Rise in Unusual and Rare Cancers in Long Covid Patients: Rural Clinic Experience with Gastrointestinal Stromal Tumors (GIST)

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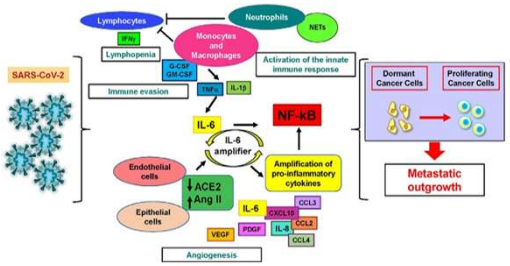
Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has shown diverse life-threatening effects, most of which are considered short-term. In addition to its short-term effects, which has claimed many millions of lives since 2019, the long-term complications of this virus are still under investigation. Like many oncogenic viruses, it has been hypothesized that SARS-CoV-2 employs various strategies to cause cancer in different organs. These include leveraging the renin angiotensin system, altering tumor suppressing pathways by means of its nonstructural proteins, and triggering inflammatory cascades by enhancing cytokine production in the form of a "cytokine storm" paving the way for the emergence of cancer stem cells in target organs. Since infection with SARS-CoV-2 occurs in several organs either directly or indirectly, it is expected that cancer stem cells may develop in multiple organs. Thus, we have reviewed the impact of coronavirus disease 2019 (COVID-19) on the vulnerability and susceptibility of specific organs to cancer development. It is important to note that the cancer-related effects of SARS-CoV-2 proposed in this article are based on the ability of the virus and its proteins to cause cancer but that the long-term consequences of this infection will only be illustrated over time.

Abnormal immune response to viral infections can indirectly trigger the secondary mutational events that promote clinical leukemia development[1]. Additionally, SARS-CoV-2 can interact significantly with the renin-angiotensin system (RAS), which has been suggested to have a role in neoplastic hematopoiesis[2-4]. Thus, we hypothesize that SARS-CoV-2 could potentially act as the second hit needed for leukemogenesis, inducing hematologic neoplasia in genetically pre-disposed individuals[5-8].

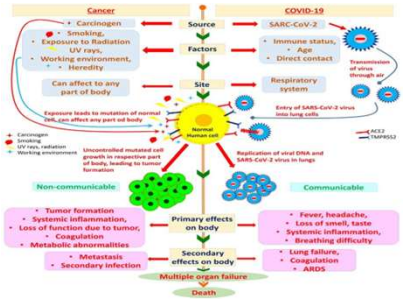


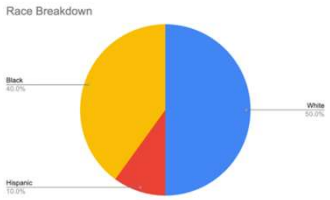
Inflammatory Response to COVID-19 and Ultimate Neoplastic Triggers[9-12]

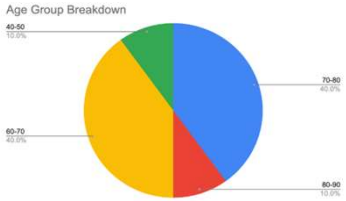
Mechanism on SARS-CoV-2 Cellular and molecular factors involved in the pathogenesis of severe COVID-19 play also multiple roles in cancer. Lymphocytes are activated during the first phase of the disease and produce interferon-gamma (IFNg), then their numbers and activity decreases, resulting in lymphopenia. Activated innate immune response cells (neutrophils and monocytes/macrophages) sustain immune evasion by depressing lymphocyte activity and hindering lymphocyte access to the tumor. They also trigger the production of interleukin-6 (IL-6), starting the systemic release of pro-inflammatory cytokines and chemoattractant by immune and non-immune cells. Interleukin-1b (IL-1b) and tumor necrosis factor a (TNF-a) further stimulate the production of IL-6. In virus-infected epithelial and endothelial cells, the downregulation of angiotensin-converting enzyme-2 (ACE2) that follows SARS-CoV-2 entry releases the brake from angiotensin II. This event stimulates additional IL-6 production by activating the IL-6 amplifier, a positive feedback loop leading to the uncontrolled production of pro-inflammatory factors. At the same time, neutrophil extracellular traps (NETs) generated by activated neutrophils physically obstruct the access of lymphocytes to inflamed tissues and promote the reawakening of dormant cancer cells. Additional cytokines increased during COVID-19 include granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF) (which stimulates neutrophil and monocyte expansion), platelet derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) (which may contribute to tumor angiogenesis). All these events may generate a microenvironment favorable to the proliferation of dormant tumor cells and to subsequent metastatic outgrowth.

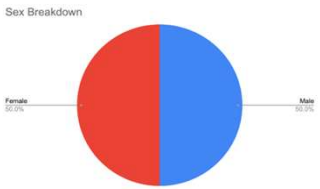
Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal malignancy (sarcoma) of the gastrointestinal (GI) tract; however, they only comprise 1–2% of all GI malignancies. GISTs originate from pluripotential mesenchymal cells committed to become interstitial cells of Cajal (ICC), which are the pacemaker cells situated between the circular and longitudinal layers of the muscularis propria along the GI tract[13]. Most tumors affect the stomach and small intestine. The incidence of GIST is 10–15 cases per million worldwide, with ~5000 cases per year in the United States[14-15]. Small incidental lesions are commonly identified during abdominal surgery, radiologic or endoscopic studies, and at autopsy[16].

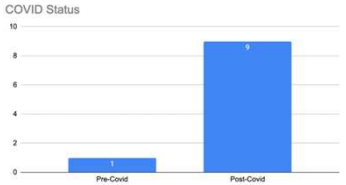
Pre Covid pandemic, our community practice has seen only one patient with confirmed diagnosis of Gastrointestinal Stromal tumor keeping up with national incidence. However, post Covid we saw 10 new patients with GIST. Of these patients, 4 had localized diseases while 6 patients had distant spread of disease including liver metastases.

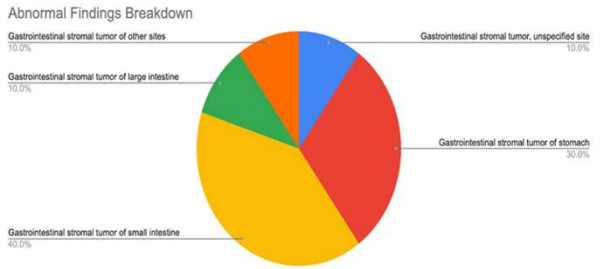












Discussion

SARS-CoV-2 induces a pro-inflammatory cytokine known as a cytokine storm. Once acute crisis is over between 4-12% of patients with severe Covid develop Long Covid. The majority of Long Covid manifestations result from chronic ongoing inflammatory cascade activation (Figure 3,4) leading to various clinical manifestations from headaches, memory loss, cardiac issues, chronic cough, Steatoses in liver to potential of neoplastic upregulation[17-34]. One of the main inflammatory cytokines participating in this process is interleukin-6 (IL-6). The extent to which IL-6 is important in the pathogenesis of COVID-19 is indicated by a high level of serum IL-6 (>32.1 pg/mL) being a prognostic factor for disease severity and poor prognosis. The association of chronic inflammation with autoimmune diseases and cancer has been already established. The IL-6 amplifier (IL-6 Amp) mechanism involves the activation of signal transducer and activator of transcription 3 (STAT3) by IL-6, and the activation of NF-κB by IL-17 or TNF-α. STAT3 activation can cause G1 to S cell cycle transition along with the induction of c-myc, pim1 and pim2 protooncogenes. The evidence of cancer progression via the activation of IL-6, STAT3, and subsequently pim1 has been illustrated in pancreatic and breast cancer. In addition, the IL-6-stimulated STAT3 signaling pathway can cause metastasis by epithelial–mesenchymal transition (EMT) in head and neck cancer. This signaling pathway can also cause angiogenesis via induction of hypoxia-inducible factor-1α (HIF-1α) and VEGF in cervical cancer. Therefore, since IL-6 activates STAT-3, which has a key role in cancer progression and inflammation, there might be a possible relationship between SARS-CoV-2 infection and the susceptibility of these patients to cancer

TNF-α also plays a critical role in initiating an inflammation cascade via NF-κB activation. Inflammation and NF-κB can cause tumors by evoking DNA damage, chromosomal instability and mutations via different processes including the production of ROS, the induction of activation-induced cytidine deaminase and the prevention of apoptosis. In addition, some viruses including Epstein-Barr Virus (EBV) stimulate NF-κB to exert their oncogenic effects. As with the IL-6/STAT3 pathway, activation of the TNF-α/NF-κB pathway enhances angiogenesis via VEGF, EMT and metastasis. The plethora of cytokines released during the cytokine storm, including interleukin-1β (IL-1β) and TNF-α, are responsible for the activation of protein kinases involved in the phosphorylation of heat shock protein 27 (HSP-27). Since HSP-27 can inhibit multiple steps involved in apoptosis it is a sign of poor prognosis in many different cancers. Therefore, TNF-α may indirectly have a key role in cancer progression.

Conclusion

Long Covid is a multi-systemic illness resulting from untamed ongoing inflammatory response encompassing, impacts on multiple organ systems, and vascular and clotting abnormalities, cardiac issues, memory lapses and autonomic dysfunction. It has already debilitated millions of individuals world-wide, and that number is continuing to grow. We are still learning about trends emerging in new cancers and rare cancers. However, due to slow development of neoplastic disorders and lack of prospective studies it may be few years before we fully understand the oncogenic potential of the Covid virus. If history teaches us anything, by now we understand the oncogenic potential of other viruses like Hepatitis, EBV, Human T-cell Lymphotropic Viruses 1 and 2, Human Papillomavirus, we need to be more cognizant of this issue as Covid Virus is ubiquitous and population-based impact may be a huge challenge.

Diagnostic and treatment options are currently insufficient, and many clinical trials are urgently needed to rigorously test treatments that address hypothesized underlying biological mechanisms, including viral persistence, neuroinflammation, excessive blood clotting and autoimmunity. There is a need to identify primary inflammatory drivers and consider interventions sooner than later.

References

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