Case Report

Severe Aplastic Anemia Secondary to SARS CoV-2 Infection- A Case Report

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Abstract

During the current COVID-19 pandemic, the assessment, and management of patients are challenging. The clinical features of COVID-19 are heterogeneous and subtle in many cases. Although Severe Acute Respiratory Syndrome Corona Virus 2 (SARS CoV-2) mainly affects pulmonary system, it has also been shown to cause abnormalities within the hematopoietic system by inducing neutropenia, lymphopenia, and in rare circumstances, central pancytopenia. Aplastic anemia is a potentially life-threatening acquired bone marrow failure syndrome which leads to central pancytopenia. The association between SARS CoV-2 and aplastic anemia is insufficiently explored in the current literature. Although the exact pathogenesis of the disorder is yet to be fully understood, it is thought to be primarily caused by post infective auto-immunity. Based on a clinical case of COVID-19 induced severe aplastic anemia and the available literature on virus induced aplastic anemia, we propose that the development of aplastic anemia in COVID-19 patients may be attributable to SARS CoV-2. We here report a case of a previously normal 4 years old child who developed severe aplastic anemia after being hospitalized for COVID-19.

Keywords: Aplastic anemia; Bone marrow transplant; COVID-19; Central pancytopenia; Immunosuppressive therapy

1. Introduction

"Coronavirus disease 2019"-COVID-19 pandemic caused by "Severe Acute Respiratory Syndrome Corona virus 2"(SARS-CoV-2) is a major public health crisis pandemic threatening humanity at this point of time. COVID-19 is continuing to spread globally. Number has surpassed 180 million cases and 4 million deaths. In India there were about 30 million cases and 4 lakh deaths. With second wave in India, a large number of children were also affected. Symptoms and signs of COVID-19 are nonspecific and mimic any viral illness. Although fever, cough, sore throat, diffuse alveolar damage and acute respiratory failure are the main features of COVID-19, children present with gastrointestinal symptoms-vomiting, loose stools and diarrhea and abdominal pain. Cutaneous manifestations like maculopapular, urtricarial and vesicular eruptions and transient livedo-reticularis and COVID-Toes (Reddish purple nodules on distal digits) are also seen predominantly in children. Very few children may progress to severe COVID-19 characterised by ARDS, sepsis and septic shock. Even presentation as meningoencephalitis is seen. Serious form of disease- MIS-C (Multisystem Inflammatory syndrome in children) temporally related to COVID-19: Condition diagnosed in children who had infection previously and also among those with active infection. Multiorgan failure includes acute kidney injury, acute liver injury and acute cardiac injury which can cause long-term damage to heart, liver and kidneys. The COVID-19 infection was found to be complicated with anemia, lymphopenia, neutrophilia, agranulocytosis, monocytopenia and atypical reactive lymphocytes, particularly in severe cases. Hence relationship between COVID-19 and aplastic anemia can be explained.

Aplastic anemia is a rare hematological condition that is characterized by pancytopenia due to bone-marrow failure. While the exact pathogenesis behind Aplastic anemia is not fully understood, it is widely accepted that this type of acquired bone marrow failure syndrome is caused by the destruction of hemato-poietic stem cells secondary to a dysregulated auto-immune response. Viral infections have been implycated as a main factor in the disease etiology. Here, we describe a rare case of a 4 year old child who was previously admitted and treated for COVID-19, and presented now with features suggestive of severe aplastic anemia. Although the causal relationship between SARS CoV-2 and aplastic anemia remains unclear, the purpose of this case report is to elucidate a possible association between aplastic anemia and COVID-19.

2. Case Description

A 4-year-old female child with previous H/O COVID-19 presented to pediatric emergency department with c/o fever since 1 day, rashes all over the body and worsening exertional dyspnea. One month back, child was admitted in another hospital with high grade fever for 5 days, bleeding from gums, blood-stained vomiting and petechial rashes over body, which she developed for the first time in her life shortly after being diagnosed with COVID-19. On clinical examination, child was found to have severe skin pallor and petechial rashes all over the body, and purpura within the oral cavity. Child was febrile (100degree F), tachycardic-(158 beats/min), RR-40/min, Spo2-99% on room air. Child was conscious and alert. (GCS-15/15) There was no icterus, no lymphadenopathy, no edema, no enlargeement of tonsils, no throat congestion. There were no signs of respiratory distress. Breath sounds were

normal, bilaterally heard in all lobes, without rhonchi or crackles. Cardiovascular system-Tachycardia with S3 gallop rhythm was present. The abdomen was soft, not distended, No organomegaly.

2.1 Evaluation during hospitalization

Blood investigations showed severe anemia (Hemoglobin of 2.5g/dl) and severe thrombocyte-openia (platelet 11000). There was no leukocytosis (total White blood cell count of 8190 leukocytes/ mm3 with neutrophils 3% /mm3 and 94% lympho-cytes/mm3. C Reactive protein was elevated-38 (normal value being less than 10), ESR-59, LDH-227(mildly elevated, normal value being less than 170). SARS COVID Antibody IgG came positive with a titre of 3.34 (>1 – positive) and IgM antibody came negative with a titre of 0.27(<1-negative). Reticulocyte count showed a value of 0.2%. Peripheral smear reported as dimorphic anemia, with absolute severe neutropenia (PMN <200/cmm), and marked thrombocytopenia. Work up for pancytopenia was started. Meanwhile child was transfused with one pint PRBC and one pint platelet. Serum B12 and folic acid levels were normal. The Direct Coombs Test(DCT)was negative. Mantoux-Negative. Tridot-Negative. Repeat hemoglobin showed an improve-ment (7.6 g/dl) and repeat platelet counts showed 18000, which dropped again after three days 13,000/cumm and 8000/cumm after another two days. Bone marrow examination was done which showed Hypocellular marrow with decrease in all hematopoietic elements with relative increase in lymphocytes. Detailed analysis of the patient's serum was negative for acute viral infections (dengue virus, hepatitis virus), but did reveal antibodies for cytomegalovirus. CMV Antibody IgG was positive with a titre of 102, normal value being less than 12. CMV IgM antibody was negative with a titre of 5 (Normal <18).

2.2 Treatment

Based on clinical findings and laboratory investi-gations child was given supportive therapy of PRBC and Platelet transfusion. Child was treated with Inj Methyl Prednisolone Pulse therapy for 3 days, followed by tab Prednisolone 2mg/kg OD. First line antibiotics were given for 5 days. Inj.Filgrastim 300 mcg (Recombinant Human Granulocyte Colony Stimulating Factor) was given 2 times (100 mcg *6 days). Inj Erythropoetin 4000 IU was given (1000 IU on alternate days *4 days). Patient's hemoglobin, neutrophil count improved after therapy, but a further drop in platelet count (8000) was observed on 10th day of admission for which child was transfused one more pint of platelet. Inj.Romiplostin was planned but was not available immediately. After 14 days, child was referred on the request of attenders to a higher centre, specializing in aplastic anemia care and bone marrow transplantation. Till this day, as per our follow up over phone no BMT was given.

Figure 1: 4Yrs Old Child with severe Acquired Aplastic Anemia.

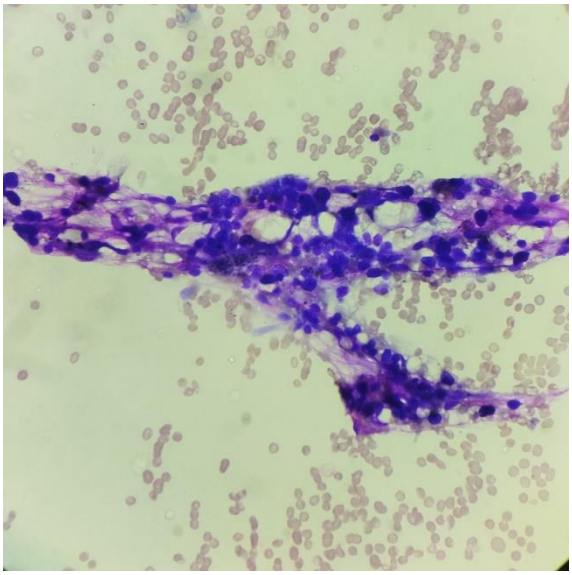

Figure 2: Bone Marrow aspiration showing hypocellularity with stromal elements with few scattered hematopoietic lineage cells.

Characteristics	Reported values
Total count	8190
Neutrophils	3
Lymphocytes	94

Hemoglobin	2.5
PCV	7
RBC	0.77
Platelet count	11,000
MCV	99.1
MCH	33
MCHC	36.2
RDW	16.9
Reticulocyte count	0.2
CRP	38
SARS CoV-2 IgG Antibody	Positive
Cytomegalovirus- IgG Antibody	Positive
SARS CoV-2 IgM	Negative
Cytomegalovirus IgM Antibody	Negative
HIV	Negative
HBsAg	Negative

Table 1: Laboratory Investigations

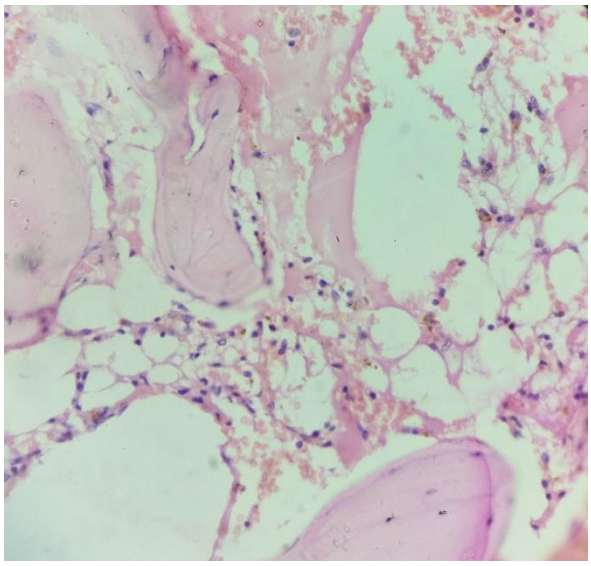

Figure 3a: Bone Marrow Biopsy specimen showing replacement of all hematopoietic lineages of adipose tissue along with areas of hemorrhages suggestive of hypocellular bone-marrow for age.

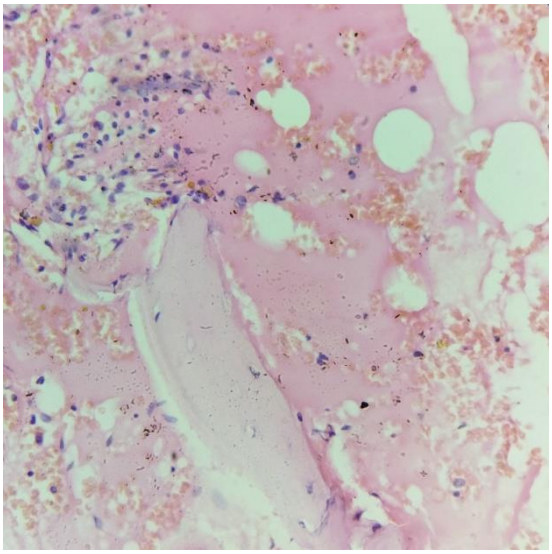

Figure 3b: Bone Marrow Biopsy specimen showing replacement of all hematopoietic lineages of adipose tissue along with areas of hemorrhages suggestive of hypocellular bone-marrow for age.

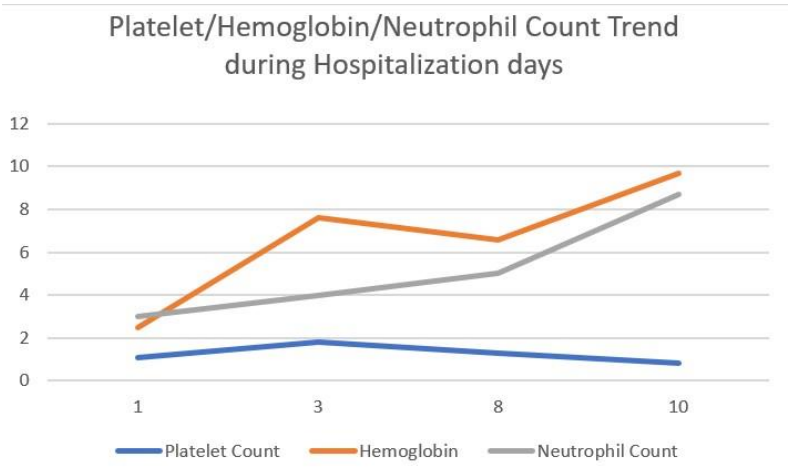

Figure 4: Platelet/Hemoglobin/Neutrophil Count Trend during Hospitalization days.

3. Discussion

COVID-19 added another dimension to hematologic disorders. This case report helps to understand the characteristics of COVID-19-related hematological problems and its correlation with clinical outcomes. Aplastic anemia is a rare and heterogeneous disorder. It is defined as pancytopenia with a hypocellular bone marrow in the absence of abnormal infiltrates, marrow fibrosis, or dysplastic changes. The majority (70-80%) of aplastic anemia cases are idiopathic. Viral infection account for a small percentage of aplastic anemia cases. The first mechanism involves destabilizing Human Pluripotent Stem Cell (HPSC) replication by modifying the expression of several vital proteins and manipulating intracellular biochemical cascades. 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) [1]. The overproduction of inflammatory cytokines in viral infections, such as IL-1ß, IL-6, TNF-α and INF-γ, has been shown to disrupt the bone marrow microenvironment, resulting in bone marrow failure. [1, 2] Viruses have also been observed to directly destroy HPSC [4]. 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 [2-4].

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. [4] The role of auto-immune cytotoxic T-cell response in causing aplastic anemia in COVID-19 patients are yet to be found out. In contrast to the other cases of COVID-19-induced bone marrow failure, our child's bone marrow could not be recovered. In COVID-19 infection, whether the patient's bone marrow is infiltrated by SARS CoV-2 virus is yet to be determined. Although the link between SARS CoV-2 and aplastic anemia in our case seems to be a temporal association, the role of viruses, SARS CoV-2, cytomegalovirus etc in causing aplastic anemia needs to be better studied.

4. Conclusion

COVID-19 is a multisystemic infection that has been associated with various hematological abnormalities. Since aplastic anemia is usually a diagnosis of exclusion with a wide variety of symptoms, there are chances that it can be misdiagnosed. The new onset aplastic anemia in our child 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 aplastic anemia secondary to COVID-19 infection. We are still in need of further reporting of the clinical presentation pattern of COVID-19 infection in children. This case highlights and adds to the growing literature surrounding the associated effects of SARS-CoV-2 infection. While the exact pathogenesis of aplastic anaemia is unknown, one theory proposes abnormal antigen stimulation and inappropriate cell activation due to increased levels of IL-17 as part of a cytokine storm leading to apoptosis, which in aplastic anaemia involves the haematopoietic stem cells. Here we cannot definetively say that the effect is causal, the close temporal relationship of this case points to the possible development of a rare haematological condition following infection with the SARS-CoV-2 virus, and to consideration of the virus being added to the array of viral infections that are known to be implicated in the pathogenesis of aplastic anaemia.

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