

A Diagnostic Dilemma of Encephalopathy in Acute Myeloid Leukemia Patient with Twice COVID-19 Infection: A Case Report

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Abstract

Background: During the COVID-19 pandemic, there was limited data about the appropriate management of acute myeloid leukemia (AML) with COVID-19 infection and the possible post-COVID-19 complications reported in acute leukemia patients.

Case presentation: We report a 52-year-old lady with AML and confirmed twice SARS-CoV-2 infection. The first infection was just after the diagnosis of AML before the administration of induction therapy, and the second infection was just after she received the salvage therapy. The COVID-19 infection was confirmed by qRT-PCR and high-resolution non-contrast computerized tomography of the chest. Unfortunately, the patient developed post-covid neurological complications, disturbed consciousness level, and encephalopathy. The COVID-19 infection may have triggered encephalopathy or exaggerated the neurological toxicity of cytarabine even in a small dose. Another possible explanation is the exaggeration of cytokine storm by the administration of granulocyte-stimulating factors used in salvage therapy.

Conclusion: Management of COVID-19 infection in AML patients faces many challenges. These patients are more vulnerable and susceptible to many complications and high mortality rates. The treatment approach needs to be tailored to overcome the interaction between the treatment adverse events and the biology of covid-19 infection.

Keywords: Acute myeloid leukemia, COVID-19, Encephalopathy

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Introduction

Worldwide, the confirmed cases of acute respiratory syndrome coronavirus 2 (COVID-19) infection exceeded 600 million and it resulted in more than 6.5 million deaths ¹. The exact incidence of COVID-19 among leukemic patients is still unknown. Malard et al. ² identified patients with

hematological disorders as a high-risk subgroup of COVID-19 infections regarding complications. Furthermore, a high mortality rate of about 37% was reported in hematological malignancies patients with COVID-19 ³.

Herein, we present a case of acute myeloid leukemia (AML) with confirmed twice SARS-CoV-2 infections (by qRT-PCR). Despite it being unclear if

the second time of COVID-19 infection in this patient represents a reactivation or reinfection, we report this case to discuss the management of an AML patient with 2 times confirmed COVID-19 infection.

Case Presentation

The patient was treated at the Department of Medical Oncology, Faculty of Medicine, Mansoura University between August 2020 and March 2021.

A 52-year-old woman presented with generalized weakness, headache, and fatigue. Her complete blood count showed leukopenia ($3.7 \times 10^9/L$), normocytic anemia (hemoglobin: 9.2 g/dl), and thrombocytopenia ($119 \times 10^9/L$). She was referred to the hematology department at our center on 24 August 2020. A diagnosis of AML-M2 was made based on bone marrow aspirate examination in addition to the flow-cytometry result. Florescent in situ hybridization analysis of both t (8:21) and t (16:16)/inv.16 was negative. The molecular study for FLT3- internal tandem duplication (ITD) mutation was negative.

During her first admission, she presented with productive cough, high-grade fever of 39 °C, elevated C-reactive protein (59 mg/L), erythrocyte sedimentation rate (1st hour of 150 mm./hr.), and serum ferritin (908 ng/ml) and the D-Dimer level was 0.72 µg/L.

High-resolution non-contrast computerized tomography of the chest showed bilateral multiple patchy areas of ground glass opacities of predominant peripheral subpleural location in all lung lobes, coping with CORADs-4 (Figure 1). The examination was otherwise normal with no consolidation, crazy paving pattern, or pleural effusion.

A nasopharyngeal swab for SARS-Cov2 was positive by qRT-PCR on August 27, 2020.

The patient received dexamethasone 8mg/12h and low molecular weight heparin, with good antibiotic coverage. Eighteen days later (15 September 2020), the patient became asymptomatic, however, her new nasal swab examination for SARS-Cov2- qRT-PCR was still positive. Her induction chemotherapy was delayed for about 2 months until the patient tested negative for SARS-Cov2 by RT-PCR on 28 October 2020. Then, she started the 7 plus 3 protocol with cytarabine 200 mg continuous infusion on days 1-7 plus doxorubicin 60 mg on days 1-3.

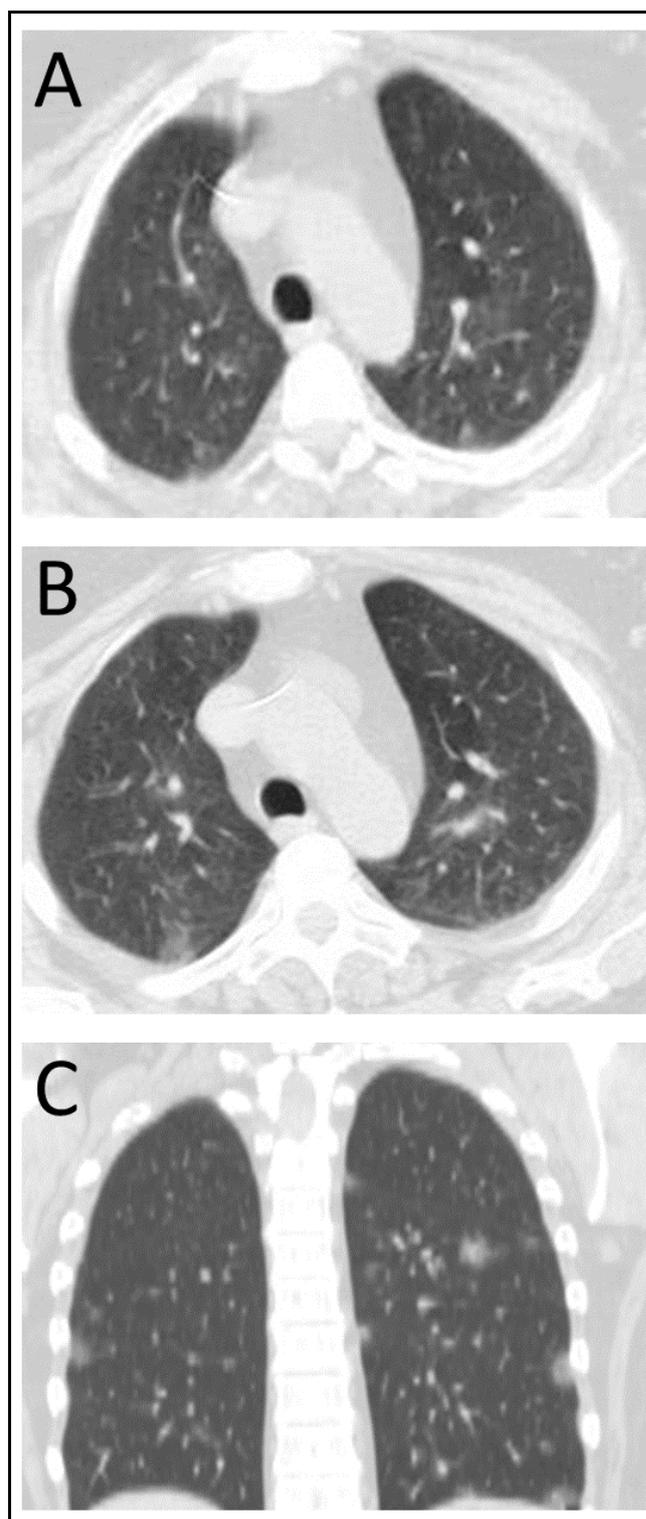


Figure 1: 1st infection non-contrast computerized tomography of the chest: A & B) Axial images, C) Coronal reformatted image.

Unfortunately, bone marrow assessment after the 1st cycle showed 44% blast cells. That is why salvage chemotherapy FLAG protocol was initiated (fludarabine 50mg D1-5, cytarabine 3 gm/12h D1-5, and granulocyte colony-stimulating factor [G-CSF] from D 1 until recovery of absolute neutrophil count) under cover of antibiotics. In December 2020,

her course was complicated by neutropenic fever, which was controlled by broad-spectrum antibiotics and an antifungal.

Unfortunately, on 10 January 2021, she presented with a disturbed conscious level, Glasgow Coma Scale (GCS) of 6/15, and her vital signs were as follows; body temperature was 37.2° C, blood pressure was 110/60, and respiratory rate was 20/minute. Oxygen saturation by pulse oximetry (SpO₂) on room air was 86%. She was admitted to the intensive care unit and intubated due to more deterioration in her consciousness level and ended up in a coma. Her complete blood count showed a white blood cell count of 1.1×10^9 /L, absolute neutrophil count of 0.16×10^9 /L hemoglobin of 9.8 gm/dl, and platelet = 18.2×10^9 /L. C reactive protein was 112 mg/L, LDH 1400 U/L, serum ferritin 7000 ng/ml, and D-dimer 1.4 µg/L, with normal chemistry and electrolyte levels. High-resolution non-contrast computerized tomography of the chest showed bilateral few areas of ground glass opacities with fine reticulonodular densities in both upper lobes (Figure 2).

Brain computerized tomography and magnetic resonance imaging were normal. Cerebrospinal fluid analysis was free. Nasal swab analysis by qRT-PCR confirmed the re-positivity of SARS-Cov2 and she was admitted to an isolation hospital for 2 weeks where she received imipenem 500mg/6h, levofloxacin 500mg/24h, dexamethasone 10mg/12h. Four days later she showed certain improvement in consciousness level after two days upon remdesivir was started with a loading dose of 200 mg on the first day followed by a 100 mg maintenance dose for another 4 days and she was extubated from the mechanical ventilator. Nasal swab SARS-Cov2-PCR was reported to be negative after three weeks. Magnetic resonance imaging of the brain

examination and cerebrospinal fluid analysis were repeated, and no abnormalities were detected. Bone marrow assessment showed 1% blast cells and she was discharged from the hospital on maintenance therapy. She was fragile and not fit for allogeneic bone marrow transplantation. She was followed by the neuro-medicine service for conversion disorder. Unfortunately, one month later she presented with relapsed leukemia. She received a second FLAG but she died due to septic shock by the end of March 2021.

Discussion

In the current AML patient, SARS-CoV-2-RNA was detected in the upper respiratory tract sample by qRT-PCR. Chest computed tomography scanning showed right lower lobe lung, and peripheral ground glass opacities, matching the typical finding of SARS-CoV-2 infection according to Simpson *et al.*⁴ and Li *et al.*⁵. The patient was proved to be positive for SARS-CoV-2 infection twice, however, it is very difficult to specify, if it is a reactivation or a new infection. The first episode has been detected before induction of remission and the second was after salvage therapy. To our knowledge there are no published reports on the management of such a complex situation at that time, also there was no evidence for delaying chemotherapy in negative COVID-19 patients. Moreover, the American Society of Hematology recommends treatment with intensive chemotherapy for newly diagnosed AML patients who are eligible for intensive therapy 6, while the European Hematology Association advised that the best approach to improve survival is to delay AML treatment, whenever possible⁷.

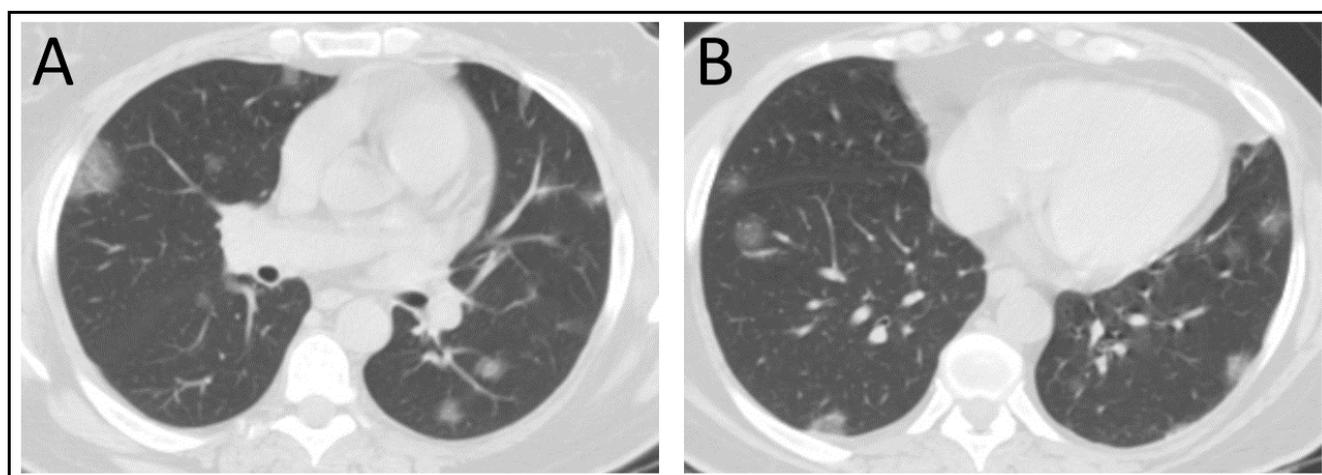


Figure 2: 2nd infection non-contrast chest computerized tomography axial images

In our case, after her first SARS-CoV-2 negativity, leukemia-specific treatment was initiated in the form of a 7 plus 3 protocol. At the time of evaluation, persistent blast cells were detected in the marrow (about 44%). Given the patient's young age, and good performance status at that time, the multidisciplinary board decision recommended intensive salvage chemotherapy in the form of FLAG protocol, based on data reported by a study conducted by Ghazy⁸.

Clinical symptoms of COVID-19 range from mild symptoms to critical courses and even death⁹. We noticed both courses of COVID-19 in our patient, the first one was mild, meanwhile, the second one was severe and even critical. This was confirmed by He *et al.*¹⁰ who reported more severe SARS-CoV-2 infections in patients with hematological malignancies.

The poor outcome of AML cases was also observed by Núñez-Torrón *et al.*¹¹ study on eight AML cases with COVID-19 who received intensive chemotherapy cycles, of them four were confirmed cases. Three of them presented with refractory adult respiratory distress syndrome and all eventually died.

After salvage therapy, our patient developed a second infection or reactivation of COVID-19 which was complicated by a deterioration of the consciousness level and encephalopathy. The diagnosis of COVID-19 encephalopathy was confirmed after the exclusion of other possible causes of impaired consciousness level like central nervous system infiltration, hemorrhage, or infection by magnetic resonance imaging of the brain and cerebrospinal fluid analysis. In addition, cytosine arabinoside-induced neurological toxicity was also a differential diagnosis. This possibility could be excluded because of the patient's age, normal kidney function, absence of cerebellar dysfunction manifestations, and a cumulative cytosine arabinoside dose of 31.5 gm. However, we do not know if the covid infection could have exaggerated the neurological toxicity of cytarabine¹².

Encephalopathy was reported to be associated with COVID-19 infection in the literature^{13, 14}. Garg *et al.*¹⁵ observed in their study that encephalopathy was usually triggered by cytokine storm secondary to COVID-19 infection. In the current case, the cytokine storm might have been precipitated by the G-CSF administration. There is a paucity of data in the literature about the safety of G-CSF

administration during the COVID-19 pandemic. Although the National Comprehensive Cancer Network recommended the use of G-CSF to fasten the hematological recovery in cancer patients¹⁶, some authors suggested that the use of G-CSF can stimulate the release of inflammatory mediators (interleukin-1 [IL-1], interleukin-6 [IL-6], and tumor necrosis factor-alpha [TNF- α]) leading to worse outcome in covid-19 patients¹⁷⁻¹⁹.

Conclusion

In conclusion, post-COVID-19 neurological sequelae in AML patients receiving chemotherapy should be expected as a consequence of either viral infection and/or exaggeration of therapy-related toxicity. More clinical studies are still recommended to draw a firm conclusion on the treatment of AML patients with concurrent COVID-19 infection.

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Authors' contribution

Conception or design: RA; Acquisition, analysis, or interpretation of data: L.M, N.F, & H.Z; Drafting the manuscript: R.A, S.A, Z.E, S.A, M.O, L.M, & G.A; Revising the manuscript: M.E, T.E, & S.S; Approval of the manuscript version to be published: All authors; Agreement to be accountable for all aspects of the work: All authors.

Conflict of interest

The authors declare that they have no conflict of interest to disclose.

Data availability

Included in the manuscript.

Ethical considerations

Not applicable.

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