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# RELAPSES IN THREE CASES OF CLASSICAL HODGKIN'S DISEASE AFTER COVID-19 INFECTION

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## ABSTRACT
In the era of COVID-19 pandemic, patients with cancer suffered because of treatment delay and interruption as well as excessive morbidity and mortality. A possible link of cancer relapses following COVID-19 infection has been mentioned in literature.
We aim to present 3 cases of adult patients with classical Hodgkin's disease who were in remission after frontline chemotherapy. All the 3 patients developed mild to moderate COVID-19 infection confirmed by PCR testing and recovered within 2-4 weeks. Confirmed relapses of Hodgkin's disease occurred in the 3 patients after 1, 3 and 4 months, respectively. A possible link awaits further studies of similar cases.

***Keywords:*** *Hodgkin's Disease, COVID-19*



## INTRODUCTION
COVID-19 pandemic that started in late 2019 affected the world population deeply in different ways. Patients with cancer had been greatly affected and many of them had their treatment plan modified or interrupted and an important number died with severe COVID-19 (Li *et al.*, 2021).
The mortality rate of cancer patients who contracted SARS-CoV-2 virus was reported to be 6% in comparison to 1% for healthy people in China. Cancer patients are reported three times more susceptible to SARS-CoV-2 infection with possible poor prognosis than individuals without cancer because of their systemic immunosuppressive state caused by the malignancy and anticancer treatments, such as chemotherapy or surgery (AACR Virtual Meeting, 2020). More than half a million people in the United States are receiving chemotherapy and more than 1.5 million people will be diagnosed with cancer. Patients who are under active chemo/radiotherapy or recently underwent stem cell transplantation are particularly at higher risk (Jyotsana & King, 2020).
SARSCoV-2 recruits proteins involved in cellular replication, DNA damage, metabolism, and epigenetic regulation that are also involved in cancer pathogenesis (Tutuncuoglu *et al.,* 2020). At the same time, COVID-19-induced inflammation may affect malignant cells and the microenvironment they reside in. Emerging evidence suggest that COVID-19 may affect a particular stage in the tumor's life cycle represented by dormant cancer cells (DCCs) (Francescangeli *et al*., 2020; De Angelis *et al.,* 2019).
Herby, we describe a series of 3 cases of Hodgkin disease who relapsed after COVID-19 infection. All of these patients were managed at the Hematology Centre/ Medical City Campus/ Baghdad/Iraq. Whether this was a coincidence or there is a causal relationship awaits further studies.

## CASE 1
L.M.Y. , A 30 years old gentleman diagnosed with classical Hodgkin's lymphoma (mixed cellularity subtype, confirmed by immunohistochemistry) stage IIIB , non bulky disease on August 2020.He was

started on ABVD protocol for two cycles, interim PET scan showed persistant active disease so he was shifted to escalated BEACOPP protocol for four cycles ended at February 2021. End of treatment PET scan showed a complete metabolic response and the patient was kept on follow up, last time seen on April 2021 and he was in a good health with no lymphadenopathy, no organomegaly and his CBC was normal.

In May 2021 he presented with fever, dry cough and generalized malaise. The swab for COVID 19 infection was positive by PCR, CRP was elevated, D-dimer 1.73 ug/ml, oxygen saturation was at the range of above 90%. He was treated with the antiviral favipiravir along with antipyretics, antibiotics and the disease course were of moderate severity, after 14 days he was free from symptoms and returned to his daily life activities.

On 22.6.2021 he presented with night sweating and fever, by examination there were cervical and inguinal lymphadenopathy, PET scan showed relapsed disease above and below diaphragm. Lymph node biopsy confirmed classical Hodgkin's disease. He received one cycle of DHAP protocol with progressive disease clinically, then received two doses of Pembrolizumab with no response, the patient died in October 2021.

**CASE 2**

S.H.U. , A 55 years old lady was diagnosed with classical Hodgkin's lymphoma ( mixed cellularity subtype) stage IVB non bulky on February 2020, confirmed by immune-histochemistry. She was started on ABVD protocol for 6 cycles and her end of treatment PET-CT scan showed a complete metabolic response .The patient was kept on follow up, last time seen on March 2021 and investigations along with examination were all normal.

On April 2021 she presented with malaise, fever and dry cough, swab for COVID 19 infection was positive by PCR. The patient was treated with antiviral favipiravir with supportive treatments and the disease course was of moderate severity, she recovered back three weeks later.

On July 2021 she presented with cervical lymphadenopathy along with night sweating, by examination there were multiple cervical and axillary lymphadenopathy, biopsy confirmed relapsed classical Hodgkin's disease , she received three cycles of ICE protocol with partial response then she was shifted to BeGeV protocol and received two doses, but she had progression of her disease. She unfortunately died in October 2021.

**CASE 3**

A.A.J., A 49-year-old lady was diagnosed as classical Hodgkin lymphoma stage IB in June 2020 after a cervical lymph node biopsy and was confirmed by immune-histochemistry. She was treated with 4 courses of ABVD. An end treatment PET-CT revealed complete metabolic response.

In April 2021 she contracted mild to moderately severe COVID-19 infection diagnosed by PCR of a nasal swab, which responded to treatment with rest, paracetamol and azithromycin. A CT scan of neck, chest and abdomen just before this episode revealed no evidence of relapse.

In August 2021 she started to have fever, weight loss and sweating. Her Hb was 10.3 gm/dl, WBC 3.4 x $10^9$/l, and platelet $183x10^9$/l. a repeat PECT-CT revealed metabolically active lymph nodes in neck, mediastinum and para-aortic regions. A lymph node biopsy confirmed relapsed Hodgkin disease and she underwent 2 cycles of ICE followed by autologous SCT.

**DISCUSSION**

There exists no clear evidence that SARS-CoV-2 is causative, related to, or modulates cancer pathobiology. Both viruses and cancers express proteins that are recognizable by host T cells and both prompt T cell mediated inflammation. A number of oncogenic (HBV, HCV, HPV, EBV, HIV) and oncolytic viruses (Coxsackievirus, reovirus, vaccinia virus, adenovirus) are known to cause and regress various cancer types, respectively (Hotchkiss & Moldawer , 2014). With regards to the biological interconnection between COVID-19 and cancer, ACE2, cytokine storm, age and coagulopathy are few

strong factors that connect COVID-19 and cancer. A deeper understanding of these connecting links may guide us in finding novel anti-viral and anti-cancer therapeutic options (Jyotsana & King ,2020).
This case series describes occurrence of relapse of 3 patients with Hodgkin disease following COVID-19 infection which was documented by PCR testing. All the 3 patients recovered fully from COVID-19 infection. The time lapse between COVID-19 infection and confirmation of relapse was 1 month for the case 1, 3 months for case 2 and 4 months for case 3. All 3 relapses were confirmed by PET-CT and lymph node biopsy. Two of the 3 patients died with active Hodgkin disease.The relatively long timelapse between COVID-19 infection and confirmed relapse is not against this speculation as COVID 19 infection can cause inflammation that can persist for a long time.This chronic inflammatory process was describes as a delayed multisystem inflammatory syndrome which has been recognized in adults that is distinct from acute COVID-19–associated hyperinflammatory syndrome ( Morris SB *et al*. ,2020)**.** These post-covid syndrome cases share proteomic findings with CIRS (Shoemaker *et al*., 2021) .

***COVID-19 and cancer reactivation***

Several factors involved in COVID-19 may play a role in the reawakening of dormant tumor cells. The strongest evidence points to neutrophil extracellular
traps (NETs) and neutrophils, which are emerging as important players in COVID-19 pathogenesis. NETs involvement in COVID-19 was first proposed upon observation of intense neutrophilic infiltration in the lungs of autopsied COVID-19 patients. The presence of NETs in COVID-19 patients was then confirmed and showed to be responsible for immunothrombosis. Acute lung inflammation and NETs have been respectively shown to trigger the exit from dormancy of breast DCCs, leading to metastasis formation (Francescangeli *et al*.,2020) ; ( De Angelis *et al.,* 2019).
COVID-19 also has been shown to lead to immune system dysregulation and the long-term significance of this in children with leukemia who develop SARS-CoV-2 infection is unknown. Given that COVID-19 is a relatively new clinical entity, there are limited data as to whether SARS-CoV-2 infection affects incidence or outcome of leukemia.
Two cases of patients with high-risk B-cell ALL (B-ALL) who developed isolated CNS relapses following confirmed SARS-CoV-2 infection are reported. COVID-19 vaccines were not yet available at the time of infection for both patients. The first case after 56 days of covid and the second after also after 56 days (Walker *et al.,* 2021).
Recent studies on the long-term clinical outcomes of COVID-19 showed a high incidence of persistent symptoms after the acute disease. The possibility that inflammatory and/or autoimmune processes may be a common consequence of SARS-CoV-2 infection raises further concerns about the risks of DCCs reawakening, which may be enhanced in chronically inflamed microenvironments (Francescangeli *et al*.,2020).
IL-6 was found to be the driving factor for tumorigenesis and anti-apoptotic signals as well as the key biomarker for the diagnosis, and prognosis evaluation of malignant tumor. Therefore, it will bring great significance to investigate not only the protective effect of IL-6 inhibitors against the inflammatory damage caused by COVID-19 but also their beneficial effects for cancer treatment. Ham et al studied the gastric cancer cell lines of MKN-1 and MKN-45 and found that the anti-IL-6 receptor monoclonal antibody tocilizumab can eliminate cancer associated fibroblasts (CAF)-mediated inhibition of apoptosis. Compared with 5-fluorouracil treatment alone, combination treatment with tocilizumab and 5-fluorouracil significantly reduced the cancer weight of CAF-mixed xenograft mice. At the present time, the interaction rate between anti-cancer drugs and anti-COVID-19 drugs is relatively modest and the therapeutic effect of anti-COVID-19 drugs on cancer patients needs to be explored according to numerous experimental and clinical data (Li *et al.* ,2021 ) ; (Ham *et al.,* 2019).
Severe COVID-19 may increase the risk of subsequent cancer recurrence by inducing the reactivation of dormant cancer cells (DCCs). According to this viewpoint, the major events occurring during severe COVID-19 such as immune-mediated tissue inflammation, impairment of T-cell and natural killer (NK)

cell activity, neutrophil hyperactivation and thrombocytosis may collectively generate a temporary pro-tumorigenic
microenvironment favourable to DCCs reawakening. Metastatic reawakening has been reported to be triggered by disruption of tissue homeostasis that usually occurs during acute or chronic inflammation. Pathogen-induced infection has been reported to promote the migration of cancer cells to metastatic sites and the reactivation of dormant metastatic cells (Francescangeli *et al*.,2020).
Immune responses in COVID-19 patients are orchestrated by proinflammatory cytokines (IL-1, IL-6, IL-8, and TNF-$\alpha$), which are also known to drive tumorigenesis (Del Valle *et al.,* 2020). Additionally, COVID-19 has been associated with T-cell depletion and activation of oncogenic pathways, including JAK-STAT, MAPK, and NF-$\kappa$B, potentially increasing the risk of cancer development (Li *et al*., 2020)**.** Hypoxia due to inflammation or virus-induced angiotensin-converting enzyme 2 depletion can induce oxidative stress and malignant transformation (Saini & Aneja 2021) ; (Al Tameemi *et al.,* 2019).
Nekooghadam et al (2021) described a 61-year-old man presented with complaints of weakness, nausea, vomiting, and epigastric pain. His past medical history was just relevant for a recent covid-19 infection presenting with symptoms of myalgia, cough, shortness of breath and weakness, about 40 days later, the patient again presented to the emergency department of our hospital complaining of a new progressive disabling weakness, accompanied by anorexia, epigastric pain, nausea, vomiting and nonbloody watery diarrhea. Subsequently, a bone marrow smears surprisingly revealed sheets of large vacuolated blasts forming more than 20% of nucleated marrow cells. The cells were morphologically compatible with acute leukemia of lymphoid linage (ALL L3) or myeloid linage (AMLM4) (Nekooghadam *et al.* ,2021).

***COVID-19 and cancer regression***

Challenor & Tucker ( 2021) reported the alleviation of lymphadenopathy in a patient with Epstein–Barr virus (EBV)-positive classical Hodgkin lymphoma after his infection with SARS-CoV-2. No corticosteroid or immunochemotherapy was given, and the underlying mechanism was probably attributed to the anti-tumor immune response induced by SARS-CoV-2 infection. This suggests a potential association between anti-viral and anti-tumor treatments and sheds light on the immunotherapy of malignant disease (Challenor & Tucker , 2021) .
Kandeel *et al* (2021) described two cases of patients who were diagnosed as AML and relapsed ALL concomitantly with COVID-19 pneumonia. Patients were not started on chemotherapy and received COVID-19 protocol with supportive measures. Approximately after one month, all evidence of AML and ALL started to disappear, and only the myelodysplastic features persisted in the first case that was diagnosed as AML.This condition may be explained that the COVID-19 infection could potentially evoke an anti-tumor immune response through cross-reactivity of the virus-specific T cells with tumor antigens, or through non-specific activation of the natural killer cells by the inflammatory cytokines produced in response to viral infection Another explanation could be that COVID-19 may act as an oncolytic virus, which is causing destruction of the tumor cells and release of the tumor-associated antigen (TAAs) from the tumor cells (Kandeel *et al.* ,2021)
Returning back to our patients, the relation between COVID-19 infection and occurrence of relapse cannot be confirmed in the light of conflicting reports. We did not measure any inflammatory markers at the time of relapse and probably its interpretation will be difficult as both Hodgkin disease and post-COVID-19 CIRS like syndrome may induce similar markers changes.
In conclusion, we believe that it is worthy to consider the possibility of a relation of relapse of malignant diseases to the effects of COVID-19 infection and further studies of similar cases in detail may give an answer.

**CONFLICT OF INTEREST**

Nothing to declare

**REFERENCES**

**Al Tameemi W, Dale TP, Al-Jumaily RM K & Forsyth NR (2019).** Hypoxia-modified cancer cell metabolism. *Frontiers in Cell and Developmental Biology*, **7**, 4.

**Challenor S, Tucker D ( 2021).** SARS-CoV-2-induced remission of Hodgkin lymphoma. *British Journal of Haematology*. **192**(3) 415. doi:10.1111/bjh.1711660

**De Angelis ML, Francescangeli F, Zeuner A (2019)**. Breast cancer stem cells as drivers of tumor chemoresistance, dormancy and relapse: new challenges and therapeutic opportunities. *Cancers* **11**(10):1569.

**Del Valle DM., Kim-Schulze S, Huang HH *et al*. (2020).** An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nature Medicine*, **26**(10), 1636–1643.

**Francescangeli F, De Angelis ML & Zeuner A (2020)**. COVID-19: a potential driver of immune-mediated breast cancer recurrence? *Breast Cancer Research* 22, 117 https://doi.org/10.1186/s13058-020-01360-0

**Ham IH, Oh HJ, Jin H *et al* (2019).** Targeting interleukin-6 as a strategy to overcome stroma-induced resistance to chemotherapy in gastric cancer. *Molecular Cancer* **18** (1) 68. doi:10.1186/s12943-019-0972-859

**Hotchkiss RS and Moldawer L (2014).** Parallels between cancer and infectious disease. *New England Journal of Medicine* **371**(4) 380– 383.

**Jyotsana N, King MR (2020).**The Impact of COVID-19 on Cancer Risk and Treatment [Published online ahead of print, 2020 Jun 29]. *Cellular and Molecular Bioengineering* **13**(4) 1-7.doi:10.1007/s12195-020-00630-3.

**Kandeel EZ, Refaat L, Abdel-Fatah R *et al.* ( 2021)** Could COVID-19 induce remission of acute leukemia?. *Hematology (Amsterdam, Netherlands)* **26**(1) 870-873. doi: 10.1080/16078454.2021.1992117. PMID: 34719343.

**Li G, Fan Y, Lai Y *et al.* (2020).** Coronavirus infections and immune responses. *Journal of Medical Virology*, **92**(4), 424–432.

**Li Y, Wang X, Wang W (2021). The Impact of COVID-19 on Cancer**. *Infection and drug resistance* **14** 3809-3816 https://doi.org/10.2147/IDR.S324569

**Morris SB, Schwartz NG , Patel P *et al.* ( 2020).** Case series of multisystem inflammatory syndrome in adults associated with SARS-CoV-2 infection - United Kingdom and United States, March-August . *MMWR Morbidity and Mortality Weekly Report* **69** (40) 1450–1456.

**Nekooghadam SM, Moradi A, Kimia KT, Pishgahi M ( 2021).** A Case of Acute Leukemia Following Remission of COVID-19 Infection; an Urge to Search for a Probable Association. *Archives of academic emergency medicine* **9** (1): e51, DOI: https://doi.org/10.22037/aaem.v9i1.1338.

**Saini G, Aneja R (2021).**Cancer as a prospective sequela of long COVID-19. *BioEssays: news and reviews in molecular, cellular and developmental biology* **43**(6) e2000331. doi: 10.1002/bies.202000331. Epub 2021 Apr 29. PMID: 33914346; PMCID: PMC8206711.

**Shoemaker R, McMahon S, Heyman A, Lark D, Westhuizen M, & Ryan J (2021).** Treatable metabolic and inflammatory abnormalities in Post COVID Syndrome (PCS) define the transcriptomic basis for persistent symptoms: Lessons from CIRS. *Medical Research Archive* **9**(7). doi: 10.18103/mra.v9i7.2493

**Tutuncuoglu B, Cakir M, Batra J *et al.* (2020).** The landscape of human cancer proteins targeted by SARS-CoV-2. *Cancer Discovery* **10** (7) 916–21.

**Walker SC, Reppucci JR, Ann Thompson M *et al* (2021).** Isolated CNS Relapse in 2 High-Risk B-cell Acute Lymphoblastic Leukemia Patients Following SARS-CoV-2 Infection. *Journal of Pediatric Hematology/oncology*. 2021 Dec. DOI: 10.1097/mph.0000000000002377. PMID: 34935738.