Case Report

Spontaneous regression of advanced hepatocellular carcinoma following COVID-19 infection and vaccination: a case report and review of literature

Cody Eslinger[1]^, Pedro Luiz Serrano Uson Jr[1], Bolni Marius Nagalo[2,3], Mitesh J. Borad[1]

[1]Department of Hematology-Oncology, Mayo Clinic Arizona, Mayo Clinic Comprehensive Cancer Center, Phoenix, AZ, USA; [2]Department of Pathology, University of Arkansas for Medical Sciences, Little Rock, AR, USA; [3]Winthrop P. Rockefeller Cancer Institute, University of Arkansas for Medical Sciences, Little Rock, AR, USA

Contributions: (I) Conception and design: MJ Borad, C Eslinger; (II) Administrative support: MJ Borad; (III) Provision of study materials or patients: MJ Borad; (IV) Collection and assembly of data: C Eslinger; (V) Data analysis and interpretation: C Eslinger, MJ Borad; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Mitesh J. Borad, MD. Department of Hematology-Oncology, Mayo Clinic Arizona, Mayo Clinic Comprehensive Cancer Center, 5881 E. Mayo Blvd., Phoenix, AZ 85054, USA. Email: borad.mitesh@mayo.edu.

Background: Spontaneous regression (SR) of cancer remains a rare phenomenon, particularly in hepatocellular carcinoma (HCC), where limited literature exists. This case report emphasizes the significance of SR in advanced HCC, shedding light on the proposed mechanisms and addressing the scarcity of documented cases in current medical literature.

Case Description: We present the case of a 67-year-old female with a history of localized HCC who underwent right hepatectomy. Surveillance imaging 4 months later revealed tumor recurrence with tumor thrombus in the main portal vein. Radioembolization was deemed unsuitable, leading to the recommendation of systemic therapy with atezolizumab and bevacizumab. Prior to receiving any treatment, the patient tested positive for coronavirus disease 2019 (COVID-19), having previously received both the messenger RNA (mRNA)-1273 vaccine series and a booster. Surprisingly, subsequent imaging 10 months after initial diagnosis showed SR of the previously identified lesions, suggesting a potential link between viral exposure, vaccination, and the observed regression. The patient eventually received treatment with atezolizumab and bevacizumab and has sustained disease control to date, 12 months after initiating treatment.

Conclusions: This unique case highlights SR of advanced HCC following COVID-19 infection, raising intriguing questions about the interplay between viral infections, vaccinations, and cancer outcomes. The patient's response in the absence of systemic therapy further underscores the complexity of HCC management and prompts further investigation into the potential immunomodulatory effects of viral infections and vaccinations on cancer regression. Understanding these interactions could have implications for tailoring treatment approaches and improving outcomes in patients with advanced HCC.

Keywords: Spontaneous regression of cancer (SR of cancer); hepatocellular carcinoma (HCC); coronavirus disease 2019 (COVID-19); case report

Submitted Jan 20, 2024. Accepted for publication Apr 12, 2024. Published online Jul 22, 2024.
doi: 10.21037/jgo-24-59
View this article at: https://dx.doi.org/10.21037/jgo-24-59

^ ORCID: 0000-0002-8057-0841.

Introduction

Spontaneous regression (SR) of cancer is a well-documented phenomenon beginning in ancient Egypt and was first described in the medical literature in 1745 (1). In 1959, Drs. Everson and Cole defined SR as "*the partial or complete disappearance of a malignant tumor in the absence of treatment or in the presence of therapy considered inadequate to exert a significant influence on the disease*", a definition still relevant by today's standards (2). The vast majority of SR in malignancies occur in the setting of preceding or concomitant infection including bacterial, fungal, viral, or protozoal illness, but can also be seen in the context of preventative vaccination (3,4).

Highlight box

Key findings

- This case study delves into host-mediated responses in a patient with advanced hepatocellular carcinoma (HCC) experiencing spontaneous regression (SR) after a second coronavirus disease 2019 (COVID-19) infection. The SR may be linked to immune-mediated antitumor responses triggered by the viral infection, including cytokine release, molecular mimicry, and programmed cell death protein 1 (PD-1) pathway inhibition. Twelve months after initiation of atezolizumab and bevacizumab, the patient has continued disease control. The use of vaccine-based therapy for advanced HCC is debated, with ongoing trials exploring alternative strategies.

What is known and what is new?

- The presented case underscores the intricate host-mediated responses in cancer patients with primary infections. The patient with recurrent HCC exhibited SR following COVID-19, suggesting a potential immune-mediated antitumor response. This supports prior literature of SR in certain subsets of cancer patients affected by COVID-19. Proposed mechanisms include cytokine release, natural killer cell activation, molecular mimicry, and PD-1 pathway inhibition, offering insights into the poorly understood phenomenon.
- Previous reports have documented cases of COVID-induced SR in both hematologic and solid cancers. This is the first report of SR specifically in HCC, which aligns with prior literature indicating that cancers responsive to immunotherapy may be more likely to experience this rare phenomenon.

What is the implication and what should change now?

- To our knowledge, this is the first report of SR in a patient with advanced HCC following COVID-19 infection. While the exact mechanism is uncertain, the profound inflammatory reaction may be a key factor. This insight into immune responses could influence future oncolytic viral therapies, especially for relapsed or advanced HCC.

Several mechanisms have been proposed as a possible explanation of SR, with data coming from patients with hematologic malignancies including leukemias and lymphomas, as well as solid tumors such as renal cell carcinoma, malignant melanoma, and neuroblastoma (5). According to a meta-analysis of advanced solid cancers with SR, malignancies that are responsive to immunotherapy may exhibit SR more frequently (6). These mechanisms are thought to be multifactorial and exist as a spectrum of host-mediated responses which include cytokine production, innate and adaptive immune responses, growth factor alterations, hormonal variations, as well as localized changes within the tumor microenvironment (5,7).

Since the onset of coronavirus disease 2019 (COVID-19), there have been numerous case reports of SR in cancer patients following primary infection or immunization. The cases published pertain to a variety of hematologic and solid malignancies including several which are considered responsive to immunotherapy as previously mentioned (8-13). There are also case reports of non-malignant lesions including a pituitary adenoma that spontaneously resolved after primary infection with COVID-19 (14). To our knowledge, there are no case reports of SR of hepatocellular carcinoma (HCC) following primary infection or immunization with COVID-19. Herein, we present a patient with advanced HCC who had SR of her malignancy following COVID-19 infection in the absence of cancer-directed therapies. We present this case in accordance with the CARE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-59/rc).

Case description

We present the case of a 67-year-old female with HCC who had a past medical history significant for hypertension, hyperlipidemia, and psoriasis, with no known history of cirrhosis or significant alcohol use history and negative viral hepatitis B and C serologies, who developed severe onset gastroesophageal reflux disease (GERD) and epigastric pain. Subsequent imaging with computed tomography (CT) abdomen and pelvis and magnetic resonance (MR) abdomen revealed multiple masses in the right hepatic lobe. The largest lesion measured 11.6 cm in greatest dimension and alpha-fetoprotein (AFP) levels at that time were noted to be 22,147 ng/mL. She underwent robotic-assisted right hepatectomy and cholecystectomy, with microwave ablation of the smaller right hepatic lesion. Pathologic evaluation confirmed moderately differentiated HCC with evidence of

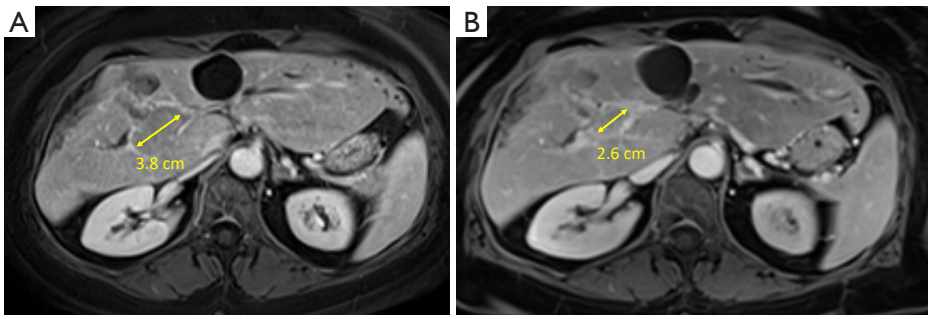

Figure 1 Changes in size of the primary lesion showing SR 4 months after relapse. CT imaging 6 months after diagnosis with axial views demonstrating (A) tumor thrombus within the main portal vein and right portal vein branches measuring up to 3.8 cm (LR-TIV) and (B) 4 months later after COVID-19 reinfection showing decreased tumor in vein lesion, now measuring 2.6 cm. SR, spontaneous regression; CT, computed tomography; LR-TIV, Liver Imaging Reporting and Data System tumor in vein; COVID-19, coronavirus disease 2019.

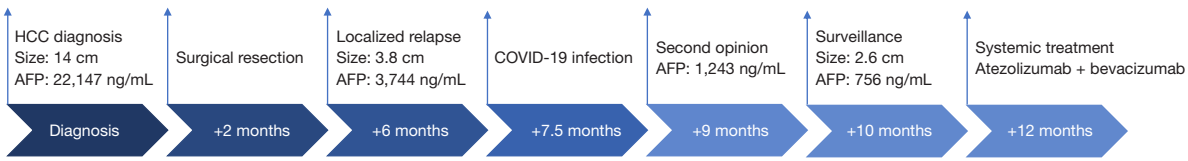

Figure 2 Timeline of events following initial diagnosis of HCC. HCC, hepatocellular carcinoma; AFP, alpha-fetoprotein; COVID-19, coronavirus disease 2019.

vascular invasion.

Approximately 4 months after her initial surgery, surveillance imaging showed findings concerning for recurrence with tumor thrombus identified in the main portal vein and right portal vein branches measuring up to 3.8 cm [Liver Imaging Reporting and Data System (LI-RADS) tumor in vein (LR-TIV)], a 1.6 cm arterially enhancing lesion inferiorly within segment 3 (LR-4) and elevated AFP (1,243 ng/mL). Notably, there were no other medications, including heparin or other potentially prothrombotic agents to explain the portal vein thrombus. Microwave ablation was attempted, however, the procedure was aborted after two large vessels were identified surrounding the lesions. Her case was evaluated at a multidisciplinary tumor board where it was recommended that radioembolization be considered. Unfortunately, the patient was not a candidate for radioembolization as the tumors did not exhibit sufficient perfusion at the time of treatment mapping. Given the advanced nature of her disease, she was recommended to receive systemic therapy with atezolizumab and bevacizumab based on the results of the IMbrave150 trial (15).

Prior to initiating systemic therapy for recurrent HCC, the patient tested positive for COVID-19 approximately 7 months after her original diagnosis. In addition to a prior COVID-19 infection in October 2020, the patient had also received the messenger RNA (mRNA)-1273 primary vaccine series against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein, as well as a booster vaccine dose before her second infection. Interestingly, repeat surveillance imaging completed 10 months after diagnosis showed SR of the two previously identified lesions. The tumor in vein previously measuring 3.8 cm now measured 2.6 cm. Although there was increased inferior extension of the tumor along the posterior aspect of the trunk of the superior mesenteric vein, the overall volume of the tumor in vein was decreased. Furthermore, the prior LR-4 lesion within segment 3 had decreased in size from 1.6 to 0.9 cm and had been downgraded to LR-3. There were no new lesions identified. AFP was also decreased from prior levels to 759 ng/mL. As before, there were no medication changes during this time frame or other documented illnesses. *Figure 1* shows the observed radiographic changes identified between the initial relapse and follow-up imaging showing SR. The patient ultimately initiated systemic treatment with atezolizumab and bevacizumab and continues to have sustained disease control after 12 months. *Figures 2,3* depict a timeline of

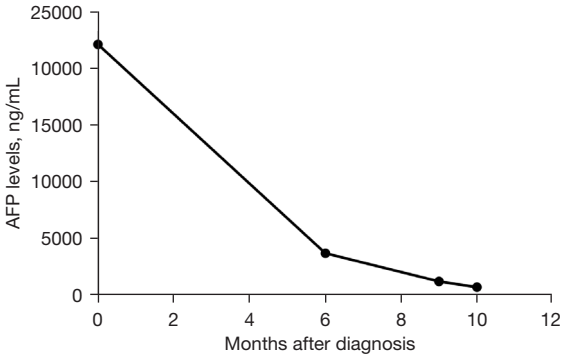

Figure 3 Trend of AFP levels over time. AFP, alpha-fetoprotein.

events and AFP levels from initial diagnosis, respectively.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent for publication of this case report and accompanying images was not obtained from the patient or her relatives after all possible attempts were made.

Discussion

The case presented highlights the complexity of host-mediated responses in patients with underlying malignancy who develop a primary infection. Our patient initially underwent partial hepatectomy with pathology demonstrating microvascular invasion, which has been shown to be an independent risk factor for recurrence (16). She ultimately developed recurrent, advanced HCC with portal vein tumor thrombus (PVTT) and a separate arterially enhancing lesion. Prior to beginning any systemic therapy, she experienced an approximate 30% reduction in the size of the LR-TIV lesion and 40% reduction in the LR-4 segment 3 lesions. In addition to the radiographic changes, the AFP levels had decreased by 80%.

Studies have demonstrated an approximate 70–75% likelihood of HCC, and more than 90% chance of malignancy with LR-TIV criteria (17-19). Due to associated risks of biopsy and strong suspicion for disease relapse, biopsy of the recurrent lesion was not completed. A month after disease relapse, and nearly 7 months into her diagnosis, the patient contracted a COVID-19 infection for the second time since the onset of the pandemic. She had also received the primary vaccine series and booster vaccine before the second infection. The exact reason for SR in this patient is unclear but is presumed to be the result of an immune-mediated antitumor response elicited by the viral infection. SR of cancer following COVID-19 is well documented but remains poorly understood.

There are a small number of reviews published that describe possible mechanisms of patients with solid and hematologic malignancies affected specifically by COVID-19 who experienced similar outcomes to the patient presented (20,21). One possible explanation is the release of inflammatory cytokines, including interleukin (IL)-12, IL-15, IL-2, interferon (IFN)-α, and IFN-β, produced as a result of COVID-19 infection which stimulates adaptive immune responses, in particular natural killer (NK) cells and cytotoxic T-cells (20). As a result of the cytokine storm, migrating NK cells express activating receptors and degranulate in part due to the downregulation of major histocompatibility complex (MHC) class I receptors within the tumor microenvironment. Other possible mechanisms for SR include molecular mimicry of tumor cells expressing heat shock proteins similar to the spike protein native to the SARS-CoV-2 virus, resulting in an antitumor response by activated cytotoxic T cells (22). A review of SR in lymphoma patients hypothesized various mechanisms including viral entry through various extracellular cluster of differentiation (CD) proteins and disruption of microtubule production resulting in cell-cycle arrest and apoptosis (21).

Another proposed mechanism for SR observed in hematologic malignancies is direct inhibition of the programmed cell death protein 1 (PD-1) signaling pathway. The spike protein has been shown via computational analysis to bind to the PD-1 receptor which may interfere with the corresponding interaction with programmed death-ligand 1 (PD-L1) (23). The mechanism for PD-1 inhibition in lymphoma is thought to be similar to the effects mediated by PD-1 monoclonal antibodies such as nivolumab and pembrolizumab. Barh *et al.* demonstrated the spike protein binds to PD-1 residues near those occupied by checkpoint inhibitors (21). Patients with HCC containing high levels of circulating and tumor-infiltrating $PD\text{-}1^{+}$ $CD8^{+}$ T cells were shown to be associated with progression following curative hepatic resection (21). Furthermore, patients with unresectable or metastatic HCC were shown to have improved outcomes with the combination of atezolizumab, a monoclonal antibody against PD-L1 and bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor, compared to sorafenib as part of the IMbrave150 trial (15). Our patient was eventually treated with this combination and has had ongoing clinical benefit.

Although SARS-CoV-2 binding to PD-1 has not been studied in HCC, the SR observed in our patient prior to treatment with immunotherapy may in part be explained by a similar mechanism.

The oncolytic potential of a SARS-CoV-2-based vaccine has also been proposed but remains controversial. The broad spectrum of possible side effects from primary infection are in part owed to the induction of cell lysis from SARS-CoV-2 internalization (24). To date, there are several Food and Drug Administration (FDA)-approved therapies for cancer treatment which work on the principle of host immune response activation. Attenuated strains of *Mycobacterium bovis* as part of the Bacillus Calmette-Guerin (BCG) for non-muscle-invasive bladder cancer (NMIBC) are internalized by local tumor cells causing inflammatory cytokine release from infiltrating T-lymphocyte and subsequent granuloma formation and tumor regression (25). A viral-based intratumoral injection therapy with oncolytic herpes simplex virus (HSV) called Talimogene laherparepvec (T-VEC) is also approved by the FDA for treatment of advanced melanoma (26). There are multiple ongoing clinical trials for advanced cancers utilizing these alternative treatment strategies and there is still much to be elucidated regarding the effect of COVID-19 on such patients.

Conclusions

To our knowledge, this is the first case report of a patient with localized HCC who developed a recurrence of her malignancy following surgical resection and eventual SR following COVID-19 infection. Although atezolizumab and bevacizumab was discussed as first-line treatment, she experienced a 30% reduction before beginning systemic therapy. A host-mediated anti-tumor response due to the profound inflammatory reaction from COVID-19 seems to be the most plausible explanation, however the exact reason and underlying mechanism is uncertain. There are certainly a multitude of patients who experienced progression of their cancer after infection or immunization with COVID-19, owing to the complex nature of the immune responses and the tumor microenvironment. This case may provide insight into future oncolytic viral therapies for relapsed or advanced HCC as part of alternative treatment strategies.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-59/rc

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-59/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-59/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent for publication of this case report and accompanying images was not obtained from the patient or her relatives after all possible attempts were made.

References

1. Le Dran HF. Traite des operations de chirurgie. Fricy; 1745.
2. Everson TC, Cole WH. Spontaneous regression of malignant disease. J Am Med Assoc 1959;169:1758-9.
3. Jessy T. Immunity over inability: The spontaneous regression of cancer. J Nat Sci Biol Med 2011;2:43-9.
4. Kucerova P, Cervinkova M. Spontaneous regression of tumour and the role of microbial infection--possibilities for cancer treatment. Anticancer Drugs 2016;27:269-77.
5. Papac RJ. Spontaneous regression of cancer: possible mechanisms. In Vivo 1998;12:571-8.

6. Ghatalia P, Morgan CJ, Sonpavde G. Meta-analysis of regression of advanced solid tumors in patients receiving placebo or no anti-cancer therapy in prospective trials. Crit Rev Oncol Hematol 2016;98:122-36.
7. Ricci SB, Cerchiari U. Spontaneous regression of malignant tumors: Importance of the immune system and other factors (Review). Oncol Lett 2010;1:941-5.
8. Buchler T, Fiser L, Benesova J, et al. Spontaneous Regression of Metastatic Renal Cell Carcinoma after SARS-CoV-2 Infection: A Report of Two Cases. Curr Oncol 2021;28:3403-7.
9. Sousa LG, McGrail DJ, Li K, et al. Spontaneous tumor regression following COVID-19 vaccination. J Immunother Cancer 2022;10:e004371.
10. Gambichler T, Boms S, Hessam S, et al. Primary cutaneous anaplastic large-cell lymphoma with marked spontaneous regression of organ manifestation after SARS-CoV-2 vaccination. Br J Dermatol 2021;185:1259-62.
11. Pasin F, Mascalchi Calveri M, Calabrese A, et al. Oncolytic effect of SARS-CoV2 in a patient with NK lymphoma. Acta Biomed 2020;91:ahead of print.
12. Antwi-Amoabeng D, Ulanja MB, Beutler BD, et al. Multiple myeloma remission following COVID-19: an observation in search of a mechanism (a case report). Pan Afr Med J 2021;39:117.
13. Kandeel EZ, Refaat L, Abdel-Fatah R, et al. Could COVID-19 induce remission of acute leukemia? Hematology 2021;26:870-3.
14. Raishan S, Alsabri M, Hanna AM, et al. Resolution of pituitary microadenoma after coronavirus disease 2019: a case report. J Med Case Rep 2021;15:544.
15. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med 2020;382:1894-905.
16. Yao LQ, Li C, Diao YK, et al. Grading severity of microscopic vascular invasion was independently associated with recurrence and survival following hepatectomy for solitary hepatocellular carcinoma. Hepatobiliary Surg Nutr 2024;13:16-28.
17. Lee YT, Wang JJ, Zhu Y, et al. Diagnostic Criteria and LI-RADS for Hepatocellular Carcinoma. Clin Liver Dis (Hoboken) 2021;17:409-13.
18. Lee S, Kim YY, Shin J, et al. CT and MRI Liver Imaging Reporting and Data System Version 2018 for Hepatocellular Carcinoma: A Systematic Review With Meta-Analysis. J Am Coll Radiol 2020;17:1199-206.
19. Kim DH, Choi SH, Park SH, et al. The Liver Imaging Reporting and Data System tumor-in-vein category: a systematic review and meta-analysis. Eur Radiol 2021;31:2497-506.
20. Bounassar-Filho JP, Boeckler-Troncoso L, Cajigas-Gonzalez J, et al. SARS-CoV-2 as an Oncolytic Virus Following Reactivation of the Immune System: A Review. Int J Mol Sci 2023;24:2326.
21. Barh D, Tiwari S, Gabriel Rodrigues Gomes L, et al. Potential Molecular Mechanisms of Rare Anti-Tumor Immune Response by SARS-CoV-2 in Isolated Cases of Lymphomas. Viruses 2021;13:1927.
22. Burgio S, Conway de Macario E, Macario AJ, et al. SARS-CoV-2 in patients with cancer: possible role of mimicry of human molecules by viral proteins and the resulting anti-cancer immunity. Cell Stress Chaperones 2021;26:611-6.
23. Meo C, Palma G, Bruzzese F, et al. Spontaneous cancer remission after COVID-19: insights from the pandemic and their relevance for cancer treatment. J Transl Med 2023;21:273.
24. Fu Y, Cheng Y, Wu Y. Understanding SARS-CoV-2-Mediated Inflammatory Responses: From Mechanisms to Potential Therapeutic Tools. Virol Sin 2020;35:266-71.
25. Chang SS, Boorjian SA, Chou R, et al. Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline. J Urol 2016;196:1021-9.
26. Andtbacka RH, Kaufman HL, Collichio F, et al. Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma. J Clin Oncol 2015;33:2780-8.

Cite this article as: Eslinger C, Uson PLS Jr, Nagalo BM, Borad MJ. Spontaneous regression of advanced hepatocellular carcinoma following COVID-19 infection and vaccination: a case report and review of literature. J Gastrointest Oncol 2024;15(4):1933-1938. doi: 10.21037/jgo-24-59

