Molecular Therapy
Oncolytics
Review

Remission of liquid tumors and SARS-CoV-2 infection: A literature review

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The coronavirus disease 2019 (COVID-19) pandemic has produced a new global challenge for patients with cancer. The disease and the immunosuppression induced by cancer therapies have generated a perfect storm of conditions to increase the severity of the symptoms and worsen the prognosis. However, a few clinical reports showcased the power of viruses to induce remission in some patients suffering from liquid tumors. Here, we reviewed six cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that resulted in cancer remission, simultaneously highlighting the strengths and the unique challenges of oncolytic virotherapy. Virotherapy has become a special case of cancer immunotherapy. This paradigm-shifting concept suggests that oncolytic viruses are not only promising agents to combat particularly immunologically suppressed, immunotherapy-resistant tumors but also that the trigger of local inflammation, such as SARS-CoV-2 infection of the respiratory pathways, may trigger an abscopal effect sufficient to induce the remission of systemic cancer.

INTRODUCTION

Reports of remissions following viral infections in patients with liquid tumors are not new occurrences. In 1904, George Dock, a hematology professor at the University of Michigan, described a 42-year-old woman with myelogenous leukemia who experienced a temporary remission of her cancer, during an episode of flu.[1] In 1953, Bierman and colleagues published a systematic review of remissions of leukemia in children following acute infections, including varicella.[2] Bluming and Ziegler reported a case study in 1971 of an 8-year-old boy who showed the characteristic rash of measles and was admitted to the hospital with right orbital swelling due to Burkitt's lymphoma.[3] The infection forced the delay of the anti-cancer therapy, but the patient remained in complete remission 4 months after the measles infection, having received treatment for the lymphoma. Measles disease has also been reported in relation to remission of Hodgkin's lymphoma.[4] Over time, these clinical reports have functioned to stimulate the study of oncolytic viruses and the development of virotherapies. Naturally, given the novelty and intense study of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), there is interest in determining whether similar liquid tumor remissions in patients have been observed following SARS-CoV-2 infection.

SARS-CoV-2 is responsible for coronavirus disease 2019 (COVID-19) and has had deleterious impacts on cancer patients, including higher risks for severe illness and related mortality.[5–7] Despite the undeniable and global negative effects on most cancer patients, clinical cases have emerged showing the paradoxically beneficial role of COVID-19 on some patients with liquid tumors. In this article, we review recent reports on the partial and complete remissions of some liquid tumors during SARS-CoV-2 infection and discuss the relevance of these cases to the field of oncolytic viruses and immunotherapy for cancer.

SARS-CoV-2 AND CANCER REMISSIONS

Case 1

Challenor and Tucker[8] reported the case of a 61-year-old male with progressive lymphadenopathy and weight loss. After a needle-core biopsy of a supraclavicular node and a fluorodeoxyglucose-positron emission tomography/computed tomography scan (FDG-PET/CT), the patient was diagnosed with Epstein-Barr virus (EBV)-positive classical Hodgkin lymphoma grade III. Shortly after the diagnosis, the patient developed a PCR-positive SARS-CoV-2 pneumonia requiring admission to the hospital, where he received ward-based care for 11 days, without administration of corticosteroid or immunochemotherapy. In a 4-month follow-up, a PET/CT scan showed widespread resolution of the lymphadenopathy, reduced metabolic uptake, and a decrease in EBV viral copies (from 4,800 to 413 copies/mL), indicative of remission.

Case 2

Pasin and colleagues reported the case of a 20-year-old male with a relapsed and refractory NK/T cell lymphoma associated with EBV infection and autoimmune hemolytic anemia.[9] The NK/T cell lymphoma was resistant to several immunochemotherapies (rituximab; pembrolizumab; l-asparaginase; dexamethasone, methotrexate, ifosfamide, asparaginase, and etoposide [SMILE]; cisplatin, dexamethasone, gemcitabine, and pegaspargase [DDGP]; and cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP]

https://doi.org/10.1016/j.omto.2022.06.006.

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chemotherapy). The patient was admitted to the hospital with a 5-day history of fatigue, fever, and dyspnea. Massive hepatosplenomegaly was palpable. CT scans showed diffuse bilateral subpleural ground-glass opacities. Laboratory tests revealed severe anemia and high hemolytic markers. An oropharyngeal swab confirmed COVID-19 infection. Treatment consisted of red-blood transfusions, methylprednisolone, oxygen, and intravenous levofloxacin. Ten days later, only partial recovery of hemoglobin, platelets, and hemolytic markers was observed, and transfusion and steroid therapy were discontinued. On day 11, an unexpected steady recovery of red-blood and platelet counts was observed. In addition, peripheral blood flow cytometry showed a remarkable reduction in the clonal NK populations from 70% to 4.2%, an inverted CD4/8 ratio, an increase in double-positive T cells, and plasma EBV-DNA significantly reduced from 229,876 to 495 copies/mL. Clinical and laboratory data suggested a remission of NK lymphoma during COVID-19 infection. On day 34, the patient had recovered from COVID-19 infection, as shown by a negative oropharyngeal swab. Intriguingly, shortly after SARS-CoV-2 clearance, the patient experienced a rapid recurrence of hemolytic anemia, fever, and spleen enlargement and a rise in NK cell count and the plasma EBV-DNA load. The authors suggested that COVID-19 infection resulted in transient remission of NK/T cell lymphoma.

Case 3

Sollini and collaborators reported the case of a 61-year-old male with follicular lymphoma who was treated with chemotherapy agent R-bendamustine.[10] During end-of-treatment [18]FDG-PET/CT, the patient was diagnosed with SARS-CoV-2 bilateral pneumonia, confirmed by a nasal swab. Images also showed a reduced para-aortic lymph nodal lesion compared with baseline, suggesting a partial response to R-bendamustine. After SARS-CoV-2 recovery, [18]FDG-PET/CT scans illustrate an increase in size and [18]FDG avidity of the para-aortic lesions. After recovering from the infection, two CT-guided biopsies were negative and scans showed a complete metabolic response, suggesting complete remission. The authors speculated that the increase in size of the nodal lesion might be considered a "flare phenomenon" occurring before the remission.

Case 4

Antwi-Amoabeng et al.[11] reported the remission of multiple myeloma (MM) in a 76-year-old woman after a single cycle of MM therapy followed by SARS-CoV-2 infection. The patient had started a cyclophosphamide, bortezomib, and dexamethasone (CyBorD) treatment regimen due to significant renal function decline. Three days after the last dose of cyclophosphamide, she presented symptoms associated with COVID-19 and tested positive by PCR of nasopharyngeal swab. A single dose of filgrastim was administered, and the patient was discharged as the fever resolved. A 5-day course of levofloxacin and acyclovir was prescribed while the patient was self-isolated. The patient returned to the emergency room with a persistent cough, fever, and decreasing blood-oxygen levels 7 days later. After admission to the hospital, the patient was treated with a 10-day course of dexamethasone (6 mg/day) and remdesivir. After 11 days, the patient was discharged with improved respiratory status. Several weeks later, a bone-marrow biopsy showed normalized trilineage hematopoiesis and laboratory studies demonstrated improvement in renal function. Flow cytometry and fluorescence *in situ* hybridization analyses showed polyclonality of plasma cells. The patient was in remission 2 months after the improvement in the disease markers. Although this patient received a single round of CyBorD therapy, the authors report that the patient's remission was equivalent to patients who receive four complete cycles of CyBorD therapy.

Cases 5 and 6

Kandeel et al.[12] reported two cases of acute leukemia that improved during COVID-19 viral infection. In the first case, a 63-year-old woman was admitted to the hospital following fever, dyspnea, and wheezy chest. A positive PCR test confirmed COVID-19 infection, with a CT showing bilateral ground-glass appearance and low blood-oxygen level, compatible with pneumonia. Laboratory tests, including bone marrow aspirate and immunophenotyping, guided the diagnosis of acute myeloid leukemia, but treatment was postponed until the COVID-19 infection had subsided. The patient received treatment with fluconazole, azithromycin, and prednisone and was discharged 5 days after the fever subsided and two negative PCR nasopharyngeal swabs. Three studies of blood counts and bone-marrow aspirate, starting 5 weeks after the hospital discharge of the patients, were compatible with the diagnosis of myelodysplastic syndrome refractory cytopenia with trilineage dysplasia. The second patient was a 28-year-old male who was diagnosed and treated for T acute lymphoblastic leukemia (T-ALL) for 6 years. The patient was initially admitted with fever, headache, and loss of smell and taste. COVID-19 infection was confirmed with nasopharyngeal swab, and the CT showed multiple bilateral ground-glass appearance. The patient presented multiple cervical lymphadenopathies. Together with blood analysis showing anemia, absolute lymphocytosis, and 30% blast cells, relapse was suspected and immunotyping analysis revealed increased expression of major histocompatibility complex class II (MHC class II) and atypical cells. The patient decided to take first COVID-19 supportive treatment, and he was treated with azithromycin and prednisone (40 mg/daily) for 5 days. Two weeks later, PCR was negative for COVID-19. After 6 weeks, the cervical lymphadenopathy has disappeared, and no atypical cells were found. Both patients have received regular follow-ups, and their disease has been in remission after a follow-up period of 12 and 5 months, respectively.

In summary, these reports highlight the probable effect of SARS-CoV-2 infection on the natural history of liquid tumors in six patients. Specifically, the response was observed in several types of cancer, including EBV-positive classical Hodgkin lymphoma grade III, NK/T cell lymphoma associated with EBV infection, acute myeloid leukemia, follicular lymphoma, T acute lymphoblastic leukemia, and MM. The remission period was followed until the time of publication, which varied from 7 weeks to 1 year. While five of the six cases showed remission, a transient improvement of an NK/T cell lymphoma was solely observed during the duration of the viral-related disease. Except for the patient in case 3, all patients suffered a severe COVID infection, including pneumonia. In some of these

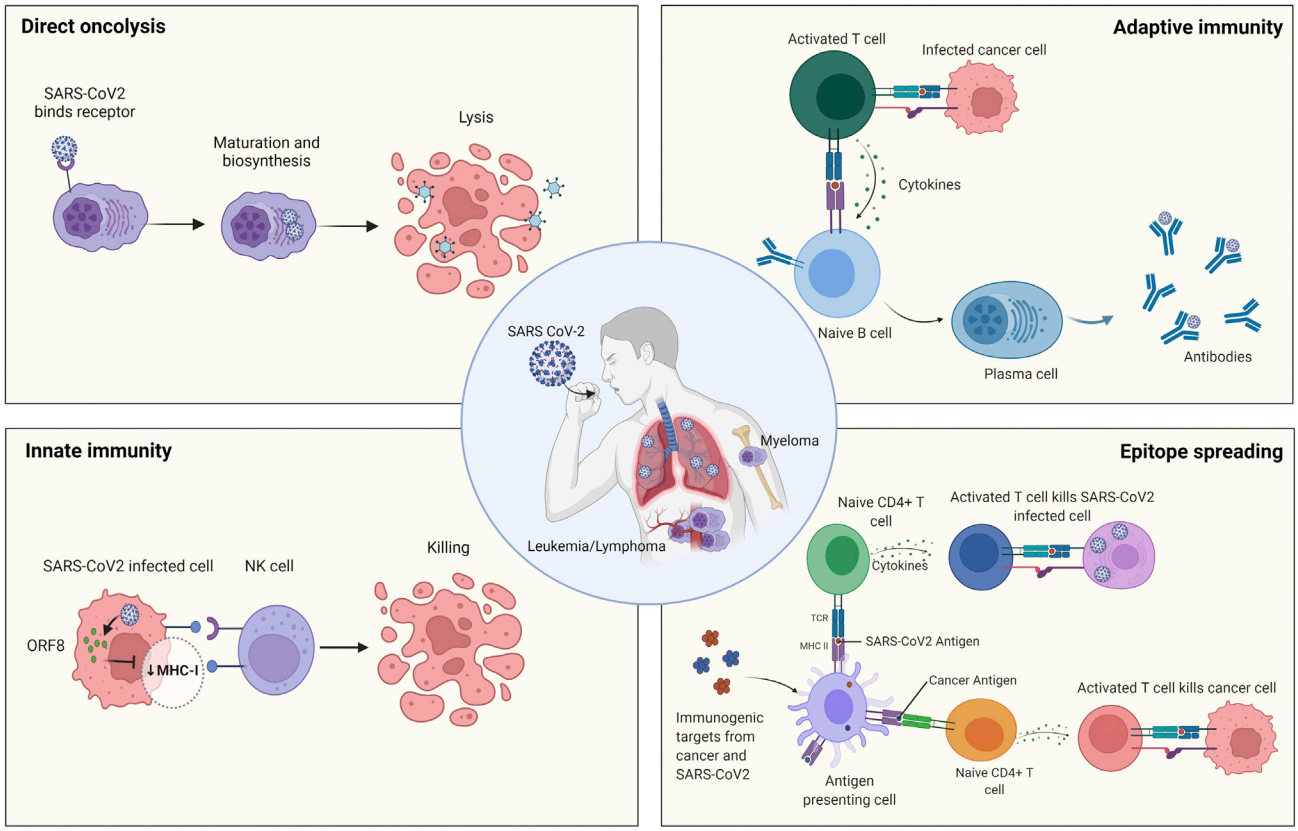

Figure 1. Schematic representation of the interface of anti-SARS-CoV-2 immunity with an anti-cancer effect

The proposed mechanisms for the anti-cancer effect include direct oncolysis (direct cell death produced by the virus replication in the infected cell), innate immunity (at least partially mediated by the action of NK cells), adaptive immunity (responses of the immune system to viral antigens in infected cells), and antigen spreading (the immune system shifts from viral antigens to cancer antigens). The figure was created with BioRender.com.

reports, the authors discussed the possible effect of the COVID treatment in the evolution of cancer. The patient reported in case 4 received dexamethasone after a first cycle of CyBorD, although in a lower dose than in a standard chemotherapeutic regimen. In the patient described in case 3, the COVID infection was diagnosed during the end-of-treatment study. The rest of the patients did not receive treatment for their cancer during the SARS-CoV-2 infection, and two patients never received cancer-related treatment.

SARS-CoV-2 AND VIROTHERAPY

Based on some of these anecdotal reports, Donia et al.[13] proposed using the SARS-CoV-2 virus in cancer virotherapy. Studies have indicated that SARS-CoV-2 infection is correlated with rapid oncolysis[14] and also suggested that direct oncolysis was combined with cross-reactivity of pathogen-specific T cells with tumor antigens, resulting in activation of NK cell populations through cytokines released in response to infection.[8] SARS-CoV-2 also encodes a protein by open reading frame 8 (ORF8) that downregulates the MHC class I,[15] serving as an activation signal for NK cells. Recently, Barh et al.[14] performed a computational analysis to uncover the molecular mechanisms underlying SARS-CoV-2-mediated tumor remission. In this study, predictive algorithms indicated that SARS-CoV-2 spike protein might bind and facilitate entry into lymphoma cells via surface markers, such as CD15, CD27, CD45, and CD152. These predictions align with the theory that SARS-CoV-2-associated inflammation included cross-reactivity of pathogen-specific T cells. A separate report describes how the SARS-CoV-2 ORF3a protein may induce cell cycle arrest, ultimately leading to apoptosis or other types of cell death.[16] These results warrant further investigation into the interactions between SARS-CoV-2 and cancer cells (Figure 1) and may eventually provide new insights into the fundamental mechanisms of the anti-cancer effect of other viruses.

Although the reported cases and the proposed mechanisms of action offered some justification for using SARS-CoV-2 as a cancer virotherapy agent, this virus might not be the ideal candidate for an oncolytic virus for several reasons. First, differently from other wild-type viruses utilized in virotherapy, such as reovirus, coronavirus infects and replicates in normal cells.[17,18] In addition, an oncolytic virus should be stable and undergo the minimum possible mutations and recombination after its administration to the patient. Therefore, the exceedingly high mutation rate of SARS-CoV-2 presents a hurdle

for recombinant vector engineering and poses a threat to patients. It is known that RNA viruses undergo mutations more frequently than DNA viruses.[19] For example, RNA viruses have mutation rates ranging from 10^{-6} to 10^{-4} substitutions per nucleotide per cell infection (s/n/c) compared with DNA viruses that range from 10^{-8} to 10^{-6} s/n/c.[20] It has been reported that RNA viruses, such as vesicular stomatitis virus (VSV), are transformed for unwanted mutations even during the cloning process and have been shown to have different mutation rates among different hosts.[21] In the clinical setting, injecting a replication-competent virus with a high mutation rate into a tumor or the bloodstream of a patient carries unnecessary risks of recombination compared with current DNA and RNA viruses used in virotherapy. Another concern associated with using SARS-CoV-2 in virotherapy is the partial viral integration into the host genome,[22] a characteristic of other RNA viruses, such as retroviruses, generating the possibility of triggering oncogenic mechanisms.[23]

VIROIMMUNOTHERAPY FOR CANCER

Currently, several viruses are being used for cancer virotherapy. Among RNA viruses, poliovirus, measles virus, Newcastle disease virus, VSV, and reovirus are some of the most promising candidates. In addition, modifications to these viruses can be explored to enhance safety and efficacy. Recombinant polio-rhinovirus chimera (PVSRIPO) has the genome backbone of the nonpathogenic PV1 Sabin vaccine strain, and replacement of its internal ribosome entry site region with that of human rhinovirus prevents it from causing polio or neurovirulence.[24] Human breast and prostate cancer xenograft models showed short PVSRIPO virus persistence in infected tumors[25] and increased type I interferon response that led to anti-tumor immunity.[26] A phase I study was conducted on 61 patients with recurrent malignant gliomas based on these results. Overall survival of patients receiving a direct intratumoral injection of PVSRIPO was 21% at 36 months, which was significantly higher than historical controls.[27] The live attenuated measles virus-Edm-Zagreb (MV-EZ) vaccine strain and its variants that express human carcinoembryonic antigen (MV-CEA) or human sodium iodide symporter (MV-NIS) have shown safety in humans. They are being tested in clinical trials for multiple cancer types, including MM, breast cancer, head and neck cancer, glioblastoma, and ovarian cancer.[28] Other RNA viruses, like the Newcastle disease virus, reovirus, and VSV, are also tested in preclinical and clinical settings and are extensively reviewed elsewhere.[29]

Compared with RNA viruses, DNA viruses possess higher genome stability and lower integration rates into the host genome. For example, the genome of adenovirus, a DNA virus, remains episomal in host cells in contrast to chromosomal integration of RNA viral genomes, such as retrovirus or lentivirus.[30] In 2005, the oncolytic adenovirus H101 was approved by China's State Food and Drug Administration for use in head and neck cancer.[31] H101 achieves tumor selectivity through deletion of the viral E1B gene that interacts with cellular p53. DNX-2401 is another oncolytic adenovirus with a 24-bp deletion in the viral E1A gene, making it selective for retinoblastoma (Rb)-deficient cells.[32] DNX-2401 has been tested in a phase I clinical trial for patients with recurrent malignant gliomas, with 20% of the patients surviving 36 months after treatment.[33] DNX-2401 is also being tested in clinical trials of children with pediatric gliomas.[34] An oncolytic herpes simplex virus (HSV) has shown encouraging clinical efficacy on pediatric malignant gliomas,[35] and another HSV virus, talimogene laherparepvec (T-VEC), was approved in 2015 by the US Food and Drug Administration (FDA) for the treatment of unresectable, recurrent melanoma.[36,37] The use of transgenes to activate the immune system during oncolytic virus infection and the utilization of cell vehicles[38] for the delivery of viruses to tumors are areas of research and are reviewed elsewhere.[39–41]

CONCLUSIONS

The six recent cases of SARS-CoV-2 resulting in cancer remission simultaneously highlight the strengths and the unique challenges of oncolytic virotherapy. Despite sharing some similarities to both gene therapy and immunotherapy, oncolytic virotherapy benefits from its unique dual modality of action: direct oncolysis from virus replication and activation of the host immune system. Selective virus replication in cancer cells multiplies the initial doses and generates an immune-activating microenvironment and the potential to generate antigen spreading. Thus, oncolytic viruses are being harnessed to combat immunologically repressed cold tumors resistant to other forms of immunotherapy, including immune checkpoint blockades and chimeric antigen receptor T cells.[42] Furthermore, incidents of COVID-19 resulting in cancer remission provide support to demonstrate the abscopal effect of virotherapy, in that local infections in the respiratory tract initiated immune responses against systemic tumors. Finally, the field of oncolytic virotherapy would also benefit from the sharing of insights gleaned from recent scientific and technological advances resulting from the study of SARS-CoV-2 pathophysiology, including computational and 3D modeling to predict virus structure, infection, and replication in cancer cells.[43,44]

DATA AVAILABILITY STATEMENT

All data are available in the main text.

ACKNOWLEDGMENTS

We thank the support from the National Institutes of Health R01CA256006 (J.F. and C.G.-M.), P50CA127001 (J.F.), the John and Rebekah Harper Fellowship (D.H.S.), and the Partnership in Cancer Science and Medicine Program at MDACC (A.V.W.). The funding bodies were not involved in the decision to publish or the preparation of the manuscript. Figure 1 and the graphical abstract of this manuscript were created with BioRender.com.

AUTHOR CONTRIBUTIONS

D.H.S., A.G., C.G.-M., and J.F. did the literature search. D.H.S., A.G., and J.F. created the figure. All authors wrote, reviewed, and edited the manuscript.

DECLARATION OF INTERESTS

C.G.-M. and J.F. report license agreements with DNAtrix, Inc. C.G.-M. and J.F. are shareholders of DNAtrix, Inc.

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