[Clinical note]

COVID-19 in a 13-year-old patient with acute lymphoblastic leukemia

Running title: COVID-19 in ALL patients

Seyed Kamal Eshagh Hossaini¹, Zahra Movahedi¹, Ahmad Hormati²,³, Hosein Heydari¹, Seyed Jalal Eshagh Hosseini⁴, Fatemeh Khodadust, MSc⁵, Mahboubeh Afifian, MSc⁶, Sajjad Ahmadpour³

¹Department of Pediatrics, School of Medicine, Hazrat-e Fateme Masoume Hospital, Qom University of Medical Sciences, Qom, Iran; ²Gastrointestinal and Liver Diseases Research Center, Iran University of Medical Sciences, Tehran, Iran; ³Gastroenterology and Hepatology Diseases Research Center, Qom University of Medical Sciences, Qom, Iran; ⁴Department of Surgery, School of Medicine, Shahid Beheshti Hospital, Qom University of Medical Sciences, Qom, Iran; ⁵Department of Rheumatology, VU University Medical Center, Amsterdam, The Netherlands; ⁶Department of Health Information Technology, Tehran University of Medical Sciences, Tehran, Iran

Corresponding author: Sajjad Ahmadpour

Gastroenterology and Hepatology Diseases Research Center, Qom University of Medical Sciences, Qom, Iran

Email: sajjadahmadpour@yahoo.com

https://orcid.org/0000-0003-4321-874X

Accepted Article
Abbreviations:

ALL: Acute Lymphoblastic Leukemia

CT: Computed Tomography

COVID-19: Coronavirus Disease 2019

rRT-PCR: real-time Reverse-Transcriptase Polymerase Chain Reaction

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2
**Key message**

**Question:** What should be considered in an immunocompromised child with coronavirus disease (COVID-19)?

**Finding:** Due to the importance of appropriately managing COVID-19 in children with cancer, the possibility of a fatal outcome should be considered in immunocompromised patients who receive chemotherapy agents.

**Meaning:** In all kinds of infections including COVID-19, disuse management and the development of international guidelines for children with cancer is challenging but important.
On March 2, 2020, a 13-year-old female patient has been admitted to Hazrat-e Fateme Masoume Hospital, Qom city, Iran with the main complaint of pallor, anemia and weight loss. Bone marrow smears show hypercellular bone marrow aspiration composed of more 50% blastic cells with high nucleus/cytoplasm (N/C) ratio, fine chromatic, 2-3 prominent nuclei and thin rim of basophilic cytoplasm. Ultimately, flowcytometry assay was confirmed acute lymphoblastic leukemia (ALL) with T-cell type. The patient was reported to have high-risk ALL. The patient underwent medication with chemotherapy agents in Table 1. On March 12, 2020, once again, the patient has been admitted to the hospital with the main complaint of fever (38.5 °C) and vomiting. Also, the patient presented gingival bleeding, cough and myalgia. Laboratory test for severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) was performed using real-time reverse-transcriptase polymerase chain reaction (rRT-PCR) that was reported positive. The cycle threshold (Ct) value was reported 25. Complementary evaluation was followed by performing chest computed tomography (CT) scan which showed a well-defined nodular ground glass opacity with diameter of 6 mm at lateral segment of RML (Figure 1 a, b). Despite lung involvement, gasometer data were in normal range. Within two weeks, all symptoms for SARS-CoV-2 were subsided. Laboratory rRT-PCR test was repeated that was reported negative (Ct value=39). Additionally, radiologic findings disappeared. On April 18, 2020, the patient has been admitted to hospital and received treatment with chemotherapy agents for third time. Three days later, the patient has been hospitalized again with the main complaint of fever (38.7 °C), abdominal pain, headache, diarrhea, and nausea, as at the beginning of hospitalization, she presented tonic-clonic seizures twice and lost consciousness as well. Drowsiness and stiff neck were evident in the patient. Chest CT scan was requested once again as revealed small bilateral peripheral consolidations with ground-glass opacity and a crazy paving pattern (Ct value=27 in
rRT-PCR). The patient underwent medication, but eventually the patient's lung turned white (Figure 1c, d) and died due to the acute respiratory distress syndrome and cardiovascular arrest.

COVID-19 and ALL

The novel Coronavirus disease 2019 (COVID-19) is affecting the entire population of the world after its outbreak in Wuhan, China [1]. It has been well documented that definitive diagnosis of COVID-19 in children is less than 2%. Relatively few pediatric COVID-19 cases were hospitalized, as mainly limited to the pediatric patients aged <1 year and those with underlying conditions [2, 3]. Acute lymphoblastic leukemia (ALL) numerate as the most common form of childhood malignancy that originates in a single B- or T-lymphocyte progenitor. It is reported that the account for the peak incidence is in early childhood [4]. So far, most of the published data on COVID-19 infection is mainly focused on children and newborns (<18 years) and there is little information about infected children with cancer, particularly ALL [4].

Treatment of ALL in COVID-19

There have not yet been any international guidelines developed to address the optimal management of ALL patients in any infectious pandemic [5]. Therefore, at the age of COVID-19, it seems that the disease management in children with ALL is sometimes challenging and of high importance. The novel Coronavirus disease 2019 (COVID-19) outbreak is rapidly affecting children with cancer, and it seems that special care is required for these patients. Regarding various case reports have described the impact of COVID-19 in the pediatric population, the impact of COVID-19 pneumonia on children with cancer need more investigation [4, 6]. So far, the medical management of children with cancer, remains unclear and poorly documented.
In a study, the clinical course of COVID-19 in childhood with acute leukemia was reported by Chen, et al [6]. The patient was reported to have high-risk ALL who on his maintenance chemotherapy neutropenic fever and cough had occurred. The child remained febrile and the requested chest CT scan for the second time 11 days after symptom onset showed progressive changes. The patient then was isolated and treated with umifenovir, ribavirin and recombinant interferon α-1b nebulized inhalations. Seven days later, the child’s blood count had recovered and the SARS-CoV-2 test result became negative; however, four days later, the test was reported positive again and he was transferred to the intensive care unit.

In this case report, we documented one COVID-19 patient with presentation of ALL. The patient underwent chemotherapy and was discharged from the hospital. After chemotherapy, the patient presented symptoms of COVID-19 infection. The results of clinical evaluation, rRT-PCR tests, as well as Ct values, confirmed the reinfection or reactivation with the SARS-CoV-2.

**How should care the risk of COVID infection in cancer patients?**

Overall, COVID-19 is very fatal for some cancer patients, but most are adults and often have other underlying conditions. Pediatric population are less likely to be infected by COVID-19 as in compared to adults, they may present mild symptoms, though in some cases, especially for patients with cancer, severe infections may occur. All kind of infection including COVID-19 could be the main cause of mortality and morbidity of leukemia patients with chemotherapy [7, 8]. In this case report, CSF evaluation, blood culture test and rRT-PCR were performed to exclude the other reasons of patient deterioration on last admission. With notice to the negative result for blood culture test, various organ involvements including; CNS (seizure and loss of consciousness), heart (tachycardia and increasing of troponin), severe increasing of ferritin and
D-Dimer, history of positive rRT-PCR, we claim that the major cause of a death may be related to the COVID-19 infection or maybe second complications of COVID-19. Multisystem inflammatory syndrome (MIS-C) in children is a serious condition that appears to be linked to COVID-19. In rare cases, MIS-C could result in permanent damage or even death. It seems that this syndrome was occurred in this patient who was infected with the COVID-19 (According to the WHO diagnostic criteria for MIS-C [9]). The exact cause of MIS-C in children with COVID-19 is not known yet, but it appears to be an excessive immune response related to the SARS-CoV-2 [10]. This case report depicts the importance and fatality of immune suppression after COVID-19 infection, which can cause reactivation or reinfection of the virus. In conclusion, both children and adults with confirmed COVID-19, the patients' medical history can play great role in the incidence of severe symptoms and even death.
Declarations

Consent to publish

Patients signed informed consent regarding publishing their data and photographs.

Availability of supporting data

All data and materials are available.

Conflict of interests

The authors declare that they have no conflict of interest.

Author Contribution

[SK Eshagh Hossaini], [H Heydari], Original draft preparation. [Z Movahedi], [A Hormati], [SJ Eshagh Hosseini], Designing, investigation. [S Ahmadpour], Writing, edit and correspondence. [F Khodadust], Language editing, [M Afifian], Collecting the data.

Compliance with Ethical Standards

Approval was obtained from the ethics committee of Qom University of Medical Sciences. The procedures used in this study adhere to the tenets of the Declaration of Helsinki (Nu: IR.MUQ.REC.1399.056).

ORCID iDs

Seyed Kamal Eshagh Hossaini https://orcid.org/0000-0002-0176-4884
Zahra Movahedi https://orcid.org/0000-0002-5847-6111
<table>
<thead>
<tr>
<th>Name</th>
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</tr>
</thead>
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<tr>
<td>Ahmad Hormati</td>
<td><a href="https://orcid.org/0000-0002-1322-1318">https://orcid.org/0000-0002-1322-1318</a></td>
</tr>
<tr>
<td>Hosein Heydari</td>
<td><a href="https://orcid.org/0000-0002-8627-9625">https://orcid.org/0000-0002-8627-9625</a></td>
</tr>
<tr>
<td>Seyed Jalal Eshagh Hosseini</td>
<td><a href="https://orcid.org/0000-0003-3139-9512">https://orcid.org/0000-0003-3139-9512</a></td>
</tr>
<tr>
<td>Mahboubeh Afifian</td>
<td><a href="https://orcid.org/0000-0002-8924-2246">https://orcid.org/0000-0002-8924-2246</a></td>
</tr>
<tr>
<td>Sajjad Ahmadpour</td>
<td><a href="https://orcid.org/0000-0003-4321-874X">https://orcid.org/0000-0003-4321-874X</a></td>
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References


Figure legend

**Figure 1.** Chest computed tomography scan (transverse plane) of the 13-year-old female patient revealing nodular ground-glass opacity and white lung on the last day of hospitalization.
Table 1. Laboratory examination results of a 13-year-old patient who had COVID-19 and acute lymphoblastic leukemia

<table>
<thead>
<tr>
<th>Test Result</th>
<th>March 2</th>
<th>March 12</th>
<th>21 April</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDH, IU/L</td>
<td>444&lt;sup&gt;a&lt;/sup&gt;</td>
<td>900&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1154&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10-12 years: 120-293</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.4</td>
<td>0.73&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>children: 0.3-0.7</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>3.2</td>
<td>39.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>60.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>quantitative &lt;6: negative</td>
</tr>
<tr>
<td>Reticulocyte count, %</td>
<td>0.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.5</td>
<td>0.4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>adults: 0.5-1.5% newborns: 2-6%</td>
</tr>
<tr>
<td>WBC, 10&lt;sup&gt;³&lt;/sup&gt;/μL</td>
<td>9000</td>
<td>2800&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>1000&lt;sup&gt;b&lt;/sup&gt;</td>
<td>9-12 years: 4500-13500</td>
</tr>
<tr>
<td>RBC, 10&lt;sup&gt;⁶&lt;/sup&gt;/μL</td>
<td>3.86&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.56&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.86&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6-12 years: 4.0-5.2</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>11.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>7.2&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>7.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>12.4-15.7</td>
</tr>
<tr>
<td>Platelet, 10&lt;sup&gt;³&lt;/sup&gt;/μL</td>
<td>26000&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8000&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>10000&lt;sup&gt;b&lt;/sup&gt;</td>
<td>150000-450000</td>
</tr>
<tr>
<td>ESR, mm</td>
<td>13</td>
<td>88&lt;sup&gt;a&lt;/sup&gt;</td>
<td>25&lt;sup&gt;a&lt;/sup&gt;</td>
<td>children: 3-13</td>
</tr>
<tr>
<td>SpO2, %</td>
<td>96</td>
<td>97.5</td>
<td>63.2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>90-100</td>
</tr>
<tr>
<td>PT, sec</td>
<td>11</td>
<td>13</td>
<td>23&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>11-13.5</td>
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<tr>
<td>PTT, sec</td>
<td>29</td>
<td>36</td>
<td>58&lt;sup&gt;a&lt;/sup&gt;</td>
<td>25-45</td>
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<tr>
<td>D-dimer, ng/ml</td>
<td></td>
<td></td>
<td>18817&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>Up to 500</td>
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<tr>
<td>Troponin I, ng/L</td>
<td></td>
<td></td>
<td>1188</td>
<td>TO&gt;100 positive</td>
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<tr>
<td>rRT-PCR</td>
<td>negative</td>
<td>positive</td>
<td>positive</td>
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| Treatment                  | Vincristine + Doxorubicin + Prednisolone + PEG Aspar | Hydroxychloroquine + Lopinavir/ritonavir + Oseltamivir + Vincristine + Doxorubicin + Prednisolone + PEG Aspar | Lopinavir/ritonavir + Oseltamivir + Levetiracetam + Methylprednisolone + IVIG + Platelets + Dopamine + FFP + Pethidine |}

<sup>a</sup>Higher than reference value
<sup>b</sup>Lower than reference value
<sup>#</sup>On April 18, 2020, after a second course of chemotherapy, the platelet, WBC, and hemoglobin values returned to normal (172000 × 10<sup>³</sup>/μL, 4.9 × 10<sup>³</sup>/μL, and 8.2 g/dL, respectively).

LDH, lactate dehydrogenase; CRP, C-reactive protein; WBC, white blood cell; RBC, red blood cell; ESR, erythrocyte sedimentation rate; PT, prothrombin time; PTT, partial thromboplastin time; rRT-PCR, reverse transcription polymerase chain reaction.

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Figure 1

(A) CT scan of the chest showing bilateral pneumonia.
(B) CT scan of the chest with no evidence of pneumonia.
(C) Fluoroscopic image of the chest.
(D) X-ray of the chest.