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Concurrent Presentation of Acute Myeloid Leukemia with COVID 19: A Diagnostic Challenge

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ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic has brought forth with it many challenges for the management and treatment of patients with hematological malignancies. Amongst the hematological malignancies in young to middle-aged adults Acute Myeloid Leukemia (AML) is one of the commonest malignancies, however occurring de-novo with COVID-19RTPCR confirmed cases, is a rare presentation to the best of our knowledge. This concomitant appearance of AML with COVID-19without any previous history is rare. We are presenting four cases of COVID-19with coexistent AML. The diagnosis was established with the correlation of flow cytometry, bone marrow examination, and radiology. Though it is known that patients with concomitant infection of leukemia and COVID-19 develop severe disease and complications, the treatment strategies should be formulated at the early onset of the infection to minimize the mortality and morbidity associated with both these conditions.

***Keywords*:** COVID-19, AML, young adults, mortality.

INTRODUCTION

COVID-19 disease caused due to infection with the novel coronavirus (SARS CoV-2) is causing havoc worldwide ever since its first appearance in Wuhan, China in December 2019. With a population of around 1.3 billion people, in a resource-limited country like ours, lacking a comparative health care system vis-vis the western world, India is tackling the worst crisis ever as the total number of infections detected daily are too high with a high mortality rate constituting a huge burden on the already shattered health care system [1]. Globally it is taking a toll on patients' physical and mental health, however, young patients with malignancies are suffering a lot due to the current situation. Although the awareness regarding the disease has increased manifold since its inception in December 2019 the treatment of patients with already suppressed immune status owing to hematological malignancies and other comorbidities is a challenge. It has been observed that the mortality, morbidity, and severity of infection associated with this disease is higher in immunocompromised patients having cancer with a case fatality rate of 5-6% [2,3]. Patients with leukemi as and COVID-19show a higher fatality rate of 37%. [2]. The time-lapse between disease presentation and diagnosis is also increased due to COVID-19as many symptoms are overshadowed due to the typical presentation of COVID-19. Therefore, the aim is to diagnose the patients with leukemia as at the very onset of disease during this pandemic as the outcome is very

poor so that the management and follow-up of the patients begin at the earliest. We hereby present case series of four patients diagnosed with Acute Myeloid leukemia (AML) with concurrent COVID-19infection:one of whom died due to the disease.

CASE REPORTS

Case 1: A 32-year-old male with no significant past medical history presented with mild fever, myalgias, exertional dyspnoea, fatigue, and bleeding gums. He recovered from covid infection without complications in home isolation month ago. Physical examination revealed mild hepatosplenomegaly. No other abnormality was detected. Venous blood samples were sent for biochemical and hematological parameters (table 1). Peripheral smear showed normocytic normochromic RBCs with marked leukocytosis with total leukocyte count 63190/ul and thrombocytopenia with platelet count 25000/cumm. Smears revealed 87% blasts of size two to three times the size of a lymphocyte. These cells had a high nucleo-cytoplasmic ratio, delicate chromatin, prominent nucleoli, and a moderate amount of cytoplasm with occasional Auer rods (figure1). A diagnosis of acute myeloid leukemia was made. Bone marrow aspirate was markedly hypercellular with blast population constituting 87%. Multiparametric flow cytometry analysis of bone marrow aspirate revealed 80% blasts on CD45 side scatter. These cells were positive for CD45, CD117, MPO, CD13, and CD33. These were negative for CD7, HLA-DR, CD14, CD3, CD4, CD5, CD10, CD19, CD20, cyCD3 and surface light chains (figure 2). A final diagnosis of Acute Myeloid leukemia was made. After the diagnosis was made patient was given induction therapy with two drugs Cytarabine (Ara-C) and Daunorubicin for seven days. The patient was in the intensive care unit for a week however patient's condition deteriorated and he could not survive.

Case 2: A 42-year-old male with no significant past medical history presented with fever, rigors and chills, fatigue, myalgias, diffuse abdominal pain, and exertional dyspnea for eight days. He had no cough, chest pain, sore throat, rhinorrhea, anosmia, or ageusia. He was febrile (axillary temperature of 101^0F) with tachycardia (120 beats/minute), normotensive (blood pressure 126/78 mmHg), and oxygen saturation 91% on room air. On physical examination, generalized pallor and mildabdominal tenderness were noted. No systemic abnormalities were detected. Nasopharyngeal and oropharyngeal swabs were sent for the SARS-COV RTPCR test which came to be positive. The very next day due to further dipping of oxygen saturation to 85% patient was admitted. Blood samples were sent for hemogram and biochemical parameters. Peripheral smear showed mild anisocytosis with macrocytic RBCs and macro-ovalocytes, leukocytosis with total leukocyte count 31820/ul. Smears revealed 47% blasts with high Nuclear: Cytoplasmic ratio, opened up chromatin, prominent 2-3 nucleoli, and occasional Auer rods with thrombocytopenia (platelet counts on smears 45000/cumm) as shown in table1. Again, a diagnosis of Acute myeloid leukemia was made. Immunophenotyping by flow cytometry was performed on peripheral blood and the gated population showed a CD45 dim population (40%of the total) of atypical cells/blasts which are positive for CD34, CD117, MPO, CD13, CD38, and CD7.CD19, CD20, CD10, CD3, CD5, and cyD3 were negative in the gated population. An impression of Acute myeloid leukemia with aberrant expression of CD38 and CD7on flow cytometry was made. Bone marrow aspirate and biopsy were performed. The marrow aspirate showed particles that were highly cellular with marrow being replaced by blasts 2 to 2.5 times the size of small mature lymphocytes having high N:C ratio, round nucleus, and fine chromatin and prominent (2-3) nucleoli and scant cytoplasm with the presence of

granules and Auer rods in some (figure 3). Suppression of erythroid, myeloid, and megakaryocytic series was also noted. The bone marrow biopsy was completely replaced by myeloblasts with few normoblasts. Occasional dyspoietic megakaryocytes were noted (figure 3). The patient is under follow-up.

Table 1. Comparison of hematological and biochemical parameters of four cases.

S.no	Parameters	Value				Reference range
		Case 1	Case 2	Case 3	Case 4	
1	Hemoglobin	12g/dl	5.90g/dl	7.1g/dl	4.6g/dl	15.0 to 17.0g/dl
2	TLC	63190/ul	31820/ul	301090/ul	652860/ul	4000.00 to 11000.00/ul
3	Platelets	0.25 lacs/cumm	0.45 lacs/cumm	0.47 lacs/cumm	0.85 lacs/cumm	1.50 to 4.50 lac /cumm
4	S. Urea	36mg/dl	32mg/dl	63mg/dl	37mg/dl	15 to 50mg/dl
5	S. Creatinine	0.6mg/dl	10.5mg/dl	1.4 mg/dl	1.2mg/dl	0.6 to 1.23mg/dl
6	Uric Acid	2.5mg/dl	6.40mg/dl	9.4 mg/dl	5.2mg/dl	3.0 to 7.0mg/dl
7	S.LDH	1870U/L	1958U/L	1630U/L	1652U/L	230-460U/L
8	S. procalcitonin	0.42ng/ml	9.84ng/ml	0.25ng/ml	0.32ng/ml	0.00 to 2.00ng/ml
9	CRP	Negative	Negative	Negative	Positive	<0.60 mg/dl
10	D DIMER	940 ng/ml	886 ng/ml	690 ng/ml	798 ng/ml	0.00-500.00ng/ml
11	S. Ferritin	874ng/ml	659 ng/ml	1000ng/ml	784 ng/ml	20 to 300 ng/ml
12	IL-6	2.5pg/dl	3.2pg/dl	2.7pg/dl	3.6pg/dl	0.0.-2.0 pg/dl

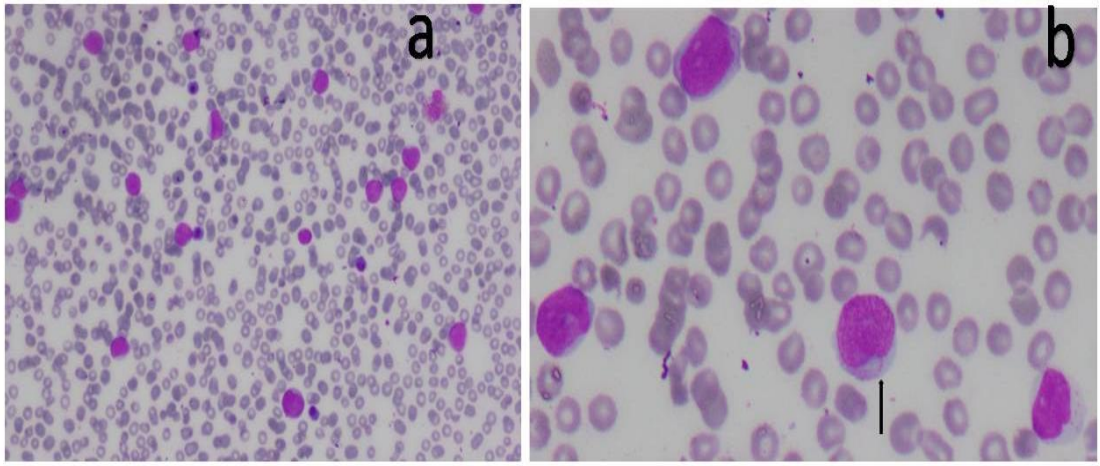

Figure1 a, b: Case 1Peripheral smear- a) smear showing normocytic normochromic RBCs with marked leukocytosis Leishman's stain, X100 b) Smear showing numerous blasts, platelets and occasional nucleated RBCs (Leishman's stain, X100), arrow showing blasts with auer rod (Leishman's stain, X600)

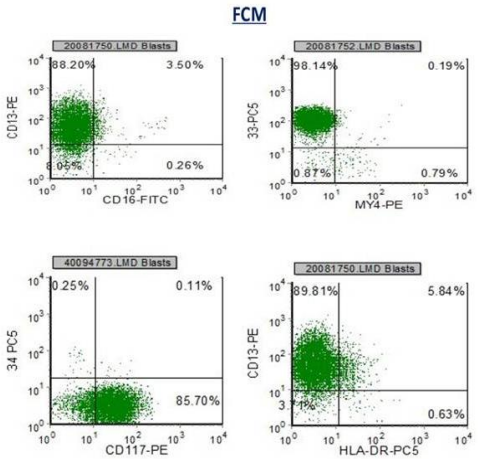

Figure 2 Case 1: Flow cytometry showing CD113, HLA-DR, CD 117 positive

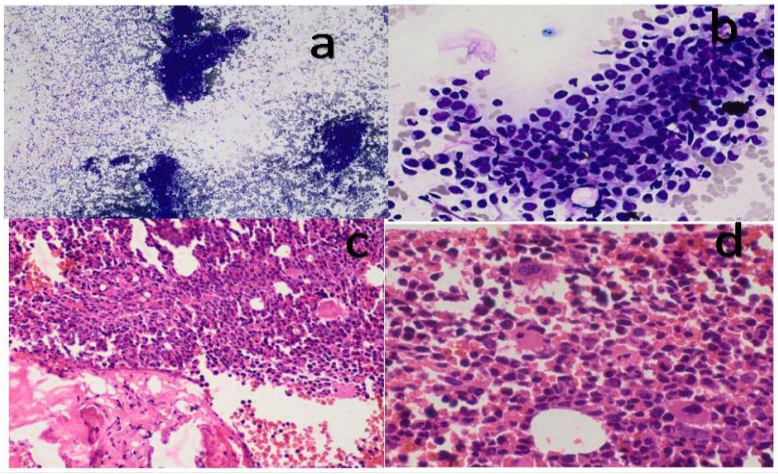

Figure 3 a, b, c, d Case 2Bone marrow aspirate-a) Smears showing high cellularity and marrow particles (Geimsa, X40) b) Smears showing marrow particle with blasts (Geimsa, X400). Bone marrow biopsy-c) Sections showing intertrabecular spaces and high cellularity (H&E, X100) d) Sections showing intertrabecular spaces and High cellularity (H&E, X400)

Case 3: A 64 Year female presented with a history of high-grade fever, breathlessness, anosmia, ageusia, abdominal pain, myalgias, fatigue, and chest pain for 7 days. The patient presented with difficulty in breathing, chest pain, and episodes of vertigo. On examination, the patient was febrile (axillary temperature 101^0F), tachycardic (120 beats/min), hypotensive (106/66 mm Hg) with oxygen saturation of 80% at room air. The patient was admitted, a detailed physical examination was done, nasopharyngeal swabs were taken for Covid 19 sampling, peripheral blood samples were taken for various hematological, biochemical, and microbiological parameters (table 1). RTPCR for COVID-19was positive. Peripheral smears revealed marked leukocytosis with the presence of 75% blasts. The blasts were 2.5 to 3.5 times the size of small mature lymphocytes with a high N: C ratio with scant to moderate cytoplasm, round to oval moderately pleomorphic nuclei showing nuclear indentations, and convolutions in some, fine chromatin and 0-4 nucleoli. Normocytic normochromic RBCs and low platelet count were seen (figure 4). Based on it, a diagnosis of acute myeloid leukemia was made. Bone marrow studies (figure 4) and flow cytometry confirmed the diagnosis and the patient was taken for chemotherapy after the covid RTPCR report came negative. The patient is under follow-up.

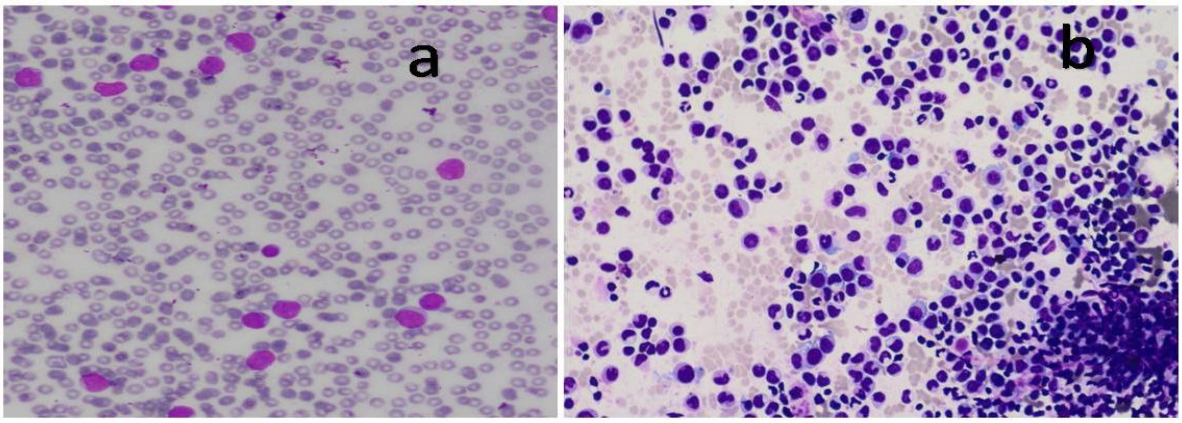

Figure 4 a, b: Case 3 -a) Peripheral smear showing numerous blasts, platelet clumps and a nucleated RBC (Leishman's stain, X 400) b) bone marrow biopsy showing increased cellularity (H&E, X100) Bone marrow aspirate) Smears showing megakaryocytes (Leishman's stain, X 400) d) Smears showing blast population (Leishman's stain, X 400).

Case 4: A 17-year-old female patient with no significant past medical history presented with a mild cough, breathlessness, episodes of high-grade fever, and chest pain for 5 days. On examination generalized pallor, febrile (temperature 102 ^{0}F), normotensive (110/76mm Hg), petechiae, and mild hepatosplenomegaly was seen. She had low oxygen saturation of 83% at room air. Nasopharyngeal/oropharyngeal swabs for COVID-19RTPCR came positive and the patient was admitted for treatment of COVID-19. High flow oxygen was administered and Venous samples were taken for hematological, biochemical, and microbiological parameters which revealed a low Hb 4.6g/dl, total leukocyte count 652360/cumm, platelet count of85000/cumm. Peripheral smear examination revealed marked leukocytosis with the presence of 80%blasts2.5 to 3.5 times the size of a small mature lymphocyte with scant cytoplasm showing granules in a few high N: C ratio, fine chromatin, 1-4 prominent nucleoli. Occasional blasts show nuclear cleaving and indentation. Red blood cells show marked anisopoikilocytosis with the presence of macrocytic cells, microcytes, and a few macro-ovalocytes, and platelets were reduced on smear. A diagnosis of acute myeloid leukemia was made. Bone marrow aspiration and biopsy were advised for confirmation along with flow cytometry for immunophenotyping. X-ray and CT scan of the chest revealed nodular ground-glass opacities in both the lungs with paraseptal emphysematous changes in both upper lobes (Figure 5).

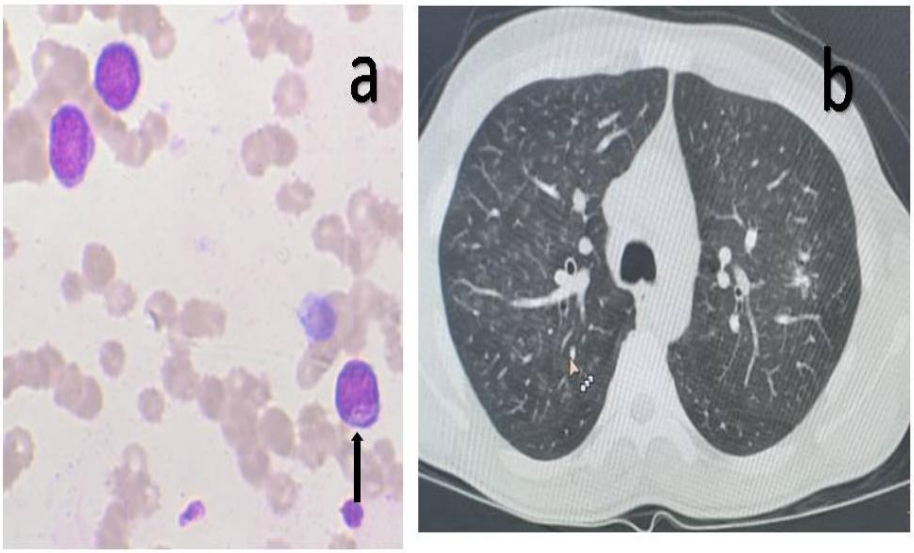

Figure 5. Case4 -a) Peripheral smear showing blasts with an auer rod (arrow)Leishman's stain, X600b) CT scan showing bilateral ground-glass opacities in both lungs

Interestingly all the patients diagnosed with AML were not having any clinical abnormality before the COVID-19infection so we feel that this is a de-novo presentation of AML with COVID-19and can only speculate about the coronavirus per se causing the hematological malignancy. However, more data is required to confirm this association, particularly the role of IL-6 and its direct effect in the causation of hematological malignancy.

DISCUSSION

Acute Myeloid leukemia (AML) is a common hematological malignancy but the occurrence of Acute myeloid leukemia with COVID-19or as a complication of COVID-19is uncommon. The diagnosis, treatment, and follow-up of patients with leukemias during this pandemic has been challenging for clinicians and pathologists due to a lack of clinical experience in such cases and diagnostic variabilities in laboratory results. On an extensive search of the literature, we

came across few studies suggesting that leukemia patients show rapid development of severe disease symptoms [4]. However, due to the paucity of literature, the exact aftermath of COVID-19inleukemia patients is still not well known [3,5]. Patients with leukemia are already immunosuppressed, myelosuppression, and may have low immunoglobulin levels, which renders them more vulnerable to COVID-19 and its complications. The concurrence of AML and COVID-19 is an extreme challenge of treating two potentially life-threatening diseases at the same time, both of which are known to cause morbid immuno-suppression.

The majority of COVID-19 patients are either asymptomatic on presentation or present with fever, fatigue, myalgias, anosmia, ageusia, cough and with disease progression, dyspnea, pneumonia, ARDS, and finally death. However, the disease presentation varies from patient to patient. All of our patients presented with similar symptoms, however, one of them had gum bleeding which is commonly seen in AML. None of our patients had any significant history and were incidentally diagnosed with AML when hemogram and other laboratory parameters were studied.

Owing to the scarcity of literature on the clinical course and outcome of SARS-CoV-2 infections in immunosuppressed cases and a coexisting malignancy, the exact disease outcome cannot be predicted and the outcome of the disease varies from patient to patient [6]. It has been mentioned that there is decreased production of interleukins (ILs), decreased proliferation, survival, and maturation of T cells caused by immunosuppressive therapy. Also, it is believed that though the risk of acquiring the virus is higher, the anti-inflammatory effects of such therapy reduce the overall severity of COVID-19 [6]. AML is also to known to impair T-cell response [6]. We note evidence supporting the link between the overactivation of T cells and severe immune injury in patients with severe COVID-19 [6].

Both humoral and cytotoxic immunity is impaired in COVID-19 due to the rapid exhaustion of helper T cells, regulatory CD4+ T cells, cytotoxic CD8+ T cells, natural killer cells, and B cells, resulting in lymphocytopenia [7]. A few studies have supported the finding of lymphocytopenia (83.2%) [7], however, none of our patients presented with lymphocytopenia.

The biochemical parameters have been associated with the severity of COVID-19 disease [8]. Few studies revealed that elevated LDH levels were associated with an increased risk of developing severe ARDS, multiple organ dysfunction syndromes, and increased mortality in COVID-19 [8,7]. Another study revealed that a cut-off value of Serum LDH level at 8.4 mg/dl point was associated with higher mortality [8]. Hypoxia and infection-induced cytokine-mediated tissue breakdown could be the cause of increased LDH and uric acid in COVID-19 patients, while in leukemia patients it can be attributed to the increased lysis of malignant cells or rapid cell turnover of malignant leukemic cells leading to increased catabolism of nucleic acids. This was in concordance with our study that all four patients had high S.LDH values and one patient showed mild elevation of serum uric acid and serum urea (Table1). High levels of IL-6 and elevated serum ferritin are associated with increased mortality from COVID-19 infection as the inflammatory response may contribute to poor outcomes [8]. This was in concordance with our study where three of our patients showed increased IL-6 levels whereas serum ferritin was elevated in all four patients(table1).

The National Cancer Research Institute (NCRI) AML working group and other experts recommended screening all the patients with AML for SARS-CoV-2 before initiating therapy regardless of symptoms [9]. NCRI AML working group recommends delaying the therapy for AML until symptoms resolve and PCR becomes negative [9]. These guidelines were kept in consideration before starting the

chemotherapy in all our patients. The chemotherapy was initiated after the patients got negative RTPCR for SARSCoV2. After the initiation of treatment, three patients are on follow up however, one died within a week of onset of treatment due to severe respiratory distress.

COVID-19infected patients with leukemia are at an increased risk of developing severe complications after receiving anticancer therapy (including chemotherapy, radiotherapy, or immunotherapy) within days of COVID-19 diagnosis [4,9]. This reinstates the severe impact of COVID-19 in patients with leukemia. Presently, accurate prognostication of AML with COVID-19 is difficult due to the paucity of studies and small sample sizes. Immunocompromised leukemia patients with COVID-19 are also at higher risk of superimposed bacterial or fungal pneumonia. It is of utmost importance to minimize the risk of COVID-19 in the immunocompromised population and initiate intensive monitoring and modified treatment strategies once the infection occurs. If these guidelines are followed during the management of leukemia in COVID-19 high-risk periods, it would help in decreasing the mortality and morbidity associated with the disease.

CONCLUSION

Concurrent presentation of AML and COVID-19 is challenging from a diagnostic and management point of view. The mutated virus is affecting large masses including the young population and the immunocompromised are always at higher risk of infection. There have been few case reports in patients with leukemia getting infected with COVID-19 but to the best of our knowledge, these are possibly the first few cases of AML occurring in concurrence withCOVID-19 infection detected incidentally without any prior history of any significant disease. These cases highlight the association of hematological malignancies with the current pandemic and also difficulty in their management.

Declaration by Authors

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