Received: 23 January 2021 | Revised: 14 February 2021 | Accepted: 17 February 2021

DOI: 10.1002/pbc.28995

Pediatric Blood & Cancer

SOCIÉTÉ INTERNATIONALE D'ONCOLOGIE PÉDIATRIQUE INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY

aspho The American Society of Pediatric Hematology/Oncology

WILEY

LETTER TO THE EDITOR

SARS-CoV-2-related multisystem inflammatory syndrome in an immunocompromised child with leukemia

To the Editor:

SARS-CoV-2 associated multisystem inflammatory syndrome in children (MIS-C) is increasingly recognised in children with clinical presentations resembling disorders ranging from toxic shock syndrome to Kawasaki disease. MIS-C is diagnosed in immunocompetent children based on the clinical and laboratory profile of the patient with history or evidence of exposure to the SARS-CoV-2 virus. A high index of suspicion is required for diagnosis of MIS-Cin cancer patients receiving immunosuppressive therapy. We describe the first case of MIS-C in a child receiving significantly immunosuppressive chemotherapy.

A 5-year-old female child was referred to the transplant team as a case of refractory acute myelomonocytic leukemia M5. She was refractory to three different courses of immunosuppressive chemotherapy regimens for acute myeloid leukemia. She was planned for experimental therapy with venetoclax and 5-azacytidine after negative SARS-CoV-2 testing by polymerase chain reaction of nasopharyngeal swab. The time line of chemotherapy is shown in Figure 1.

On day 2 of hospital admission, she developed high grade fever, maximum of 39.4°C with no focus. She was maintaining normal oxygen saturation in room air and chest had no added sounds on auscultation. Her abdomen was soft and she had no evidence of mucositis. Her complete blood count showed haemoglobin 8 mg/dl, total white cell count 30,500/mm^3 with absolute neutrophil count 610/mm,[3] 68% blasts and platelets 12,000/mm^3; procalcitonin was 2.12 mg/ml; and lactate 2.3 mmol/L. Blood cultures were taken and she was started on meropenem and amikacin.

On hospital day 3 (day 2 of illness), she was tachycardic with a heart rate up to 150 beats/min during an afebrile period, and a new onset S3 gallop was heard on auscultation.

A chest radiograph showed clear lung fields but was suggestive of cardiomegaly (Figure S1A). 2D echocardiography reported a structurally normal heart with mild concentric left ventricular hypertrophy and a dilated left ventricle. Ejection fraction was 61%.

On hospital day 4 (day 3 of illness), she had two episodes of loose stools with no vomiting. Premature ventricular contractions were present on the ECG monitor (Figure S1B). She was febrile and tachycardic with no respiratory distress. Her chest had no added sounds and abdomen was soft with no tenderness.

Procalcitonin had escalated over 48 h from 2.12 ng/ml at illness onset to 28.21 ng/ml, and C-reactive protein increased from 48 to 192 mg/L but blood cultures had no growth. Suspecting myocarditis, we measured creatine phosphokinase myocardial band, which was elevated at 349 U/L (normal range ≤ 25 U/L).

During a fever spike, she had an episode of oxygen desaturation to 93% in room air and was started on supplemental oxygen delivered by a face mask at 4 L/min. Given the rapid worsening of clinical condition with high inflammatory markers and cardiac involvement, we considered evaluation for MIS-C. SARS-CoV-2 antibodies were positive (total titer 2.11) with ferritin of 56,458 ng/ml, interleukin-6 85 pg/ml, and d-dimer 4704 ng/ml. She fulfilled the CDC/WHO criteria for MIS-C and was started on steroids and enoxaparin prophylaxis. Methylprednisolone was given at a dose of 10 mg/kg/dose. The time line of chemotherapy and signs of MIS-C are shown in Figure 1.

On hospital day 7, after three doses of methylprednisolone, her ectopic heart beats had resolved and inflammatory markers were resolving (ferritin decreased to 6200 ng/ml; interleukin-6 5.56 pg/ml, C-reactive protein 51 mg/l, and procalcitonin 1.3 ng/ml) (Supplementary Figure 2A and B). Antibiotics were discontinued and steroids were tapered and stopped over 2 weeks. Unfortunately, her disease was refractory to venetoclax and azacytidinetherapy with total white blood cell counts escalating to 172×10^9/L, so she was discharged home for palliation.

There is one case of MIS-C published in a child with acute lymphoblastic leukemia prior to chemotherapy.[1] No case of MIS-C has been reported following immunosuppressive or myelosuppressive therapy for cancer (Table S1). The syndrome has not been described in cancer patients probably because of overlap between infection and inflammation and lack of recognition of an emerging syndrome over other usual infections in children receiving immunosuppressive therapy. In haematology-oncology patients, gastrointestinal symptoms are common postchemotherapy during the phase of febrile neutropenia and cardiotoxic chemotherapy can contribute to cardiac dysfunction making diagnosis challenging. Therefore, a high index of suspicion is required for diagnosis of MIS-C in this group of patients.

The pathophysiology of MIS-C is unknown. However, the timing of presentation of cases of MIS-C in relation to the peak of COVID-19 pandemic and the presence of antibodies suggest that this inflammatory syndrome is not mediated by direct viral invasion.[2–7] Multiple possible mechanisms have been suggested for an immune response that results in MIS-C including molecular mimicry,[8] viral superantigens that activate an immunological host response to virus-infected cells, mediated by antibodies or T cells[3] or by macrophages.[9,10] Our patient had received chemotherapy including fludarabine and cytarabine for acute

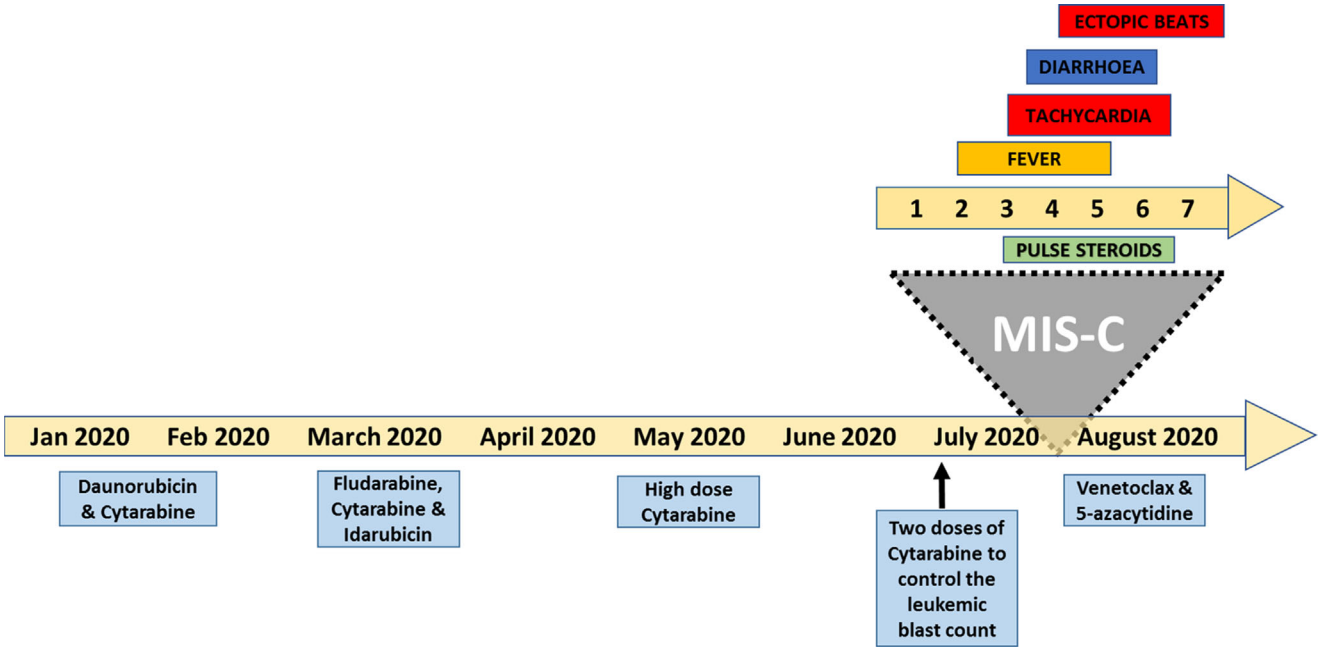

FIGURE 1 Time line of chemotherapy and signs of MIS-C according to day of illness

myeloid leukemia. She mounted an immune response resulting in MIS-C despite several courses of potent immunosuppressive and myelosuppressive chemotherapy.

Cellular mechanisms of MIS-C are not fully understood but laboratory work alludes to FcγR1-mediated macrophage activation (where FcγR is Fc-gamma receptor).[11,12] We speculate role of monocytic blasts that typically express high levels of FcγR1 in causing MIS-C in our patient.[13] Our patient had MIS-C with cardiac involvement despite immunosuppressive chemotherapy and responded to anti-inflammatory dose of steroids, that is, steroid dose used for macrophage activation syndrome.[14] Patients with MIS-C also respond to intravenous immunoglobulin possibly by stimulating inhibitory Fc receptors of macrophages.[2–6]

We present the first case of MIS-C in a patient treated with immunosuppressive chemotherapy for cancer. Cases such as this may help us understand the cellular mechanisms of MIS-C as countries face the second/third wave of the pandemic. Awareness of MIS-C in this patient population will ensure early use of high-dose steroids.

AUTHOR CONTRIBUTIONS

Ambreen Pandrowala and Prashant Hiwarkar designed the study, collected the data, and wrote the manuscript; Honey Panchal collected the data; Sangeeta Mudaliar, Minnie Bodhanwala, Shakuntala Prabhu, Shreepal Jain, and Jayashree Mishra were actively involved in patients care; all authors approved the manuscript.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

Ambreen Pandrowala[1]
Honey Panchal[2]
Sangeeta Mudaliar[3]
Minnie Bodhanwala[2]
Shakuntala Prabhu[4]
Shreepal Jain[4]
Jayashree Mishra[4]
Prashant Hiwarkar[1,3]

[1] *Department of Blood and Marrow Transplantation, Bai Jerbai Wadia Hospital for Children, Mumbai, India*
[2] *Department of Pediatrics, Bai Jerbai Wadia Hospital for Children, Mumbai, India*
[3] *Department of Haematology, Bai Jerbai Wadia Hospital for Children, Mumbai, India*
[4] *Department of Cardiology, Bai Jerbai Wadia Hospital for Children, Mumbai, India*

Correspondence
Prashant Hiwarkar, Department of Blood and Marrow transplantation, Bai Jerbai Wadia Hospital for Children, Mumbai 400012, India.
Email: phiwarkar@nhs.net

ORCID

Minnie Bodhanwala https://orcid.org/0000-0002-3301-3858
Prashant Hiwarkar https://orcid.org/0000-0001-7504-3521

REFERENCES

1. Al-Haddad F, Ali A, Al-Sharrah D, Atyani S, Saleh H, Ali MA. Newly diagnosed acute lymphoblastic leukemia in a child with COVID-19

complicated By MIS-C: a case report from Kuwait. *Blood*. 2020;136(Supplement 1):24-25.
2. Riphagen S, Gomez X, Gonzalez-Martinez C, et al. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet*. 2020;395(10237):1607-1608.
3. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet*. 2020;395:1771-1778.
4. Cabrero-Hernández M, García-Salido A, Leoz-Gordillo I, et al. Severe SARS-CoV-2 infection in children with suspected acute abdomen: a case series from a tertiary hospital in Spain. *Pediatr Infect Dis J*. 2020;39:e195-e198.
5. Belot A, Antona D, Renolleau S, et al. SARS-CoV-2-related paediatric inflammatory multisystem syndrome, an epidemiological study, France, 1 March to 17 May 2020. *Euro Surveill*. 2020;25(22). https://doi.org/10.2807/1560-7917.
6. Feldstein LR, Rose EB, Horwitz SM, et al. Overcoming COVID-19 investigators; CDC COVID-19 response team. Multisystem inflammatory syndrome in U.S. children and adolescents. *N Engl J Med*. 2020;383(4):334-346.
7. Shobhavat L, Solomon R, Rao S, et al. Multisystem inflammatory syndrome in children: clinical features and management-intensive care experience from a pediatric public hospital in western India. *Indian J Crit Care Med*. 2020;24(11):1089-1094.
8. Cheng MH, Zhang S, Porritt RA, et al. An insertion unique to SARS-CoV-2 exhibits superantigenic character strengthened by recent mutations. *bioRxiv*. 2020. https://doi.org/10.1101/2020.05.21.109272
9. Liu L, Wei Q, Lin Q, et al. Anti-spikeIgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection. *JCI Insight*. 2019;4(4):S6.
10. Schwartz M. MIS-C: post-infectious syndrome or persistent infection? *Lancet Infect Dis*. 2020. https://doi.org/10.1016/S1473-3099(20)30786-6
11. Nakra NA, Blumberg DA, Herrera-Guerra A, Lakshminrusimha S. Multi-system inflammatory syndrome in children (MIS-C) following SARS-CoV-2 infection: review of clinical presentation, hypothetical pathogenesis, and proposed management. *Children*. 2020;7(7):69.
12. Gruber CN, Patel RS, Trachtman R, et al. Mapping systemic inflammation and antibody responses in multisystem inflammatory syndrome in children (MIS-C). *Cell*. 2020;183(4):982-995.e14.
13. Scott CS, Bynoe AG, Linch DC, et al. Membrane Fc-IgG and C3b receptors on myeloid leukaemia cells: a comparison with cytoplasmic acid naphthyl acetate esterase cytochemistry. *J ClinPathol*. 1983;36(5):555-558.
14. Boom V, Anton J, Lahdenne P, et al. Evidence-based diagnosis and treatment of macrophage activation syndrome in systemic juvenile idiopathic arthritis. *PediatrRheumatol Online J*. 2015;13. https://doi.org/10.1186/s12969-015-0055-3

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.