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COVID-19 in patients with acute leukemia: Two cases with different outcomes

1. Introduction

The novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that causes coronavirus disease 2019 (COVID-19) leads to serious complications in individuals with certain comorbid conditions [1]. There have been only few cases reported specifically looking at the severity and outcomes of COVID-19 in patients with hematologic malignancies [2]. We are presenting 2 patients, one with acute lymphoblastic leukemia (ALL) and the other with acute myelogenous leukemia (AML) who were diagnosed with COVID-19. Both patients were pancytopenic from underlying leukemia and chemotherapy, had similar presentation and were admitted during the same period of time. They received a similar treatment but had different outcomes.

2. Patient 1

On April 8th 2020, a 60-year-old female presented to the emergency room (ER) with one week history of fever. She had a history of B-cell ALL diagnosed a year ago. She failed treatment after 5 cycles of hyper CVAD (3 of part A and 2 of part B), and now was on her 3rd cycle of salvage blinatumomab. Her globulins were in the range of 1.3–2.4 g/dL and her CD4/CD8 ratio was 0.4. She achieved remission as confirmed by recent bone marrow biopsies revealing hypocellular marrow with no evidence of leukemic cells. She did however develop leukopenia for which she was receiving antimicrobial prophylaxis with valacyclovir, fluconazole and levofloxacin. Comorbidities included type II diabetes mellitus. Patient's vital signs included temperature of 39.6 °C, BP of 110/64 mm Hg, heart rate of 114 bpm and SaO2 of 98% on room air. Laboratory data are mentioned in Table 1. Chest X-ray was normal. Blood cultures drawn 2 days prior to presentation grew Staphylococcus hominis in one set and Staphylococcus epidermidis in the other. Patient was started on meropenem and vancomycin. Blood cultures drawn in the ER were negative for bacterial growth but grew Candida parapsilosis from both her peripheral vein as well as central line. Anidulafungin was added and her central line removed. She continued to spike fever and on day 3 of hospital admission a CT scan of chest and abdomen was done and the only finding was scattered minimal ground glass opacities in both her lungs. Although patient denied any exposure history to COVID-19, based on the CT appearance, SARS-CoV-2 (Roche's Cobas NAA test) nasopharyngeal swab was done which came back positive. She was then placed on airborne isolation precautions and was started on hydroxychloroquine and azithromycin. On day 8, she became hypoxic requiring high flow oxygen at 12 liters per minute (LPM) and was transferred to ICU. She was encouraged to self-prone to improve her oxygenation. Repeat chest CT scan showed diffuse bilateral groundglass opacities (Fig. 1). On day 11, she was intubated and placed on mechanical ventilation, started on norepinephrine for hypotension. She retested positive for COVID-19. She continued to have worsening hypoxemia, requiring 80% FiO2 with a PEEP of 10 cmH2O on the ventilator. Her inflammatory markers were elevated and she received 2 doses of intravenous tocilizumab 400 mg, intravenous solumedrol 80 mg every 6 h for 4 days, then 40 mg every 12 h for total of 12 days. On day 13 of her admission, she also received convalescent plasma. Since her immunoglobulins were low (Table 1), she received a dose of 30 gram of intravenous immunoglobulins. After receiving tocilizumab and steroids, patient remained afebrile until her death. She remained on ventilator for 18 days without improvement and her family decided to make her comfortable. She died on day 34 of her admission after she was compassionately extubated.

3. Patient 2

On April 16th 2020, a 63-year-old female presented to the ER with fever, fatigue, dysuria and syncopal episodes for 2 days. She had a history of refractory AML (FLT3 TKD positive), which was diagnosed about 8 months ago. No other significant comorbidities were present. She failed to achieve complete remission with 7 + 3 regimen and was started on single agent gilteritinib for the past 4 months, although was not fully compliant. She had chronic pancytopenia for which she was receiving antimicrobial prophylaxis with levofloxacin, fluconazole and acyclovir. She had similar febrile episode 10 days prior to this visit, and during that admission, she tested negative for SARS-CoV-2 virus and was treated for E. Coli urinary tract infection. Patient's vital signs included temperature of 40 °C, BP of 110/60 mm Hg, heart rate of 100 bpm, SaO2 of 92% on 2 LPM oxygen. See laboratory data in Table 1. Of note, her globulin was always in the normal range of 2.8–3.5 g/dL. Her peripheral blast count was 20%. Chest X-ray was normal. She was started on cefepime, vancomycin, anidulafungin and acyclovir for neutropenic sepsis. On day 2, since she continued to spike fever, CT scans of chest/abdomen/pelvis were done, and it showed scattered ground glass opacities in both the lungs (Fig. 1). This prompted us to test for SARS-CoV-2 virus which came back positive. She was isolated and started on azithromycin and hydroxychloroquine. On Day 3, she was transferred to ICU as her hypoxemia worsened and she required heated high flow oxygen at 60 LPM and 100% FiO2. She received inhaled epoprostenol, a dose of intravenous tocilizumab 400 mg, transfusions per institutional guidelines and gilteritinib was restarted with daily dexamethasone (given to prevent potential differentiation syndrome) for the treatment of her AML. On Day 10, her oxygenation improved, and she was transferred to the floor. On Day 14, she was discharged home. Her blood counts continued to improve, the CD4/CD8 ratio was normal at that stage at 2.3 and she became transfusion independent.

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Table 1
Laboratory data for patient 1 and patient 2.

Patient 1	**4/8/20**	**4/16/20**	**4/22/20**	**4/29/20**	**5/05/20**	**5/12/20**
WBC 10^3cells/ mm^3(3.7–11)	0.8	2	3.1	1.5	2.1	0.6
ANC 10^3cells/ mm^3 (1.5–8)	0.3	1.58	2.5	1.4	1.7	0.37
ALC 10^3cells/ mm^3 (1–4.5)	0.2	0.1	0.4	0.1	0.2	0.1
Hb gm/dL (12.2–14.9)	9.1	9	9.2	7.6	7.8	8.7
Platelets/ mm^3 (150–400)	37	24	27	40	20	45
Ferritin ng/ mL (13–150)	1786	2921	5605	3642	3731	3057
IgG mg/dL (586–1602)				142		
IgM mg/dL (26–217)				13		
IgA mg/dL (87–352)				11		
Procalcitonin ng/mL (0–0.08)	0.14			0.09		0.04
CRP mg/L (0–4.9)	<0.3					<0.3
Fibrinogen mg/dL (228–518)	452	561	394	100	162	142
Patient 2	**4/17/20**	**4/19/20**	**4/21/20**	**4/24/20**	**4/26/20**	**4/28/20**
WBC cells/ mm^3(3.7–11)	1.6	0.9	0.5	1	0.7	1.3
ANC 10^3cells/ mm^3 (1.5–8)	0.6	0.3	0.17	0.2	0.02	0.05
ALC 10^3cells/ mm^3 (1–4.5)	0.45	0.2	0.14	0.3	0.27	0.39
Hb gm/dL (12.2–14.9)	6.9	9.4	8.7	8.2	8.2	8.7
Platelet cells/ mm^3 (150–400)	30	40	21	21	17	18
Ferritin ng/ mL (13–150)	6957	11,795	18,061	11,727	12,341	9677
Procalcitonin ng/mL (0–0.08)	0.47			0.08		0.04
CRP mg/L (0–4.9)	112	213	265	84	5.8	1.3
Fibrinogen mg/dL (228–518)	762	732	611			

Abbreviations: WBC, white blood cell count; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; Hb, hemoglobin; CRP, C-reactive protein.

4. Discussion

Both our patients with underlying leukemia were neutropenic at the time of presentation. Febrile neutropenia is a serious complication encountered in leukemic patients and is usually treated with broad spectrum antimicrobial therapy. Persistent febrile episodes despite being on appropriate antibacterial and antifungal regimen prompted us to perform CT scans in our patients. While the patients did not have any significant respiratory signs, symptoms or exposure history, the pathognomonic ground glass opacities on CT chest prompted us to test for SARS CoV-2 that came back positive, indicating a silent smoldering infection in the immunocompromised patients. In a cohort study of 128 hospitalized patients with hematological malignancies in Wuhan, China, 13 patients (10%) developed COVID-19 [2]. Most of them were suspected to have COVID-19 based on the pulmonary ground glass opacities seen on CT scans [2]. The masking of clinical and biochemical data in leukemic patients who cannot mount an adequate immune response, results in longer incubation period and a delayed diagnosis of COVID-19 [3]. The case fatality of COVID-19 in patients with hematological malignancies is high. In the above cohort study, 8 patients (62%) died [2]. A New York hospitals system that treated 218 patients with cancer and COVID-19 found that the case fatality rate was 37% (20/54 total patients) for patients with hematologic malignancies and patients with myeloid malignancies showed a trend towards higher mortality compared to lymphoid malignancies [4]. In a case series of 4 patients with therapy naive B cell-chronic lymphocytic leukemia and COVID-19, 3 patients died despite aggressive supportive treatment [5]. Patients with severe lymphopenia (< 500/uL) are more likely to be in the ICU and have a worse prognosis [6, 7].

Our first patient with B-cell ALL responded well to the second line treatment with blinatumomab, CD19+ *B* cell ablative therapy, achieving complete remission with negative minimal residual disease. However, the B cell ablation from blinatumomab resulted in persistent pancytopenia, severe lymphopenia, and severe hypogammaglobulinemia. COVID-19 has been reported to be associated with cytokine release syndrome (CRS) and secondary hemophagocytic lymphohistiocytosis (sHLH) which is characterized by unremitting fever, pancytopenia, elevated ferritin and acute respiratory distress syndrome (ARDS) [8]. Interestingly, the filgrastim 300 mcg that was given for two days to treat the persistent fever and neutropenia resulted in worsening of her respiratory symptoms, possibly related to increase in neutrophil activity adding to the CRS seen in COVID-19 patients. The effect of the use of growth factors to alleviate neutropenia in cancer patients with COVID-19 is not known, however, a published case report in which a lung cancer patient was treated for 5 days with granulocyte colony stimulating factor (G-CSF), had full recovery with favorable outcome [9]. We believe our patient had worse outcome due to persistent severe lymphopenia, low CD4/CD8 ratio and severe hypogammaglobulinemia, and possibly delay in delivering of the anti-inflammatory treatments. On the other hand, our second patient with persistent pancytopenia related to her underlying AML and no comorbidities made full recovery despite persistent leukemia and a lower neutrophil count than our first patient. This patient, unlike the first case, had evidence for intact immune system including normal globulins and normal CD4/CD8 ratio. Another favorable difference is that this patient received dexamethasone to prevent differentiation syndrome once she restarted on gilteritinib, which may have suppressed the inflammatory response associated with COVID-19 infection. Although there are few published reports indicating patients with myeloid malignancies and COVID-19 have a higher mortality [10], our patient with active AML and pancytopenia made a full recovery highlighting the need for additional studies to further delineate risk factors contributing to mortality in this subgroup of patients.

According to the presentation of our two cases, it is important to note that the early signs of COVID-19 are usually not apparent on routine chest x-rays and CT imaging may be needed for early detection [11]. Our cases also illustrate the need for high index of suspicion for COVID-19 in actively treated leukemic patients and practice strategies to reduce the risk of infection and increase surveillance for early detection. Furthermore, factors such as lymphopenia, low CD4/CD8 ratio, hypogammaglobulinemia and comorbidities may contribute to worse outcomes of

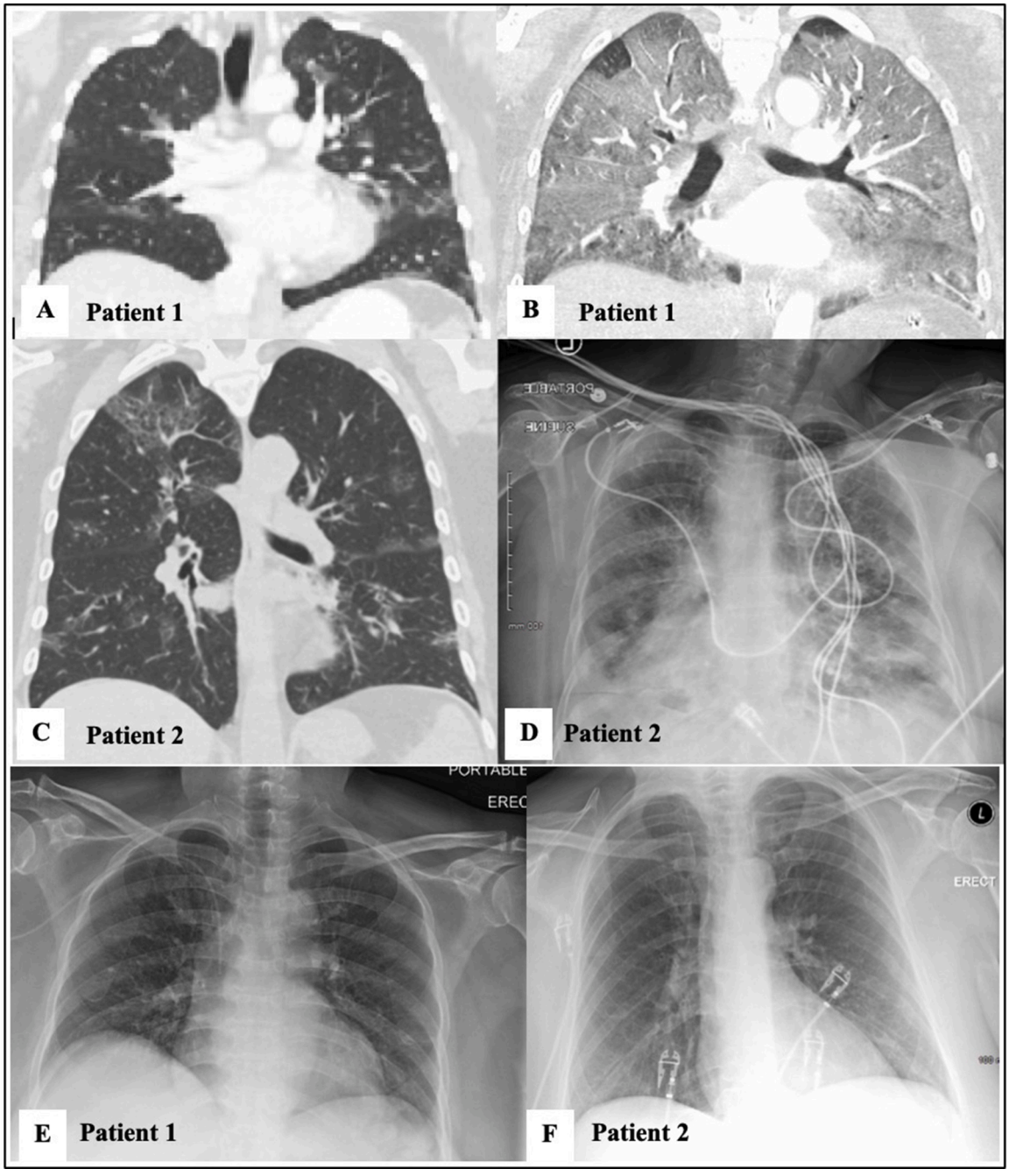

Fig. 1. Imaging findings A- CT chest on day 3, showing patchy ground glass infiltrates in patient 1. B- On day 8, CT chest showing diffuse bilateral groundglass opacities in patient 1. C- CT chest done on day 2 showing bilateral scattered ground glass opacities in patient 2. D- Chest X-ray done on day 7 showing worsening bilateral airspace opacities in patient 2. E- Normal admission Chest X-ray in patient 1. F- Normal admission Chest X-ray in patient 2.

COVID-19 patients with acute leukemias.

Declaration of Competing Interest

The authors whose names are listed above certify that they have NO affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript. The authors have no conflicts of interest to disclose.

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