

## Atypical Presentation of COVID-19 as Acute Leukemia: A Case Report

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**Abstract:** In the absence of respiratory system involvement, COVID-19 patients developing ARDS can clinically mimic other diseases including acute leukemia due to presence of atypical lymphocytes in peripheral blood smear and increased serum lactate dehydrogenase and serum uric acid levels. Herein, we report a case who was initially suspected to have acute leukemia based on his atypical symptoms without any respiratory system involvement and deranged laboratory parameters and finally, diagnosed with COVID-19. Our patient presented with fever, myalgia, gum bleed, and petechiae. On clinical and laboratory evaluation, he was suspected to have acute leukemia based on markedly deranged serum lactate dehydrogenase and serum uric acid and the presence of atypical cells in peripheral blood smear and bone marrow. On day 3 of hospitalization, he developed respiratory symptoms, breathing difficulty which progressed to ARDS, and subsequently, he succumbed to his illness. His real-time reverse transcriptase-polymerase chain reaction test for severe acute respiratory syndrome coronavirus-2 yielded positive results. Also, Flow cytometry and fluorescence in situ hybridization studies for leukemia workup did not show any abnormalities. Although we are reporting the findings of only a single case, we aim to enhance and contribute further to the understanding of this novel infection.

### INTRODUCTION

Recently some studies have reported the presence of atypical lymphocytes in peripheral blood smear and increased serum lactate dehydrogenase (LDH) and serum uric acid (UA) levels in COVID-19 patients developing ARDS.<sup>[1-6, 7]</sup> These findings, along with the presence of non-specific symptoms of fever, myalgia, gum bleed, and petechiae without any respiratory system involvement or negative travel and contact exposure history can be mistaken for Acute Leukemia, especially in a peripheral healthcare setup where specialized investigations like Real-time reverse transcriptase-polymerase chain reaction (rRT-PCR), Flowcytometry (FCM) and Fluorescence in situ hybridization (FISH) are not easily available. Herein, we report a case who was initially suspected to have acute leukemia based on his atypical symptoms without any respiratory system involvement and deranged laboratory parameters and finally, diagnosed with COVID-19. Patient's consent was obtained after he was tested positive for COVID-19 for academic purpose.

### Case report

Our patient, a 35-yr-old male presented to the Emergency Department with a history of fever, myalgia, gum bleeding, petechiae on the face, and both, upper and lower limbs, for the past 15 days. No history of Influenza-like illness or respiratory system involvement. No recent history of international or domestic travel or any contact exposure with COVID-19 suspect or confirmed patients. On examination, he was found to be febrile (axillary temperature 101 F) and had tachycardia (Pulse rate 132/min), normal respiratory rate (26/min), and his blood pressure was 134/80 mmHg. His general physical examination revealed him to be of average height and built for an age without any icterus or lymphadenopathy. His routine laboratory investigations showed decreased Hemoglobin (Hb 9 g/dl), elevated total white blood cell counts with lymphocytic leucocytosis (TLC-21000/cu mm, P24, L75), and reduced platelets (90,000/cu mm). Among deranged biochemical parameters were markedly increased Serum UA 15 mg/dl and Serum LDH 12000 IU/L. On repeat testing after 8 hours, his Serum UA was 14.5 mg/dl and Serum LDH was 11800 IU/L. Peripheral blood smear examination revealed normocytic normochromic red blood cells and large atypical lymphoplasmacytic cells (size 20-30 $\mu$ ) with high Nuclear: Cytoplasmic ratio, 2-5 nucleoli, mildly condensed chromatin, and a thin rim of deeply bluish cytoplasm resembling leukemic blasts. [Fig1, A-F] Myeloperoxidase stain was done on

Received :19.12.2020  
 Received in revised form :-  
 Accepted :21.02.2021  
 Available online :03.05.2021

#### Keywords:

COVID-19  
 Coronavirus  
 Atypical lymphocytes  
 Lactate dehydrogenase  
 Acute leukemia

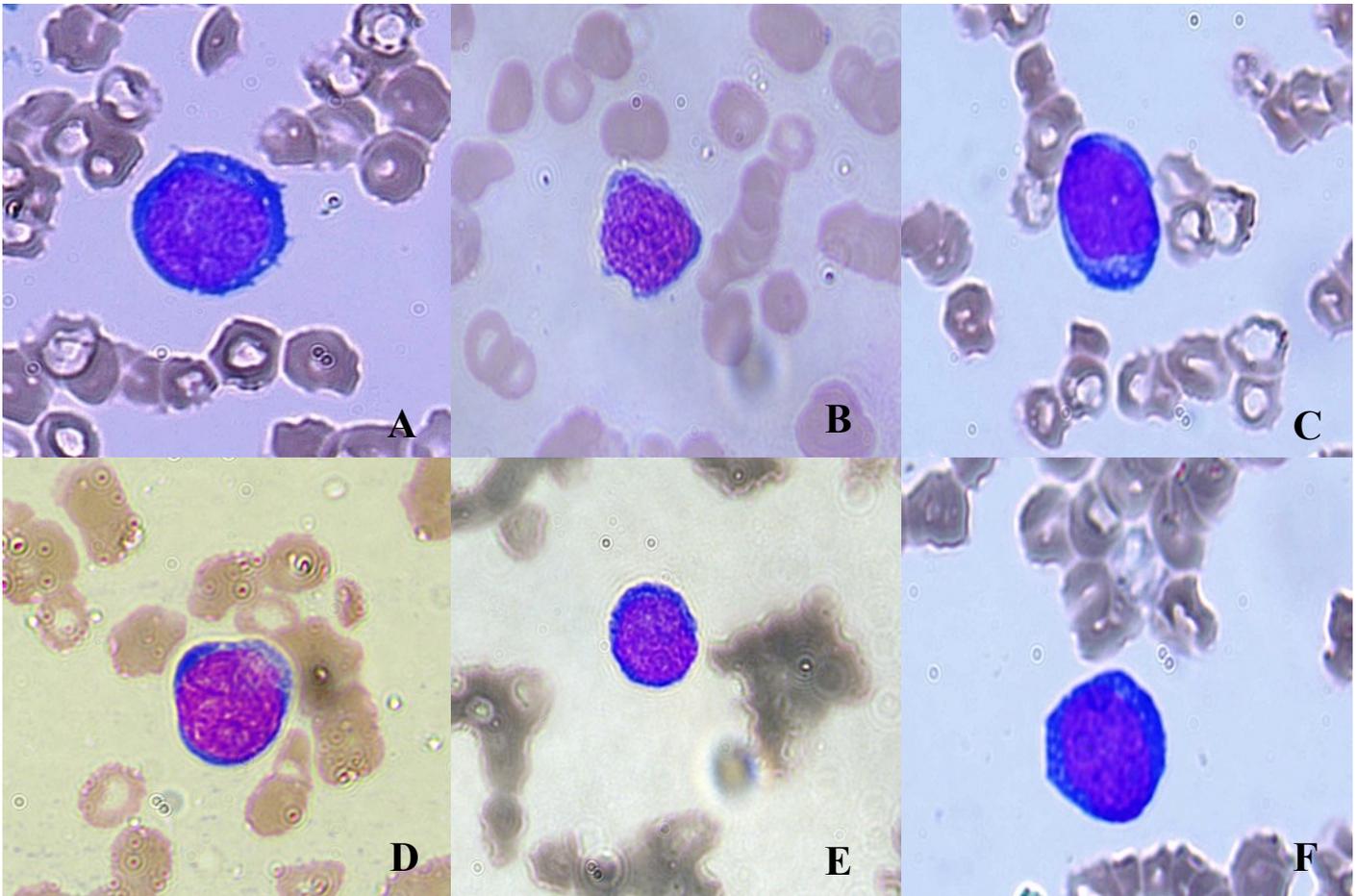
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<http://dx.doi.org/10.29228/jamp.48437>

*Int J Acad Med Pharm*,  
 2021; 3 (2); 189-191



fresh peripheral blood smear which was negative. Based on his symptomatology, presence of atypical lymphoplasmacytic blastoid cells in the peripheral smear, and markedly increased Serum LDH and UA, a probable diagnosis of Acute Leukemia was offered. His bone marrow aspirate also showed a preponderance of similar atypical lymphoplasmacytic blastoid cells. Subsequently, the patient's samples were sent to a higher center for FCM and FISH for confirmation and typing of Leukemia. On day 3 of his hospitalization, our patient suddenly developed shortness of breath, and oxygen saturation dropped to 70 % in room air. Considering the prevalent COVID-19 scenario, his nasopharyngeal swab and throat swab was taken and sent

for real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) for SARS-CoV-2 which turned out to be positive. In the meantime, His FCM and FISH Cytogenetics analysis reports for acute leukemia were negative for any blasts or cytogenetic abnormality. On the same day, the Patient's condition rapidly deteriorated with worsening respiratory symptoms, progressively decreasing oxygen saturation, development of hypotension, acute respiratory distress syndrome(ARDS), and sepsis and though, he was intubated and put on invasive ventilatory support along with supportive treatment but eventually, he succumbed to his illness.



**Figure 1 (A-F) :** Atypical lymphocytes showing high N: C ratio, mild to moderate opened up chromatin, prominent nucleoli nuclei and dark blue cytoplasm, (Both rows ,Leishman Stain x 400)

## DISCUSSION

Clinically, the majority of COVID-19 patients are either asymptomatic or initially present with fever and myalgia progressing to dyspnea, ARDS, multi-organ failure, and death. However, our patient presented with fever, myalgia, gum bleed, and petechiae which are more commonly seen with acute leukemia.

Pathogenesis of COVID-19 involves functional impairment of both, humoral and cytotoxic immunity against viral infection and rapid exhaustion of helper and regulatory CD4+ T cells, cytotoxic CD8+ T cells, B cells, and natural killer (NK) cells resulting in lymphocytopenia seen in COVID -19 patients<sup>1</sup>. In one study, the vast majority of patients presented with lymphocytopenia (83.2%),<sup>2</sup> however, it was not seen in our patient.

Recently, few studies have reported the presence of atypical lymphocytes in COVID-19 patients<sup>4,5</sup>. Atypical lymphocytes are a heterogeneous group of reactive lymphocytes commonly seen in

peripheral blood with viral infections such as Influenza, Dengue fever, Epstein-Barr virus (EBV), and Cytomegalovirus infections due to polyclonal proliferative lymphoid immune response to antigenic stimulation<sup>5,8</sup>. They can be either lymphoplasmacytic type or Downey II cells-like and morphologically resemble actively proliferating T-lymphocytes produced in response to infected B-lymphocytes mimicking leukemic blasts<sup>8</sup>. Few studies have reported a strong association of the presence of atypical lymphoplasmacytic cells with SARS-CoV-2 infection while on the contrary, the classical Downey II-like cells, which are generally more common in other viral infections, are paradoxically less common<sup>5,9</sup>. In a study done on 33 SARS-CoV-2 patients, 25 patients showed Atypical lymphocytes, out of which, twenty exhibited lymphoplasmacytic features<sup>5</sup>. In another study done on 32 COVID-19 patients, 23 patients showed atypical lymphocytes out of which 16 patients exhibited lymphoplasmacytic lymphocytes<sup>9</sup>. On retrospective analysis, the atypical cells seen in our patient were indeed atypical lymphoplasmacytic cells which

resembled leukemic blasts.

Among various biochemical parameters, serum LDH and Serum UA have been associated with the severity of COVID-19 disease. In one study, LDH was elevated in 41% of COVID-19 patients<sup>2</sup> while in a pooled analysis of 9 published studies (n=1532 COVID-19 patients), elevated LDH levels were associated with a ~6-fold and ~16-fold increase in odds of developing severe disease and mortality in COVID-19 patients, respectively<sup>3</sup> Similarly, another study reported that Serum UA level at 8.4 mg/dl cut off point had 89% sensitivity and 80% specificity predicting higher mortality, more severe ARDS, and frequent occurrence of multiple organ dysfunction syndromes<sup>10</sup>. On the other hand, In one study, increased LDH and UA were seen in 96.6% and 83.3% leukemic patients, respectively<sup>7</sup>. The probable reason of increased LDH and UA in COVID-19 patients can be attributed to hypoxia and infection-induced cytokine-mediated tissue breakdown while in leukemia patients, they are increased due to leukemic cell lysis, or to increased rapid cell turnover of malignant cells resulting in increased nucleic acid catabolism<sup>3,7,8</sup>.

### Conclusion

Our understanding of COVID-19 is still evolving and this case highlights another tangential clinical presentation of this disease among myriad others. This case stresses the importance of atypical presentation of COVID-19 which can be mistaken for acute leukemia, especially in a peripheral healthcare facility with limited availability of special investigations.

### Acknowledgements

None.

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