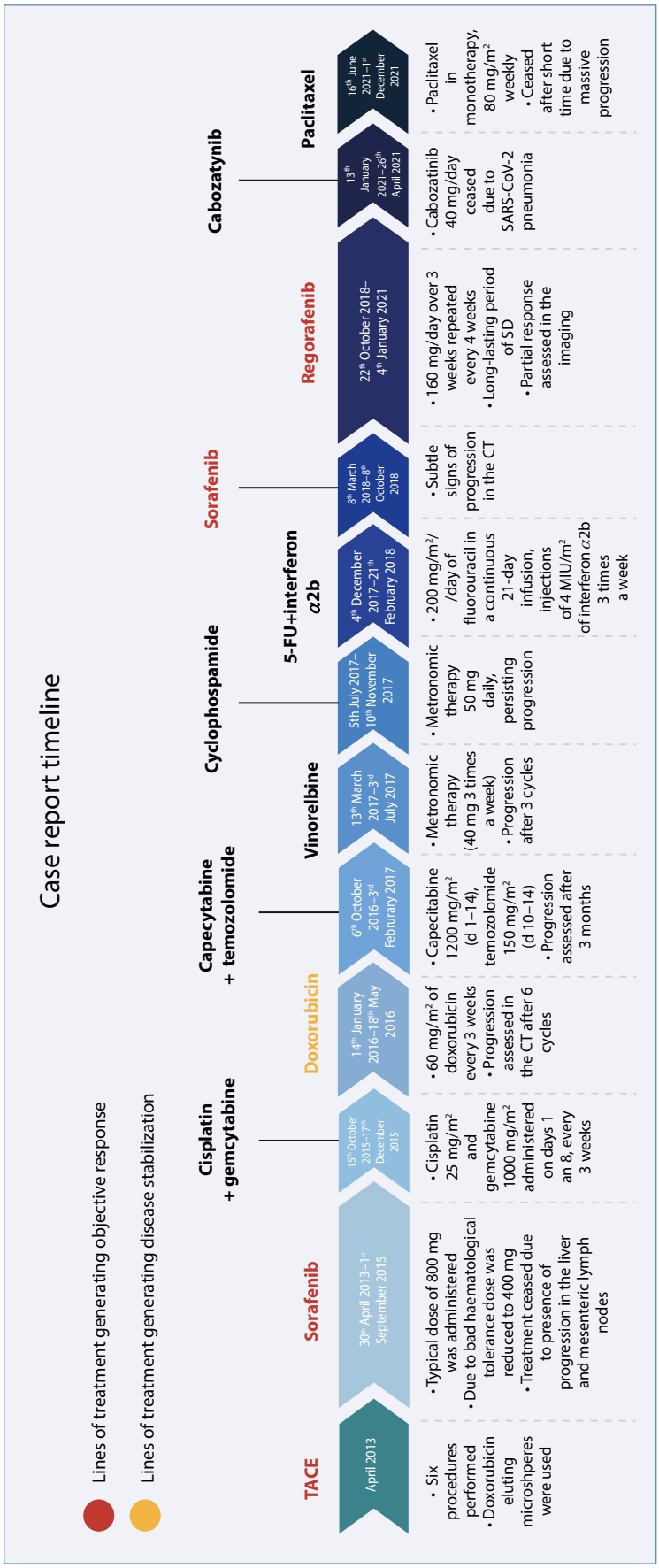

Figure 3. Fibrolamellar hepatocellular cancer (FLHCC) case report timeline; CT — computed tomography; SD — stable disease

Table 1. Overview of clinical trials focusing on fibrolamellar subtype of hepatocellular carcinoma (FLHCC) treatment

Treatment regimen	Type of study	Status	Citation
5-FU + IFN-α-2B	Phase II trial	Completed	Patt et al. [21]
Everolimus Leuprolide + letrozole Leuprolide + everolimus	Phase II trial	Completed	El Dika et al. [23]
ENMD-2076	Phase II trial	Completed	Abou Alfa et al. [24]
Fusion-VAC-XS15 + atezolizumab	Phase I trial	Recruiting	Walz et al. [25]
DNAJB1-PRKACA fusion kinase peptide vaccine + + nivolumab + ipilimumab	Phase I trial	Recruiting	Yarchoan et al. [26]
KAT-101	Phase I/II trial	Recruiting	[27]
5-FU + IFN-α-2B + nivolumab	Phase II/III trial	Recruiting	Gottlieb et al. [28]
Pembrolizumab	Phase II trial	Recruiting	O'Neill et al. [29]
Atezolizumab + bevacizumab + cyclophosphamide + pharmacokinetic-guided sorafenib	Phase I/II trial	Recruiting	Gartrell et al. [30]
Cisplatin ± other agents	Phase II/III trial	Recruiting	Tiao et al. [31]
Sapanisertib + Ziv-Aflibercept	Phase I trial	Active/not Recruiting	Naing et al. [32]
Sunitinib	Phase II trial	Terminated	Faivre et al. [33]
DRP-104 + durvalumab	Phase I/II trial	Not yet recruiting	Baretti et al. [34]

5-FU — 5-fluorouracil

In clinical practice, FLHCC treatment mimics regimens used in HCC and hepatoblastoma. Due to dissimilarities between these cancers, therapies have variable efficacy in FLHCC [37].

During treatment, our patient received 11 lines of therapy in total (Fig. 3). It is worth noticing that during these 8 years, the patient was in overall good health, with ECOG performance status not exceeding 1 (apart from the last year of life). The patient gave his informed consent to each line of treatment and was eager to cooperate. The response to the different lines of treatment was diverse, and predominantly disease stabilization was achieved. The overall response to all lines of treatment combined with the general low dynamics of the disease was sufficient to provide him with a good quality of life. The longest response was obtained with TACE, sorafenib, and regorafenib, with the last therapy also generating a partial response. Rechallenge with sorafenib was justified by the lack of better treatment options and the hope that the tumor lost its acquired resistance to sorafenib, as there is preclinical evidence that potential resistance mechanisms can be potentially reversible [38]. Apart from another single case report [39], we are not aware of prior studies investigating re-challenge therapy with sorafenib in this setting. Shortly afterward, the drug was exchanged for regorafenib, which had not been administered earlier due to its unavailability in the European Union before 2017 [40]. Regorafenib, despite its similarity to sorafenib, was shown to be more effective in consecutive HCC treatment lines [41, 42].

The patient's response to the rechallenge of multikinase inhibitors was definitely surprising. It is hard to say which factor played its key role in providing this long-lasting partial response. Tumor resistance mechanisms to multikinase inhibitors come from genetic, epigenetic, and metabolic changes in tumor cells [43]. Furthermore, the epithelial-mesenchymal transition (EMT) and the presence of cancer stem cells (CSCs) also play a key role in predicting response in sorafenib treatment [43]. Attempts have been made to overcome resistance to sorafenib in HCC with a combination of sorafenib and other anticancer regimens. These have provided diverse results and have not resulted in changes in clinical practice. Multikinase inhibitors with additional mechanisms of action, such as regorafenib and cabozantinib, have been developed and are considered the standard option in HCC patients pretreated with sorafenib, but they have not been adequately researched in FLHCC [43].

Recent studies report good efficacy of immunotherapy in HCC treatment [44, 45]. Today, immunotherapy is the standard of care in the first line of treatment for unresectable HCC [46]. Those regimens were not tested in the FLHCC patient population. The patient described in this study did not receive this innovative treatment due to its unavailability at the time.

Fibrolamellar subtype of hepatocellular carcinoma is a rare and exceptional type of primary liver cancer that is often overlooked. All its traits, such as the lack of specific risk factors and the unique molecular profile, underline its distinctiveness from HCC. Therefore, it

is vital to recognize FLHCC as a unique type of liver malignancy. Accordingly, there is an urgent need to develop individual treatment regimens for FLHCC. Due to the rarity of FLHCC, data on the subject are limited.

We hope that more FLHCC-related research will be done in the future which will lead to the development of guidelines helping in clinical practice.

Article Information and Declarations

Ethics

Article have been conducted according to the principles stated in the Declaration of Helsinki.
All authors have read and agreed to the published version of the manuscript.

Author contributions

B.T.W.: formal analysis, investigation, resources, data curation, writing — original draft preparation; M.U.-B.: formal analysis, investigation, resources, writing — original draft preparation; P.M.P.: conceptualization and patient selection, methodology, investigation, resources, data curation, writing — original draft preparation.
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Conflicts of interest

B.T.W. and M.U.B.: declare no conflicts of interest.
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Supplementary material

None.

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