

## Diffuse Variant Hepatocarcinoma. Case Report

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### Abstract

Hepatocarcinoma is the most common primary liver neoplasm, it is mostly related to liver cirrhosis, and its presentation without concomitant chronic liver disease is rare; however, there is a percentage of non-cirrhotic patients who develop the disease. We present the clinical case of a 24-year-old female patient, with no medical history, who consulted for long-term recurrent mild abdominal pain. After complementary studies, a liver tumor was detected, with alpha-fetoprotein of 974 ng/dl. The definitive pathology report reports a diffuse variant hepatocarcinoma. Given the rarity of presentation, it is decided to present the case.

**Keywords:** Hepatocarcinoma; Hepatocelular Carcinoma; Ecuador

### Introduction

Hepatocarcinoma is the most common primary liver neoplasm, currently the fourth leading cause of cancer-related death worldwide [19]. There is a higher prevalence in men than in women, with a 3: 1 ratio, and it generally occurs in older adults around 60 years of age; however, it can also occur in children and young adults [25]. Its incidence varies, but is increasing, its mortality is around 700,000 deaths a year globally [4,7]. The most affected population is patients with chronic hepatitis B infection [21]. An increase in numbers has been seen in developing countries such as Latin America [13]. The prognosis remains poor, with a 5-year survival rate of 18% [25]. In Ecuador, hepatocarcinoma ranks eighth in the male gender, with an incidence of 4.7 and mortality of 4.5 per 100,000 inhabitants and in the female gender it ranks 10 with an incidence of 6.5 and mortality of 6.3 per 100,000 inhabitants [12].

Morphologically, there are three main types of hepatocellular carcinoma: nodular carcinoma associated with cirrhosis with well-defined nodules, the massive type that is not associated with cirrhosis, with or without nodules, and the diffuse type that presents several small, poorly defined and disseminated nodules in the liver and that represents 7 - 13% [2]. There are 5 morphological subtypes: fibrolamellar, scirrhous, undifferentiated carcinoma, lymphoepithelioma-like carcinoma and sarcomatoid. In addition, there are architectural patterns such as: trabecular pattern (plaque), pseudoglandular pattern (acinar), and compact pattern, with cytological variations such as: pleomorphic cells, clear cells and fat change. Mixed tumors such as hepatocholangiocarcinoma may also appear [16,20]. Fibrolamellar

carcinoma is rare, represents 0.85-16%, occurs in young women without a liver history, is not associated with cirrhosis or high levels of alpha fetoprotein, is described as polygonal hepatocytes, eosinophilic and with abundant fibrous stroma, and have a better prognosis [2,9].

Molecularly, mutations in TP53, high-grade tumor and high levels of alpha-fetoprotein, chromosomal instability and poor prognosis are described in hepatocarcinoma; or it can present with CTNNB1 mutations, gene expression similar to that of normal hepatocytes, low-grade tumor, and low rate of vascular invasion [13,25].

Risk factors for cirrhosis or chronic liver disease are considered risk factors for hepatocarcinoma, within these, hepatitis B and C, alcohol consumption, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, diabetes, environmental exposures, genetic disorders, obesity, metabolic syndrome, diet and other lifestyle factors [21].

There are factors associated with a decrease in the risk of developing hepatocarcinoma, such as metformin through the decrease in liver lipogenesis, statins and dietary factors associated with high consumption of monounsaturated fats, fish, white meat, fiber, coffee [26].

The clinical presentation is asymptomatic, or it may be an incidental finding through imaging tests. The symptoms presented in advanced stages are: jaundice, anorexia, weight loss, abdominal pain, hepatomegaly, encephalopathy, bleeding, or manifest as paraneoplastic syndromes such as hypercholesterolemia, erythrocytosis, hypercalcemia, hypoglycemia, diarrhea, skin manifestations such as dermatomyositis, pemphigus sign Leser Trélat [25].

For the diagnosis, in high-risk patients, it is confirmed with the image criteria of contrast abdominal computed tomography or magnetic resonance imaging with contrast, for patients who are not at high risk, a biopsy is performed. Staging studies are performed with blood tests and imaging to determine metastasis to the lungs, bone, adrenal glands, or peritoneum [26].

Blood tests for staging liver cancer include: hepatitis panel, bilirubin, transaminase, alkaline phosphatase, prothrombin time, albumin, urea nitrogen, complete blood count, creatinine, serum alpha-fetoprotein [26]. Alpha-fetoprotein as a diagnostic tool is not as effective, since neoplasms such as cholangiocarcinoma or metastases of gastrointestinal origin can elevate its levels, so a confirmatory biopsy should be performed [10]. Serum alpha-fetoprotein levels  $\geq 400$  ng/ml in high-risk patients are almost diagnostic with a specificity of 95% [3].

There are other additional biomarkers that can be used alone or in combination with serum alpha-fetoprotein such as de-gamma-carboxy-prothrombin and culinary lens agglutinin-reactive alpha-fetoprotein (AFP-L3), and others such as plasma microRNAs, methylated DNA markers and circulating tumor cells; in addition, the combined use of biomarkers such as the GALAD score (sex, age, AFP-L3, AFP, and prothrombin-des carboxy, have shown promise in patients with early-stage hepatocarcinoma [17].

The differential diagnosis is made with benign hypervascular hepatic masses such as hepatocellular adenoma, dysplastic nodule, hemangioma, intrahepatic cholangiocarcinoma, congenital hepatic fibrosis, vascular forms of portal hypertension, and hepatic neuroendocrine tumors [21].

Management depends on staging, resectability, presence of comorbidities, functional status, and metastatic burden. The treatment approach is based on the staging of the disease according to the Barcelona Clinic Liver Cancer BCLC staging system, the clinical presentation and the patient's decision. Definitive and curative treatment is liver resection, liver transplantation, and ablation. When there is no resectability option, without evidence of metastasis, the option of liver transplantation is considered, while those who are not eligible for transplantation, locoregional therapy with ablation, radiotherapy, systemic therapy is considered [26]. The Milan criteria for liver transplantation are: single lesion less than or equal to 5 centimeters, 2 to 3 lesions less than 3 centimeters, no evidence of macrovascular involvement or extra-hepatic disease, for which less than 10% recurrence is expected, and 70% 5-year survival [18,26].

Early stages such as A according to the BCLC, reach remission of the disease in up to 70%, and in case of resection, there is a recurrence of 40 to 100% at 5 years [4]. The intermediate stage BCLC-B, present multifocal or disseminated tumors, if their liver function is preserved it is considered transarterial chemoembolization (TACE), which has been shown to increase survival time [7]. Trans-arterial radioembolization (TARE) has shown similar results to TACE with better tolerance, but it does not yet have broad scientific support, but it may be indicated in patients with contraindications to TACE [8].

There are very few treatment options in advanced stages, so it has not been possible to determine a therapeutic option, advanced hepatocarcinoma corresponds to stage C of BCLC, has vascular invasion and/or extra-hepatic alteration [4]. Sorafenib is considered the only treatment to prolong survival in patients with preserved liver function, since chemotherapy has not been shown to be effective and is in disuse. End stage D tumors, very advanced with deterioration of the general condition and / or Child Pugh stage C, have a survival of less than 3 months [1].

After diagnosis, an extension and prognostic study should be carried out, the degree of liver dysfunction can be evaluated with the Child-Pugh or MELD classification, however, prognostic systems that evaluate only one dimension of the disease (tumor extension, liver function, or symptoms associated with cancer), are inaccurate and only aid in the detection of terminal illness [11].

### Presentation of the Case

A 24-year-old female patient, mestizo, Ecuadorian nationality, doctor by profession, without personal or surgical pathological antecedents; within her family pathological history, her paternal grandfather died with pancreatic cancer. Obstetric gynecological history without relevant findings. She does not refer to alcohol, tobacco or drug use.

He comes to the hospital medical consultation of the Gastroenterology service for a recurrent abdominal pain, for a year, that intensifies in the last 72 hours of moderate intensity (VAS 6-10), located in the right hypochondrium and right iliac fossa, accompanied by nausea and vomiting for a yellowish-looking occasion.

On physical examination the patient was conscious, oriented, hydrated, without neurological focus, normal cardi thoracic evaluation, without relevant findings. Soft, depressible abdomen, slightly painful on palpation, hepatomegaly is evident on palpation at the expense of the left lobe, in the epigastrium and right hypochondrium region, air-fluid noises present. Normal extremities, no evidence of edema. Positive Fist-percussion maneuver. Elemental neurological examination preserved.

Complementary tests were requested, as well as blood tests that reflected a decrease in hemoglobin (11.5) and erythrocyte count (3.68). Preserved kidney function, blood glucose and electrolytes within normal parameters. Amylase (53) and lipase (22). Within the liver laboratory panel, transaminases ALT (98.1) - AST (165.7), GGT (428), alkaline phosphatase (148), total bilirubin (1.61), direct (0.69) and indirect (0.92) bilirubin are evidenced. Interleukin 6, procalcitonin and C-reactive protein without alteration.

Negative hepatitis B and C profiles are performed. In addition, tumor markers were performed: normal carcino-embryonic antigen (0.60), normal CA-125 (15.68), normal CA 19-9 (14.12) and elevated alpha-fetoprotein (974).

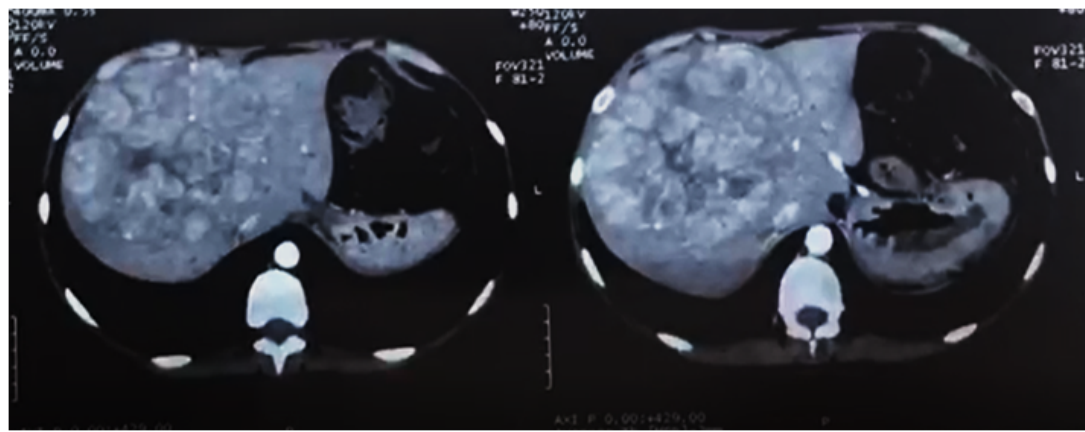
In the examinations, abdominal US showed the presence of an enlarged liver of 19.8 cm in length, hyperechoic, with irregular borders, poorly defined and with solid characteristics, and an area suggestive of necrosis, concluding with a liver mass with a tumor appearance.

Abdominopelvic CT is requested, showing a lesion measuring 122 x 115 x 123 mm, hypodense, heterogeneous, with multilobed contours, solid content, tumor aspect, in addition to central hypodense areas of probable necrosis; In addition, there is an additional exophytic lesion in the liver segment 4B, with the same characteristics previously described, measuring 58 x 58 x 66 mm in its largest diameters, it is defined as hepatocarcinoma under study, for which several studies and medical procedures are requested.

A bone scan is performed, which is normal and negative for blast-type metastatic bone disease. In addition, an upper gastrointestinal endoscopy plus biopsy is performed, which shows moderate upper hemorrhagic gastropathy, moderate erythematous antral gastropathy, and moderate bile reflux. A colonoscopy is performed, where lymphoid hyperplasia of the ileum is evidenced. Abdominal Angiotac is performed, where areas of decreased contrast uptake are evidenced, suggesting areas of necrosis, as well as a lesion with a diameter greater than approximately 19 cm, with multiple afferent vessels originating from the hepatic arterial circulation. In the portal phase, there is an extrinsic displacement and compression of the main portal vein, dilation of the intrahepatic portal veins and multiple perilesional veins that converge towards the main portal vein.

A liver biopsy is performed, which shows structural alterations, atypical mitoses, intracytoplasmic cholestasis, intracytoplasmic and extracytoplasmic cholestasis, positive for hepatocarcinoma, diffuse variant.

It is concluded that due to the extension of the tumor tissue that encompasses this vital organ, it has a poor prognosis in the medium term.



**Figure:** Source: Data from the patient's medical history. Gastroenterology Service of the Hospital Instituto Ecuatoriano de Seguridad Social-IESS. Prepared by: Authors of the article.

## Discussion

Hepatocarcinoma is more common in men than in women, with the exception of lamellar carcinoma, where a higher frequency has been described in young women. On the other hand, diffuse hepatocarcinoma, which represents 7 - 13% of cases, is considered very rare, little studied and reviewed in the literature. This case is presented as a sign of a behavior different from hepatocarcinoma, with an advanced stage.

There are several inherited disorders associated with hepatocarcinoma such as hereditary hemochromatosis, alpha 1 antitrypsin deficiency, acute intermittent porphyria [11]. Furthermore, its presentation varies according to hepatitis carriers, exposure to environmental toxins and/or potentially protective effects of estrogens mediated by interleukin 6 inhibition [23]. Due to the age of presentation, a lamellar type hepatocarcinoma could be thought, however, it was determined that it does not comply with the characteristics and typical behavior of the same, and the diffuse variant in which there is high levels of alpha-fetoprotein was determined, by the infiltration into the liver parenchyma.

The main differential diagnoses of liver carcinoma in young patients include adenoma, focal nodular hyperplasia and nodular regenerative hyperplasia, and an unusual variant of mixed hepatocarcinoma with a classic and fibrolamellar component has been described [20].

With the passage of time there are increasingly better diagnostic techniques, however, it continues to be a diagnostic challenge and challenge in the interpretation of results even for pathology, since it requires a detailed and meticulous study of tumor cytology and architecture, histochemical studies and immunohistochemistry [20].

For the management of the patient, it was determined as unresectable, without the option of surgical treatment, due to the extension of the tumor and underlying liver alteration, patients who undergo any treatment have a high risk of progression to liver failure, and of having an impact on long-term survival. Systemic chemotherapy is not well tolerated by patients with liver dysfunction, clinical studies of chemotherapy in advanced hepatocarcinoma have been carried out in various populations, since until 2008 there was no effective therapy in advanced stage patients or failure of local therapies, molecular agents Like sorafenib, it has shown better survival being first-line, in addition, combined therapy with atezolizumab plus bevacizumab has been shown to be superior to first-line sorafenib, changing the treatment landscape; however, they are very expensive agents and not easily accessible [5].

Patients in advanced-terminal stage with an ECOG 3-4, and short life expectancy, should perform a multidisciplinary management, focused on improving the quality of life, symptomatic palliative management, based on the nutritional field, pain management and scope psychological [22].

New drugs have been approved for the treatment of hepatocarcinoma, in phase 3 and immunotherapy studies, there are currently more management options, studies combined with immune therapies are being carried out, but more studies are still required to determine their optimal time as adjuvant therapies or first or second line agents; In addition, advances in DNA and RNA sequencing techniques have provided information about the mechanism of hepatocarcinogenesis and its progression for a better therapeutic approach [14].

Global strategies for the management of hepatocarcinoma should be considered, such as: prevention of infection by Hepatitis B and C, treatment of chronic hepatitis B, liver disease C and liver disease; in addition to reducing dietary and metabolic risk factors, and improving detection, early diagnosis through surveillance and management programs in hepatocarcinoma, especially in developing countries [27]. Sorafenib has been considered as an alternative in developing countries with limited resources, but lowering the cost of drugs would be essential for its wide use [24].

Hepatocarcinoma is one of the main contributors to the burden of morbidity and mortality in various parts of the world, especially in developing countries, where resources for medical and social care are limited [27]. There is a shortage of livers available for transplantation, patients who meet resectability criteria and have adequate liver reserve have good results with 53% survival at 5 years, however, patients who remain on the waiting list can receive locoregional therapy while wait, some patients progress and die while waiting for a transplant [6].

Late diagnosis is related to a lack of adequate screening, considering that it is a frequent pathology and that is associated with high mortality, since it has only been described that 30% of patients with hepatocarcinoma are diagnosed in the screening phase and can be treated in stages. early disease [4].

Palliative treatments go hand in hand with optimizing quality of life and information about the disease and prognosis, along with symptom control, psychosocial support, and spiritual care for the patient and her family [15].

## Conclusion

- Diffuse hepatocarcinoma is a rare entity in young adults, whose diagnosis is generally made in advanced stages of the disease when its prognosis is poor, it has been shown that there are atypical forms of behavior and presentation.

- Priority should be given to early detection in the screening phases, and the global strategies described above should be implemented in patients with risk factors, to reduce morbidity and mortality rates.
- New research challenges have been proposed to improve the diagnosis and therapeutic approach of hepatocarcinoma.

### Conflict of Interest

None.

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