

COVID-19 in Children with Cancer: A single Low-Middle income center experience

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Abstract

Background: Coronavirus disease-2019 (COVID-19) could be associated with morbidity and mortality in immunocompromised children. Objective: To measure the frequency of SARS-CoV-2 infection among hospitalized children with cancer and detect the associated clinical manifestations and outcomes. Methodology: A prospective non-interventional study including all hospitalized children with cancer conducted between mid-April and mid-June 2020 in Ain Shams University hospital, Egypt. Clinical, laboratory and radiological data were collected. SARS-CoV2 infection was diagnosed by RT-PCR tests in nasopharyngeal swabs. Results: Fifteen of 61 hospitalized children with cancer were diagnosed with SARS-CoV-2. Their mean age was 8.3 ± 3.5 years. Initially, 10(66.7%) were asymptomatic and 5(33.3%) were symptomatic with fever and/or cough. Baseline laboratory tests other than SARS-CoV-2 RT-PCR were not diagnostic; the mean absolute lymphocyte count was $8.7 \pm 2.4 \times 10^9/L$, C-reactive protein was mildly elevated in most of patients. Imaging was performed in 10(66.7%) patients with significant radiological findings detected in 4(40%) patients. Treatment was mainly supportive with antibiotics as per the febrile neutropenia protocol and local Children Hospital guidance for management of COVID-19 in children. Conclusion: Pediatric cancer patients with COVID-19 were mainly asymptomatic or with mild symptoms. A high index of suspicion and regular screening with nasopharyngeal swab in asymptomatic hospitalized cancer patients is recommended.

Introduction:

Coronavirus disease 2019 (COVID-19) is a viral respiratory illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the first case was detected in December 2019. (1) The COVID-19 pandemic has rapidly escalated into a global crisis. (2) The first case registered in Egypt was in February 2020 and since that date, the numbers have been increasing and by mid-June 2020, 47,856 cases of SARS-CoV-2 and 1766 deaths have been reported by the Ministry of Health (3).

Children are usually develops mild disease (4), a Chinese analysis of 2135 confirmed or suspected cases of COVID-19 among children revealed that 55.4% developed mild symptoms or were asymptomatic and only 5.4% had severe illness compared with 18.5% of adult cases. (5)

Viral infections in general are associated with increased morbidity and mortality in immunocompromised children. (6) Data on the clinical features and outcomes of immunocompromised children with cancer who are infected with SARS-CoV-2 are scarce. Knowledge from previous influenza A H1N1 pandemics suggests that those vulnerable immunosuppressed children are likely to be infected and to develop manifestation as an increased number of cases are described with time. (7,8)

Although isolation as an inpatient is common practice for children who are receiving intensive chemotherapy or stem cell transplant, most children with cancer are treated in the outpatient setting, and hospital visits

or intermittent hospital admission are unavoidable for appropriate delivery of therapy. Risk of exposure to SARS-CoV-2, either in the hospital or the community setting, has resulted in widespread anxiety among families of children with cancer. (9)

The primary objective of this study was to measure the frequency of SARS-COV-2 infection among hospitalized children with cancer, while the secondary objective was to identify the associated clinical manifestations and outcomes in those with confirmed SARS-COV2 infection.

Methodology

Study design

A prospective non-interventional study was carried out at the Hematology Oncology Department, Children's hospital, Ain-Shams University, Cairo, Egypt. The study sample was obtained using a non-probability convenience sample including all hospitalized children with cancer with confirmed SARS-COV-2 between mid-April and mid-June 2020. The study was approved by the Research Ethics Committee, Faculty of Medicine, Ain Shams University [FMASU P25a /2020] in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments in humans, 2013 and was registered on clinicaltrials.gov [NCT04404244].

Study Procedures:

A written signed and dated informed consent and assent were obtained from each caregiver and patient if applicable before inclusion in the study. Patient clinical report forms included demographic data, full medical history, concurrent medications and epidemiological data (history of contact to a COVID-19 case, history of travel), as well as the underlying oncological disorders and cause of admission. In addition, physical examination, vital signs (blood pressure, heart rate and temperature) and blood oxygen saturation were assessed and recorded.

Baseline Laboratory investigations included complete blood count (CBC) using Sysmex XT-1800i (Sysmex, Kobe, Japan), examination of Leishman stained smears for differential white blood cell (WBC) count, liver (alanine amino transferase (ALT), total and direct bilirubin) and kidney function tests (serum creatinine), CRP using Cobas Integra 800 (Roche Diagnostics, Mannheim, Germany), serum ferritin using Immulite 1000 Analyzer, Siemens Healthcare Diagnostics, Marburg, Germany), lactate dehydrogenase (LDH) and coagulation test (D-dimer, prothrombin time and INR). COVID-19 was confirmed by SARS-CoV-2 reverse Transcription Polymerase Chain Reaction (RT-PCR) test by nasopharyngeal (NP) swab. Chest X-ray and/or computed tomography (CT) scan of the chest was performed.

During admission, whenever unexplained fever and/or respiratory symptoms developed or COVID-19 was suspected, chemotherapy during admission was revised and individualized decisions were taken, NP swab (in patients with platelet count at least $30 \times 10^9/L$) was repeated, and chest X-ray and/or CT chest were performed. In addition, CBC with differential counts, CRP and serum ferritin level, coagulation test and routine bacteriological study, blood culture and other symptoms/signs-based cultures were performed.

On discharge, a thorough physical examination was performed, date of discharge, period of admission and the outcome were recorded.

Results

Over the study period between mid-April and mid-June 2020, sixty-one children with cancer were admitted to the Pediatric Hematology Oncology department, Children's hospital, Ain Shams University. They were 38 (62.2%) males and 23 (37.7%) females. The underlying diagnosis was mainly acute lymphoblastic leukemia (ALL) (n=42, 68.9%), bone tumor (n=4, 6.5%), lymphoma (n=4, 6.5%), neuroblastoma (n=2, 3.3%), central nervous system (CNS) tumors (n=3, 4.9%), hemophagocytic lymphohistiocytosis (HLH) 2 (n=2, 3.2%), retinoblastoma (n=1, 1.6%), Wilms tumor (n=1, 1.6%), germ cell tumor (n=1, 1.6%) and rhabdomyosarcoma (n=1, 1.6%). All patients were admitted either for their due chemotherapy cycle (n=29, 45.7%) or for a

concurrent illness that required supportive care (n=33, 54.3%). Forty-six (75%) patients were discharged safely and 4 (6.5%) died during the admission.

Children with cancer diagnosed with SARS-COV-2

Fifteen patients were diagnosed with SARS-COV-2 by NP swab during the study period; 9 (60%) boys and 6 (40%) girls. Their mean age was 8.3 ± 3.5 years. Their residence mainly in the catchment area of the hospital (8 (53.3%) from Cairo, 2 (13.4%) from Qalyubia, 1 (7%) from El-Fayoum and four were from other governates (1 Suez Canal, 3 Beni-Sweif). Five (33.3%) patients had a positive history of exposure to confirmed SARS-CoV2 positive cases. NP Swab was performed for 3 out of 13 care-givers and it returned positive. The underlying diagnosis of those 15 patients was mainly hematological malignancies; ten (76.9%) were diagnosed with ALL (n=8, 61.5% had Pre B and n=2, 15.3% had T-cell), 1 (6.7%) had acute myeloid leukemia, 1 (6.7%) had lymphoblastic lymphoma, and 1 (6.7%) had post-transplant Hodgkin Lymphoma. Two (13.4%) of these 15 patients had other malignancies; 1 (6.7%) had high risk medulloblastoma and 1 (6.7%) had Ewing's sarcoma.

Clinical picture

Regarding the clinical picture, 10 (66.7%) were asymptomatic (six patients were newly diagnosed with cancer and three were admitted for chemotherapy and one was screened preoperatively for excisional lymph node biopsy for suspicion of relapse). One of the ten asymptomatic cases who presented at his initial diagnosis found to have a mediastinal mass and malignant pleural effusion on the initial diagnostic work-up. The other five (38.4%) symptomatic patients were admitted for supportive care; 4 presented with fever and 1 presented with cough and dyspnea as illustrated in Figure1. During admission, out of ten asymptomatic children, five remained asymptomatic and the other 5 developed mild symptoms, mainly fever (n=5), cough (n=3), headaches (n=2), myalgia (n=1), fatigue (n=1), and pruritis (n=1).

Laboratory results

Regarding the laboratory results, there was a wide range of lymphocyte count which is attributed to the presence of three newly diagnosed patients with acute leukemia within the study and the detected lymphocytopenia present in 50% of patients. D-dimer was performed in seven patients and was elevated in all of them. LDH was also elevated in all the examined cases. The mean serum creatinine was 0.7 mg/dl, which was elevated only in one newly diagnosed patient with high TLC count and picture of tumor lysis. C-reactive protein (CRP) was mildly elevated in all, except in three patients with a mean of 24.3 mg/dl. Laboratory data of the 15 patients with confirmed SARS-CoV2 infection are summarized in Table 1. Creatine kinase was done for 2 patients; 36 and 41 U/l (reference range 20-200). One patient was isolated at home, whose parents refused doing further laboratory tests, except for a CBC before biopsy.

Radiological data

Among the 15 patients with confirmed SARS-CoV2 infection, 10 (66.7%) performed radiological assessment with significant radiological findings detected in four (40%) patients. One patient had only a plain chest x-ray, which showed bilateral pulmonary infiltrates. Three had an initial plain chest x-ray followed by high resolution CT-scan (HRCT), which was abnormal in one of them revealing bilateral mosaic appearance and left lobar consolidation. Six patients had HRCT from the start and showed abnormal finding in two patients.as illustrated in Figure 2.

Treatment

Treatment was mainly supportive with antibiotic according to the febrile neutropenia protocol and the local Children Hospital, Ain shams University guidance for management of COVID-19. Supportive treatment was mainly in the form of maintaining adequate hydration and nutrition, ensuring adequate sleeping hours, antipyretics (paracetamol), vitamin C (50 mg 1-3 year and 100 mg over 3year), zinc 5-10 mg for young children and 10-15 mg for older children, vitamin D 3 (400-600 IU) below 1 year, and (600-800 IU) for older children in addition to lactoferrin sachet once daily.

Treatment of COVID-19 as per the local children's hospital guidance includes the following medications: 1) azithromycin 10 mg/kg once on day one max dose 500mg /dose followed by 5 mg/kg (max 250 mg/dose) once daily for 5 days, 2) hydroxychloroquine 6.5 mg/kg orally every 12 hours (max: 600 mg/dose) for two doses, followed by 3 mg/kg orally every 12 hours (max: 200 mg/dose) for a total of 5-10 days, 3) ceftriaxone 100 mg/kg/dose once daily for 5 days max daily dose 2 gm, and 4) anticoagulation prophylaxis (Enoxaparin) <2 months: 0.75 mg/kg SC q12h , [?]2 months: 0.5 mg/kg SC q12hr if D dimer between 500-1000 ng/ml.

Outcome

Out of the 15 patients with confirmed SARS-CoV2 infection, eight (53.3 %) were discharged after their RT-PCR test results became negative, four (26.6 %) are still admitted in isolation, one (6.7 %) patient was isolated at home and managed through the hospital on-call services. The duration of hospital stay ranged from 1-24 days (mean 10.2+/-8.1) as illustrated in Figure 1.

Mortality

During the study period two death were reported, one of them was 13 years old female who presented on May 16, 2020 with pancytopenia and severe menorrhagia for which she started hormonal therapy with GnRH agonist and platelet transfusion with good initial response, eventually she was diagnosed with ALL pre B. NP swab was performed on the following day and she was confirmed with SARS-CoV-2 and her CT scan was normal. She was transferred to Elobour isolation hospital and treated with supportive treatment, azithromycin, oseltamivir, and hydroxychloroquine. No anticoagulation was started due to persistent thrombocytopenia. After 12 days of her first presentation to hospital she was deceased due to the underlying cancer before commencing anti-leukemic therapy because SARS-CoV-2 RT-PCR was still positive.

Discussion

COVID-19 was declared by World Health Organization as a public health emergency of international concern (10) and despite the worldwide spread, clinical patterns of COVID-19 particularly among children remain largely unclear. (5) The clinical spectrum of COVID-19 could range from being asymptomatic to developing severe acute respiratory distress. (2) In the current study, despite of the immunocompromised status of the hospitalized patients with cancer, 66.7% were asymptomatic at admission and 33.3% had mild symptoms. This is in comparison to 4.4% and 50.9% respectively in large Chinese study in which 731 patients were confirmed positive by laboratory testing. (2)

While other coronaviruses can produce more severe disease in immunocompromised children with increased risk with coexisting pulmonary disease or concurrent lower respiratory tract infection (6,11), the severity of children's COVID-19 cases was milder than adult. (2) A systemic review of 110 immunosuppressed patients, mostly presenting with cancer, along with transplantation and immunodeficiency, they seemed to have a favorable disease course, as compared to the general population, 72 (65.5%) recovered (discharged or inpatients) or did not require intensive care and 6 (5.5%) needed intensive care or invasive ventilation and 23 (20.9%) died. (12) In an Italian pediatric haemato-oncology clinic, SARS-CoV-2 infection was detected in 4 out 170 patients at the molecular level; three of them were asymptomatic. (13)The clinical course and outcome of SARS-CoV-2 was reported to be more favorable in children than in adults (1) A possible explanation that children might have less severe disease was attributed to the lower expression of ACE2 receptor and present with a different inflammatory response, with higher numbers of B and T regulator cells, involved in immune tolerance and leading to a less inflammatory immune response. (14)

The detrimental impact of COVID-19 pandemic on childhood cancer may be delay in diagnosis (15), delay in starting treatment, the detrimental impact of infection on children with cancer, and the uncertainty about decision for chemotherapy in PCR-positive asymptomatic patients. Universal testing of asymptomatic cancer patients may help safe continuation of treatment. (16)

As regards the treatment, all the patients received supportive care in addition to antivirals or antibiotics guided by radiological findings and symptom progression (according to Children's hospital and MOH guidelines). With the large diversity of therapeutic options, (17) whether a different treatment approaches in

children with cancer on chemotherapy is not adopted. The important decision is the proper time to start anticoagulation, the main concern is that childhood cancer is predisposing for thrombosis (18). Whether early start of anticoagulation for COVID-19 or delay usage as that it might be an immune thrombosis related to neutrophil extracellular traps (19); yet it is acceptable that in both cancer (20) and COVID-19 (21), D-dimer level is the most important laboratory result in decision for anticoagulation.

As for total and differential leucocytic count, there was wide variability; lymphocytopenia was present in 50% of patients compared to 3.6% in a previous study that is evaluating children infected with SARS-CoV-2 and treated at the Wuhan Children's Hospital. (11) Although lymphopenia was associated with severe disease (22) which was not consistent with the clinical manifestations of our patients group, yet the high frequency of lymphopenia might be attributed to the underlying cancer, chemotherapy and the wide variation could be due to the inclusion of three newly diagnosed patients with hematological malignancy.

The radiological findings in our patients were mainly ground glass opacities (GGO), not necessarily affecting the periphery, consolidation (lobar) and interstitial infiltrates. This finding is in agreement with Chen et al, 2020 who reported that initially, chest radiography findings can show signs of pneumonia, such as small irregular lung opacities and interstitial alterations, usually affecting peripheral areas. The authors also reported that chest computed tomography also exhibits GGO and segmental consolidation in both lungs while pleural effusion being uncommon. (23) However, correlation of radiological findings with COVID-19 severity in the current study may not be applicable due to small sample size.

Conclusion :

Pediatric oncology patients with SARS-COV-2 infection in this study were mainly asymptomatic or with mild symptoms. A high index of suspicion with mild symptoms and regular screening by NP swab in asymptomatic hospitalized cancer patients admitted for intensive chemotherapy and initiation of treatment, guided by laboratory data is recommended. More studies are required to report the incidence, outcomes and therapeutic decisions of SARS-COV-2 in pediatric patients with cancer.

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Figure Legend

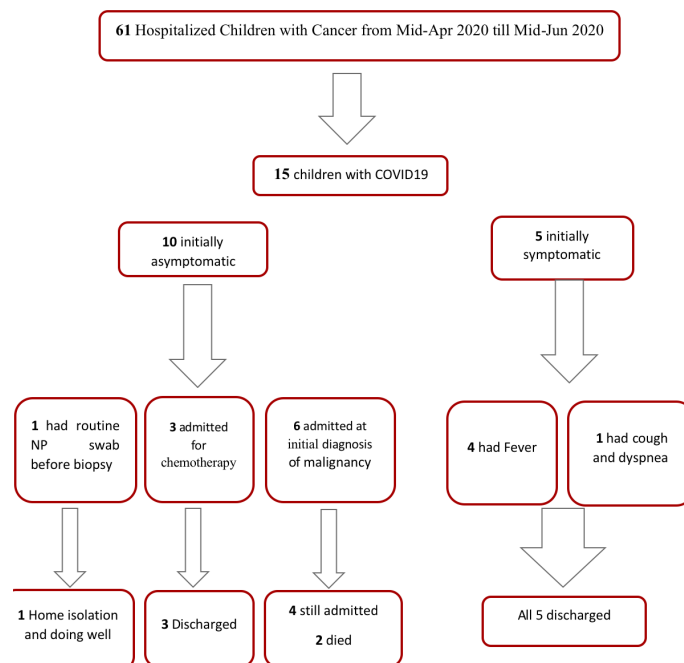


Figure 1: Consort Diagram presenting admitted children with cancer, SARS-COV-2 results and outcome

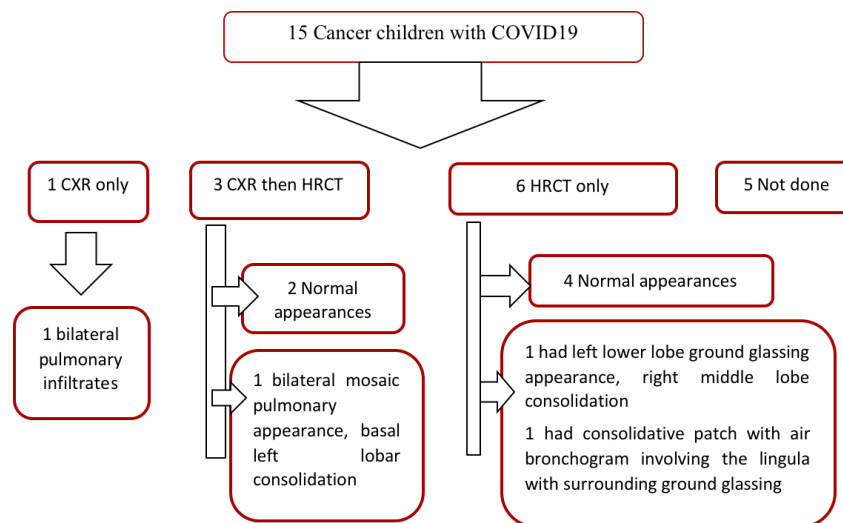


Figure2: Consort Diagram showing radiologic findings in children with cancer and COVID positive by RT-PCR

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Table 1.docx available at <https://authorea.com/users/351657/articles/476209-covid-19-in-children-with-cancer-a-single-low-middle-income-center-experience>