

Peer Review File

Article Information: <https://dx.doi.org/10.21037/jgo-24-59>

Reviewer A

Very interesting case of spontaneous regression of HCC after COVID 19 infection. Have you seen any other info regarding COVID 19 and tumor regression?

Does the pt have HBV or HCV related HCC?

Reply: Thank you for the feedback. Authors have included previously published cases of COVID-19 induced tumor regression. Please refer to introduction, paragraph 3. The patient was negative for viral hepatitis serologies, refer to case description paragraph 1.

Reviewer B

The authors presented a case of spontaneous regression of hepatocellular carcinoma in a patient after COVID-19 infection.

The presentation of the case needs to be improved. First of all, this is a regression of portal vein thrombosis after a previous right hepatectomy for HCC. Furthermore, the patient had a first COVID-19 infection and a subsequent vaccination in 2020.

The true regression finding is the decrease in alpha-feto-protein. Did the patient receive heparin therapy during follow-up? evidence of a covid-19/regression effect is lacking.

figure 2: add the date year/month to be more clear.

Where was the HCC recurrence nodule? or it was only a PVTT?

Reply: This is correct, the patient had tumor thrombus (i.e. recurrent tumor in the vein and not blood clot in the vein) in the main portal vein and right portal vein branch with LI-RADS criteria (LR-TIV). The sequence of events was clarified in the discussion to avoid confusion. We have also added the findings of AFP reduction to support evidence of COVID-19 regression. Percentage of LR-TIV associated with HCC was added to the discussion. There was no use of heparin or other potentially prothrombotic medications used during this time frame consistent with this being tumor in vein, and not clot in vein. This was added to the case description (paragraph 2). In addition to the LR-TIV lesion, there was a LR-4 lesion in segment 3 (case description, paragraph 2), which was ultimately downgraded to LR-3 (case description, paragraph 3). Verbiage in the discussion regarding the use of “lesion” was changed to LR-TIV and LR-4, respectively, to avoid confusion. The authors would prefer avoiding months and years along the timeline (Figure 2) to preserve patient anonymity.

Reviewer C

I have seen valuable cases in which COVID-19 infection may have been involved in the spontaneous regression of hepatocellular carcinoma. Some additional information would be needed.

major

Is it a recurrence to begin with? Is it being judged solely on the basis of tumor markers? What happened to the ablated lesion? Is a histological diagnosis unnecessary, or are other modalities such as PET scans necessary? Overall, imaging findings seem to be lacking.

Reply: This was designated a recurrence due to both radiographic findings and AFP levels. The reduction of AFP levels was added to the discussion to strengthen the argument of spontaneous regression. The right hepatectomy was completed at an outside hospital. This was excluded in the manuscript for brevity. Discussion of the likelihood of HCC recurrence with LI-RADS TIV criteria was added (discussion, paragraph 2). Biopsy and other diagnostic workup including PET were not undertaken given that available imaging findings and AFP elevation already established recurrence and also that risk of biopsy in vascular territory would have not been clinically warranted.

Various mechanisms have been considered for spontaneous resolution, but have other factors besides COVID infection been ruled out?

Reply: An additional sentence was added to the case description (paragraph 3) which mentions no other medications or illnesses were documented from recurrence to spontaneous regression.

minor

• Ablation of a right lobe lesion seems unlikely in a patient who has undergone right lobe resection. Is it a mistake for the left (page 3 line 87-89)?

Reply: Our patient underwent right hepatectomy and is considered a partial right lobectomy. Various sources will report a right lobectomy as an “extended right hepatectomy.” Right hepatectomy involves resection of segments V-VIII, whereas right lobectomy (extended right hepatectomy) involves resection of all segments lateral to the umbilical fissure (IV-VIII, and sometimes I). This was also excluded from the manuscript as authors considered this out of scope.

• Do you need details of vascular invasion? Is it portal or venous? Was there a portal vein tumor plug at the time of initial surgery? (page 3 line 89-90)

Reply: Recurrence in the liver was identified as tumor in vein (LR-TIV), or a type of portal vein tumor thrombus, and suspected HCC. The discussion was amended to include clarification of the radiographic findings and LIRADS criteria.