Multiple and Rare Cancers Presenting Simultaneously In The Same Patient Post Covid 19 Infection: Case Report and Review of Literature

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Abstract

Multiple primary cancers are defined as 2 or more malignancies that arise independently of each other in the same or different organs. While patients with up to cancers are not unusual to find, patients with three or more cancers are rare. Even rare is the simultaneous presence of all three cancers. We report a patient with three separate primary cancers (Squamous cell carcinoma of Epiglottis, adenocarcinoma of lung and hepatocellular cancer in the liver) post Covid. He was reported to have multiple episodes of Covid 19 (Sars-CoV-2) confirmed with labs studies consistent with Long Covid. Also, his comprehensive genomic profiling repeatedly carried out in view of resistance to treatment confirmed new mutations appearing in his genome possibly indicative of multi-dimensional impact of Long Covid.

Case Report

A 74-year-old Caucasian male presented with three separate primary cancers (SCCA of epiglottis, Adenocarcinoma of Lung and primary hepatocellular carcinoma in liver) in 2020 fall. He was a non-smoker and has not had any biological or environmental risk factors for any of these cancers. He received standard of care (SOC) treatment and initially responded well. However, with recurrent episodes of Covid 19, he progressively worsened and passed away in December 2024 after nearly 49 months of battle against cancer. He was fully functional though and was able to enjoy life to the fullest.

Conclusion

Multiple cancers from separate primary sites (3 or more) are rare occurrences. What is even more rare is that all three cancers are presented at the same time. In the context of Long Covid and inflammation, this becomes a matter of concern as evidenced by progressive development of newer genomic alterations (including pathogenic variants). This case report highlights a cautionary approach post covid for more vigilance and prospective research in patients with established Long Covid symptoms confirmed with lab studies.

Introduction

There is a noticeable increase in the synchronous and metachronous new cancers post covid due to multiple factors from immunosuppression to inflammation to mitochondrial dysfunction resulting from Covid 19 infection[1]. Typically, the incidence of multiple primary cancers ranges from 3% to 5%; most of them are two sequential cancers. It is important to separate metastases from primary site. Three or more separate primary cancers are extremely rare. Our extensive literature search concluded that the incidence of such cases with 3 or more primary sites is only about 0.3% of all malignant tumors.[2,3]

The multiple primary cancer in the same patient is thought to be due to a combination of genetic and environmental factors. The Covid 19 pandemic has created quite a lot of public health challenges due to poorly understood long term sequelae post infection also known as PASC (Post-Acute Sequelae of Covid) or Long Covid. While the surge in new cancers is being attributed to lack of timely access to cancer screening, we, as well as others, have noticed a surge in both rare cancers and new cancers in younger patient population. We have also noticed a surge in the number of patients with two or more cancers at our center. Our understanding of chronic post-acute covid tissue impact is getting little clearer as well as the final common pathways to explanation on Long Covid hoovers around sequelae of chronic inflammatory changes leading to tissue damage. Now also the evidence is emerging indicative of potential carcinogenic potential of inflammatory changes induced by Long Covid.[4-6]

Potential underlying mechanisms that may explain carcinogenic potential of Long Covid associated carcinogenesis.[4-14]

1) Chronic Inflammation: Persistent inflammatory responses may result in DNA damage, promote cellular proliferation, and inhibit apoptosis leading to higher risk of carcinogenesis
2) Epigenetic changes: PASC results in
3) Oxidative stress: Elevated oxidative stress with Long Covid from past infections are linked to an increased risk of cancer through DNA damage
4) Mitochondrial damage
5) Immune dysregulation: COVID-19 triggers immune responses, including cytokine storms, which results in chronic inflammation

There is paucity of research and on-going studies to assess carcinogenicity of Long Covid on a large-scale population based studies. Findings from[1] Ozgur et al indicate the need for increased cancer surveillance in COVID-19 survivors as well as patients with documented evidence of Long Covid. In the post-COVID-19 period, inflammation associated with excessive cytokine release, especially interleukin-6, genetic and epigenetic changes, and co-infections with oncogenic viruses such as Epstein-Barr virus or human papillomavirus may be triggering the development and progression of cancer. Our case report narrated in the following section highlights all the aspects of need to better understanding Long Covid and inflammation connection highlighted by three synchronous and metachronous cancer as well as evolving findings of newer pathogenic variants in genomic profile of this patient.

Case Report

A pleasant 74-year-old Caucasian male with h/o long standing thyroid nodules (he chose never to have them biopsied) developed progressive hoarseness of voice and cough in October 2020. Prior to this, he had had three different documented infections with Covid 19. He went to Ear, Nose, and Throat (ENT) surgeon who identified a mass in his epiglottis. He underwent a biopsy of the mass. Biopsy revealed Squamous cell carcinoma (SCCA) of the head and neck. He underwent staging scans prior to treatment. His scan revealed metachronous lesion in his left lung in the hilar region almost 3x4 cms. He underwent biopsy of the same and was found to have adenocarcinoma of the lung with distinct pathological features from his head and neck primary cancer that was squamous cell carcinoma. Simultaneously he was also found to have a small mass in his liver. Patient elected to hold off on additional biopsies due to multiple trips required to go back and forth to the hospital (due to his own perceived concerns for repeated Covid infections). With his having SCCA of supraglottic larynx with finding of a left upper lobe (LUL) lesion on PET which has turned out to be a second primary based on lung biopsy showing adenocarcinoma.

We discussed the implications of this second diagnosis and the influence this has on his treatment. Given the presence of two primaries simultaneously, we discussed options for his lung cancer, surgery vs. Stereotactic body radiation therapy (SBRT). He chose to proceed with SBRT, and I think this is a reasonable approach as we need to try and treat both cancers in a relatively expeditious fashion. He received SBRT w/ 5 fractions to the lung tumor and then we moved promptly to treatment of supraglottic cancer with fractionated radiation therapy plus chemotherapy. We reviewed the rationale for this approach, and we went over side effects of therapy and anticipated outcomes. He expressed a good understanding of his diagnoses and treatment options.

He initially received 6 cycles of concurrent chemoradiotherapy to his supraglottic region. After 6 weeks of rest, he started receiving immunotherapy with pembrolizumab. He has had a stable phase for about 12 months when he started developing progressive abdominal pain. His imaging studies in the summer of 2022, revealed progression in the size of his lesion in liver. This time he agreed to have it biopsied. Biopsy of this mass revealed evidence of hepatocellular carcinoma.

Below is the list of genomic findings in chronological order:

Genomic Findings from tumor in epiglottis: (Fall 2020)

Immunotherapy Markers: The Tumor Mutation Burden (TMB)is low; MS-Stable.

Molecular Markers: A clinically significant variant in the KAT6B gene.

Copy Number Alterations: Segmental loss of 11q22.1q25 which includes ATM, whole q arm loss of 13q12.11q34 (BRCA2, RB1), a

Whole chromosome 17 loss (TP53, BRCA 1). Focal gain of 11p15.5 which includes HRAS and whole q arm gain of 8q11.21q24.3

Germline testing: (early spring 2021)

PALB2 NM_024675.3 c.2096C>G p.S699C Heterozygous (one copy) Variant Of Uncertain Significance Susceptibility To Breast And Pancreatic Cancer (PALB2-Related) / Fanconi Anemia Group N Autosomal Dominant/ Autosomal Recessive

Genomic findings in September 2021 from Blood:

CHEK2 R145fs*16 # PRKARIA splice site 769+1G>A TP53 C238F

G**enomic findings from Liver biopsy:** (late summer 2022)

c-124C>T N/A TERT Promoter variant VAF = 20% Tier II: other findings CCND1, CDKN2A, CDK4, CTNNB1, KRAS, NRAS, TP53

Genomic Findings in September 2024 from Blood:

CHEK2 R145fs*16 ; PRKAR1A s; RAD21; TET2 01680* ; TP53 C238F, P151A

Discussion and Conclusion

The risk of getting multiple primary cancers is increasing along with the increasing number of cancer survivors. About one-third of cancer survivors over the age of 60 have been diagnosed with another primary cancer. As the number of cancer survivors and the elderly increases, the occurrence of multiple primary cancers is also likely to increase. Multiple authors 15-20 have reported case studies of three or more cancers as attributable to several different factors. However, due to the rarity of these findings, a definite conclusion cannot be reached as to true cause of multiple primaries. In addition, majority of these case reports are based on the development of sequential cancers rather than synchronous or metachronous development. Bittorf et al 20 reported in their 50,000 plus patients, metanalysis that the incidence of those with more than 2 malignancies accounted for 0.1%.

Our case report is distinct from most of the published literature. First, he had evidence of three separate primary cancers totally different biologically and in non-contiguous tissue plane. Secondly, we noticed progressive development of newer genomic findings with both pathogenic variance and therapeutic considerations. Third and the most important aspect of his situation is the ongoing recurrent evidence of Long Covid based on symptoms and corresponding laboratory findings indicative of the same.

While this is a single case report with very limited implications for population level implications, in the light of more awareness coming to our learning about Long Covid, there is a need to have large scale prospective real world evidence studies to identify and follow patients with Long Covid with a view to look at carcinogenic potential of this virus.

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