LETTERS TO THE EDITOR

Systemic therapy with lenvatinib in advanced hepatocellular carcinoma: what to do in the case of a complete radiologic response?

To the Editor,

We read with great interest your recent paper by Cosma et al [1]. The study evaluated the efficiency and tolerability of lenvatinib in patients with advanced hepatocellular carcinoma (HCC), including those with liver cirrhosis and impaired liver function, in a real-world setting. Thus, lenvatinib is a useful treatment in daily clinical practice, even in patients with mild impaired liver function, producing an effective response and improving overall survival (OS) and progression-free survival (PFS). In a dynamic approach, our work aims to support the role of lenvatinib as an effective treatment for patients with advanced HCC, showing its applicability in the concepts of therapeutic hierarchy and treatment stage migration, even as a bridging neoadjuvant therapy to liver transplantation.

We observed the efficacy of this treatment in a male patient, 59-year-old, with an increasing HCC lesion of 56 mm in the caudate process and peripheral satellite lesions detected by computed tomography (CT) (Fig. 1a), left portal vein tumour thrombosis (PVTT), VP3 according to the Liver Cancer Study Group of Japan (Fig. 1b) and alpha-fetoprotein (aFP) = 3415 ng/ml. Following a multidisciplinary discussion, the patient started systemic therapy with lenvatinib in April 2020 and presented six months (Fig. 1c) and a year (Fig. 1d) later, in May 2021, no active tumour or PVTT on the CT scan and persistent biological complete tumour response (aFP of 3.9

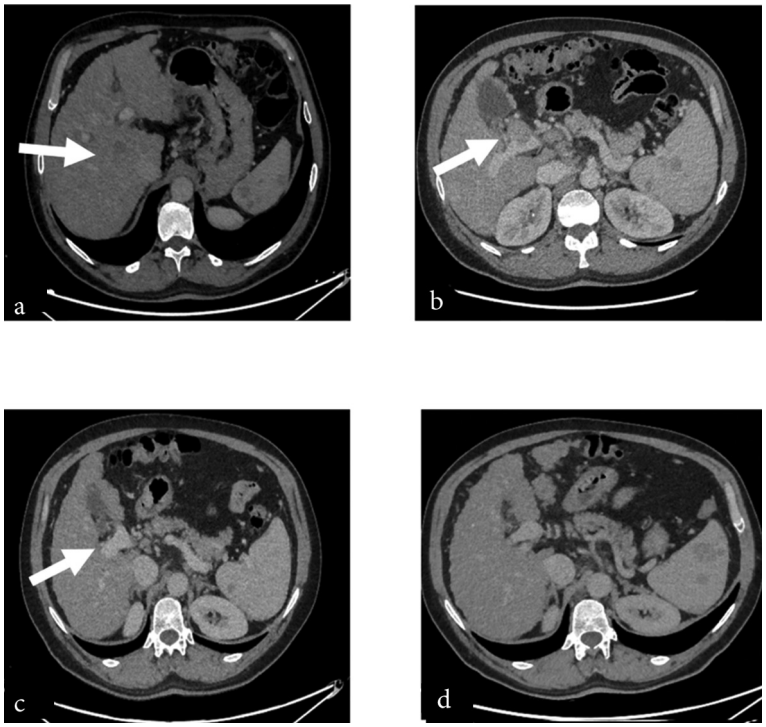

Fig. 1. Computed tomography scans: a) hepatocellular carcinoma in the caudate process and peripheral satellite lesions; b) left portal vein tumour thrombosis; c) no active tumor or left portal vein tumour thrombosis six months later; d) no active tumor or left portal vein tumour thrombosis one year later.

ng/ml). Therefore, in October 2022, the patient was evaluated for possible liver transplantation.

A few years ago, the standard treatment of intermediate/advanced-stage HCC patients included exclusively non-curative options. The recent advancement in target therapies and biological agents has promoted the concepts of treatment strategy migration and therapeutic hierarchy [2]. In fact, despite the initial burden of the disease, patients with favourable responses to locoregional and systemic therapies can be successfully submitted to surgical procedures with curative intents, with significantly longer 3- and 5-year OS rates.

The efficacy of lenvatinib has been demonstrated in recent randomised clinical trials (RCTs) comparing lenvatinib with sorafenib [1, 3]. In addition, a few case reports have shown remarkable long-lasting responses in selected initially unresectable HCC. At present, it is still debatable whether patients with initially unresectable HCC and PVTT presenting a significant tumour regression following locoregional and systemic therapies should be considered for liver transplantation. Even if solid recommendations are not yet available, recent case reports [4] have documented the safety and favourable oncological outcomes of liver transplantation for selected HCC patients with PVTT.

Therefore, the question should be how to select patients likely to present sustained tumour response. As the response to a single treatment could be heterogenous [5], several diagnostic and prognostic tools, such as the analysis of specific tumour mutations or circulating biomarkers, may improve our comprehension of tumour response rate, facilitating the implementation of personalised medicine [5].

Whereupon surgical resection or liver transplantation with curative intent remains a possibility, even for initially unresectable HCC. Future research should focus on identifying biomarkers able to predict tumour response to specific treatments, promoting more precise and personalised treatments.

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Bezafibrate in severe liver toxicity due to ibrutinib

To the Editor,

A 70-years-old, presented at our clinic with 4-weeks history of fatigue, jaundice, and pruritus. Five years ago, he had undergone an autologous hematopoietic stem cell transplantation for the treatment of mantle cell lymphoma (MCL) which recurred 4 months ago with new lymph nodes and spleen lesions on the PET-CT scan and biopsy. Thus, he started treatment with Ibrutinib (Imbruvica) 560 mg/day with good clinical response. His past medical history included also hypothyroidism treated with Euthyrox 50 mcg/day, former smoking, and coronavirus disease 2019 (COVID-19) pneumonia two months ago treated in our hospital with Tocilizumab and steroids.

On examination, marked jaundice and mildly enlarged spleen on palpation were noted. No liver enlargement, encephalopathy and other signs of chronic liver disease were present. Blood analyses demonstrated elevated hepatocellular liver enzymes up to 2-3 times normal levels, alkaline phosphatase 250 U/L (normal ranges 30-120 U/L), and total bilirubin 31 mg/dL (normal range 0.2-1.2 mg/dL), direct bilirubin 24 mg/dL (normal ranges 0-0.5mg/dL), albumin 3.1 g/dL (normal ranges 3.2-4.6 g/dL), creatinine 1.46 mg/dL (normal ranges 0.7-1.3 mg/dL), INR 1.35, hemoglobin levels of 10 g/dL (normal ranges 13-17 g/dL), platelets 129,000 (normal ranges (130,000-400,000). Virologic and immunologic tests were negative, IgG4 level was in normal range. Liver ultrasound, abdominal computed tomography and magnetic resonance cholangiopancreatography revealed no abnormalities. Liver biopsy demonstrated portal and lobular inflammation, necrosis areas with macrophages infiltrating lobules, and portal and perisinusoidal fibrosis. Liver biopsy findings raised the suspicion of a drug induced liver injury (DILI); hence, Ibrutinib was stopped.

The patient was initiated treatment with ursodeoxycholic acid (UDCA) 900 mg/day with no response. Later cholestyramine 12 g/day was added without improvement. Later on, Bezafibrate 400 mg/day was added with rapid clinical and laboratory improvement.

Ibrutinib is an orally available, potent irreversible inhibitor of Bruton's tyrosine kinase, a key kinase important for signal

transduction in the B-cell receptor pathway. Inhibition of this pathway prevents B cell activation, differentiation and proliferation. Ibrutinib has been approved by FDA for the treatment of MCL in 2013, for chronic lymphocytic leukemia in 2014, for Waldenstrom's macroglobulinemia in 2015 and for marginal zone lymphoma and chronic graft-versus-host disease in 2017 [1].

Ibrutinib is generally a well tolerated drug with rapid and durable response but has some adverse events. The most common adverse effects are diarrhea, upper respiratory tract infection, bleeding, fatigue and cardiac side effects. Prior to FDA approval in 2015, there was no evidence of hepatotoxicity caused by ibrutinib. However, with widespread use of Ibrutinib since 2015, multiple rare cases of severe hepatic injury associated with Ibrutinib treatment were reported [2]. In these cases, the latency to onset of liver injury varied from several weeks to 9 months and the pattern of injury was hepatocellular with early onset of hepatic failure. In all previously reported cases liver function tests improved with drug cessation, and most cases fully recovered.

Bezafibrate, showed in previous studies a biochemical and clinical response in patients with primary biliary cholangitis who had had an inadequate response to UDCA alone (3). In addition, some reports showed improvement of laboratory parameters and pruritus in patients with primary sclerosing cholangitis. Indeed, Bezafibrate is even considered recently as a preferred treatment for patients with pruritus even for dermatologic etiologies [4, 5].

We presented a rare case of ibrutinib-induced severe liver injury that did not improve with drug cessation alone. We have also shown the possible role of bezafibrate as a treatment of DILI with cholestatic features. According to our knowledge, this is the first report that describes the effectiveness of bezafibrate in such patients.

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A novel controllable cannula with a short flexible tip for reintervention after stent-by-stent placement in malignant hilar biliary obstruction

To the Editor,

Bilateral placement of a self-expandable metal stent (SEMS) is generally recommended for the management of an unresectable malignant hilar biliary obstruction [1, 2]. However, approximately 50% cases require reintervention for recurrent biliary obstruction, which is very challenging [3, 4] Appropriate selection of two SEMS lumens without passing the stent mesh is the most difficult step after stent-by-stent (SBS) deployment [5]. A novel controllable cannula (Zeon Medical, Tokyo, Japan) has a unique flexible tip, which bends 90° upwards and downwards (Fig. 1) owing to the presence of a movable fulcrum located 15 mm from the tip. Therefore, it may be helpful for reintervention after SBS placement.

A 73-year-old woman with gallbladder carcinoma who had undergone bilateral SBS placement in the right anterior and left hepatic ducts developed obstructive jaundice with cholangitis due to recurrent biliary obstruction. Therefore, reintervention was attempted. We were able to successfully select the right SEMS lumen using a standard catheter with an angle-tip guidewire. However, we could not successfully select the left SEMS lumen due to the gap between the bile duct and distal end of the SEMS (misalignment of stent axis and bile duct axis). Therefore, we inserted a novel controllable cannula and bent its tip towards the left SEMS to adjust the axis. Subsequently, guidewire insertion into the left SEMS without passing the mesh was successfully achieved (Fig. 2). Finally,

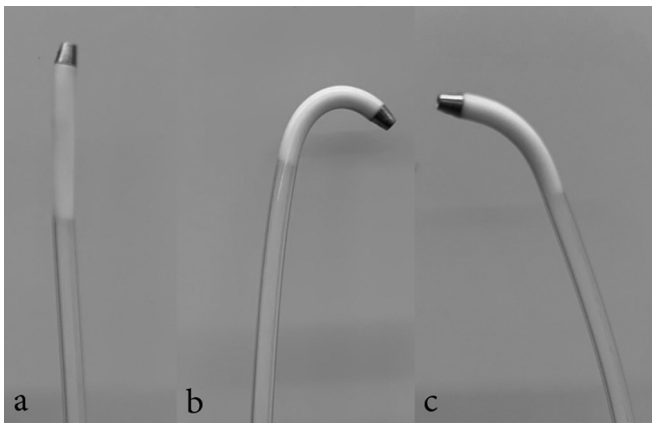

Fig. 1. A novel controllable cannula (Zeon Medical, Tokyo, Japan) has a short flexible tip (a), which can bend 90° upwards (b) and downwards (c) owing to the presence of a movable fulcrum located 15 mm from the tip, which has a diameter of 1.4 mm.

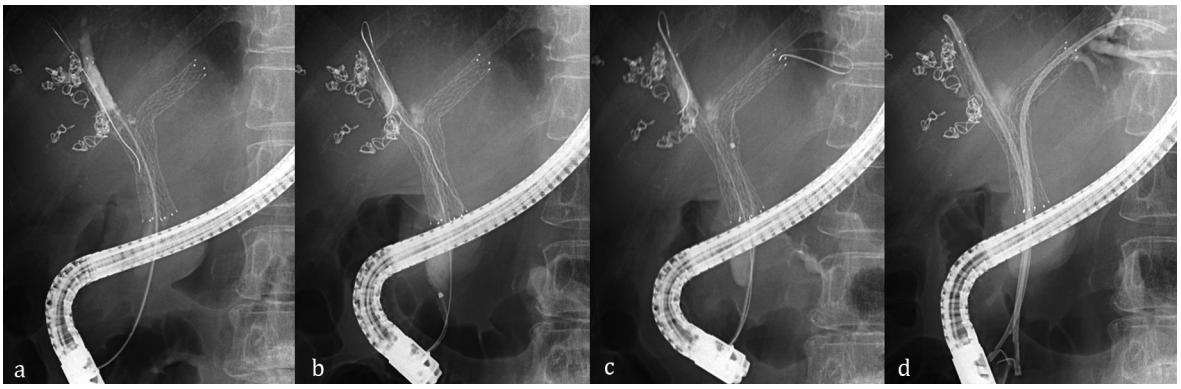

Fig. 2. The right SEMS lumen is successful selected using a standard catheter with an angle-tip guidewire (a). There is a gap between the lower end of the left stent and bile duct (misalignment of stent axis and bile duct axis); therefore, the tip of the catheter cannot face the stent direction and the guidewire passes the stent mesh (b). By moving the tip of the novel cannula toward the left stent, it is possible to appropriately select the left stent lumen without passing the mesh (c). Finally, two plastic stents are placed bilaterally (d).

bilateral placement of two plastic stents was performed, and clinical success was achieved without any adverse events.

This novel cannula has a large range of tip motion and a very short bent tip; therefore, it can be moved even in narrow bile ducts. Selection of the lower end of the SEMS after SBS deployment is a good indication of the effectiveness of this novel cannula.

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Genetic predisposition to celiac disease in a Greek case-control study: a preliminary study

To the Editor,

Celiac disease (CD) is a well-known autoimmune disease that is triggered in genetically predisposed individuals by gluten. Celiac disease is a complex genetic disorder in which the interplay of multiple genes is involved in its manifestation. Although high-risk HLA types are responsible for at least 35% of the disease risk, this percentage alone stands insufficient as to fully explain CD etiology [1]. To date, there is one study from Greece reported genotypic and allelic distribution of HLA-DR/DQ in a pediatric CD cohort [2].

Our study included 27 patients with CD and 68 healthy controls. The characteristics of the study population is presented in Table I. As expected, most patients presented

Table I. Characteristics of the study population

	Cases (N= 27)	Controls (N= 68)	p
Age	40 (16.5)	46 (21.5)	0.181
Weight (kg)	60.2 (18.8)	67.4 (20.8)	0.034
Height (m)	1.63 (0.100)	1.65 (0.123)	0.413
Sex (F)	22	54	1
BMI	22.5 (4.5)	23.9 (4.88)	0.054
WC (cm)*	80.3 ± 13.8	82.8 ± 10.6	0.356
HC (cm)	99 (8)	102 (10.9)	0.063
WHR	0.78 (0.125)	0.8 (0.0924)	0.512
Age of CD onset *	31.9 ± 13.7	-	-
Typical CD (Yes|No)	16|10	-	-
Marsh Classification (type 0, type I, type II, ≥type III)	1|6|3|8	-	-

*parametric variable; parametric quantitative variables are depicted as mean (±standard deviation: SD), non-parametric quantitative variables as median (interquartile range: IQR) and categorical variables as numbers. Statistical analyses: t-test for parametric continuous variables), Mann–Whitney test for non-parametric continuous variables and chi-square test p-value for categorical variables.

symptoms of bloating (52%) and diarrhea (44.4%) prior to being diagnosed with CD. Hashimoto's thyroiditis (HT) was present in 33.3% of patients. As it is well known, CD often coexists with HT [3].

Two hundred and sixteen SNPs were retrieved when querying "celiac disease" term in the GWAS Catalog search panel. Thirty-six SNPs out of 216 were detected in our genotypic data. After conducting SNP association test with disease outcome (adjusting for age and sex), we confirmed the harmful effect of rs2187668-HLA-DQA1 (OR=8.333, 95%CI: 2.9-23.94, p<0.001) and of rs10903122-RUNX3 (OR=2.155, 95%CI: 1.017-4.567, p=0.045) with CD odds ratio (OR) >1 in our Greek sample. The polymorphisms' genetic frequencies are in Hardy-Weinberg Equilibrium (HWE). The effect allele frequencies are 58.42% for rs10903122 (G) and 13.37% for rs2187668 (T). Previous studies have highlighted the well-known association of rs2187668-HLA-DQA1 with CD. HLA-DQA1 dysfunction leads to a failure of the immune response to the gluten protein, resulting in the destruction of tissues [4]. RUNX3 regulates the development of CD8+ T lymphocyte in the thymus [5]. To assess the contribution of both genetic variants we created a Genetic Risk Score (GRS) (by summing the number of risk alleles at each locus (0, 1, 2)) and a wGRS (by multiplying the number of risk alleles at each locus (0, 1, 2) by its OR) were constructed based on two previously reported SNPs that were found statistically significant with CD odds in our sample.

The medians of GRS (p=1.9E-05) and wGRS (p=7.2E-06) were significantly higher in cases than controls. Moreover, GRS and wGRS were divided into low and high-risk levels based on their median cutoff values (GRS, median:1, wGRS, median: 2.155). In cases, the high-risk individuals of GRS and wGRS were 81%, while their difference with the controls were detected to be significant (Fig.1).

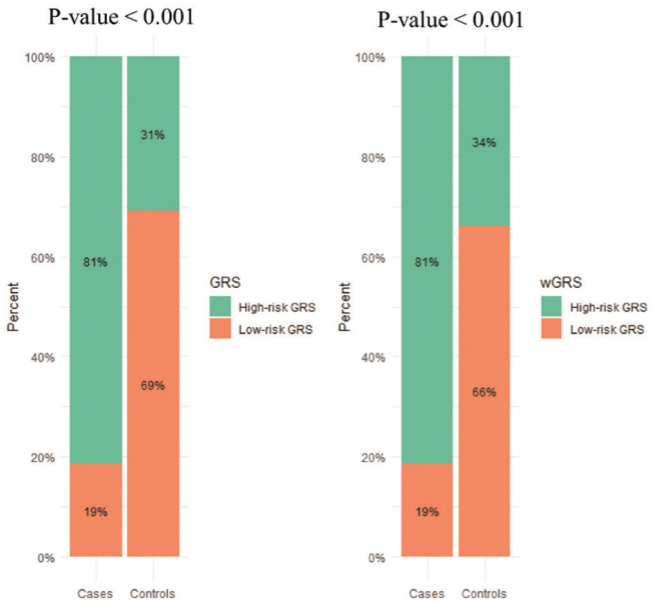

Fig. 1. Bar graphs showing the percentage of low and high-risk Genetic Risk Score (GRS) (left) and wGRS (right) in cases and controls, respectively. The Chi-square test was used to compare the differences between the groups.

The GRS and wGRS were associated with CD odds in an unadjusted model (GRS: OR=3.992, 95%CI: 1.937-8.225, p<0.001; wGRS: OR: 2.884, 95%CI: 1.763-4.720, p<0.001) and after adjusting for age and gender (GRS: OR=3.942, 95%CI: 1.893-8.209, p<0.001; wGRS: OR: 2.843, 95%CI: 1.722-4.693, p<0.001).

In conclusion, the present study confirmed that genetic risk factors tend to have an additive effect on CD in this Greek sample. However, the small sample size limited the ability to detect more SNP-associations with CD. Therefore, a larger sample would allow the creation of GRSs with more SNPs. Hence, larger studies are needed to validate our findings.

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The silent slayer of the liver: primary hepatic angiosarcoma

To the Editor,

A 69-year-old gentleman, a known diabetic and a sculptor by occupation, was under evaluation for colicky abdominal pain for 2-3 months. The patient was incidentally diagnosed with a focal liver lesion (FLL) in segment V of the liver on an abdominal ultrasonography. Alpha-fetoprotein (AFP) level was normal. Abdominal contrast enhanced computed tomography (CECT) showed isolated hypodense 6x4x6 cm FLL in segments V and VI with mild enhancement in arterial and progressive

enhancement in portovenous phases suggestive of LI-RADS V lesion (Fig 1A). On positron emission tomography (PET) no other metabolically active lesions were noted. Ultrasound guided biopsy of the lesion was performed and histological examination reported a high grade malignant vascular lesion. Resection of the liver segments V and VI was performed. The macroscopic appearance revealed a subcapsular tumour with infiltrating margins, areas of haemorrhage and necrosis. Histopathology showed an infiltrating tumour composed of anastomosing vascular channels. Tumour cells had epithelioid to spindle shape, vesicular nuclei, marked pleomorphism and abnormal mitosis (Figs. 1C, 1D). Large areas of haemorrhage and necrosis were noted within the tumour. Immunohistochemistry (IHC) showed strong diffuse tumour positivity for markers CD31 (Fig. 1E) and CD34 (Fig. 1F). From all the above features the lesion was diagnosed as a primary hepatic angiosarcoma (PHA).

Angiosarcoma is an aggressive malignant soft tissue tumour arising from the endothelial cells of blood vessels. Primary hepatic angiosarcoma is rare and accounts for 0.1-2% of all primary liver malignancies [1, 2]. It usually occurs in the sixth to seventh decade with male preponderance [3]. Cases of hepatic angiosarcoma are asymptomatic or with nonspecific symptoms and diagnosed incidentally.

History of exposure to harmful chemicals might indicate the diagnosis. About 25% cases of PHA are associated with known etiologies. Chemicals such as vinyl chloride has an association with PHA with a hazard ratio of 10-15 folds [1]. Our patient was sculpture by occupation and had prolonged exposure to vinyl chloride. It was observed that PHA associated with vinyl chloride exposure showed TP53 mutation [4, 5]. Chaudhary et al. [4] reported 11 out of 61 cases of PHA in Great Britain between 1975-1987 which were associated with vinyl chloride exposure. Kielhorn et al. [5] reported 197 cases of liver angiosarcoma associated with vinyl chloride exposure between 1985-1999. After 1999 measures were taken to cease the exposure, but as these chemicals have a long latent period (20-22 years) tumours were still detected [5]. Other chemicals associated with PHA can be prolonged exposure to anabolic steroids, radiation, thorium dioxide, arsenic and oral contraceptives [3].

Specific radiology diagnosis of PHA is difficult as they show variable features. There are no specific tumour markers indicating the diagnosis of PHA. Vascular nature of tumour makes it difficult to biopsy. False negative biopsy results are also observed due to necrotic and haemorrhagic foci in tumour [3]. Surgical resection remains a promising early treatment in patients with PHA. Histopathology examination of the resected tumour remains the gold standard for diagnosis. Characteristic microscopic features of epithelioid and spindle cells lining vascular channels and showing marked pleomorphism and abnormal mitosis were noted in our case. Common IHC markers such as CD34 and CD31 have about 87% sensitivity

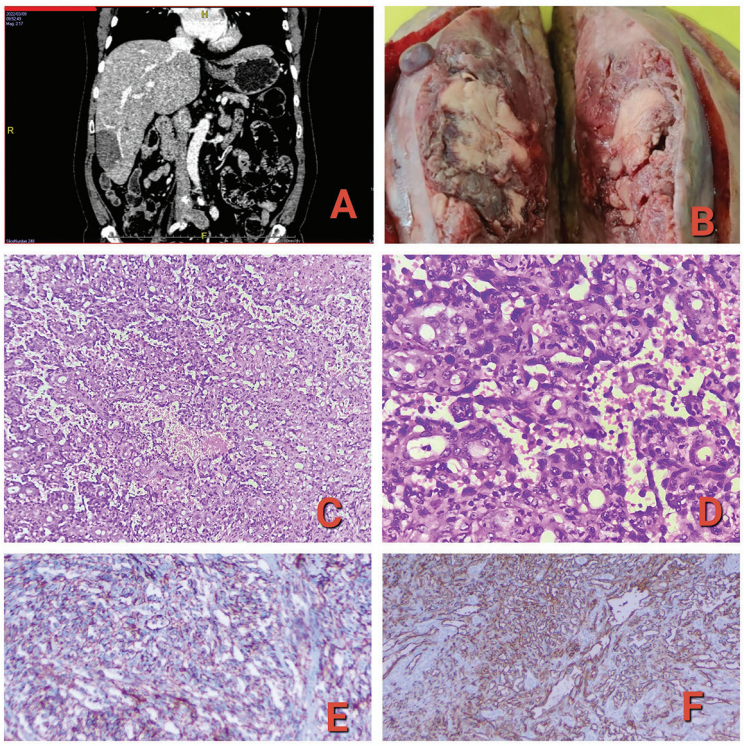

Fig. 1. A) Contrast enhanced computed tomography, portal phase: isolated hypodense 6x4x6cm focal liver lesion in segments V and VI with progressive enhancement in portovenous phases – LIRADS V; B) Resected liver segments V and VI with a large tumour showing areas of haemorrhage and necrosis; C, D) Microscopic examination (H&E staining): tumour composed of infiltrating anastomosing vascular channels with epithelioid and spindle tumour cells; E) Microscopic examination, immunostaining: CD 31 positive tumour cells; F) CD 34 positive tumour cells.

[1]. CD34 and CD31 performed in our case showed strong diffuse positivity, thus confirming the diagnosis.

The complications observed in patients with PHA are haemorrhage followed by spontaneous tumour rupture, acute liver failure, disseminated intravascular coagulation [1, 3, 5]. Primary hepatic angiosarcoma has very poor prognosis. Survival of patients without treatment is 1-6 months. Patients undergoing surgical resection may have a survival of up to 17 months [1]. Thus partial surgical resection of the liver to remove the tumour remains the best treatment for PHA.

Primary hepatic angiosarcoma should be considered as possible diagnosis in patients with prolonged chemical exposure, absence of cirrhosis and normal serum AFP levels. Early diagnosis and proper surgical management is necessary. Histopathology and immunohistochemistry are the gold standard for the diagnosis of angiosarcoma.

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