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NOVEL ID CASES

Pancytopenia and Profound Neutropenia as a Sequela of Severe SARS-CoV-2 Infection (COVID-19) With Concern for Bone Marrow Involvement

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Pancytopenia and neutropenia due to coronavirus disease 2019 (COVID-19) are rare. Here we report a case of neutropenia as a sequela of COVID-19 with concern for bone marrow infiltration. The patient was successfully treated with granulocyte colony-stimulating factor.

Keywords. COVID-19; GCSF; neutropenia; pancytopenia; SARS-CoV-2.

Cancer patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have increased morbidity and mortality when compared with the rest of the population [1, 2]. SARS-CoV-2 viremia and pancytopenia from infiltration of the bone marrow (BM) constitute a rare coronavirus disease 2019 (COVID-19) manifestation. We report a case of neutropenia as a sequela of COVID-19 with concern for bone marrow infiltration. Therapeutic approaches to pancytopenia in the context of COVID-19 are unknown, and use of granulocyte colony-stimulating factor (GCSF) is controversial due to concern for increased morbidity and mortality [3–5].

CASE PRESENTATION

A 44-year-old Mexican man with B-cell acute lymphocytic leukemia (ALL) in remission, chronic hepatitis B infection, and liver cirrhosis presented to the emergency room on July 2020 complaining of cough and dyspnea for 2 days. He had completed hyper-CVAD (alternating cycles of cyclophosphamide, doxorubicin, vincristine, dexamethasone, methotrexate, and cytarabine) chemotherapy followed by POMP (mercaptopurine, methotrexate, prednisone, and vincristine) maintenance therapy 48 days before admission. Vital signs revealed a temperature of 101.8°F and oxygen saturation at 84% on room air. Laboratory workup showed bicytopenia (white blood cell count 1390 cells/μL and platelet count 42 000 cells/μL). His absolute neutrophil count (ANC) was normal (3140 cells/μL) (Figure 1). His inflammatory markers were elevated (C-reactive Protein [CRP] 15.53 mg/dL, D-dimer 0.6 mg/L, ferritin 5100 ng/mL). A diagnosis of COVID-19 was confirmed via polymerase chain reaction (PCR) of a nasopharyngeal (NP) swab. His disease progressed to acute respiratory distress syndrome (ARDS) and distributive shock requiring mechanical ventilation and vasopressors. The patient was admitted during the peak of the pandemic, with a statewide remdesivir shortage and inaccessibility to convalescent plasma therapy (CPT) due to high demand. He received empiric broad-spectrum antibiotics (including vancomycin, cefepime, and later piperacillin/tazobactam), methylprednisolone 40 mg (that was tapered over 30 days), prophylactic trimethoprim/sulfamethoxazole, and acyclovir. On hospital day 13, he was extubated.

His hospital course was complicated by persisting fevers and mild hypoxia. On hospital day 17, he developed diarrhea and worsening pancytopenia. He finally received CPT on day 20. Nonetheless, his symptoms persisted, and he developed profound neutropenia with ANC <500 cells/μL on hospital day 37 (Figure 1). Cefepime and micafungin were started empirically for febrile neutropenia. Microbiology workup for his diarrhea, including *Clostridium difficile* antitoxin test and gastrointestinal pathogen panel PCR, was negative. Extensive computed tomography (CT) imaging of his thorax, abdomen, and pelvis was unrevealing.

The patient had a BM biopsy on hospital day 40. SARS-CoV-2 and cytomegalovirus (CMV) qualitative PCR from BM aspirate yielded positive results for both viruses, whereas Epstein-Barr virus PCR and herpes simplex virus PCR were negative. Immunohistochemistry was negative for CMV, and histopathology failed to demonstrate CMV-related cytopathic effects. Moreover, his BM was normocellular (40%), with no evidence of ALL recurrence or hemophagocytosis. Low-level CMV viremia (<200 copies/mL) was detected the day of the bone marrow biopsy, as well as SARS-CoV-2 viremia (56 copies/mL; Viracor Eurofins, Lees Summit, MO, USA). Our attempts to culture SARS-CoV-2 from blood and BM were unsuccessful. Hemophagocytic lymphohistiocytosis (HLH) was considered with fevers >38.5°C, splenomegaly to 22.5 cm, peripheral cytopenias, and ferritinemia (>9000 ng/mL); however, his triglycerides were normal, and his BM biopsy was inconsistent with this diagnosis. Furthermore, the patient was already receiving steroids at the time, and further diagnostics

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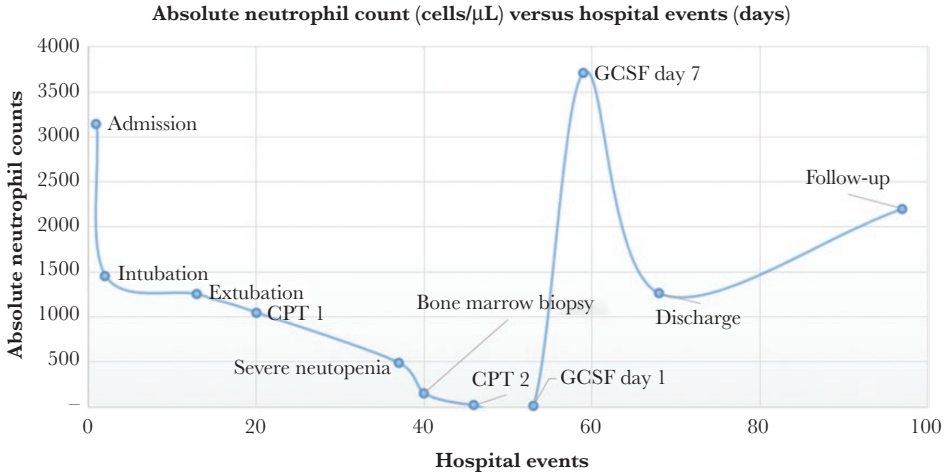

Figure 1. ANC (cells/μL) vs hospital events (days). The patient presented with normal ANC, which abruptly declined by the time he required intubation for his severe COVID-19. His ANC continued to decrease slowly thereafter, reaching a severe neutropenia threshold that resolved after GCSF administration. Follow-up labs demonstrate a normal ANC. Abbreviations: ANC, absolute neutrophil count; COVID-19, coronavirus disease 2019; CPT, convalescent plasma therapy; GCSF, granulocyte colony-stimulating factor.

including natural killer cell activity and interleukin-2 receptor were not pursued. CMV reactivation was considered; however, given negative CMV immunohistochemistry of BM specimen with lack of CMV cytopathic effects, lack of improvement after 5 days of ganciclovir, and normal colonoscopy (performed on hospital day 56 after profound neutropenia resolution), this diagnosis was excluded.

Given SARS-CoV-2 viremia with persistent systemic symptoms and negative repeat SARS-CoV-2 IgG, a second CPT was administered on hospital day 46 with a probable diagnosis of SARS-COV-2-related pancytopenia and neutropenia. Fevers, pancytopenia, neutropenia, diarrhea, and mild hypoxia persisted. Hence, on hospital day 53, a 7-day course of GCSF was started. After receiving GCSF, the patient defervesced, and his ANC recovered 5 days later (Figure 1). Additionally, his diarrhea improved, with a reduction in SARS-CoV-2 viremia from 56 copies/mL on hospital day 46 to 20 copies/mL on hospital day 60, though the authors acknowledge that this may represent variation in the test rather than true improvement. The patient was discharged home on day 68 of hospitalization, with improved yet unresolved pancytopenia and ongoing hypoxia requiring supplemental oxygen. Throughout the hospital course, our patient failed to seroconvert, with negative anti-SARS-CoV-2 IgG testing on 7 separate instances, the last on hospital day 60. Follow-up laboratory tests 28 days postdischarge (illness day 97) revealed an ANC of 2200 cells/μL (Figure 1).

DISCUSSION

Our case presents a middle-aged Hispanic man with underlying hematological malignancy in remission who developed SARS-CoV-2 viremia and probable BM infiltration after surviving COVID-19 cytokine storm. This case could represent the second documented case of BM disease and viremia due to COVID-19 [6] and the first case of profound neutropenia directly related to COVID-19 prompting myeloid maturation arrest. Medications including vancomycin, piperacillin/tazobactam, entecavir, cefepime, trimethoprim/sulfamethoxazole, acyclovir, and ciprofloxacin were administered before profound neutropenia development; however, discontinuation of these agents did not halt pancytopenia or neutropenia progression or improve his syndrome.

Cancer patients with COVID-19 have a higher likelihood of death, with the highest mortality in the hematologic malignancies subgroup [1, 2]. In 1 meta-analysis, the pooled estimated death rate from 5 studies of 24 patients with cancer and COVID-19 was 20.83% [2]. Cancer patients are also more prone to COVID-19 infection than the average population due to cancer immunosuppression, anticancer drugs, radiotherapy, and surgical treatment [1, 2].

The pathophysiology of COVID-19 is not well elucidated. However, it has been stipulated that in addition to direct viral damage, uncontrolled inflammation contributes to disease severity, along with high CRP levels, ferritin, and D-dimer [7]. Also, cytokine patterns are predictive of COVID-19 survival and mortality independent of demographics and comorbidities [7]. Numerous reports suggest that individuals affected by severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) have dysregulated cytokine production from both innate and adaptive immune cells, allowing progression to multi-organ dysfunctional syndrome (MODS) and ARDS, and SARS-CoV-2 appears to behave similarly [8].

Interestingly, our patient neither developed anti-SARS-CoV-2 IgG nor improved despite 2 CPTs. Further randomized control trials are required to substantiate the optimal time of initiation, dosage, titer, duration, and safety of this therapy, especially in the immunocompromised [9]. We believe that given our patient's impaired humoral immunity and probable development of myeloid maturation arrest due to SARS-CoV-2 infection, seroconversion was halted. Typically, seroconversion occurs in most patients by day 14 [9]. Our attempts to isolate the virus from blood and BM did not prosper. So far, no virus isolation from stool, blood, urine, or BM has been documented [10].

Several authors have recommended caution with GCSF use for neutropenia treatment in COVID-19 due to an associated increased need for oxygen supplementation, cytokine storm, and death [3–5]. In a case series, 3 patients who received GCSF developed severe COVID-19 within 72 hours of administration, emphasizing the need for larger studies. However, our patient improved with GCSF. One key reason for this difference could be the timing of GCSF. Our patient received GCSF on illness day 56, several weeks after recovering from his cytokine storm, the time frame when GCSF use could result in adverse events. Interestingly, a case of mild SARS-CoV-2 infection presenting as neutropenic fever and successfully managed with GCSF was documented [11]. Nevertheless, it was not reported for how long the patient was having COVID-19 symptoms, and no BM studies were mentioned.

We proved with cumulative clinical evidence the hypothesis that CMV was an innocent bystander. We feel it is also important to remark that his syndromic COVID-19 sequelae appeared to follow a natural course, despite adding and discontinuing antibiotics and antivirals for therapy or prophylaxis. In terms of therapy, no immediate clinical benefit from CPT was observed. Tocilizumab was not considered, as our patient was past his cytokine storm period. Lastly, the use of GCSF for neutropenia management in COVID-19 patients is controversial due to the risk of precipitating cytokine storm and death [3–5]. Nonetheless, it seems to be a safe therapeutic alternative after the cytokine storm has resolved. In our patient, notable clinical improvement was observed after GCSF was commenced, with apyrexia, reduced oxygen requirements, ANC recovery (Figure 1), and SARS-CoV-2 viral load reduction.

In conclusion, while our paper is limited by an inability to culture SARS-CoV-2 from BM, we believe it invites further research, particularly regarding the usage of GCSF for prolonged and profound neutropenia. Additionally, SARS-CoV-2 PCR of blood and BM specimens should be considered for diagnostic purposes if pancytopenia or neutropenia evolve in COVID-19 patients presenting with typical symptoms. This case highlights the importance of understanding the temporal relationship between COVID-19 and neutropenia, as treatment approaches might be on opposite ends of the spectrum, from immune de-activation to immune re-activation.

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Patient consent. The authors confirm that the patient's written consent was obtained.

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