



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Contents lists available at ScienceDirect

Pediatric Hematology Oncology Journal

journal homepage: <https://www.elsevier.com/journals/pediatric-hematology-oncology-journal/>



COVID-19 in children with severe aplastic anemia

Dhwane Thakkar ^a, Neha Rastogi ^a, Mohammad Ramzan ^b, Satya Prakash Yadav ^{a,*}

^a Pediatric Hematology Oncology and Bone Marrow Transplant Unit, Cancer Institute, Medanta- The Medicity, Gurgaon, India

^b Rehmat Fertility and Child Care Centre and NeoKids Hospital, Jodhpur, India



ARTICLE INFO

Article history:

Received 21 November 2021

Received in revised form

6 May 2022

Accepted 18 May 2022

Available online 21 May 2022

Keywords:

COVID-19

Severe aplastic anemia

Children

Immunosuppressive therapy

ABSTRACT

Introduction: Coronavirus disease 2019 (COVID-19) affects children but mostly has mild course. There is meagre published data on the impact of COVID-19 illness in children with Severe Aplastic anemia (SAA). We describe our experience of managing COVID-19 in children with SAA.

Method: Three children of SAA who developed SARS-CoV-2 infection are included in this study.

Results: Patient 1 was post Immunosuppressive therapy (IST) for SAA and had an asymptomatic course and uneventful recovery. Patient 2 was several months post IST with no response and had an asymptomatic COVID-19 illness but had delayed viral clearance, however he succumbed to bacterial sepsis soon after. Patient 3 was awaiting IST and while he contracted severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) infection, he had symptomatic COVID-19 illness followed by bacterial and fungal sepsis to which he succumbed. Conclusion: COVID-19 in children with SAA can be mild to fatal course and virus may have delayed clearance. It can lead to delay in therapy of SAA.

© 2022 Pediatric Hematology Oncology Chapter of Indian Academy of Pediatrics. Publishing Services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

The world is facing an unprecedented pandemic due to COVID-19 caused by SARS-CoV-2. This poses several challenges in the management of children suffering from life threatening conditions like SAA. While patients with SAA are more susceptible to infections due to neutropenia, the infections are likely to run a more severe course due to the immunosuppression caused by the treatment [1,2]. However, experience with the COVID-19 illness has highlighted that the severity of the course of illness is linked more so with the hyperinflammatory state that the illness confers and the immune mediated multiorgan involvement and injury [3]. There is paucity of published data on how children with SAA fare when they contract SARS-CoV-2 infection. We describe here, our experience of COVID-19 illness in 3 children of SAA.

2. Methods

We describe the course of SARS-CoV-2 infection and COVID-19

illness in three children with SAA. Stress cytogenetics was done to rule out Inherited bone marrow failure in all 3 patients. Genetic testing for Inherited Bone marrow failure syndromes was done for patient 2 and was negative. The other 2 patients did not opt for genetic testing. These patients did not have a matched sibling donor for Hematopoietic Stem cell transplant (HSCT) and hence were planned for Immunosuppressive Therapy (IST). In all three, SAA was diagnosed before the diagnosis of SARS-CoV-2 infection. The diagnosis of SARS-CoV-2 infection was made by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) test on nasopharyngeal swab sample. Patient 1 and 2 were from Centre 1 and Patient 3 from Centre 2. Written informed consent was taken from parent/guardian of the patients for treatment and for incorporating their data for analysis. All Pediatric Hematology Oncology patients were routinely screened for SARS-CoV-2 infection by RT PCR every fortnightly at both the centres. If the patient was found positive for SARS-CoV-2, further monitoring and management was based on their clinical condition.

3. Results

Patient 1 was a 9.5 years old girl, who was found to have SARS-CoV-2 infection in April 2021 during routine fortnightly screening for the infection as part of the COVID-19 surveillance protocol followed at Centre 1. The detection of SARS-CoV-2 infection was 5

* Corresponding author. Pediatric Hematology Oncology & BMT Unit, Cancer Institute, Medanta- The Medicity, Gurgaon, Haryana, 122001, India
E-mail address: satya_1026@hotmail.com (S.P. Yadav).

Peer review under responsibility of Pediatric Hematology Oncology Chapter of Indian Academy of Pediatrics.

weeks after diagnosis of SAA and 2 weeks after completion of horse Anti-Thymocyte Globulin (hATG) as part of IST. She was on Cyclosporine and Eltrombopag for SAA at the time of diagnosis of SARS-CoV-2 infection. She had an asymptomatic course and had a negative RT PCR swab test 10 days from diagnosis. The details of her blood counts at the time of diagnosis of SARS-CoV-2 infection are mentioned in Table 1. During her COVID positive status, blood investigations were not done as she was asymptomatic and she was monitored by teleconsultations by phone twice a week. She is alive and healthy at last follow-up which is 8 months from the diagnosis of SAA and is transfusion independent.

Patient 2 was a 10.5 years old boy, who was a diagnosed case of SAA, post hATG IST with no response to IST. He did not have a matched family donor for HSCT and was on supportive care with packed red blood cell (PRBC) and platelet transfusions while awaiting parental decision on definitive treatment with second round of IST or alternate donor HSCT. He was diagnosed with SARS-CoV-2 infection in September 2020 which was 9 months post his IST. He was on Cyclosporin. Eltrombopag was tried for this patient however withdrawn in view of transaminitis. He was diagnosed with SARS-CoV-2 infection during routine fortnightly screening as part COVID-19 surveillance protocol followed at Centre 1. His blood counts at diagnosis of SARS-CoV-2 infection were as mentioned in Table 1. He had a delayed clearance of SARS-CoV-2 infection, RT PCR turning negative, 28 days from the diagnosis of infection. During this period of 28 days, he did not have any clinical concerns like fever, respiratory or gastrointestinal symptoms. He received PRBC and platelet transfusions during this time as needed. On the day that his SARS-CoV-2 RT PCR turned negative, he developed fever and pain abdomen with difficulty in breathing. He was admitted to hospital and received intravenous fluids, IV antibiotics and other supportive care. RT PCR for SARS-CoV-2 was repeated and was negative. He had high inflammatory markers (Ferritin 24000 ng/ml, CRP 346 mg/L). He required supplemental oxygen followed by mechanical ventilation. Blood culture grew Klebsiella pneumoniae. He succumbed within 24 h of admission to refractory septic shock with abdominal sepsis and pneumonitis with multiorgan

dysfunction.

Patient 3 was a 9 years old boy, diagnosed with SARS-CoV-2 infection 10 days after his diagnosis of SAA in January 2021. He had not yet received IST. He was symptomatic with fever, cough, sore throat. His blood workup at diagnosis of SARS-CoV-2 infection is summarized in Table 1. CT scan chest was done which showed minimal haziness of both lung fields with COVID-19 Reporting and Data System (CO-RADS) score 5/15. He received intravenous Immunoglobulins (IVIG), Azithromycin and supportive care including PRBC and platelet transfusions. Remdesvir was not given due to unavailability. His SARS-CoV-2 RT PCR became negative after 2 weeks. SARS-CoV-2 negativity was confirmed by a repeat test. He improved symptomatically initially but went on to develop pseudomonas sepsis and invasive pulmonary aspergillosis infection subsequently. Child had persistent fever with cough and repeat chest CT scan showed pulmonary cavitory lesions. Serum Galactomannan and Bronchoalveolar lavage galactomannan was positive. Work up for tuberculosis was negative. Blood culture was negative for fungus. He also had raised inflammatory markers (CRP-190 mg/L, Ferritin 2200 ng/ml, IL6- 420 pg/ml, D-dimer 600 ng/ml). 2D Echocardiography (ECHO) was normal. He was treated with Voriconazole initially and Liposomal Amphotericin-B was added later. Blood culture grew Pseudomonas aeruginosa and he received IV Antibiotics as per the sensitivity. Repeat IVIG was given along with symptomatic treatment but eventually he succumbed to pulmonary fungal infection and pseudomonas sepsis 7 weeks after diagnosis of SARS-CoV-2 infection.

Two out of the three patients in our small series had an unfavourable outcome. MIS-C was not considered to be the cause of mortality in these two patients since it occurred soon after the SARS-CoV-2 infection and both the patients had documented bacterial and fungal infections that led to sepsis, shock and death. Though not attributable only to SARS-CoV-2 infection, the post infection immune dysregulation in addition to the SAA could have been contributory to the susceptibility to poor outcome.

Table 1
Demographic and Clinical Profile of the three children with Severe Aplastic Anemia and COVID-19.

S.No.	Age	Gender	Duration b/w diagnosis of AA and SARS-COV-2 positivity	Definitive treatment for AA	Duration from IST to COVID-19	Response to immunosuppressive therapy	Comorbidities	Course of COVID-19 illness	Symptoms of COVID-19 illness
1	9y 8 m	F	5 wk	IST	3 wk	Yes	none	asymptomatic	None
2	10y 7 m	M	17 m	IST	9 m	No	none	asymptomatic	None
3	9y	M	10 d	None	NA	NA	none	symptomatic	fever, sore throat, cough
S.No.	TLC at diagnosis of SARS-CoV-2 inf (/ μ l)	ANC at diagnosis of SARS-CoV-2 inf (/ μ l)	ALC at diagnosis of SARS-CoV-2 inf (/ μ l)	Platelet count at diagnosis of SARS-CoV-2 inf (/ μ l)	Chest X ray during COVID-19 illness	CT scan chest			
1	4930	720	4072	10000	not done	not done			
2	1770	129	1570	7000	not done	not done			
3	650	40	610	30000	abnormal	abnormal			
S.No.	Hospitalization needed for COVID-19 illness	Total duration of hospitalization (days)	Respiratory support needed for COVID-19	Specific treatment for COVID-19 illness	Duration between SARS-CoV-2 positive and negative report (days)	Outcome	Cause of death	Death after how many days from positive SARS-CoV-2 RT PCR	
1	No	none	none	none	10	alive	NA	NA	
2	No	1	none	none	28	dead	Refractory septic shock (Klebsiella infection, Abdominal sepsis and Pneumonitis) with MODS	30	
3	yes	51	none	IVIG	14	dead	Pulmonary aspergillosis with pseudomonas sepsis	49	

y-years; m-months; wk-weeks; d-days; F-female; M-male; μ -microliter; inf-infection; TLC- Total Leucocyte count; ANC- Absolute Neutrophil Count. ALC- Absolute Lymphocyte Count; MODS- Multi-Organ Dysfunction Syndrome.

4. Discussion

SAA is a rare but life-threatening disease [4,5]. During the recent COVID-19 pandemic, many of the SAA patients also got the SARS-CoV-2 infection. Since these patients are immunocompromised, whether there is a higher risk of contracting SARS-CoV-2 infection or they are susceptible to severe COVID-19 illness is unclear. While on the other hand, there is another prevalent thought that these patients may have a milder illness considering that the severity of illness in COVID-19 is to a great extent due to the hyper-inflammatory state which these patients of AA might not be able to have due to their immunosuppressed state [3]. Literature is limited to case reports and small series only. The three patients that we describe, span a full spectrum of possible outcomes. Patient 1 got the infection soon after completion of the IST and had an asymptomatic course and recovered well. Patient 2 in our series was post IST with no response and he had an asymptomatic course during the time that he was positive for SARS-CoV-2 infection however he developed bacterial sepsis and died of septic shock soon after. Patient 3 in the series was a newly diagnosed patient of SAA who contracted the SARS-CoV-2 infection soon after diagnosis and had a torrid course with bacterial and fungal infection and succumbed to them.

The spectrum of SARS-CoV-2 infection and COVID-19 illness has been quite perplexing with asymptomatic infection to life threatening and fatal illness. There is paucity of literature on course of this infection and illness in patients of SAA, more so in children. Akcabelen YM. and colleagues described a 14 years old boy with AA awaiting MSD HSCT who developed COVID-19 illness with mild symptoms and recovered well [6]. Figlerowicz M. et al. described a 6 years old girl who was diagnosed with SARS-CoV-2 infection and AA simultaneously and considered it as COVID-19 associated AA. She received treatment with IVIG, Azithromycin, antiviral Lopinavir + Ritonavir, high dose steroids and convalescent plasma. With this, the SARS-CoV-2 infection got eliminated and she was then planned to receive definitive therapy for AA [7]. Chakravarthy R. et al. described two patients who presented with SARS-CoV-2 infection coincident with new SAA diagnosis. These two patients did not show resolution of peripheral cytopenias and bone marrow hypocellularity pointing more towards typical immune mediated pathogenesis of SAA with COVID-19 illness rather than post-viral myelosuppression. Both patients showed good response to IST hATG with Cyclosporine and became transfusion independent. The second patient also received Eltrombopag for thrombocytopenia [8].

Nicastro E. et al. reviewed the literature for impact of SARS-CoV-2 infection and COVID-19 illness on children who are immunosuppressed for various different conditions like hematologic and oncologic conditions, chronic renal or gastrointestinal disorders, rheumatologic conditions, etc. They opined that the pediatric cancer patients have overall good COVID-19 outcomes, but they are still slightly worse than the general population. They also summarized that the innate and adaptive immune response, rather than direct virus induced damage are the main factors for pulmonary and extrapulmonary inflammation and tissue injury. In complex conditions like cancer patients, the overall fragility and multiorgan involvement contribute to the higher severity in addition to the immunosuppressed status and immunosuppressive therapy. They suggested that immunosuppressive medications should not be withdrawn and scheduled therapies should not be delayed in such children for the fear of SARS-CoV-2 infection [3]. Similar observations were made by Minotti C. et al. and D'Antiga L. earlier, for immunosuppressed children and adults [9,10].

Paton C. et al. described their experience of 5 patients of AA, age range 21–61 years, who developed SARS-CoV-2 infection. Out of 5,

four patients had already received IST and had partial count recovery before the COVID-19 illness. However, one patient had simultaneous diagnosis of AA and SARS-CoV-2 infection and his hATG was delayed for 3 months until a negative SARS-CoV-2 PCR test was obtained, Cyclosporine and Eltrombopag was given. He responded well to IST. All the five patients, recovered fully from COVID-19 illness. Two patients had post-viral complications [5]. Avenoso D. et al. surveyed the clinical features and outcome of 23 patients (age range 20–77 years), 20 of whom had pre-existing AA and 3 patients had new onset AA after SARS-CoV-2 infection. Out of 20, two patients showed progressive decline in all the haematological indices; consistent with overt relapse (confirmed by bone marrow hypocellularity) and decline in blood parameters not meeting relapse criteria in 15 patients, but requiring treatment. One patient in their cohort died as a consequence of infectious complications due to relapsed AA. They demonstrated that SARS-CoV-2 infection can jeopardise the residual haematopoiesis during AA [11]. Similar experience of SARS-CoV-2 infection in adult AA patients has been published from other parts of the world.

We acknowledge that ours is a small cohort of three children with AA who developed SARS-CoV-2 infection and COVID-19 illness. However, in the wake of meagre published literature on how these SAA children fare if they develop COVID-19 illness, we believe that our experience adds to important knowledge about the same. We resonate the expert consensus that definitive treatment should be delivered to these patients without delay and without the fear of severe illness should they happen to contract SARS-CoV-2 infection. However, we do believe that these children form a high-risk group for whom COVID-19 illness may add to the overall fragility and decline in the residual hematopoietic status and may contribute to adverse outcome.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Ethical statement

Informed consent of parents obtained.

Declaration of competing interest

The authors have no conflict of interest to declare.

References

- [1] Rasmussen SA, Thompson LA. Coronavirus disease 2019 and children: what pediatric health care clinicians need to know. *JAMA Pediatr* 2020 Aug 1;174(8):743–4. <https://doi.org/10.1001/jamapediatrics.2020.1224>. PMID: 32242896.
- [2] Borrelli M, Corcione A, Castellano F, Fiori Nastro F, Santamaria F. Coronavirus disease 2019 in children. *Front Pediatr* 2021 May 28;9:668484. <https://doi.org/10.3389/fped.2021.668484>. PMID: 34123972; PMCID: PMC8193095.
- [3] Nicastro E, Verdoni L, Bettini LR, Zuin G, Balduzzi A, Montini G, Biondi A, D'Antiga L. COVID-19 in immunosuppressed children. *Front Pediatr* 2021 Apr 29;9:629240. <https://doi.org/10.3389/fped.2021.629240>. PMID: 33996683; PMCID: PMC8116542.
- [4] Young NS. Aplastic anemia. *N Engl J Med* 2018 Oct 25;379(17):1643–56. <https://doi.org/10.1056/NEJMra1413485>. PMID: 30354958; PMCID: PMC6467577.
- [5] Paton C, Mathews L, Groarke EM, Rios O, Lotter J, Patel BA, Young NS. COVID-19 infection in patients with severe aplastic anaemia. *Br J Haematol* 2021 Jun;193(5):902–5. <https://doi.org/10.1111/bjh.17415>. Epub 2021 Apr 29. PMID: 33928632; PMCID: PMC8165020.
- [6] Akcabelen YM, Koca Yozgat A, Parlakay AN, Yarali N. COVID-19 in a child with severe aplastic anemia. *Pediatr Blood Cancer* 2020 Aug;67(8):e28443. <https://doi.org/10.1002/pbc.28443>. Epub 2020 Jun 15. PMID: 32539221; PMCID: PMC7323031.
- [7] Figlerowicz M, Mania A, Lubarski K, Lewandowska Z, Szużewski W, Derwich K,

- Wachowiak J, Mazur-Melewska K. First case of convalescent plasma transfusion in a child with COVID-19-associated severe aplastic anemia. *Transfus Apher Sci* 2020 Oct;59(5):102866. <https://doi.org/10.1016/j.transci.2020.102866>. Epub 2020 Jul 1. PMID: 32636116; PMCID: PMC7328608.
- [8] Chakravarthy R, Murphy ML, Ann Thompson M, McDaniel HL, Zarnegar-Lumley S, Borinstein SC. SARS-CoV-2 infection coincident with newly diagnosed severe aplastic anemia: a report of two cases. *Pediatr Blood Cancer* 2021 Nov 12:e29433. <https://doi.org/10.1002/pbc.29433>. Epub ahead of print. PMID: 34767303.
- [9] Minotti C, Tirelli F, Barbieri E, Giaquinto C, Donà D. How is immunosuppressive status affecting children and adults in SARS-CoV-2 infection? A systematic review. *J Infect* 2020 Jul;81(1):e61–6. <https://doi.org/10.1016/j.jinf.2020.04.026>. Epub 2020 Apr 23. PMID: 32335173; PMCID: PMC7179496.
- [10] D'Antiga L. Coronaviruses and immunosuppressed patients: the facts during the third epidemic. *Liver Transplant* 2020 Jun;26(6):832–4. <https://doi.org/10.1002/lt.25756>. Epub 2020 Apr 24. PMID: 32196933.
- [11] Avenoso D, Marsh JCW, Potter V, Pagliuca A, Slade S, Dignan F, Tholouli E, Mittal S, Davis B, Tauro S, Kesse-Adu R, Griffin M, Payne E, Gandhi S, Kulasekararaj AG. SARS-CoV-2 infection in aplastic anaemia. *Haematologica* 2021 Oct 21. <https://doi.org/10.3324/haematol.2021.279928>. Epub ahead of print. PMID: 34670361.