

Delayed cancer diagnoses and high mortality in children during the COVID-19 pandemic

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To the Editor,

While the effects of the SARS-CoV-2 virus on infected patients are increasingly documented, the indirect consequences for uninfected patients are less well-described¹. We report five cases of children who presented critically ill to two United States tertiary referral centers (Children's Hospital of Philadelphia (CHOP); Lucile Packard Children's Hospital at Stanford (LPCH)) in April 2020. All patients tested SARS-CoV-2 negative and experienced delays in cancer diagnosis due to the COVID-19 pandemic with grave consequences.

Each patient required emergent life-saving interventions shortly after presentation (Table), including resuscitation following cardiac arrest (N=2), emergent intubation (N=4), and emergent pericardiocentesis for tamponade (N=1). Two patients died within days of presentation. Although pediatric cancers can present with severe initial findings, the clustered frequency and acuity of these recent initial presentations is striking.

Coinciding with the rapid rise in regional COVID-19 cases and initiation of stay-at-home orders, both institutions noted significant changes in the timing and severity of new patient presentations. The first COVID-19 case in Pennsylvania was reported on March 6, 2020. Despite a five-year historical mean of 2.96 days between new leukemia patients, CHOP did not see any patients with a new leukemia diagnosis for thirty-five days (March 2, 2020 to April 6, 2020). Comparatively, the longest gap from 2015-2019 was eighteen days. Thus, it was notable when two patients subsequently diagnosed with acute lymphoblastic leukemia (ALL) presented on consecutive days to the pediatric intensive care unit (PICU) after having cardiac arrests at local hospitals in April. Similarly, LPCH noted an increase in the percentage of patients requiring prolonged PICU care at

diagnosis. In April 2020, 75% of new leukemia/lymphoma diagnoses required PICU care, compared to a historic monthly average of 12% during 2018-2019 (previous maximum 40%).

Pediatric cancers are relatively rare, and thus delays in diagnosis can occur². However, our experience suggests that additional factors specific to the ongoing COVID-19 pandemic contributed to care delays and higher patient acuity. The family of one patient expressed reluctance to seek care due to fear of COVID-19 exposure. The other four patient families had repeated contact with the healthcare system prior to ultimate diagnosis. This suggests that healthcare system factors may play a role, including decreased referrals to emergency departments or laboratories, and transition to alternative evaluation methods such as telemedicine. Diagnostic bias may also occur, since presenting signs of malignancy (fever, malaise, and respiratory symptoms) can initially be mistaken for symptoms of COVID-19. Furthermore, endemic areas have reported that children are less likely to become critically ill from COVID-19 disease as compared to adults³, which may delay referral of children for emergency services or laboratory studies.

Two patients had multiple telehealth visits prior to in-person evaluations. Telemedicine utilization among primary and acute care providers is increasing during the pandemic⁴. The limitations of telemedicine, including lack of ability to detect critical physical exam findings such as unstable vital signs, pallor, and hepatosplenomegaly, are underscored by these cases. For example, after two telehealth visits and one visual assessment outside the primary care provider's office, patient 1 re-presented hours later to a local emergency department with overwhelming sepsis that progressed to cardiac arrest and brain death. Such an outcome is particularly difficult given the extremely favorable prognosis of childhood ALL. Indeed, the pediatric cancer diagnoses presented

here are highly curable in North America with expected cure rates ranging from 67% to over 95% depending on diagnosis⁵.

These cases illustrate the indirect impact of this pandemic on morbidity in COVID-19 negative patients for whom care delays can be fatal. We highlight the unintended consequences of a pandemic-transformed healthcare system for a vulnerable pediatric population. More work is critical to quantify these consequences and to develop solutions that protect severely ill but treatable children, while also balancing public health and the needs of those infected during this COVID-19 pandemic.

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For Peer Review

Table: Clinical characteristics, presentation, and outcomes of children newly diagnosed with cancer who presented in critical condition

Patient	Age (yrs)	Sex	Symptoms at presentation	Onset of symptoms	# Visits prior to diagnosis			Presumed diagnosis	Time from initial presentation to diagnosis	Oncologic diagnosis	SARS-CoV-2 RT-PCR assay	Notable laboratory / radiologic findings	Clinical course	Survival Status
					Tele-health	PMD / urgent care	ED							
1	4	F	Fevers, emesis, hallucinations	3 weeks	2	1	1	Viral syndrome	2 weeks	B-cell ALL	Negative x 2	WBC 1,000 /uL blasts 1.6% Hgb 2.3 g/dL platelets 3,000 /uL lactate 13 mmol/L uric acid 19 mg/dL Blood culture positive for Group G strep Many clusters of bacterial organisms on BMA	Presented in shock. Cardiac arrest with multisystem organ failure. Brain herniation. Hemodialysis delayed due to COVID-19 related staffing shortages.	Deceased (HD 5)
2	16	M	Fevers, cough, emesis, diarrhea, dyspnea	4.5 weeks	0	1	2	Asthma flare and acute otitis media	4 weeks	B-cell ALL	Negative x 3	WBC 1,000 /uL blasts 26% Hgb 3 g/dL platelets 77,000 /uL lactate 15 mmol/L uric acid 11.5 mg/dL	Presented in respiratory distress. Cardiac arrest with multisystem organ failure. Small cerebral hemorrhages.	Alive
3	17	F	Abdominal pain, cough, palpitations	2.5 weeks	4	0	1	Gastritis	2 weeks	Stage III DLBCL	Negative x 1	Echocardiogram: large circumferential pericardial effusion with right atrial and ventricular collapse CT chest: large anterior mediastinal mass	Presented in cardiac tamponade. 1.5 L malignant pericardial fluid emergently drained.	Alive
4	10	F	Shortness of breath, lethargy and cyanosis	3 days	Reported parental reluctance to present to care				3 days	T-cell lymphoblastic lymphoma	Negative x 2	pH of 6.9 pCO2 100 lactate of 9.2 CT chest: large anterior mediastinal mass	Presented in respiratory distress and obtunded. Emergently intubated.	Alive
5	8	M	Fevers, throat pain, pallor, bruising, vomiting, fatigue, and eye pain	4 weeks	0	2	0	Tonsillitis	4 weeks	AML	Negative x 1	WBC 365,000 /uL blasts 89% Hgb 6.1 g/dL platelets 28,000 /uL INR 1.7 fibrinogen 191	Presented with altered mental status. Status epilepticus and emergent intubation. Intracranial hemorrhage and herniation.	Deceased (HD 5)

AML - acute myeloid leukemia; ALL - acute lymphoblastic leukemia; BMA - bone marrow aspirate; DLBCL - diffuse large b-cell lymphoma; ED - emergency department; EMS - emergency medical services; HD - hospital day; Hgb- hemoglobin; PMD - primary medical doctor; WBC - white blood cell