Deficient DNA mismatch repair and persistence of SARS-CoV-2 RNA shedding: A case report of Hereditary Nonpolyposis Colorectal Cancer with COVID-19 infection.

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Case Report

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Abstract

Background:

Several independent risk factors have been reported to influence viral shedding following COVID-19 infection, but host related molecular factors have not been described yet. We report a case of a cancer patient with Lynch syndrome (hereditary nonpolyposis colorectal cancer, HNPCC) who manifested SARS-COV-2 PCR (polymerase chain reaction) positivity for at least 54 days after contracting mild COVID-19 illness and propose that deficient mismatch repair (MMR) may have a role in the prolonged SARS-CoV-2 RNA shedding.

Case Presentation:

A patient with Lynch syndrome was on surveillance for metastatic adenocarcinoma after completion of palliative chemotherapy in October 2019. Between the period of April 2020 to June 2020, he required multiple admissions addressing several clinical needs mainly related to his underlying malignancy. These included progressive disease in the interaortocaval lymph nodes leading to recurrent episodes of upper gastrointestinal bleeding, dehydration resulting in acute kidney injury and a short-lived episode of pyrexia. A SARS-COV-2 PCR of the nasopharyngeal swab (NPS) was positive at his initial admission with mild COVID-19 symptoms. He remained positive on subsequent admissions when tested routinely for SARS-COV-2 without demonstrating any obvious clinical features of COVID-19 infection.

The MMR pathway, a component of DNA damage response (DDR), is impaired in Lynch syndrome due to an inherited genetic mutation. This pathway is also required for viral clearance from the host cells following certain RNA viral infections like influenza virus and other coronaviridae. Here we provide current understanding of the importance of DDR deficiencies in the clearance of RNA virus and suggest how this may play a similar role in the clearance of COVID-19 as evident in our case that demonstrated persistent positivity.

Conclusion:

The importance of understanding the scientific basis of extended viral shedding during the COVID-19 pandemic is now centre-stage in the establishment of robust track and trace services to allow the recovery and function of societies and economies. We propose that deficient-MMR may contribute to the persistence of SARS-CoV-2 RNA shedding. Future studies could open new avenues for research and may give rise to epidemiological or early therapeutic interventions.

Background

Preliminary reports show that the median duration of shedding for severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) is 20 days (Interquartile range [IQR]17-24 days) (1). However, it can last longer for the hospitalized patients with severe COVID-19 infection. Several independent risk factors have

been identified to be responsible for the prolonged SARS-CoV-2 ribonucleic acid (RNA) viral shedding(2-4), which can be up to 34 days (IQR 24-40 days). These include obesity, age ≥65 years, male sex and invasive mechanical ventilation. It is not known whether particular viral or host related molecular mechanisms are involved in the efficiency of SARS-CoV-2 RNA clearance by the host cells, though literature exists on the contribution of DNA MMR (mismatch Repair) pathway in the antiviral response to other RNA viruses, e.g. influenza, coronavirus (5). Herein, we report a case of hereditary nonpolyposis colorectal cancer (HNPCC) that, after contracting mild COVID-19 infection manifested prolonged polymerase chain reaction (PCR) test positivity for SARS-COV-2. We propose that deficient-MMR (dMMR) may have a role in the persistent shedding of SARS-CoV-2 RNA.

Case Presentation

The case is a 69-year old man with HNPCC (Lynch Syndrome), with a history of pancolectomy and Ileo-rectal anastomosis in 2004, completion proctectomy and ileostomy for pT1 adenocarcinoma in the rectal remnant in 2012 and nephroureterectomy for pT1 grade 3 transitional cell carcinoma of the left ureter in 2014. In 2016, he received radical external beam radiotherapy for a T3aN0M0 prostate adenocarcinoma.

On the 17th of January 2018, he underwent a Whipple's procedure and a small bowel resection for contemporaneous pT3aN1(1/21) M0 adenocarcinoma of the ampulla and pT3 adenocarcinoma of the duodenum. He was left with a high output stoma. His body mass index (BMI) was 25. He was on anticoagulants for recurrent venous thromboembolism (VTE) and had no other comorbidities.

Surveillance imaging in June 2019, demonstrated metastases to the interaortocaval lymph nodes. He received FOLFOX4 chemotherapy till October 2019 and subsequently remained stable.

On April 4th, 2020, he presented with recurrent episodes of bleeding per ileostomy and a 2-day history of fever, lethargy and dry cough. His highest recorded temperature was 37.5 ◦C. He was not breathless and his oxygen saturation was 99% on air. His CURB-65 score was 3 [Urea 8.8 mmol/l, diastolic blood pressure (BP) 60 mm (Hg) and age >65]. He was anaemic (haemoglobin 80g/l), leukopenic (WBC 3.3x10^9/L) and lymphopenic (0.75x 10^9/L). His coagulation screen was normal and his blood type was A-positive. He tested positive for SARS-CoV-2 PCR nasopharyngeal swab (NPS). Computed tomography of the chest/abdomen/pelvis showed peripheral patchy ground glass appearance, primarily in the right lower lobe of the lung. There was evidence of disease progression with enlarged aorto-caval nodes that were now invading the adjacent Roux limb. He received red blood cell transfusions, intravenous fluids and antibiotics. His anticoagulation was withheld. He continued to manifest melena with tachycardia (100/min) and hypotension (BP 96/56 mmHg). He received further transfusion, tranexamic acid for 2 days and palliative haemostatic radiotherapy (20 Gy in 5 fraction) to the aorto-caval mass. A SARS-CoV-2 PCR NPS on day 24 was positive. His symptoms improved and he was discharged.

He was readmitted three weeks later with dehydration, reduced stoma output and acute kidney injury. There were no symptoms of COVID-19, however, his NPS was still positive for SARS-CoV-2 (Day 54). He improved with supportive treatment and was discharged after 5 days.

In June 2020, he was seen for a short-lived pyrexia. Chest X-ray was normal. No obvious infective cause was found. SARS-CoV-2 PCR (day 63) from NPS was negative. His COVID-19 total antibody level was consistent with the exposure to SARS-CoV-2.

Discussion And Conclusion

The median duration of viral shedding is 2-3 weeks in mild COVID-19 disease (1). In the above-mentioned case, it persisted for at least 54 days though he recovered from mild COVID symptoms. Other than being a male and older than 65years, he had no risk factors for extended SARS-CoV-2 RNA shedding.

HNPCC is an autosomal dominant genetic condition of inherited mutations causing impaired/deficient DNA mismatch repair (dMMR).

The DNA MMR pathway is a component of DNA damage response (DDR). It is required for innate cellular antiviral response and control of cellular fate following Influenza A Viral infection (5) (Fig. 1). This pathway prevents the accumulation of oxidative DNA lesions in the antiviral gene foci and thereby contribute to non-lytic viral clearance and cell survival in club cells which is a subset of respiratory epithelial cells in lungs (5). A higher level of DNA MMR activity allows repair of virus induced damage and facilitate the transcriptional expression of these antiviral genes (5).

During their life cycle, the RNA viruses can induce significant DNA damage/genetic instability in the host cells. This has been shown for Human immunodeficiency virus 1, Human T-cell lymphotropic virus, Hepatitis C virus (HCV), Infectious bronchitis virus, Influenza A virus (IVA), Chikungunya virus, Sindbis virus, La Crosse virus, Rift valley fever virus and Avian Reovirus (6). They manipulate components of the DDR pathway which allow their pathogenesis and propagation (6).

Some RNA viruses (e.g. IAV, HCV and alphaviruses) are known to activate DNA damage response and also cause downregulation of the DNA MMR pathway (5, 7). It has been found that while the IAV generally leads to reduction of DNA MMR in the infected host cells, club cells have the unique ability to maintain normal levels of DNA MMR and thereby survive the infection. Suppression of the DNA MMR pathway in the club cells with recombinant IVA strain prevents club cell survival and causes an increase in the severity of viral disease in vivo (5). This points to the role of the MMR pathway to promote genes responsible for viral clearance in the infected cells (Fig. 1). Therefore, it is possible that a connection exists between dMMR and persistent positivity for viral shedding following SARS-CoV-2 infection; where the host repair mechanism is affected following oxidative damage and impaired MMR, resulting in reduced viral clearance.

The long or short-term clinical significance of our observation is noteworthy. Although, this patient manifested only mild COVID-19 disease and mounted an antibody response within an expected time-course, he had shed the virus for 54 days. We have not found any on-going post-COVID morbidity separate to the symptoms from his underlying malignancy and treatment.

This unique case of a cancer patient may shed light on the association of deficient MMR and prolonged positivity for SARS-CoV-2. Future study could open new avenues for research. In the present day, with the existence of robust and swift assays such as next generation sequencing and whole genome sequencing, identifying such individuals at the earliest may give rise to epidemiological interventions (such as targeted prolonged quarantine/self-isolation) or early therapeutic interventions such as the use of antivirals.

SARS-COV-2 PCR assay

Roche Cepheid assay was used for nasopharyngeal swabs tested for SARS-COV-2.

Abbreviations

ATR	ATM and Rad3 related
BP	Blood pressure
CHK	Checkpoint
COVID-19	Coronavirus disease 2019
CURB-65	Confusion, blood Urea nitrogen, Respiratory rate, Blood pressure, Age 65 or older
DNA	Deoxyribonucleic Acid
dMMR	Deficient mismatch repair
DDR	DNA damage pathway
FOLFOX	Folinic acid, flurouracil, oxaliplatin
Gy	standard dose Gray
Hb	Haemoglobin
HCV	Hepatitis C virus
HNPCC	Hereditary Nonpolyposis Colorectal Cancer
IAV	Influenza A virus

IQR	Inter quartile range
M	Metastases
MMR	Mismatch Repair
N	lymph Node
NPS	Nasopharyngeal swab
PCR	Polymerase Chain Reaction
ROS	reactive oxygen species
RNA	Ribonucleic Acid
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
Ss	single strand
T	Tumour
WBC	White Blood Cell

Declarations

Ethics approval, consent to participate and Consent for publication

The patient has provided us with signed written consent for this report.

Competing interests

None of the authors has any conflict of interest to disclose concerning this case.

Availability of data and materials

No supporting data to access for this case report.

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Authors’ contribution

AM proposed the concept, prepared, and edited manuscript. FH[a,b] collected data, prepared, and edited manuscript. FH[c] constructed the figure, edited and reviewed manuscript. PL collected data and reviewed manuscript. All authors read and approved the final manuscript.

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Not applicable

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Figures

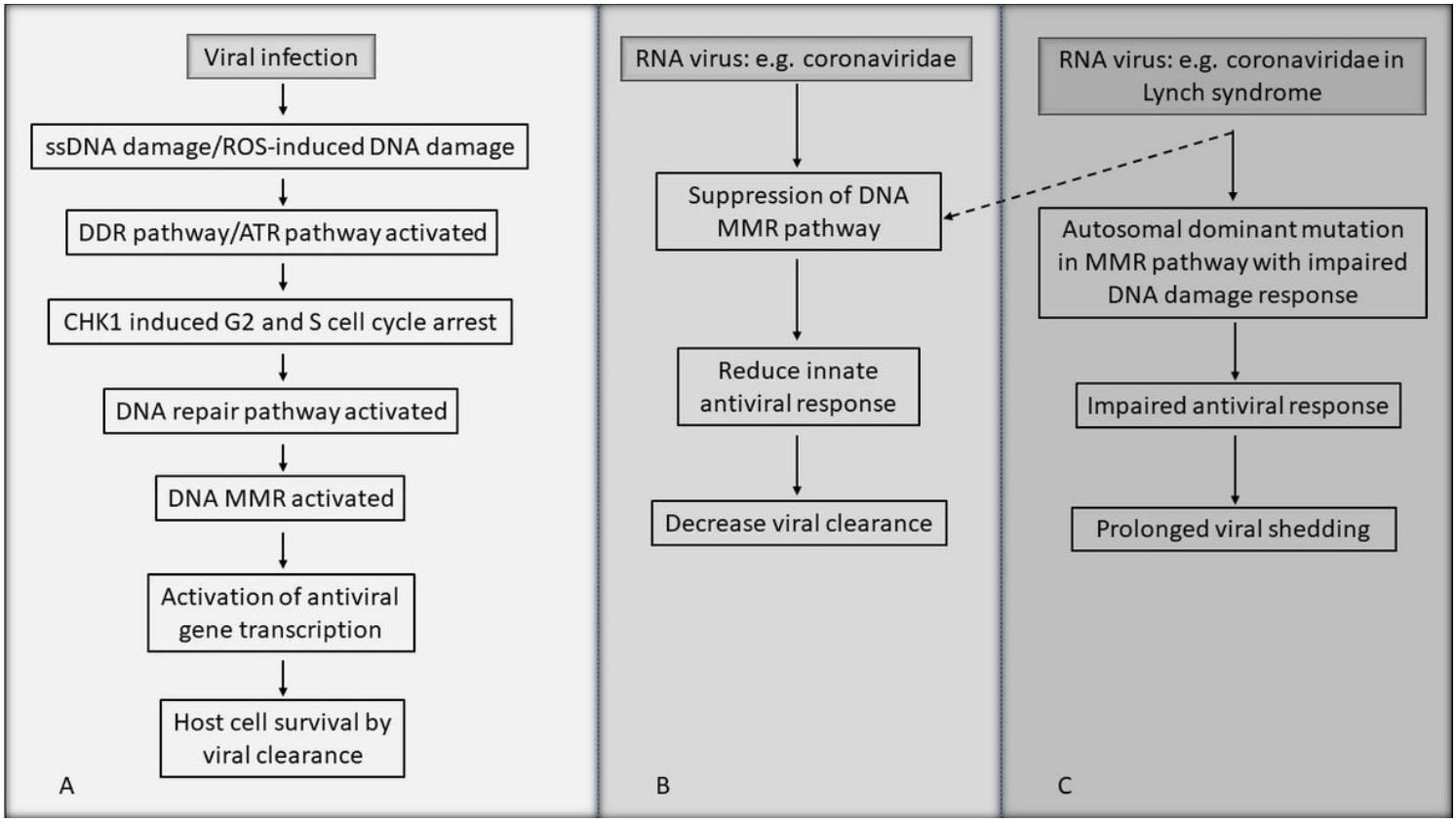

Figure 1

Cellular viral clearance response after viral infection. Schematic representation of cellular viral clearance response after viral infection (A), in case of coronaviridae (B) and in this patient with Lynch syndrome (C). ss (single strand), ROS (reactive oxygen species), DDR (DNA damage repair), ATR (ATM and Rad3 related), CHK (Checkpoint), MMR (mismatch repair).