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Spontaneous regression of hepatocellular carcinoma: focusing in the associated risk factors

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HIGHLIGHTS

- Spontaneous regression (SR) in hepatocellular carcinoma (HCC) is rare, and the objective was to review all cases HCC presenting SR in Southern Brazil.
- Data of all patients with HCC were retrospectively reviewed looking for the occurrence of SR.
- There were five cases of SR, highlighted one case occurring after COVID-19 infection in a patient with cirrhosis, emphasizing the most common mechanisms like hypoxia and immunological.
- In conclusion, this phenomenon will possibly contribute to a better understanding of the pathophysiological mechanisms of HCC.

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**ABSTRACT – Background** – Spontaneous regression (SR) is defined as the

partial or complete disappearance of a tumor, in the absence of a specific treatment. Evidence of the SR in hepatocellular carcinoma (HCC) is rare.

Objective – The authors aimed to review all the cases of SR of HCC in two reference centers of Southern Brazil, highlighting the main characteristics. **Methods** – Data of all patients with HCC were retrospectively reviewed looking for the occurrence of SR in patients from two tertiary centers in Southern Brazil, in the last five years. The diagnosis of cirrhosis was established according to clinical, laboratory and imaging data, as well as upper endoscopy or histopathological examination when necessary. The diagnosis of HCC was based on typical findings according to radiologic criteria (LIRADS) or histopathological examination. Spontaneous regression was defined as a partial or complete involution of a HCC in the absence of a specific therapy. **Results** – From all cases of HCC in the last 5 years (n=433), there were five cases of SR. Three (60%) were men, the mean age was 62.6 (50.0-76.0) years, and the etiology was HCV in 3 (60%). Complete regression was observed in three patients (60%), one patient (20%) presented partial regression, and one (20%) relapsed and died. The time of follow-up varied between 12 and 21 months. In this presentation, it was highlighted one case of SR observed after COVID-19 infection in a patient with cirrhosis. The possible mechanisms involved in this situation were reviewed, emphasizing the most common like hypoxia and immunological. There were also one patient submitted to a surgical procedure as a possible factor involved and three patients without obvious risk factors. **Conclusion** – This phenomenon will possibly contribute to a better understanding of the pathophysiological mechanisms of HCC.

Keywords – Liver cancer; hepatic cancer; hepatitis C virus infection.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common malignant neoplasm and the third leading cause of neoplastic death in the world. Among primary liver malignancies, HCC accounts for 70–85% of cases, and is associated with chronic liver disease and/or cirrhosis in 70–90% of cases. Around 80% of cases occur in developing countries⁽¹⁾.

In Brazil, a national epidemiological survey evaluated 1405 patients with HCC in 29 centers across the country. Regarding the stages, 43%, 35% and 22% of patients were in early, intermediate, and advanced stages respectively⁽²⁾.

In our center, when evaluating 453 cirrhotic patients, HCC was diagnosed in 75 (16.6%) patients, with an incidence of 2.6% in the 1st year, 15.4% in the 5th year and 28.8% in the 10th year⁽³⁾.

Spontaneous regression (SR) of a malignant tumor is defined as the partial or complete disappearance of a tumor, in the absence of treatment, or through a therapy considered to be inadequate or without influence on the disease⁽⁴⁾. Despite the epidemiological difficulties to estimate the incidence of SR in neoplasms in general, a prevalence of around 1 in 60,000–140,000 cases is estimated (being more common in renal carcinomas, melanomas and neuroblastomas)⁽⁵⁾. Evidence of the spontaneous regression in HCC is rare, with about 100 cases reported in the literature^(6,7). The definitive mechanism of SR is not elucidated, but the two most considered theories are related to induction of ischaemia and the immunological response⁽⁸⁾.

In the present study, the authors aimed to evaluate the all cases of SR of HCC in two reference centers of Southern Brazil, describing the main characteristics and possible mechanisms associated, highlighting one case of SR in a cirrhotic patient after COVID-19 infection.

METHODS

Under institutional review board approval, the data of all patients with HCC were retrospectively reviewed looking for the occurrence of SR in patients attended in two tertiary centers for treatment of liver diseases in Southern Brazil, in the last 5 years.

The diagnosis of cirrhosis was established according to clinical, laboratory and imaging data, as well as upper digestive endoscopy, or histopathological examination when necessary.

The diagnosis of HCC was based on typical findings according to radiologic criteria (LIRADS)⁽⁹⁾ or histopathological examination when necessary. Spontaneous regression was defined as a partial or complete involution of an HCC in the absence of a specific therapy.

Clinical data (sex, age, etiology of liver disease, time of follow-up) the characteristics of the tumor (size, histologic type, associated portal thrombosis, evidence of metastasis, liver imaging reporting and data system - LI-RADS, relapse), alpha-fetoprotein level, Child-Turcotte-Pugh (CTP) score, Model for End-Stage Liver Disease (MELD) score pre and post SR were evaluated.

Data are presented as mean values (and variation), or frequency (and percentage).

RESULTS

From the 433 cases of HCC identified in the two reference centers, five cases of SR were identified.

The most interesting case, which must be highlighted, was a male patient, 59 years old, with cirrhosis by HCV (treated and with sustained virological response). A computed tomography (CT) showed a cirrhotic liver with voluminous nodular images, the largest measuring 12 cm (LIRADS 5) in segment VI. A hypodense nodular lesion was also observed in the spleen (6.4 cm). Tumor thrombosis of the right branch of the portal vein was present. A nodular image of 4.8 cm suggesting peritoneal carcinomatosis was identified. Chest CT on the same occasion showed numerous nodular lesions (up to 1.0 cm), suggesting metastases. Alpha-fetoprotein (AFP) >60,000 ng/mL. One month after he was infected with COVID-19. Shortly after clinical recovery from COVID-19, a new imaging exam was performed for reassessment, showing a significant reduction in the volume in segment VI (6.3 cm). It also showed a smaller volume and impregnation of the tumoral thrombus of the right portal branch, a reduction of the spleen lesion (5.4 cm), of the extrahepatic nodule (3.3 cm) and of the nodules at the lung bases. The magnetic reso-

nance image (MRI) in the same period confirmed the findings of CT (FIGURE 1). On this occasion, considering the unusual nature of the condition, a liver biopsy of the tumor area was performed, showing extensive necrosis associated with an area of fibrosis with mononuclear infiltrate, formation of histiocytic aggregates and reactive ductular proliferation, without viable tumor. It was not observed evidence of immune response activation such as the proliferation of macrophages or lymphocytes (FIGURE 2).

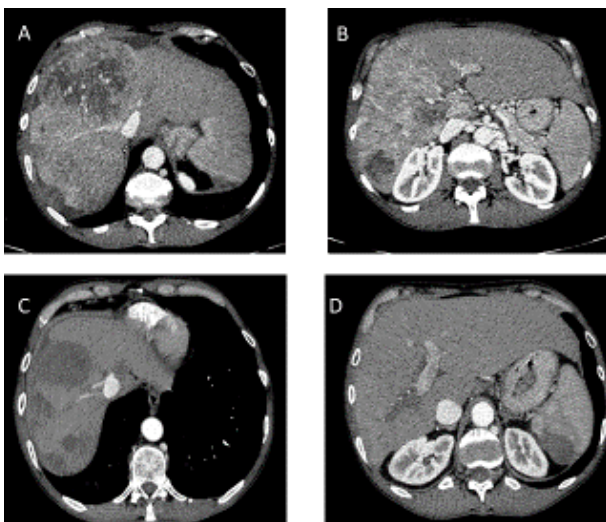


FIGURE 1. CT showing the spontaneous regression of HCC after COVID-19 infection (patient #1). A) HCC in the transition of segments VIII e IV. B) Tumoral thrombe inside the portal vein right branch. C) Regression of enhancement and reduction of the size of the tumor. D) Reduction of diameter of portal vein right branch and lack of enhancement of tumoral thrombe.
CT: computed tomography; HCC: hepatocellular carcinoma.

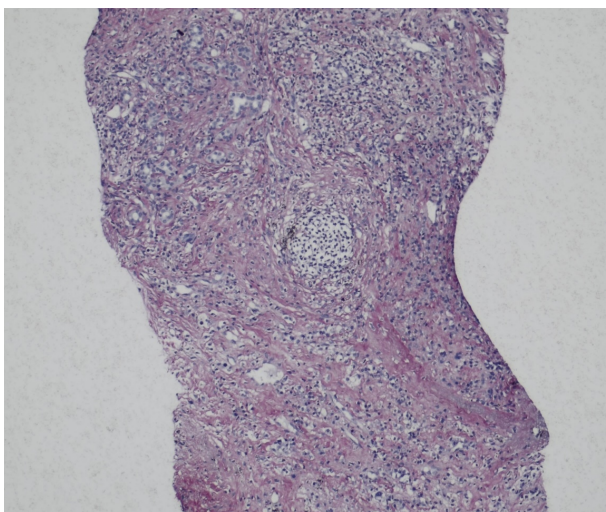


FIGURE 2. Picosirius. Extensive area of necrosis and fibrosis (patient #1).

A new MRI almost one year after showed an additional reduction of lesions in the right hepatic lobe, suggesting intra-lesional necrosis/hemorrhage (4.5 cm). The portal trunk and left branch, as well as the superior mesenteric and splenic arteries are patent. There was a further reduction of the dimensions of the lesion in the spleen (3.5 cm) and in the AFP level (2.36 ng/mL) in the last reassessment.

The main characteristics of all patients presenting HCC with SR are described in TABLE 1. Three (60%) were men, the mean age was 62.6 (50.0–76.0) years, the etiology was HCV in 3 (60%), 4 (80%) were cirrhotic, 3 (60%) presented with tumors greater than 5 cm diameter. One of the patients (20%) relapsed and died during the follow-up period. Complete regression was observed in three patients (60%), one of these was transplanted. There is also one patient (20%) with partial regression that is in the waiting list for liver transplation. Only two patients (40%) underwent liver biopsy. The alpha-fetoprotein level was within the reference level in only one patient (20%). The time of follow-up varied between 12 and 21 months. Most were Child A, with a MELD score ranging from 8 to 10 points. Just one patient (20%) presented portal trombozes and metastasis.

The most relevant event possibly related to SR was observed in the patient that presented COVID-19 infection. There were also three patients without obvious risk factors and one patient with renal tumor submitted to nephrectomy as a possible factor involved.

DISCUSSION

Spontaneous regression of HCC has been already reported^(8,10-16), and the first description of SR in HCC occurred in 1972⁽¹⁰⁾. Regardless of the methodology used, a systematic review evaluating 10 trials and 1,640 patients revealed a prevalence of SR in patients with HCC of up to 0.4%⁽¹¹⁾.

The most interesting situation described in the present study is the patient which presented a temporal relationship with SARS-CoV-2 infection. At the best of our knowledge, this is the first case of HCC SR related to COVID-19 infection described in the literature.

TABLE 1. Characteristics of the five patients presenting HCC with SR.

Characteristics	#1	#2	#3	#4	#5
Sex	Male	Female	Male	Male	Female
Age (years)	59	76	68	60	50
Etiology of liver disease	HCV/ alcohol	NASH	HCV	HBV	HCV
Cirrhosis	Yes	No	Yes	Yes	Yes
Maximum size of tumor (cm)	12.0	13.5	3.9	6.7	1.7
Relapse	No	Yes	No	No	No
Clinical course	Complete regression. Alive.	Relapse and death	Complete regression. Alive. Submitted to liver transplant	Partial regression. Alive. In liver transplant waiting list	Complete regression. Alive.
Histology	Necrosis, fibrosis and mononuclear infiltrate	No	Explant: Encapsulated 2 cm necrotic tumor	No	No
Maximum AFP (ng/mL)	60,000	7,951	5.9	26,409	453
Time of follow-up (mo)	12	21	12	16	12
Child score	A	-	B	A	A
MELD score	10	-	9	8	10
Portal thrombosis	Yes	No	No	No	No
Metastasis	Yes	No	No	No	No
Related event	Covid-19 infection	No	No	Renal tumor/ Nephrectomy	No

HCV: hepatitis C virus; NASH: non-alcoholic steatohepatitis; HBV: hepatitis B virus; AFP: alpha-fetoprotein; mo: months; MELD: model for end stage liver disease.

The second case is a description of a SR in a patient with NASH and HCC without cirrhosis. It must be emphasized that in patients with NAFLD, up to 50% of patients with HCC may not have clinical or histological evidence of cirrhosis⁽¹⁷⁾. The third case was a cirrhotic patient that presented a complete SR, who was subsequently submitted to liver transplantation with a good evolution. The fourth was a patient that presented an event that can be possibly related to SR of HCC, a kidney neoplasm and further surgical procedure to remove the kidney and the tumor. This patient is in the waiting list for liver transplantation for now. The last case presented a complete regression of the tumor and is alive in the last evaluation.

In the present series, three (60%) patients presented HCC larger than 5 cm. In fact, there is a controversy about the size of HCC presenting SR in the literature. Many authors reported SR in patients with HCC greater than 5 cm^(7,15,18-20), but others^(8,10,14,21) reported HCC smaller than 5 cm. Also, Arjunan⁽²²⁾ observed HCC greater than 5 cm in 66.7% of the six cases reported, but Sakamak⁽²³⁾ in only 33% when reviewing 24 cases.

The main mechanisms possibly related to HCC SR has been studied by image examination and the clinical course, in addition to histological and immunological findings, but it remains unclear. The main possible mechanisms proposed in the literature are tumor hypoxia and systemic immunological or inflammatory reactions, but other factors may be considered.

The malignant tissue is more sensitive to ischemic changes than normal tissue. Many mechanisms as rapid growth of tumor, vascular compression, disruption of blood supply, arterioportal fistula, invasive procedures (as hepatic angiography or surgical trauma), hemodialysis, portal arterial or vein thrombosis or the systemic hypoperfusion from bleeding, can lead to necrosis and SR in a patient with HCC probably due to hypoxia^(7,8,16,18-23).

In the casuistry in focus, only the patient with COVID-19 infection had portal thrombosis and metastasis that reduced after the SR of the primary hepatic lesion. The phenomenon of reduction or disappearance of portal thrombus or of metastasis was previously described in many reports^(7,14,18,20,22). Portal

vein tumor thrombus is one sign of advanced HCC, and may be a possible event related to HCC SR. The massive main portal vein tumor thrombus decrease portal blood flow, and the arterioportal shunt decrease blood supply from the hepatic artery to the tumors. These disturbances of the blood circulation may induce hypoxia of tumors and precipitate the tumor regression. It is also undeniable that some systemic inflammatory response to HCC also precipitates a tumor regression. This is because the long relapse-free survival cannot be explained by tumor hypoxia alone⁽¹⁸⁾.

Also, there was one patient submitted to a surgical trauma (nephrectomy) that could be a possible phenomenon related to the occurrence of SR.

The elevated levels of cytokines such as interleukines, interferon-gamma and tumor necrosis factor (TNF)-alpha have been documented in patients with SR of HCC. Measurement of inflammatory cytokines may help to elucidate the mechanism of this phenomenon^(10,13,19,24,25). In the context of immunological reactions, the improvement of immune system activities is considered. Immune stimulation is supposed to be caused by bacterial products, enzymes, hormones, traumatic events (like surgical procedures) or infections^(7,19-21).

Other factors that has been related to SR HCC, although with poor evidences, are abstinence from alcohol, metabolic factors (weight loss or improved diabetic control) and miscellaneous (drug effects as antidepressants or androgens/estrogens, smoking, vitamin K administration or alternative medicine)^(7,14-16,19,21,23).

Recently, SR of neoplasms has been reported related to the infection with SARS-CoV-2 in one patient with Hodgkin lymphoma⁽²⁶⁾ and another patient with chordoma⁽²⁷⁾. The authors suggest that the SARS-CoV-2 infection triggered an anti-tumour immune response, as has been described with other infections in the context of high-grade non-Hodgkin lymphoma⁽²⁸⁾. The putative mechanisms of action include cross-reactivity of pathogen-specific T cells with tumour antigens and natural killer (NK) cell activation by inflammatory cytokines produced in response to infection^(22,23,26,27).

Specifically in the case of COVID-19 infection, a

possible mechanism could also consider the genetic instability of the neoplastic cell, which provides a continuous modulation, producing populations of cells with variable immunogenicity. So, there could then be a potentiation of the immune function of tracking foreign cells (immunovigilance) and also of innate and adaptive responses that are more effective in combating abnormal cells⁽²⁵⁾.

In the SR associated with infection, it is essential to know whether the pathogen is intra or extracellular. The pathogen associated molecular patterns (PAMPS) of extracellular pathogens lead to activation of neutrophils, macrophages, activation of the complement system, opsonization and subsequent T helper (Th) 2 adaptive response. In relation to intracellular pathogens, there is a Th1 response, with activation of macrophages, NK cells, neutrophils and subsequent adaptive response via cytotoxic T lymphocytes, and production of TNF-alpha⁽²⁴⁾. In case of infection not directly related to tumor cells, cross-reaction between pathogen antigens and tumor antigens may occur. Antibodies against this antigen can either enhance direct cell destruction or enhance tumor antigen presentation to T cells, inducing an antitumor response⁽²⁹⁾.

In the patient with COVID-19 infection of our series, pathological findings revealed no evidence of immune response activation such as the proliferation of macrophages or lymphocytes.

The authors would like to acknowledge the study's limitations, considering the small sample size and heterogeneity of cases.

In conclusion, this study highlighted the interesting interaction between the SARS-CoV-2 infection and the SR of HCC. However, a causal relationship between SARS-CoV-2 infection and the spontaneous regression of HCC based on a solitary case cannot be established in a unrestricted manner. A better understanding of this phenomenon and of the biology of this complex tumor will possibly contribute to a better understanding of the pathophysiological mechanisms of HCC.

Authors' contribution

Tovo CV and Mattos AA: conceptualization, project administration, supervision, investigation, me-

thodology, formal analysis, writing, original draft, writing, review and editing. Ribas CR, Sartori GDP and Coral GP: data curation, formal analysis, investigation, methodology, writing, original draft, writing, review and editing. Suwa E: data curation, investigation, methodology, writing, original draft, writing, review and editing.

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RESUMO – Contexto – A evidência da regressão espontânea (RE) no carcinoma hepatocelular (CHC) é rara. **Objetivo** – Revisar todos os casos de RE de CHC em dois centros de referência do Sul do Brasil, destacando as principais características. **Métodos** – Os dados de todos os pacientes com CHC foram revisados retrospectivamente buscando a ocorrência de RE em pacientes de dois centros terciários do Sul do Brasil, nos últimos 5 anos. O diagnóstico de cirrose foi estabelecido de acordo com dados clínicos, laboratoriais e de imagem, além de endoscopia digestiva alta ou exame histopatológico quando necessário. O diagnóstico de CHC foi baseado em achados típicos de acordo com critérios radiológicos (LIRADS) ou exame histopatológico. A RE foi definida como uma involução parcial ou completa de um CHC na ausência de terapia específica. **Resultados** – Do total de casos de CHC nos últimos 5 anos (n=433), houve cinco casos de RE. Três (60%) eram homens, a média de idade foi de 62,6 (50,0–76,0) anos, a etiologia foi vírus da hepatite C em 3 (60%). A regressão completa foi observada em três pacientes (60%), um paciente (20%) apresentou regressão parcial e um (20%) apresentou recidiva e evoluiu a óbito. O tempo de seguimento variou entre 12 e 21 meses. Nesta apresentação foi destacado um caso (20%) de RE observado após infecção por COVID-19 em paciente com cirrose. Foram revisados os possíveis mecanismos envolvidos nesta situação, enfatizando os mais comuns como hipóxia e imunológicos. Houve também um paciente submetido a procedimento cirúrgico como possível fator envolvido e três pacientes sem fatores de risco evidentes. **Conclusão** – Este fenômeno possivelmente contribuirá para uma melhor compreensão dos mecanismos fisiopatológicos do CHC.

Palavras-chave – Câncer de fígado; tumor hepático; infecção pelo vírus da hepatite C.

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