Immune responses and therapeutic challenges in paediatric patients with new-onset acute myeloid leukaemia and concomitant COVID-19

Acute myeloid leukaemia (AML) is a medical emergency often presenting with hyperleucocytosis, coagulopathy and pulmonary infiltration necessitating emergent initiation of therapy. AML with concomitant severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection presents a unique challenge given the lack of evidence-based guidelines or historical experience. While cohort studies have shown early serological responses to SARS-CoV-2 in healthy adults, little is known about the serological responses to infection in patients with AML and the impact of chemotherapy on this response. In the present study, we detail the clinical presentations, treatments, serological and virological responses, and outcomes of two adolescents who presented with AML and concurrent coronavirus disease 2019 (COVID-19).

Two adolescents presenting with AML and COVID-19 were enrolled on an Institutional Review Board-approved protocol to collect prospective/residual specimens used for SARS-CoV-2 serological and virological testing. Nasopharyngeal (NP) real-time reverse transcription polymerase chain reaction (RT-PCR), antibody testing by enzyme-linked immunosorbent assay (ELISA), live-virus focus reduction neutralisation assay-mNG, surface plasmon resonance (SPR) assay and viral genetic sequencing were performed (Data S1). Patient details, treatment and outcome data were abstracted from medical records.

Patient 1 was a 16-year-old Caucasian male with a history of classical Hodgkin lymphoma who presented with fever, cough and hyperleucocytosis [white blood count (WBC) 176 × 10^9/l]. His NP SARS-CoV-2 RT-PCR test was positive and peripheral blood flow cytometry (PBFC) confirmed a diagnosis of therapy-related AML. He received hydroxyurea, followed by cytarabine starting on hospital day (HD) 3. Treatment for COVID-19 included hydroxyurea, remdesivir and supplemental oxygen (Fig 1).

On HD4, the patient had detectable immunoglobulin (Ig) M and IgG antibodies to SARS-CoV-2 (Table I). The patient did not become lymphopenic throughout his COVID-19 course and maintained detectable binding and neutralising antibodies to SARS-CoV-2. SPR demonstrated that binding antibodies to the pre-fusion conformation of S, the receptor-binding domain (RBD) and S2 subunits all peaked by HD26. The patient had detectable IgM, IgA and IgG1 titres in the final sample on HD70 (Figure S1). He cleared the virus on HD16. Bone marrow (BM) on HD20 showed rare blasts on morphology in the setting of pancytopenia, with no disease detected by flow cytometry. He received additional chemotherapy with azacitidine and gemtuzumab starting on HD26. His treatment complications included bacteremia and perirectal abscess with Pseudomonas aeruginosa and Epstein–Barr virus (EBV) viraemia resulting in multi-organ failure and death on HD74.
Table I. Laboratory results for Patient 1 (A) and Patient 2 (B).

| Days from COVID-19 symptom onset | Hospital day | Absolute lymphocyte count, /µl | IgM antibody titre | IgG antibody titre | SARS-CoV-2 NeutAb | SARS-CoV-2 RT-PCR S protein Ct value | RT-PCR ORF1ab Ct value |
|---------------------------------|-------------|--------------------------------|-------------------|-------------------|-------------------|-------------------------------------|-----------------------|
| **(A)**                         |             |                                |                   |                   |                   |                                     |                       |
| 3                               | 0           | 1763*                          | N/A               | N/A               | N/A               | Positive                            | 13-1                  |
| 7                               | 4           | 696*                           | 804               | 1327              | 236               | N/A                                 | 17-7                  |
| 19                              | 16          | 590                            | 720               | 3436              | 193               | Negative                            | N/A                   |
| 29                              | 26          | 880                            | 467               | 4790              | 91                | Negative                            | N/A                   |
| 37                              | 34          | 510                            | 312               | 5621              | 85                | N/A                                 |                       |
| 45                              | 42          | 770                            | 179               | 3781              | 37                | N/A                                 |                       |
| **(B)**                         |             |                                |                   |                   |                   |                                     |                       |
| 10                              | 0           | 4496†                          | –                 | –                 | Positive          | 13-1                  | 13-9                  |
| 14                              | 4           | 1330†                          | 85‡               | 619§              | 10‡               | Positive                            | 17-7                  | 18-2                  |
| 22                              | 12          | 85                             | 487               | 10                | Positive          | N/A                                 | N/A                   |
| 27                              | 17          | 85                             | 200†              | 10                | Positive          | 14-6                  | 15-5                  |
| 35                              | 25          | 770                            | 3263              | 559               | Positive          | 29-2                  | 36-9                  |
| 41                              | 31          | 1535                           | 33562             | 2763              | Positive**        | 24-8                  | 24-7                  |
| 45                              | 35          | 1506                           | 33326             | 4379              | Positive††        | 33-4                  | 32-4                  |
| 58                              | 48          | 1310                           | N/A               | N/A               | Negative          | N/A                                 | N/A                   |

NeutAb, neutralising antibody; RT-PCR, reverse transcription polymerase chain reaction; Ct, cycle threshold; N/A, not available.

*>95% peripheral myeloblasts.
†>85% peripheral myeloblasts 90%.
‡Negative titre.
§Received convalescent plasma on hospital day 2 and 3.
¶Received convalescent plasma on hospital day 12 and 13.
**RT-PCR done on hospital day 33.
††RT-PCR done on hospital day 40.
Patient 2 was a 19-year-old obese (body mass index of 32 kg/m²), Hispanic male who presented with fever, cough, dyspnoea and hyperleucocytosis (WBC count 67 × 10⁹/l). His NP SARS-CoV-2 RT-PCR test upon admission was positive and PBFC confirmed a diagnosis of AML. He began induction chemotherapy with cytarabine, daunorubicin and etoposide (ADE) on HD2 and he clinically deteriorated on HD4 requiring intubation and mechanical ventilation. For treatment of COVID-19, he received convalescent plasma (CP), remdesivir, tocilizumab and therapeutic plasma exchange (Fig 1).

The patient was lymphopenic by HD5 and showed no immune response to SARS-CoV-2 with absence of IgM antibodies, waning IgG (post CP) and undetectable neutralising titres (Table I). Concurrently, the patient’s NP RT-PCR remained positive with low cycle-threshold (Ct) values. Coinciding with haematological recovery on HD25, the patient demonstrated a serological response with rising IgM, IgG, neutralising antibody titres and SARS-CoV-2 RT-PCR Ct values until his first negative NP RT-PCR result on HD48. His SPR antibody profiling demonstrated class switching (Figure S1) and coincided with robust increases in binding and neutralising titres with haematological recovery. Genetic sequencing and phylogenetic analysis of his SARS-CoV-2 virus from saliva on HD23 indicated that the sequence clustered with clade 20B,3 which was relatively uncommon in virus from saliva on HD2 and he clinically deteriorated on HD4 requiring intubation and mechanical ventilation. For treatment of COVID-19, he received convalescent plasma (CP), remdesivir, tocilizumab and therapeutic plasma exchange (Fig 1).

In the present report, we highlight both the therapeutic challenges in treating COVID-19 and AML concomitantly and describe the immune response in the setting of myelo-suppressive chemotherapy. The viral clearance of the two patients negatively correlated with the intensity of chemotherapy given for each and likely contributed to the overall severity of COVID-19. Paediatric recommendations for the management of AML and COVID-19 are not well defined. Use of a ‘mild’ induction regimen (MAG) in nine patients with AML and COVID-19 in Brazil was recently described to have excellent outcomes.4 While reduced-intensity regimens are a valid approach, they preclude response-based risk assignment in AML but warrant further investigation in the setting of concomitant COVID-19.

SARS-CoV-2 evolution within immunocompromised patients with prolonged virus replication has been described.5,6 Although our investigation was limited to one time point, we did observe within-sample SARS-CoV-2 variants for Patient 2. The functional importance of these variants is unclear; however, future studies into the intra-host variation of SARS-CoV-2 genotypes are needed in the immunocompromised population. Furthermore, Ct values associated with RT-PCR testing for SARS-CoV-2 could provide indirect assessment of viral load.7 Lower median Ct values in adults with cancer correlated with higher rates of mortality.8 Patient 2’s Ct values remained <25 until HD17 suggesting a high viral load. While PCR Ct values have limitations based on sample collection and instrumentation, serial measurements could be used for clinical correlation.9

Limitations of our present study include the small number of patients, which limits generalisability of the data. Co-existing factors such as underlying obesity and race may have contributed to a worse outcome in Patient 2.10,11 In addition, absence of serological immunity at presentation and administration of CP in Patient 2 confounds interpretation of serological results. Investigation into early immune responses is warranted in this population as they may serve as prognostic indicators at the time of presentation.

In conclusion, our experience demonstrates that patients with AML and COVID-19 can mount immune responses to SARS-CoV-2 even in the face of immune suppression by chemotherapy; however, the intensity of chemotherapy may play a role in the response. Longitudinal research is needed in this vulnerable population to better understand response to SARS-CoV-2 infection and now vaccination.

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Author contributions

Pratik A. Patel designed the research study, performed the research, analysed the data and helped write the paper. Gabrielle Grubbs, Stacey L. Lapp and Venkata V. Edara performed the research and analysed the data. Christina A. Rostad, Evan J. Anderson and Surender Khurana formed the research and analysed the data. Christina A. Rostad, Evan J. Anderson and Surender Khurana designed the research study, performed the research and analysed the data. Himalee S. Sabnis analysed the data and helped write the paper. All authors made substantial contributions to research design, or acquisition, analysis or interpretation of data, drafting the paper or revising it critically and approval of the submitted and final versions of the paper.

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Conflict of interest

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Supporting Information

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

Fig S1. Antibody kinetics in serum following SARS-CoV-2 infection.

Fig S2. Phylogenetic tree of SARS-CoV-2 sequence for Patient 2.

Fig S3. Scatter plot indicates the frequency of intra-host single nucleotide variants (iSNVs) across the SARS-CoV-2 genome.

Table S1. Intra-host single nucleotide variants (iSNV) of patient 2’s SARS-CoV-2 sequence.

Data S1. Supplementary Information.

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