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New Onset Aplastic Anemia after a COVID-19 Infection: A Case Report

Vikram Sumbly*, Raheel Siddiqui, Mohsen Alshamam, Tamara Kurbanova, Vincent Rizzo

Internal Medicine, Icahn School of Medicine at Mount Sinai, Queens Hospital Center, Jamaica, United States
*Corresponding author: vikram.sumbly@gmail.com

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Abstract Aplastic anemia (AA) is a potentially life-threatening acquired bone marrow failure syndrome which leads to central pancytopenia. Although the exact pathogenesis of this disorder is yet to be fully understood, it is thought to be primarily caused by auto-immunity. Unlike other viruses, the association between SARS CoV-2 and AA remains insufficiently explored in current literature. Based on the few cases of COVID-19-induced central pancytopenia and the available literature on virus-induced AA, we propose that the development of AA in COVID-19 patients may be attributable to SARS CoV-2. We report the case of a 29-year-old female that developed AA after being hospitalized for COVID-19. She had a favorable clinical outcome after several courses of immunosuppressive therapy.

Keywords: *Aplastic anemia, COVID-19, bone marrow transplant, immunosuppressive therapy*

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1. Introduction

Aplastic anemia (AA) is a rare hematological condition that is characterized by central pancytopenia due to bone marrow failure. While the exact pathogenesis behind AA remains poorly understood, it is widely accepted that this type of acquired bone marrow failure syndrome is caused by the destruction of hematopoietic stem cells (HPSC) secondary to a dysregulated auto-immune response. More than 50% of all AA cases are idiopathic in nature; however, chemotherapy, ionizing radiation and viral infections have also been implicated in this disease's etiology. [1] The most common infectious agents are the hepatitis virus, human immunodeficiency virus (HIV), cytomegalovirus (CMV), Parvovirus B19 and Epstein-Barr virus (EBV). [2,3] While severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) mainly affects the pulmonary system, it has also been shown to cause disturbances within the hematopoietic system by inducing neutropenia, lymphopenia and, in rarer circumstance, central pancytopenia. [4] Here, we describe a rare case of AA in a young woman who was previously hospitalized for COVID-19 pneumonia. Although the causal relationship, if any, between SARS CoV-2 and AA remains unclear, the purpose of this case report is to elucidate a possible association between AA and this viral infection.

2. Case Report

A 29-year-old female with a medical history of seizure disorder and recent COVID-19 infection presented herself to the emergency department with complaints of worsening exertional dyspnea, decreased exercise tolerance, non-bilious non-bloody vomitus and mucosal bleeds that had been taking place over the course of two weeks. Several months earlier, the patient was admitted to another hospital with similar symptoms, which she developed for the first time in her life shortly after being diagnosed with COVID-19. Vital signs revealed a blood pressure of 109/45 mmHg, a heart rate of 90 beats per minute, a respiratory rate of 17 breaths per minute, a temperature of 98.7 F and an oxygen (O2) saturation of 100% on room air. The physical examination revealed significant skin pallor, delayed capillary refill, petechiae on all her limbs, and wet purpura within the oral cavity. Laboratory results revealed a white blood cell (WBC) count of 3.39 $x10^3$ cell/µl (reference: 4.8-10.8 $x10^3$cell/µl), hemoglobin of 3.1 g/dL (reference range: 12.0-16.0 g/dL) and platelets of $1x10^3$cells/µl (reference: 150-450x10 cell/µl). APTT was 28.8 and INR was 1.1. D-dimer, fibrinogen, fibrin split products and COVID PCR were negative. The patient was immediately started on prednisone and given one unit of platelets and packed red blood cells (PRBC) before being admitted to the step-down unit. Hematology was consulted and recommended that the patient receive multiple units of PRBC and platelets to keep her hemoglobin greater than 7g/dL and platelet count greater than 10x10 cells/µl. (Figure 1- Figure 3).

The patient was weaned off levetiracetam and placed on phenobarbital. Further lab tests showed an absolute reticulocyte count of 0.0009 x 10^6 and LDH of 192 U/L. The direct antiglobulin test (DAT) test was negative.

There was growing concern for AA, but the patient refused a bone marrow biopsy and aspirate. Analysis of the patient's bone marrow from her previous hospitalization revealed a hypocellular marrow (20-30%) with severely decreased megakaryocytes, erythroid precursors, granulocytic precursors and iron stores (Figure 4-Figure 6).

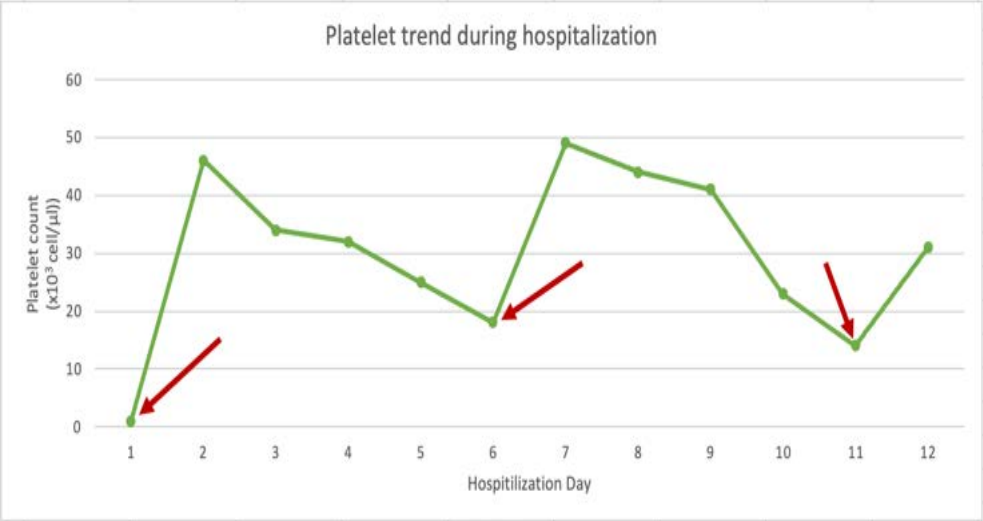

Figure 1. Platelet trend during hospitalization. Red arrows indicate the days the patient received platelet transfusions

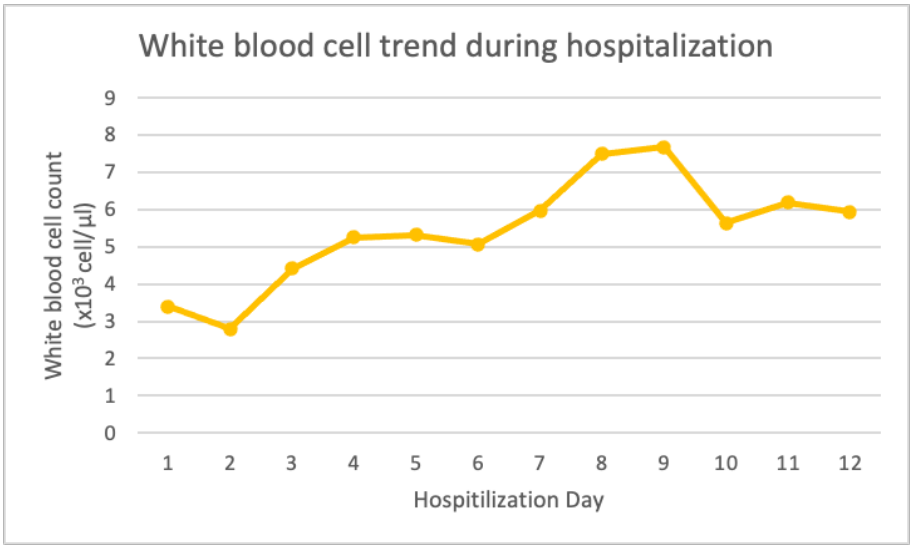

Figure 2. WBC trend during hospitalization

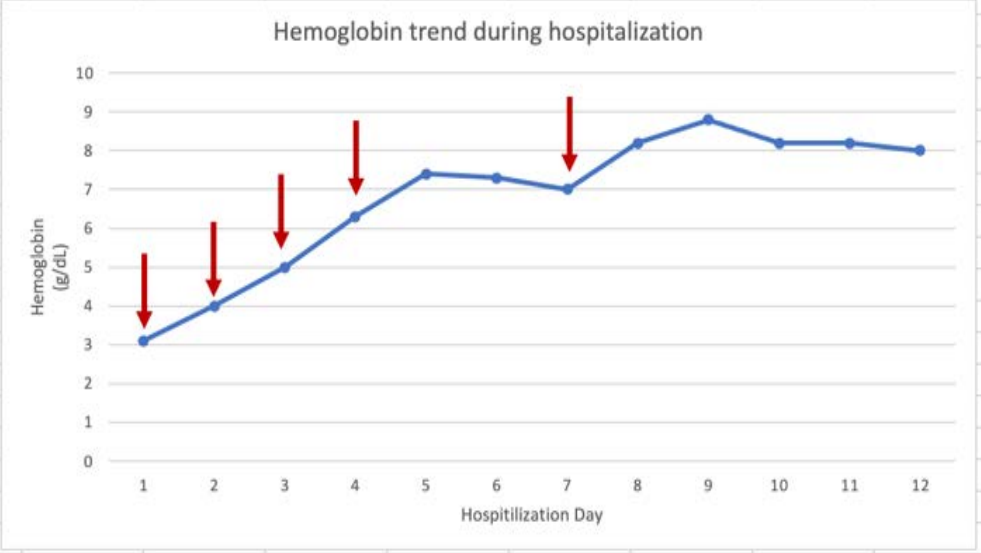

Figure 3. Hemoglobin trend during hospitalization. Red arrows indicate the days the patient received PRBC transfusions

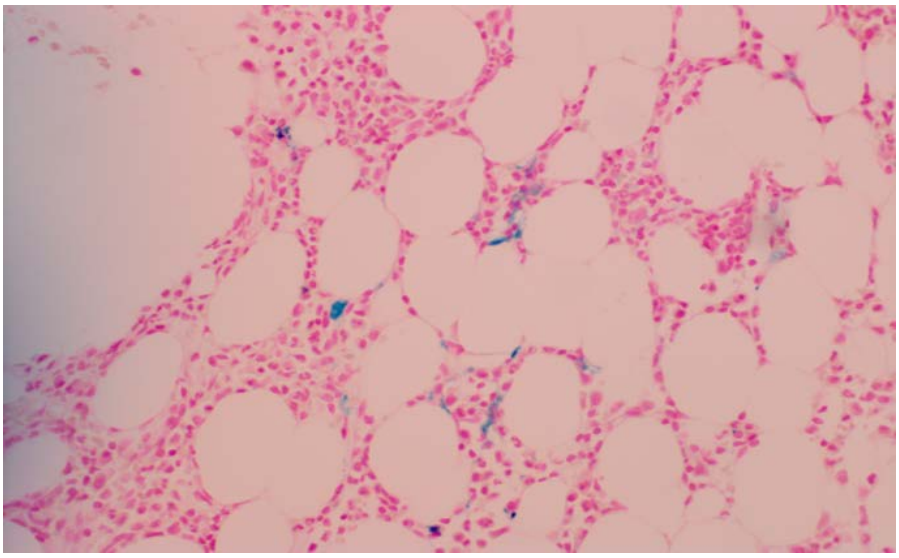

Figure 4. Hypocellular bone marrow for age with focal areas of trilineage hematopoiesis with maturation. H&E, 4x; insert, 20x

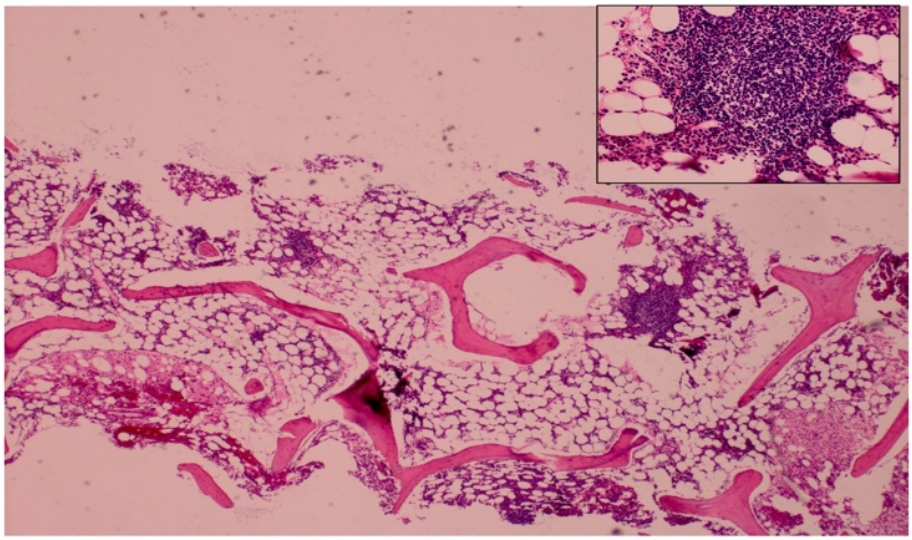

Figure 5. Iron stain reveals iron stores are present

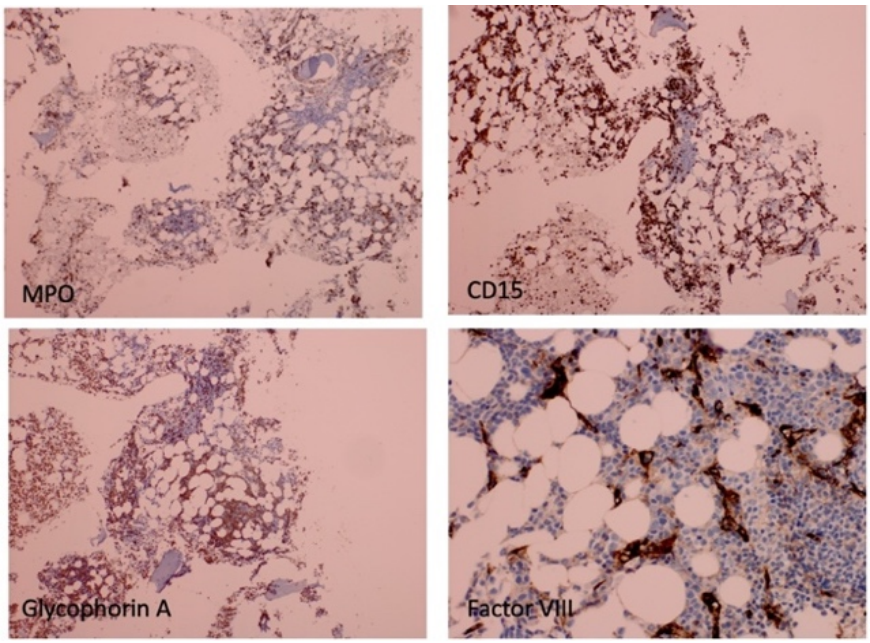

Figure 6. Immunohistochemical stains reveal mild myeloid hyperplasia with decreased number of megakaryocytes. MPO and CD15 reveal myeloid cells, glycophorin A reveals erythroid cells and factor VIII reveals rare megakaryocytes

Table 1. Viral antibody titers

Cytomegalovirus (CMV IgG)	Positive	Hepatitis B	Negative
Parvovirus B19 IgG	Positive	Hepatitis C	Negative
Epstein-Barr Virus (EBV) VCA	Positive	Human T-lymphotropic virus-1 (HTLV-1)	Negative
SARS CoV IgG	Positive	Human T-lymphotropic virus-1 (HTLV-1)	Negative
Human immunodeficiency virus-1 (HIV-1)	Negative	Syphilis	Negative
Human immunodeficiency virus-2 (HIV-2)	Negative	Toxoplasmosis	Negative

Detailed analysis of the patient's serum was negative for any acute viral infections, but did reveal antibodies for cytomegalovirus (CMV), parvovirus B19, Epstein-Barr Virus Viral Capsid Antigen (EBV VCA) and SARS- CoV (Table 1).

The patient's hemoglobin and platelet count did not respond to the prednisone regimen; hence it was subsequently discontinued. She continued to receive PRBC and platelet transfusions throughout her hospital stay. The patient was discharged after twelve days of hospitalization and was scheduled to receive weekly PRBC and platelet transfusions on an outpatient basis. She was also referred to a bone marrow transplant center specializing in AA care.

A follow-up bone marrow biopsy done at the bone marrow transplant center revealed a persistently hypocellular marrow. A cytogenetic analysis, AML fluorescent in-situ hybridization (FISH) and myeloid NGS assay were all within normal limits. Flow cytometry did not reveal any lymphoproliferative disorder. Genetic testing was negative for any congenital bone marrow failure syndrome.

The patient was again admitted to the hospital three months after her initial discharge so that she could receive immunomodulation therapy, which consisted of anti-thymocyte globulin (ATG), cyclosporin (CSA), eltrombopag (EPAG) and prednisone for ten days. She was then continued on CSA 400mg twice daily, EPAG 150mg daily and a prednisone 85mg daily. The patient responded well to therapy as her hemoglobin and platelet count remained above 8.0 g/dL and $20x10^3$ cells/µl.

3. Discussion

Viral illnesses account for a very small percentage of all AA cases.[5] According to *King and Goodell*, there are numerous ways a viral illness can cause AA. [6] The first mechanism involves destabilizing HPSC replication by modifying the expression of several vital proteins and manipulating intracellular biochemical cascades. [6] It is also suggested that HPSC, once exposed to viral pathogen-associated molecular patterns (PAMPs), can undergo apoptosis after expressing different types of pattern recognition receptors (PRR). [6] The overproduction of inflammatory cytokines in viral infections, such as IL-1ß, IL-6, TNF-α and INF-γ, has also been shown to disrupt the bone marrow microenvironment, resulting in bone marrow failure. [6,7] Viruses have also been observed to directly destroy HPSC. [8]

COVID-19 is a multisystemic infection that has been associated with various hematological abnormalities. The exact mechanism behind COVID-19-induced bone marrow aplasia has yet to be fully elucidated, but it appears to be multifactorial. There have been several cases of severe central pancytopenia associated with COVID-19. [9,10,11] While most cases were transient and did not require bone marrow biopsies, *Issa et al*. revealed that it was possible for SARS-CoV2 to directly infiltrate the bone marrow and physically cause marrow failure. [12] It has yet to be determined if any of these cases were caused by an auto-immune cytotoxic T-cell response.

To the best of our knowledge, there have been no other cases attempting to associate SARS CoV-2 with AA. Unlike the other cases of COVID-19-induce bone marrow failure, our patient's bone marrow never recovered. It would have been interesting to determine if our patient's bone marrow was infiltrated by SARS CoV-2. Although the link between SARS CoV-2 and AA in our case seems to be a temporal association, the role of viruses in causing AA needs to be better studied.

4. Conclusion

Since AA is often a diagnosis of exclusion with a wide array of symptoms, it can easily be misdiagnosed. It is still not clear as to why our patient developed AA after her COVID-19 infection. The new onset of AA in our patient could have been caused by a mechanism that we know very little about, therefore further studies should be done to better understand the association and pathophysiology of AA secondary to COVID-19 infection.

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