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COVID-19 in a patient with chronic myelomonocytic leukemia: a twisting tale

TO THE EDITOR: Chronic myelomonocytic leukemia (CMML) is a rare disease characterized by persistent clonal monocytosis. Specific features of CMML, such as autoimmunity and a tendency to mount a brisk leukemoid reaction, could be potentially relevant during the COVID-19 pandemic [1]. In this report, we describe a case of CMML with COVID-19 and discuss the relevant evidence-based management considerations.

A 30-year old man was diagnosed with CMML-2 at our hospital in December 2019. Bone marrow (BM) examination showed marked granulocytic hyperplasia, monocytosis, 5% blasts, and the absence of dysplasia (Fig. 1A). BM biopsy showed grade-1 reticulin fibrosis. Peripheral blood (PB) showed 6% blasts. Whole exome sequencing of PB revealed the following mutations (mutant allele, %): FLT3-TKD (30.7%), ASXL1 (49%), SETBP1 (51%), NRAS (4.4%), and CBL (10%). Treatment with hydroxyurea (30 mg/kg/day) resulted in a ~50% reduction in spleen size and reasonably controlled total leucocyte counts (TLC) to ~30–40×10⁹/L. In June 2020, he presented with a 2-week history of low-grade fever, joint pain, fatigue, and abdominal discomfort. An abdominal examination revealed significant hepatosplenomegaly. CBC showed a hemoglobin level of 7.9 g/dL, TLC of 451×10⁹/L (14% monocytes, absolute lymphocyte count/ALC- 10×10⁹/L, and 7% myeloblasts), and platelets- 27×10⁹/L. BM revealed 5–6% blasts, showed marked granulocytic hyperplasia, dysplasia, and evidence of toxic granules and vacuolation in the granulocytic series suggestive of leukemoid reaction (Fig. 1B). Antinuclear anti-

bodies were positive. A direct anti-globulin test was negative. The ELISA-based PB cytokine profile revealed elevated levels of IL-6 (12.0 pg/mL, normal <7 pg/mL) and TNF-α (1153.0 pg/mL, normal <29.4 pg/mL), and normal levels of IL-1β level. Coagulogram showed prolonged PT (INR-1.62) and APTT (46 sec, control <34 sec), both of which failed to correct in the mixing study. Lupus anti-coagulant was negative. Factor assay showed reduced Factor X activity (31%, normal range, 50–100%), suggesting an acquired factor X inhibitor. The fibrinogen level and activity of other clotting factors were normal. D-dimers were elevated. The patient denied any history of surgery. Infection screening, including viral markers, HIV, blood cultures, and work-up for malaria, typhoid, and tuberculosis, was unremarkable. COVID-19 testing of nasopharyngeal and oral samples by RT-PCR was negative on 10-7-2020. Therefore, an autoimmune etiology was considered for leukemoid reaction, an acquired factor X inhibitor, and the pro-inflammatory state. The hydroxyurea dose increment worsened the thrombocytopenia and failed to achieve an organ response. The factor X inhibitor disappeared after leucoreduction with hydroxyurea. Considering the patient's young age, good performance score, and progressive disease, we started FLT3-mutated AML-like intensive chemotherapy (IC) with '7+3' plus midostaurin on 15-7-2020. On day-7, the patient had febrile neutropenia (FN) and diarrhea, due to neutropenic enterocolitis (NEC). FN and NEC were treated with broad-spectrum antibiotics and empirical antifungals. Midostaurin (50 mg BID) and G-CSF were started from day-8 onwards. Infection screening, including assessing procalcitonin, serum galactomannan, blood and stool cultures, and stool for *Clostridium difficile* toxin were negative. Due to intense myelosuppression, midostaurin was withheld on day-14. The patient complained of cough on day-14, due to which we performed CT of the chest and abdomen. The CT scan was clear, except for a few tiny lung nodules. On day-15, the patient experienced worsening respiratory distress and hypoxemia (SpO₂-85% despite 90% FiO₂). On the same day, CBC showed absolute lymphopenia, a sudden surge in neutrophils (10-fold increase), and a 5-fold increase in neutrophil: lymphocyte ratio (NLR). Considering the possibility of G-CSF-induced acute respiratory distress syndrome (ARDS), G-CSF administration was stopped. A repeat COVID-19 test on the nasopharyngeal sample on day-15 using RT-PCR was positive. The patient was shifted on mechanical ventilation in the intensive care unit and was treated with dexamethasone, hydroxychloroquine, and azithromycin in addition to supportive care, including platelet transfusions. The patient succumbed to respiratory failure on day-16. Anti-COVID-19 therapies such as Remdesivir, convalescent plasma, or anti-cytokine drugs could not be administered due to non-availability. The complete clinical course of the patient is shown in Fig. 1C.

Hyperleucocytosis (TLC > 100×10⁹/L) at diagnosis is uncommon in CMML, but occasionally manifests during leukemoid reaction [2, 3]. Patients with proliferative CMML have

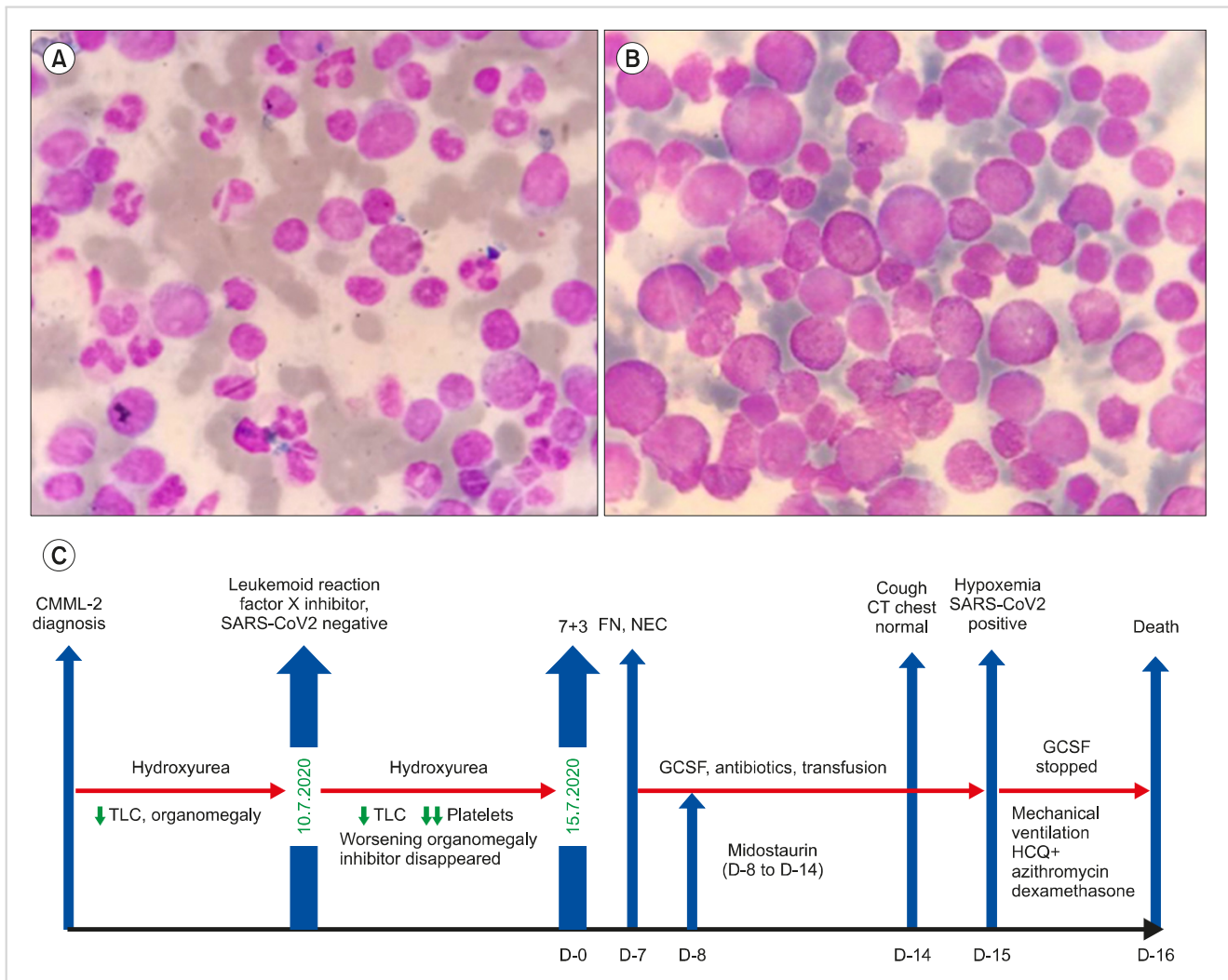


Fig. 1. (A) Ramanovsky stained bone marrow smears showing myeloid series and monocytosis ($\times 100$), (B) Ramanovsky stained bone marrow smears showing marked myeloid hyperplasia with hypergranulations ($\times 100$), and (C) diagrammatic representation of the complete clinical course of the patient.

Abbreviations: CMML, chronic myelomonocytic leukemia; FN, febrile neutropenia; GCSF, granulocyte colony stimulating factor; HCQ, hydroxychloroquine; NEC, neutropenic enterocolitis; SARS-CoV2, severe acute respiratory syndrome coronavirus 2; TLC, total leucocyte count.

been shown to have an inflammatory milieu, including elevated levels of IL-6 and TNF- α , which drives the leukemoid reaction sometimes seen in these patients following surgery and infections/inflammation [2-4]. Autoimmune manifestations are seen in about 30% of CMML patients [1, 5]. Acquired hemophilia A has been occasionally reported in association with CMML, which usually disappears following CMML treatment [5]. Acquired X inhibitor has never been reported in CMML, and it could represent an autoimmune phenomenon. Although prolonged coagulation times due to disseminated intravascular coagulation (DIC) could be associated with leukemia, failure of both PT and APTT to correct in the mixing studies in our case suggested the presence of an acquired factor inhibitor rather than DIC. Unlike AML, mutations in FLT3 are rare in CMML (<5%), and are not prognostically relevant, but provide a potential

therapeutic target [1]. Since midostaurin does not possess significant single-agent activity we decided to combine it with IC [6].

The current case highlights several insights into the interactions between COVID-19 and CMML. 1) SARS-CoV-2 enters the host cells via its receptor, angiotensin converting enzyme 2 (ACE2) expressed on the respiratory epithelium, GI tract, kidneys, and central nervous system. Because of the high expression of ACE2 on monocytes, patients with CMML appear to be particularly susceptible to COVID-19 [4, 7]. Therefore, it is likely that the leukemoid reaction in our patient was incited by SARS-CoV-2. COVID-19 was missed before IC due to false-negativity of the RT-PCR-based assays [8]. Although the median incubation period of COVID-19 is 5 days (range, 2.1-11.1 days), prolonged incubation period up to 25 days has been reported in patients

Table 1. Summary of evidence-based discussion points regarding management of patients with CMML during COVID-19 pandemic.

- 1 Patients with CMML represent an especially vulnerable population to acquire COVID-19, and needs particular attention to prevent COVID-19 infection [4].
- 2 COVID-19 could mount brisk leukemoid reaction in patients with CMML. In addition to routine infection screen, test of COVID-19 by RT-PCR could be performed in such cases.
- 3 Prolonged incubation period of COVID-19 in patients with haematological malignancies coupled with false-negative RT-PCR report of SARS-CoV-2 could cause potential diagnostic delays. Repeat testing may be considered after 1 week to confirm the absence of COVID-19 in such cases [8, 9].
- 4 Lymphopenia in serial CBC might hint towards the possibility of COVID-19 in patients with CMML-SARS-CoV-2 [10].
- 5 During COVID-19 pandemic, 'wait and watch' could be considered for CMML patients with asymptomatic disease. Hydroxyurea could be considered for patients with proliferative CMML in whom treatment is indicated [18].
- 6 In addition to standard infection screen, testing for COVID-19 may be considered in patients with FN, or diarrhea [10-12, 19].
- 7 Whenever possible, use of G-CSF should be avoided in COVID-19 positive FN cases due to the risk of worsening pulmonary inflammation, and inducing ARDS [16].
- 8 Patients with CMML with COVID-19 could have extreme cytokine elevation. Use of anti-cytokine monoclonal antibodies may represent potential treatment strategies to treat COVID-19 in CMML patients [4].

Abbreviations: ARDS, acute respiratory distress syndrome; CBC, complete blood count; CMML, chronic myelomonocytic leukemia; COVID-19, coronavirus disease 2019; FN, febrile neutropenia; G-CSF, granulocyte-colony stimulating factor; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome novel coronavirus-2.

with hematological malignancies [9]. 2) Whereas ALC at the time of leukemoid reaction was elevated, retrospective evaluation of the subsequent CBC revealed lymphopenia, which was unmasked after leucoreduction with hydroxyurea. ALC could be normal during the initial incubation period of COVID-19, and decrease later during the symptomatic phase [10]. 3) Negative baseline RT-PCR results, absence of respiratory symptoms at the FN onset, and presence of prominent diarrhea delayed the COVID-19 testing in this case. Both FN and diarrhea could also be COVID-19 related since standard infection work-up for the FN, and diarrhea was unrevealing. Diarrhea could be an initial manifestation of COVID-19 in about 10–30% of cases [11], and has been shown to correlate with disease severity in some reports [12]. 4) A CT scan of our patient at the onset of respiratory symptoms was normal, except for a few tiny nodules. Retrospective studies have shown that CT scan of the chest could be normal in about 56% of patients if performed within 2 days of symptom onset. Lung nodules in patients with FN are generally associated with fungal infection. Moreover, pulmonary nodules are distinctly uncommon in COVID-19 [13]. Therefore, the CT chest in our case missed the suspicion of COVID-19. 5) Severe COVID-19 is characterized by a cytokine storm that mediates endothelial damage and coagulopathy, and causes ARDS [14]. COVID-19 related cytokine storm could have compounded the baseline pro-inflammatory milieu of our patient, and the resultant hypercytokinemia led to ARDS and respiratory failure. Our observation lends support to the similar hypothesis proposed earlier [4]. However, this hypothesis could not be confirmed due to our inability to evaluate the cytokine profile or use anti-cytokine directed treatment for ARDS. 6) Hypoxemic respiratory failure became evident on day-15 coinciding with neutrophil recovery and simultaneous COVID-19-positivity. G-CSF was stopped at day-15 considering the

possibility of worsening pulmonary inflammation from neutrophil recovery [15]. Moreover, G-CSF administration in patients with moderate-severe COVID-19 has been postulated to exacerbate pulmonary inflammation resulting from increased NLR [16]. Increased NLR has been identified as a poor prognostic marker in patients with COVID-19 [17].

In addition to the novel finding of acquired factor X inhibitor in a very young patient with proliferative CMML, the current case illustrates several aspects that are potentially relevant during the COVID-19 pandemic. Only a few cases of CMML with COVID-19 have been reported to date [4, 18]. Highlights of the relevant evidence-based discussion points from this case are summarized in Table 1 [4, 8-12, 16, 18, 19].

Ankur Jain, Aditi Jain, Pooja Prasad, Sumita Chaudhry, Monica Sharma, Jitender Mohan Khunger, Dipender Kumar Gupta, Sumita Saluja
Department of Hematology, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India

Correspondence to: Sumita Saluja
Department of Hematology, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi 160017, India
E-mail: drssaluja@gmail.com

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Outcomes of patients with essential thrombocythemia and unnoticed thrombocytosis prior to diagnosis

TO THE EDITOR: Arterial and venous thromboses are major clinical events in patients with essential thrombocythemia (ET) [1, 2]. ET is often detected in individuals with newly diagnosed cerebrovascular or cardiovascular thrombosis [3, 4]. While many patients experience thrombosis prior to the diagnosis of ET [5], some patients have unnoticed thrombocytosis prior to the diagnosis of ET, suggesting a delay in the diagnosis of this disorder [6]. The possible effects of delayed diagnosis on the clinical course of ET have not been well addressed. We reviewed the status of delayed diagnosis of ET and its clinical outcomes. The medical records of patients with ET who visited Chungnam National University Hospital from January 1993 to June 2019, in whom a complete blood count (CBC) was performed at least once prior to the diagnosis of ET, were reviewed retrospectively. CBC was performed prior to the diagnosis of ET in 32 of 179 patients. Of these 32 patients, 26 had thrombocytosis (platelet count $\geq 450.0 \times 10^9/L$), which was neither noticed nor managed. Of these 26 patients, thrombocytosis was overlooked by physicians in 23 (88.5%) cases, ignored by the patient in 2 (7.7%) cases, and not completely evaluated due to pregnancy in 1 (3.8%) case. At the time of initial detection of thrombocytosis, the probability of ET was high in 24 (92.3%) patients because there were no reasons for reactive thrombocytosis. Diagnostic triggers of ET included examination of another health problem in 11 (42.3%) patients, a routine health check-up in 9 (34.6%) patients, and thrombotic events in 6 (23.1%) patients. The median time from initial detection of thrombocytosis to the diagnosis of ET was 2.3 (range, 0.6–12.8) years. During the delay, white blood cell counts and hemoglobin levels did not change (from $10,286 \pm 4,744 \times 10^9/L$ to $12,089 \pm 4,717 \times 10^9/L$, $P=1.100$ and from 13.7 ± 1.6 g/dL to 12.5 ± 2.9 g/dL, $P=0.065$, respectively). However, platelet counts increased significantly (from $657.0 \pm 193.5 \times 10^9/L$ to $914.0 \pm 295.7 \times 10^9/L$, $P=0.001$),