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(CASE REPORT)

Bone marrow suppression, a rare presentation of Sars-CoV-2 infection in a child living in a low-income country: A case report with literature review

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Abstract

Background: COVID -19 is a clinical condition caused by the Coronavirus SARS-CoV-2. It was a global pandemic which affected both adults and children during its outbreak in 2019. Bone marrow suppression is an uncommon but significant complication observed in paediatric patients which can worsen morbidity and mortality. Furthermore, given the fact that the marrow suppression may mimic other diseases such as leukaemia, a high index of suspicion is imperative for prompt diagnosis and treatment.

Case Presentation: We describe the diagnostic evaluation and management of a 5-year-old female with bone marrow suppression as a complication of SARS-CoV-2 infection. She presented with fever and paleness of the body. Initial examination showed severe pallor with tachycardia and tachypnoea. Investigations revealed pancytopenia with reticulocyte count at lower limit of normal. Peripheral blood film showed reduction of all three cell lines. Bone marrow aspiration showed a hypocellular marrow for the age of the child. Immunoglobulin M (IgM) for COVID-19 was found to be positive. Patient's clinical condition has markedly improved as haematologic parameters have returned to near normal and has not needed any transfusion for about 1 year.

The diagnosis of bone marrow suppression following SARS-CoV-2 infection requires a good history, physical examination, high index of suspicion and extensive investigations. Management entails recurrent transfusions, corticosteroids and supportive treatment.

Keywords: COVID-19; SARS-CoV-2; Bone marrow suppression; Immunoglobulin M; Case report

1. Introduction

COVID -19 is an illness caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2). It was a global pandemic which affected both adults and children during its outbreak in 2019. The clinical manifestation of COVID-19 in children is generally reported to be less severe and have a better outcome when compared to adults.[1] Factors responsible for the reduced severity in children include immunity due to routine live vaccines and frequent viral infections, cross immunity to other coronal virus infections as well as the absence of ageing related immune-senescence. Children also have good lung regenerative capacity which could explain the early recovery from COVID-19.[2] Though respiratory and gastrointestinal symptoms have been the primary focus; bone marrow suppression is an uncommon but significant complication observed in paediatric patients. The pathogenesis of bone marrow suppression in COVID-19 is multi-factorial, and this includes direct viral invasion, immune-mediated damage, and the effects of systemic inflammation.[3]

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Some case reports have documented [4,5] that bone marrow suppression in children with COVID-19 may vary, ranging from mild cytopenia to severe pancytopenia which is marked by decreased production of blood cells, leading to conditions such as anaemia, leukopenia, and thrombocytopenia.

Managing children with SARS-CoV-2-induced pancytopenia can be challenging, and clinical findings can be vague, mimicking other diseases such as aplastic anaemia, leukaemia, and megaloblastic anaemia especially in young children.

2. Case presentation

A 5-year-old female presented to our facility with a 6-month history of paleness of the body and fever of 2 days duration. There was no history of trauma, blood loss, weight loss, joint or bone pains. Patient's blood group is O positive and haemoglobin genotype AA. Weight was 18kg. She had been transfused thrice in a peripheral hospital within a period of 6 months because of the recurrent anaemia.

On physical examination she was severely pale, febrile, anicteric, not cyanosed and with no significant peripheral lymphadenopathy. She had tachycardia and tachypnoea with a pulse rate of 124 beats/ minute and respiratory rate of 50 cycles/ minute respectively. Her abdomen was full and moved with respiration with a palpable liver that was 4cm below the right costal margin, smooth surface, sharp edged but not tender. There was no splenomegaly. Venous blood was collected under strict asepsis and analysed in the hospital's research laboratory. Complete blood count (CBC) on presentation showed haemoglobin (HB) of 4.2 g/dl, white cell count of 2,800 cells/mm^3 with absolute neutrophil count of 210 cells/ mm^3 and platelet count of 43,000 cells/mm^3. Peripheral blood film showed moderately reduced red blood cells on film with mild anisopoikilocytosis. Mostly normochromic, normocytic cells; tear drop, poikiloctytes, target cells and hypochromic cells. White blood cells were severely reduced on film with neutrophils having 2-5 nuclear segments and fine cytoplasmic granules. Lymphocytes were mostly small - sized forms with a rim of basophilic cytoplasm and clumped nuclear chromatin appearance. Platelets were severely reduced on film.

Reticulocyte count was the lower limit of normal while serum electrolytes, urea and creatinine were normal. Urinalysis and urine m/c/s were essentially normal as well as Lactate dehydrogenase (LDH) level.

Bone marrow aspiration (BMA) done due to recurrent pancytopenia showed markedly hypocellular marrow for age. Fragments were adequate but with markedly reduced trails. Erythropoiesis was severely depressed on film. Megaloblastoid, normoblastic and micro normoblastic forms noted. Dysplastic features such as erythroid primitive cell binuclearity. Cytoplasmic bridging also noted on film. Myelopoiesis was reduced on film with sequential maturation, and occasional giant myelocytes seen. Lymphopoiesis was active with lymphoid precursor cells constituting < 5% of marrow nucleated cells. Megakaryopoiesis was depressed on film. Plasma cells were seen with < 3% of marrow nucleated cells. Iron stain was positive for marrow iron.

She received several transfusions of platelet as well as fresh whole blood on account anaemia, thrombocytopenia and neutropenia reoccurring over the next few weeks. She also received subcutaneous Granulocyte Colony Stimulating Factor for the neutropenia.

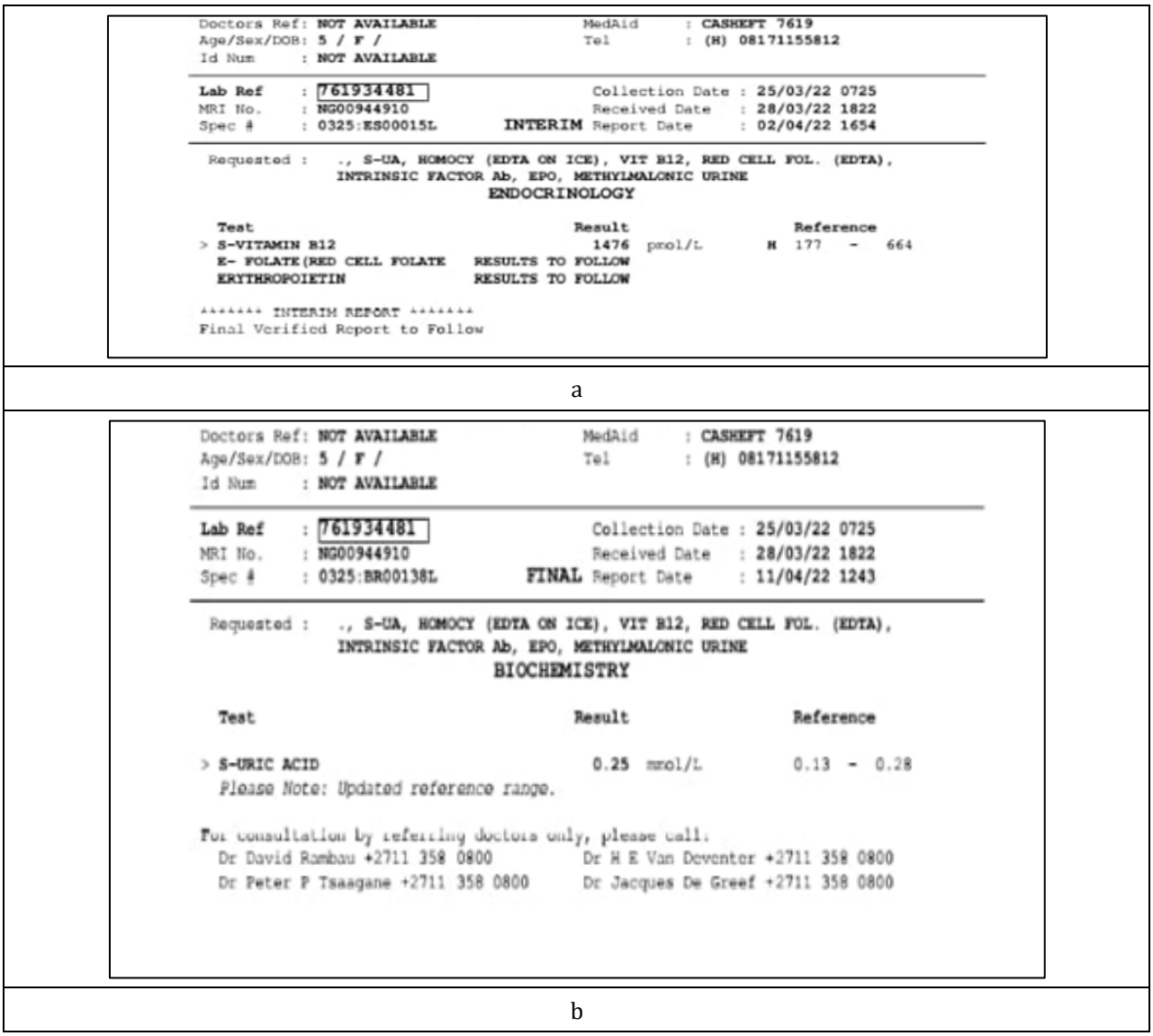
Further investigations carried out to determine the cause of bone marrow failure included serum uric acid, homocysteine levels which were normal, serum vitamin B12 level was markedly elevated, and red cell folate level was within normal range. Intrinsic factor antibody was negative. EBV, HIV, and parvovirus were all negative. This led to a suspicion of bone marrow failure from COVID-19. Thereafter, IgM for COVID-19 was done and found to be positive.

In view of the reticulocyte count which was at the lower limit of normal; CBC, peripheral blood film, BMA which showed pancytopenia; negative viral assay and positive IgM for COVID-19, a definitive diagnosis of bone marrow failure secondary to COVID-19 was made and patient was commenced on tablet prednisolone 20mg 12hourly with chronic transfusion.

Her clinical condition improved though haematologic parameters are slowly returning to normal and our patient has not required any transfusion for about one year.

Table 1 cell indices during treatment

Day	Hemoglobin(g/dl)	White blood cell(/l)	Platelet count(/l)
D1	4	5500	29000
D6	8.4	2100	117000
D10	11.2	4700	40000
D16	11.9	3300	78000
D28	11.1	6500	45000
D31	11.6	3500	43000
D59	7.2	5800	59000
D65	11.0	3600	126000
D95	9.9	2400	49000
D151	11.3	3300	102000
D155	12.7	7900	77000



Doctors Ref: NOT AVAILABLE
Age/Sex/DOB: 5 / F /
Id Num : NOT AVAILABLE

MedAid : CASKEFT 7619
Tel : (H) 08171155812

Lab Ref : 761934481
MRI No. : NG00944910
Spec # : 0325:ES00015L

Collection Date : 25/03/22 0725
Received Date : 28/03/22 1822
INTERIM Report Date : 02/04/22 1654

Requested : ., S-UA, HOMOCY (EDTA ON ICE), VIT B12, RED CELL FOL. (EDTA), INTRINSIC FACTOR Ab, EPO, METHYLMALONIC URINE

ENDOCRINOLOGY

Test	Result		Reference
> S-VITAMIN B12	1476	pmol/L	H 177 - 664
E- FOLATE(RED CELL FOLATE	RESULTS TO FOLLOW		
ERYTHROPOIETIN	RESULTS TO FOLLOW		

******* INTERIM REPORT *******
Final Verified Report to Follow

a

Doctors Ref: NOT AVAILABLE
Age/Sex/DOB: 5 / F /
Id Num : NOT AVAILABLE

MedAid : CASKEFT 7619
Tel : (H) 08171155812

Lab Ref : 761934481
MRI No. : NG00944910
Spec # : 0325:BR00138L

Collection Date : 25/03/22 0725
Received Date : 28/03/22 1822
FINAL Report Date : 11/04/22 1243

Requested : ., S-UA, HOMOCY (EDTA ON ICE), VIT B12, RED CELL FOL. (EDTA), INTRINSIC FACTOR Ab, EPO, METHYLMALONIC URINE

BIOCHEMISTRY

Test	Result		Reference
> S-URIC ACID	0.25	mmol/L	0.13 - 0.28

Please Note: Updated reference range.

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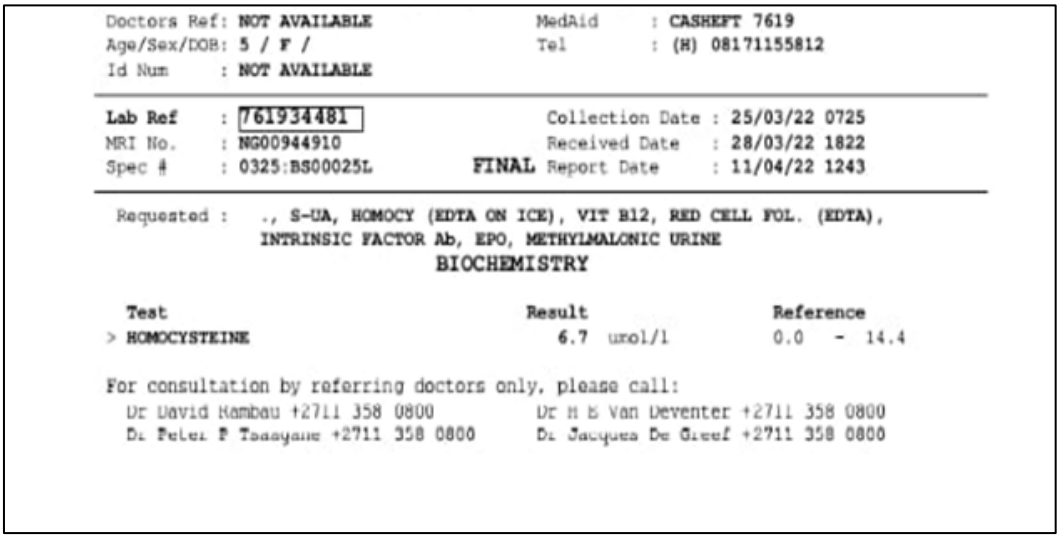

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Tel : (H) 08171155812

Lab Ref : 761934481
MRI No. : NG00944910
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Received Date : 28/03/22 1822
FINAL Report Date : 11/04/22 1243

Requested : ., S-UA, HOMOCY (EDTA ON ICE), VIT B12, RED CELL FOL. (EDTA), INTRINSIC FACTOR Ab, EPO, METHYLMALONIC URINE

BIOCHEMISTRY

Test	Result	Reference
> HOMOCYSTEINE	6.7 umol/l	0.0 - 14.4

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Dr Jacques De Greef +2711 358 0800

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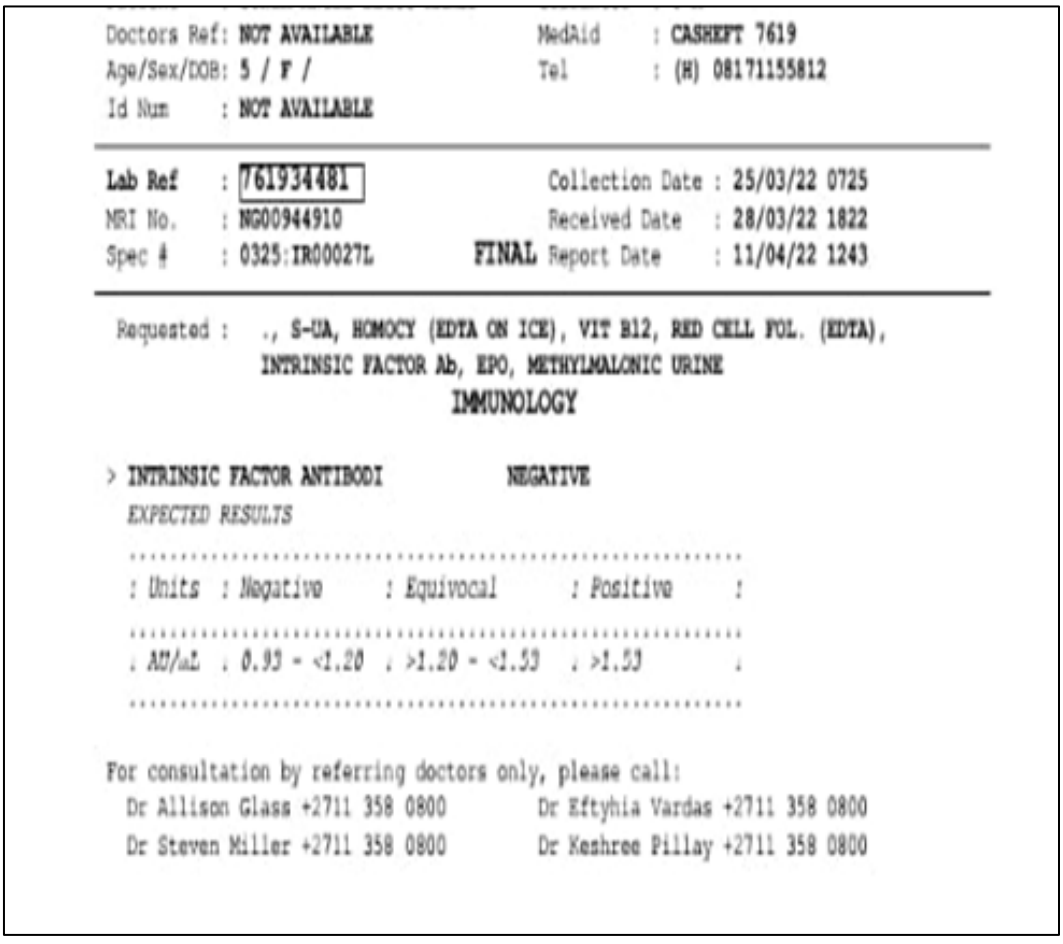

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Tel : (H) 08171155812

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Received Date : 28/03/22 1822
FINAL Report Date : 11/04/22 1243

Requested : ., S-UA, HOMOCY (EDTA ON ICE), VIT B12, RED CELL FOL. (EDTA), INTRINSIC FACTOR Ab, EPO, METHYLMALONIC URINE

IMMUNOLOGY

> INTRINSIC FACTOR ANTIBODI NEGATIVE

EXPECTED RESULTS

: Units	: Negative	: Equivocal	: Positive
: AU/mL	: 0.93 - <1.20	: >1.20 - <1.53	: >1.53

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Dr Eftyhia Vardas +2711 358 0800
Dr Steven Miller +2711 358 0800
Dr Keshree Pillay +2711 358 0800

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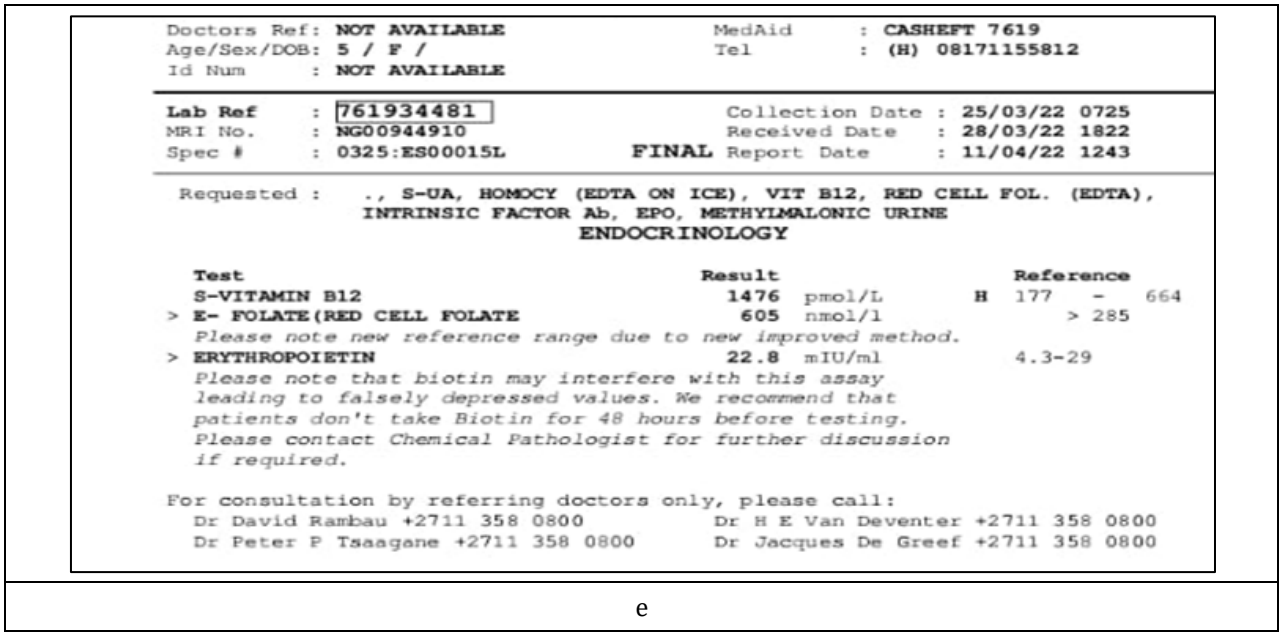

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Received Date : 28/03/22 1822
FINAL Report Date : 11/04/22 1243

Requested : ., S-UA, HOMOCY (EDTA ON ICE), VIT B12, RED CELL FOL. (EDTA), INTRINSIC FACTOR Ab, EPO, METHYLMALONIC URINE

ENDOCRINOLOGY

Test	Result			Reference
S-VITAMIN B12	1476	pmol/L	H	177 - 664
> E- FOLATE(RED CELL FOLATE	605	nmol/l		> 285
Please note new reference range due to new improved method.				
> ERYTHROPOIETIN	22.8	mIU/ml		4.3-29

Please note that biotin may interfere with this assay leading to falsely depressed values. We recommend that patients don't take Biotin for 48 hours before testing. Please contact Chemical Pathologist for further discussion if required.

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e

Figures 1 a, b, c, d, e Results of investigations

3. Discussion

The COVID-19 pandemic significantly affected global health. Children generally had mild clinical manifestations when compared to adults, however, there have been reported cases of severe illness, including those complicated by bone marrow suppression. Studies have shown that COVID-19 affects the haematopoietic system and haemostasis which results in various haematological abnormalities including lymphopenia, thrombocytopenia, and leukopenia and hyper coagulopathy. [3,6] Notably, neutropenia is more frequently reported in paediatric patients suffering from COVID-19 infection unlike in adults.[4] There are few case reports on SARS-CoV-2 induced pancytopenia. Poudel *et al,* [5] in India reported a case of an 11-year-old male who presented with fever of 5 days and laboratory workup showed pancytopenia with positive SARS-CoV-2 IgG antibody test. However, haematologic parameters improved over 96 hours and his cell-lines returned to baseline. This is in contrast to our patient who was transfused with RBCs and platelet concentrate and was also placed on corticosteroid therapy. Haematologic parameters are slowly returning to normal and our patient has not required any transfusion for about one year.

The mechanisms underlying bone marrow suppression in children with COVID-19 are multifaceted. SARS-CoV-2, the virus responsible for COVID-19, may directly invade hematopoietic stem cells or stromal cells in the bone marrow, disrupting normal haematopoiesis. Immune-mediated mechanisms, including cytokine storm and dysregulated immune responses, also contribute to bone marrow suppression. Elevated levels of inflammatory cytokines such as IL-6, IL-1β, and TNF-α can impair hematopoietic progenitor cell function and induce apoptosis, leading to decreased production of red blood cells, white blood cells, and platelets.[3]

The clinical manifestations of bone marrow suppression in children with SARS CoV-2 may include anaemia evidenced by fever, pallor, fatigue, and tachycardia; thrombocytopenia evidenced petechiae, bruising, and bleeding tendencies. Our patient presented with history of recurrent fever and paleness of the body. In a retrospective study conducted in Turkey, it was reported that the average platelet level of children with COVID-19 was significantly lower than others, and platelet reduction was more obvious in severe COVID-19 children and this was statistically significant ($p < 0.05$).[6] Although our patient had pancytopenia, however similar to the study in Turkey, the platelets were the slowest to show recovery despite multiple transfusions with platelet concentrate.

Diagnostic investigations for bone marrow suppression in children with COVID-19 include complete blood count (CBC) to identify cytopenia; reticulocyte count to assess bone marrow response, and bone marrow biopsy for definitive diagnosis. Additional tests such as inflammatory markers (CRP, ESR), and viral load assays may provide insights into the underlying pathophysiological processes. Bone marrow aspiration and biopsy remain the gold standard for evaluating marrow cellularity and architecture in suspected cases. [3] In our patient, reticulocyte count was at lower limit of normal and ESR was raised. Viral assay was requested Hepatitis B surface antigen, Hepatitis C, HIV and covid IgM were done and the patient was positive to COVID-19 IgM.

The treatment of bone marrow suppression in paediatric COVID-19 patients involves supportive care and specific interventions aimed at addressing the underlying causes. Supportive care includes blood transfusions for severe anaemia, antimicrobial therapy for infections, and platelet transfusions for significant thrombocytopenia. Immunomodulatory therapies, such as corticosteroids and intravenous immunoglobulin (IVIG), may be considered to mitigate immune-mediated marrow suppression. Additionally, antiviral treatments and monoclonal antibodies targeting SARS-CoV-2 can be employed to reduce viral load and inflammatory responses. [2]

Priyanka *et al* [7] in India reported the case of a 6-year-old female with complaints of high-grade fever, cough, and generalized body ache, easy fatigability, loss of weight and appetite. In our case, the patient presented with fever and paleness of the body however, her weight was adequate and there was no loss of appetite. The case reported by Priyanka et al, had anaemia and leukopenia on haematological examination while other parameters were within normal limits. Further investigations for the patient showed RT-PCR for COVID was done which was negative for COVID antigen but IgG titre for COVID-19 was positive. This is comparable to our patient who also had leukopenia, anaemia and thrombocytopaenia, with positive tests for COVID-19 IgM. Ranjima *et al*, [4] also in India reported a case of a 4-year-old female who presented with fever, rashes, and worsening exertional dyspnoea. However, she has been admitted previously on account of bleeding gum, blood-stained vomitus and petechial rash. In contrast, there was no history of bleeding in our patent and she was otherwise well until presentation to our facility. Fortunately, both patients responded to treatment and did not require bone marrow transplantation.

Here, we report the case of a 5-year-old female with primary complaints of fever, paleness of the body with pancytopenia as manifestations of COVID-19 infection. She was treated with corticosteroids and chronic transfusions. However, patient has been off the steroids for a few months and has not needed any transfusion of blood products in past one year. Bone marrow parameters have returned to near normal. She has remained asymptomatic till date and is still on follow up with the Paediatric Haemato- Oncology unit.

4. Conclusion

Bone marrow suppression, although relatively uncommon, represents a critical complication of COVID-19 infection in children. Due to its rarity in children, diagnosis may be difficult or delayed. Understanding its mechanisms, clinical presentations, and appropriate diagnostic and therapeutic strategies is essential for optimizing care and improving the outcome in affected paediatric patients.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no competing interests.

Statement of ethical approval

The present work does not contain any studies performed on animals /humans subjects by any of the authors.

Statement of informed consent

The written informed consent was sought and received from the parent of the child for the publication of the clinical details.

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Authors Contributions

UPI conceptualization and critically reviewed and approved final draft of the manuscript for submission. EC, CE, OE, LE and UO critically reviewed the manuscript and approved the final draft.

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