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Case Report

Spontaneous regression of hepatocellular carcinoma: what three cases of regression and disease reoccurrence can tell US ☆,☆☆

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ABSTRACT

Hepatocellular carcinoma (HCC) is a highly morbid disease both in the United States and worldwide. Chronic liver inflammation puts people at risk of developing HCC. As chronic liver disease prevalence increases in the United States there can be an expected rise in HCC. Spontaneous regression of HCC is a rare phenomenon but can provide much needed information on how to better understand disease characteristics and progression. The two proposed theories that may explain spontaneous regression are tumor hypoxia and immunologic reaction. In these cases, we describe 3 patients with heavy disease burden at presentation who showed spontaneous regression of cancer. The patient's characteristics correlate most with systemic immunologic reaction resulting in spontaneous regression. Unfortunately, all of these patients had disease recurrence shortly after regression. By studying patient data in cases of spontaneous regression, we can gain a better understanding of disease progression and which exogenous or endogenous factors determine HCC mortality. With this knowledge we hope to better characterize how spontaneous regression occurs, and how we can use this information to help in developing treatment options in the future.

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Introduction

Hepatocellular carcinoma (HCC) is the fourth most common causes of cancer related deaths worldwide [1] and the sixth most common cause of cancer related death in the United States [2]. HCC develops through many years of exposure and chronic liver inflammation from diseases such as hepatitis B (HBV) and hepatitis C (HCV) infection, non-alcoholic fatty liver disease, and alcoholic liver disease [3]. The incidence of HCC has plateaued in recent years across the United States, [4] but as the prevalence of non-alcoholic fatty liver disease rises, a proportionate increase in HCC cases is expected. Although there are many treatment options available for HCC, prognosis remains poor, with a 33% five-year survival rate of localized disease and <5% survival rate of advanced disease [1]. Despite the poor prognosis HCC portends, there are a few reported cases of spontaneous regression of HCC with or without treatment measures. Cases of spontaneous HCC regression are rare but understanding unique patient characteristics in these scenarios affords an opportunity to better understand the behavior of HCC and may open a window to exploring new therapeutic strategies. In this series, we report 3 cases of HCC with spontaneous regression followed by subsequent recurrence.

Case descriptions

Case 1

A 64-year-old male (Case 1) presented with sepsis secondary to necrotizing pneumonia, and was incidentally found to have multiple low attenuated masses in the right lobe of the liver on a computed tomography (CT) Scan (Fig. 1). Alpha fetoprotein (AFP) at the time was elevated to 146 ng/mL (Normal range = 10-20 ng/mL). This patient underwent a biopsy of the lesion, and findings were consistent with HCC. After review of the initial images, there was concern for lung metastasis and patient was advised to undergo a lung biopsy. Prior to lung biopsy, the patient suffered a stroke, thus halting further workup. Several months later when the patient followed up for his HCC, there was near complete spontaneous regression of the liver masses (Fig. 1) and lung nodules. AFP at this time had declined to 76 ng/mL despite the patient receiving no treatment. Three months following the regression, his AFP rose to 198.5 ng/mL indicating recurrence. Imaging at that time demonstrated soft tissue enhancement immediately adjacent along the capsule (Fig. 1), likely the source of recurrence.

Case 2

A 65-year-old male with known cirrhosis due to chronic HCV infection presented with encephalopathy and lethargy for several weeks (Case 2). An ultrasound of the abdomen showed multiple bi-lobar liver lesions including a large multilobulated right hepatic lobe lesion in a subcapsular location suspected to represent multifocal HCC. At the time AFP was 200,000 ng/mL. CT scan of the chest, abdomen, and pelvis with contrast confirmed the ultrasound findings. The large multilobulated right hepatic lobe lesion was Liver Imaging Reporting and Data System (LI-RADS) category 5 which is diagnostic for HCC [5]. The case was then presented at a multidisciplinary tumor board, including a hepatologist, liver radiologist, and oncologist. The board determined that the patient was not a candidate for systemic or catheter directed treatment given poor functional capacity at the time of presentation; he was subsequently referred to hospice. Over the course of 15 months in hospice the patient made significant functional gains. This unexpected recovery prompted an AFP recheck which revealed a significant reduction to 67 ng/mL. A CT scan showed reduction in infiltrative disease with near complete resolution of the massive infiltrative right hepatic lobe mass that previously measured around 13 cm, but a persistent left hepatic lobe mass measuring 4.8 cm (Fig. 2). As a result, the patient was discharged from hospice with close surveillance. Three months following discharge, his AFP rose to 101 ng/mL, and his CT scan showed recurrent disease with a LI-RADS 5 lesion in the subcapsular location (Fig. 2) on the right side, and mildly increased size of the left hepatic lobe lesion to 5.3 cm.

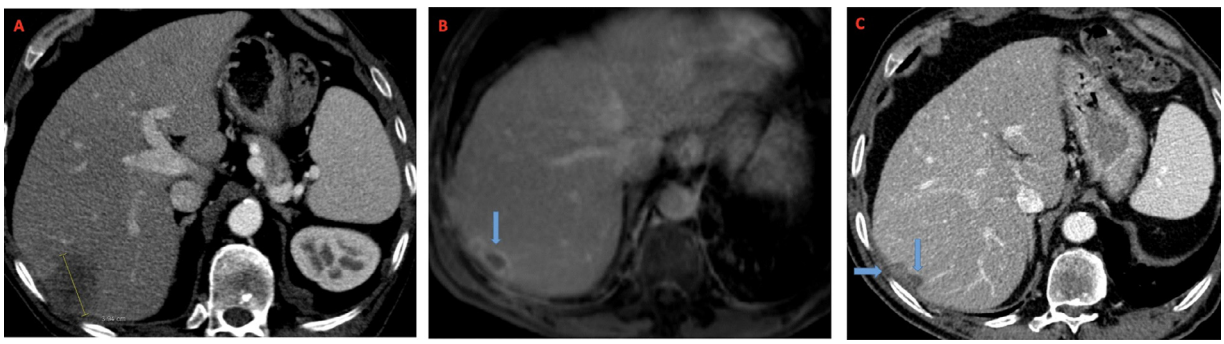

Fig. 1 – Case 1: 1. Initial CT demonstrating the dominant tumor in a subcapsular location of segment 7 of the right hepatic lobe measuring 3.9 cm. 2. MRI sequence demonstrating interval marked reduction in size (1.4 cm) in the previously seen largest lesion (arrow). 3. CT image 3 months after follow-up MRI (at the time of biochemical recurrence) demonstrating continued reduction in size of the lesion (vertical arrow, now 0.8 cm) but with a new 1.3 cm soft tissue enhancing lesion immediately adjacent along the capsule (horizontal arrow).

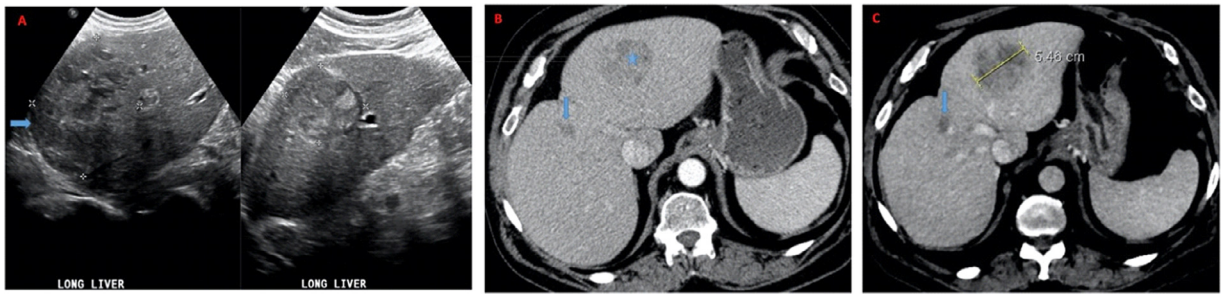

Fig. 2 – Case 2: 1. Image right: Longitudinal ultrasound image of the right hepatic lobe demonstrative infiltrative tumor measuring up to at least 10.7 cm on this image (outlined by calipers). Note extensive subcapsular tumor (arrow). Image left: Longitudinal ultrasound image of the left hepatic lobe demonstrative a solid tumor measuring 4.5 x 4.8 cm (outlined by calipers). 2. CT axial image 15 months later after functional recovery in outlining near complete resolution of previously seen infiltrative masses in the right hepatic lobe and segment 4 while there is no change in tumor in the left hepatic lobe (star). 3. Portal venous phase CT axial image 3 months later (AFP 67→101 ng/mL) slight growth in the tumor in the left hepatic lobe (star). The arrow points to the tiny residual site on the right.

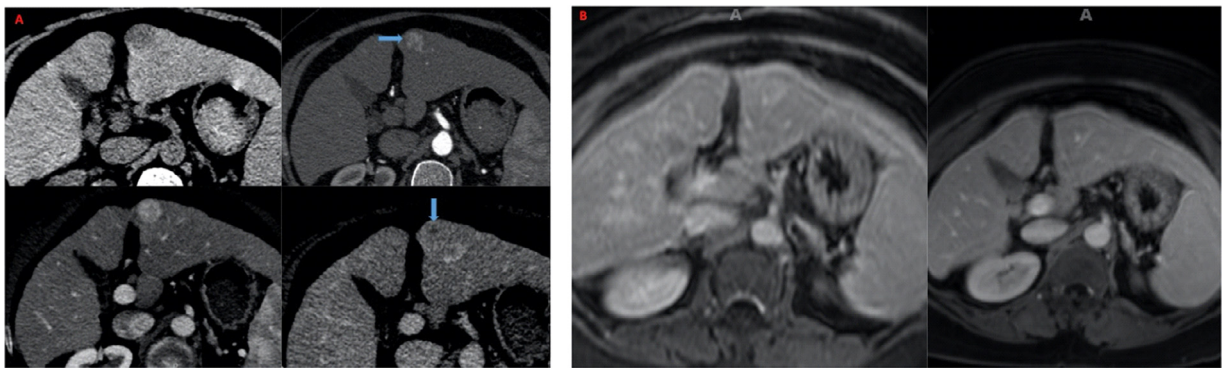

Fig. 3 – Case 3: 1. Multiphasic CT of the abdomen obtained during surveillance imaging demonstrating a new 2 cm lesion LI-RADS 5 in segment 2 (horizontal arrow denotes APHE and vertical arrow denotes non-peripheral washout compatible with LI-RADS 5). 2. Multiphasic MRI of the abdomen obtained 8 (left) and 11 (right) months after the initial exam demonstrating complete resolution of the previously seen mass, and capsular retraction.

Case 3

A 57-year-old female with known cirrhosis due to HCV infection and prior HCC in remission presented due to an increase in AFP (Case 3). The patient had previously been diagnosed with HCC, and treated three years prior to this presentation with surgical wedge resection. Six months later, her AFP levels that had been stable at 7-8 ng/mL increased to 20.7 ng/mL which prompted an ultrasound. The imagining showed a new 1.7 cm mass of the left hepatic lobe concerning for HCC. Subsequent MRI with contrast of the abdomen and pelvis confirmed a LI-RADS 5 subcapsular lesion with 2 surrounding LI-RADS 3 and LI-RADS 2 lesions (Fig. 3) which was diagnostic for HCC [5]. The patient was then evaluated by hepatology and recommended to undergo surgical resection of the subcapsular tumor. Due to overall low performance status it was recommended that she be medically optimized and undergo rehabilitation in preparation for surgery. The patient was ultimately deemed a poor surgical candidate and referred for radiation segmentectomy. Repeat imaging prior to a planned hepatic angiogram showed spontaneous regression of the 2 cm LI-RADS 5 lesion (Fig. 3). AFP had also decreased from 27.2 ng/mL to 5.5 ng/mL. The patient was then followed every 3 months and showed stable lesions for 27 months following regression. However at 27 months after regression, the surveillance ultrasound showed a new 6.5 cm hepatic mass involving segments IV, VII, and V. Patient declined cancer treatment at the time and was subsequently transitioned to hospice.

Discussion

Spontaneous regression of HCC is exceedingly rare with recently reported incidence of <1% of those with disease [6] in a large center study. Herein, we present three cases that outline an exceedingly rare phenomenon and offer some insight into how HCC may regress (see Table 1). Of the cases presented at our center in a multidisciplinary conference for HCC over 3-year (2016-2019), there were three cases of spontaneous regression. The diagnosis of HCC in these cases was made through both imaging and tissue. The American Association

Table 1 – Patient characteristics.

	Case 1	Case 2	Case 3
Age at diagnosis	64	65	55
Gender	Male	Male	Female
Race/Ethnicity	Asian	White, non-Hispanic	Asian
Likely etiology for HCC	Chronic Hepatitis B	Chronic Hepatitis C, Cirrhosis	Hepatitis C, Cirrhosis
Other Comorbidities	Type II DM Hypertension Hyperlipidemia Asthma	Type II DM Hypertension Asthma Tobacco Use	Nonischemic cardiomyopathy COPD Hyperlipidemia Smokeless tobacco use
Largest lesion at diagnosis	5.8 cm	10.7 cm	2 cm
Location of hepatic lesions	Subcapsular lesions in segment VII	Subcapsular lesion in segment IV	Subcapsular lesion in segment III
Metastatic disease	Yes – Lung	No	No
Max AFP ng/mL	146	200,000	27.2
Method of Diagnosis	Biopsy of metastatic lesion	Multiphasic CT with contrast LI-RADS Criteria	Multiphasic MRI with contrast LI-RADS Criteria
Diagnosis to proven regression	4 months	15 months	6 months
Time from disease regression to recurrent disease	3 months	3 months	27 months

for the Study of Liver Diseases (AASLD) guidelines for diagnosis of HCC outlines that for patients with chronic liver disease who are at high risk of developing HCC and have imaging findings (characterized by LI-RADS) on multiphasic, contrast enhanced CT or MRI consistent with HCC biopsy is not required for diagnosis [7]. All of the patients in this series were at high risk of developing HCC based on their pre-existing liver disease [7]. Case 1 had chronic hepatitis B, Cases 2 and 3 had cirrhosis of the liver. LI-RADS is a comprehensive system with several algorithms that provides a standardized approach to the interpretation of liver lesions with high specificity and positive predictive value for HCC [8]. A LI-RADS 5 lesion has a near 100% specificity for HCC in high risk patients thereby imaging alone is diagnostic for HCC in patients with this interpretation [9]. In Case 1 tissue diagnosis was obtained although in Cases 2 and 3 the imaging criteria for diagnosis was met thereby biopsy was not indicated.

Of the 3 cases, all had lesions located peripherally in the subcapsular portion of the liver. Spontaneous regression occurred on average at 12.5 months, with the shortest time to regression of 4 months (Case 1). Recurrence occurred in 3/3 of the cases on average at 16.5 months, with the longest time to recurrence at 27 months (Case 3). Size did not appear to be a factor in regression, the dominate lesions ranged from 2 cm to 13 cm. Similarly tumor burden did not seem to be a factor as it ranged from a single lesion (Case 3) to distant metastasis (Case 1). All of the patients had no disease modifying treatment in the time between diagnosis and regression, and had other comorbid diseases that may have contributed to their overall morbidity and mortality had they pursued aggressive HCC treatment. Case 1 and Case 2 were poorly controlled in their diabetes. Case 3 had severe non-ischemic cardiomyopathy.

A limitation to our case studies is that the time from spontaneous regression to recurrence of disease is unclear for Cases 1 and 2. Case 3 was the only patient who was closely followed after spontaneous regression and lived disease free for 2 years which may be the longest time to recurrence of disease in these 3 cases. Case 3 had disease that did not recur at the site of the initial tumor, so this may likely represent a new malignancy rather than true recurrence. Another limitation is the lack of tissue diagnosis in Case 2 and Case 3. Imaging advancements for liver diseases and hepatic tumors has improved noninvasive diagnostic capabilities so that multiphasic CT and MRI imaging has replaced the need for biopsy for many cases of HCC including those in our study [7]. One characteristic that is similar in all 3 cases is the subcapsular location of hepatic lesions. Although each of the patients had more than one primary liver lesion and Case 1 had distant metastatic disease, all cases had a primary subscapular lesion which regressed without treatment.

Two major methods of spontaneous regression have thus far been proposed, tumor hypoxia and immunologic reactions [10]. Tumor hypoxia has been described more commonly in those with local disease, whereas immunologic reactions have been found in metastatic disease [11]. We theorize the peripheral and subcapsular tumor characteristic in the patients in our series may have contributed to the spontaneous regression. The more peripheral location could predispose the tumor to ischemia given the more tenuous blood supply, particularly in cirrhotic livers and subcapsular masses [12]. Furthermore, the subcapsular location and potentially local disruption of the capsule may predispose a lesion for immunologic presentation.

Tumor hypoxia has also been suggested by systemic etiologies [13]. Case 1 had severe sepsis which led to the cancer diagnosis and preceded the spontaneous regression so sepsis seems unlikely as a causative factor. Case 3 did not have a significant hypoxic event and although had severe systolic dysfunction (ejection fraction of 20%) this degree of low systemic perfusion also seems unlikely to lead to significant tumor hypoxia and ischemia.

Another proposed theory of immunologic regression of disease is improved diabetic control [10]. In this series, both Cases 1 and 2 were poorly controlled diabetics with A1c $>$ 8 and are thus discordant with the theory. Other proposed mechanisms are via smoking and alcohol cessation [13]. In our series, Case 2 had been on nicotine replacement therapy and abstained from alcohol use for his entire hospice period.

What is known is that there is a very complex interplay in the immunological processes within the diseased liver where

HCC arises, and we are only recently beginning to understand this complex process, and there are likely a multitude of factors at play [14]. We also know that as immunotherapy is emerging, a greater understanding of the factors involved in spontaneous regression will provide a framework to study further therapies for HCC.

How these cases developed recurrent disease is also unclear. In the literature there have been a few cases that have shown recurrence of disease, but overall disease-free survival for patients with spontaneous regression is quite favorable [15]. Underlying liver inflammation is likely a contributing factor. Cases 1 and 2 did not have resolution of their viral hepatitis, and Case 3 had cirrhosis. Additionally, as demonstrated by this case series, recurrence in 2/3 cases was at the site of original disease, thus the regression is likely not complete on a pathologic level even when there is a near-complete or complete radiologic or biochemical regression. These cases show that patients with spontaneous regression still require close surveillance as recurrence eventually occurred in all cases (3/3).

As opposed to previously published cases, 2 of the 3 cases in this series had disease recurrence soon after regression. It is also possible that whatever immune response that occurred to resolve the disease was suppressed and ultimately led to disease recurrence. It could also be that when the patient presents with very advanced disease such as in Case 1 (metastatic disease) and Case 2 (extensive bilateral multifocal and AFP >200,000), the recurrence is likely to occur more quickly mirroring the unfavorable prognosis of an advanced initial presentation. While an initial presentation with limited disease, such as in Case 3, may confer a more favorable period of disease regression. Given the limited cases of spontaneous regression, it is difficult to draw conclusions but it appears treatment for sites with complete radiographic response may still be warranted and close surveillance is critical. Studies on host immunity and possible role of immune response in these patients need to be conducted to better understand why regression occurred and what changed to cause recurrent disease.

Conclusions

We present a rare phenomenon of spontaneous regression of HCC with subsequent recurrence of disease in three cases. Although limited conclusions can be drawn, one similarity between the 3 cases was the subcapsular location of the liver lesions. Further characterization of spontaneous regression could play an important role in improving therapeutic strategies in the future. Studying this phenomenon closely may provide some information on better treatment options going forward.

Patient consent statement

All study participants have provided written informed consent prior to inclusion in this study. Copies of the informed consent are available to the authors upon request from the journal.

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