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LETTER TO THE EDITOR

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Aging and therapy-related hypogammaglobulinemia causing pneumonia: An overlooked curable entity in the chaotic COVID-19 pandemic

To the Editor,

There are multiple reports that the chaos caused by the coronavirus disease-2019 (COVID-19) pandemic has diverted our attention and priorities from some other equally or more important diseases.[1] Amidst the COVID-19 pandemic, in any respiratory illness, causing pneumonia or sinusitis, the first thing that predominates our thought process is the possibility of COVID-19. It becomes more obvious in the emergency department setting, as triage staff is provided with preset COVID-19 pathways and scores defining patient's categorization in most hospitals. For example, with a known diagnosis of cancer who presents with cough and fever with pneumonia, a high probability of COVID-19 is assigned and nasopharyngeal swabs (NPS) are sent on priority for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR). If one test comes negative, still another swab is sent with a high probability of COVID-19 in the mind. Due to discomfort, some patients may not be cooperative enough to obtain a proper NPS.[2] Moreover, obtaining NPS is a potentially risky procedure for healthcare workers. Hence, despite using proper personal protective equipment, an anxious proceduralist may lack the zeal to perform a high-quality swab. Although gargle lavage has been proposed as a safer and possibly more yielding procedure[2] but is not adopted yet in practice. All these factors further delay ruling out the possibility of COVID-19.

During such chaotic periods, we often neglect aging and therapy-related hypogammaglobulinemia that could be causing pneumonia or sinopulmonary infection in the elderly population. SARS-CoV-2 may cause infection by chance in such a patient. Despite the fact that we do not have any specific COVID-19 therapies, all efforts and time are diverted toward COVID-19 management protocols, instead of a multidirectional approach to include a more curable hypogammaglobulinemia-related bacterial pneumonia. Another factor that may lead to such an erroneous path in hematological cancer patients, and some autoimmune disorders, is the presence of lymphopenia due to therapies targeting lymphocytes (specifically B cells), as lymphopenia is an established high-risk factor for the development of severe COVID-19 disease in the elderly.[3]

Hypogammaglobulinemia can be observed at extremes of age.[4,5] Hypogammaglobulinemia is reported in the elderly population.[5] Buckley and Dorsey[5] reported a gradual decrease in Immunoglobulin G (IgG) and IgM concentrations with aging, IgG decreased considerably from third through the sixth decade. This deficiency is also discovered in blood banks in ~4% of cases of ABO blood group discrepancy reflected by missing or weak ABO isoantibodies during reverse grouping.[6]

Hypogammaglobulinemia in adults may be seen in hematological malignancies, particularly chronic lymphocytic leukemia (CLL) and multiple myeloma (MM). [7] In CLL, 27%-52% of patients have hypogammaglobulinemia[8] and transiently in 38.5% of patients after anti-CD20 therapy.[9] Other causes include immunosuppressive therapies, viral infections,[10] radiation, and immunoglobulin deficiency related to enteropathies, renal, or cutaneous loss.[7] When a cause cannot be identified, the condition is labeled as a primary immune deficiency; most frequently a diagnosis of common variable immunodeficiency is made.[10] Secondary hypogammaglobulinemia is estimated to be 30 times more frequent than primary hypogammaglobulinemia.[7]

Blot et al[11] compared between severe and mild hypogammaglobulinemia (gamma globulin levels <5 g/L, and ≥5 to <6.4 g/L, respectively) in a retrospective observational study that included 389 adult patients (age range 52-82 years). They reported a similar etiology and infection risk in both groups. The main etiologies included hematological malignancies.[11] The incidence of hypogammaglobulinemia-related infections in both groups was ~22/100/year ($P = .17$), where 78% of these were pulmonary infections ($P = .12$).[11] No etiology of hypogammaglobulinemia was found in 27.76% of the patients.[11] We speculate it could be attributed to a primary deficiency or simply be a reflection of aging.

Hypogammaglobulinemia fosters infections especially encapsulated *Streptococcus pneumoniae* or *Haemophilus influenzae* infections in more than one-third of the patients.[12] Valdamalai et al[13] reported a 38% prevalence of hypogammaglobinemia in patients with community-acquired pneumonia.[13] Interestingly, Cowan et al[14] in a retrospective cohort of invasive pneumococcal disease patients, found that 72.2% of those with an underlying hematological malignancy (CLL, lymphoma, and MM) had hypogammaglobulinemia. Timely diagnosis before the development of a serious infection is the key to reducing infection burden and is dependent on appropriate screening and recognition of risk factors. Intravenous immunoglobulin (IVIg) therapy may be required, even in milder hypogammaglobulinemia for severe and recurrent infections.[7,11,15]

This commentary was initiated by real-life scenarios that we recently came across. A 71-year-old man, with non-Hodgkin

lymphoma on chemoimmunotherapy, who presented with fever and pneumonia. After staying for 3 days in the designated area for suspected COVID-19 patients, he was found to be SARS-CoV-2 negative. His condition had deteriorated while waiting to complete COVID-19 related protocols. Fortunately, he was confirmed to have severe hypogammaglobulinemia for which IVIg was given along with antibiotics for pneumonia in the intensive care unit setting.

In another scenario, a 64-year-old man with diffuse large B cell lymphoma, who was in complete remission for the last 3 years after chemoimmunotherapy, presented with cough and dyspnea along with a history of fever and bilateral lower lobe infiltrates. He was found to be SARS-CoV-2 positive by PCR on NPS in addition to hypogammaglobulinemia. After a dose of IVIG, he was managed for the possibility of bacterial pneumonia along with supportive therapies for COVID-19. We believe that aging and underlying disease or therapy-related hypogammaglobulinemia leading to pneumonia may be overlooked during the COVID-19 chaos. We have to remain vigilant for these easily treatable possibilities instead of unidirectional efforts searching for COVID-19.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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