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LETTER TO THE EDITOR

COVID-19 and acute promyelocytic leukemia: similar clinical spectrum and diagnostic challenges

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COVID-19 is an infectious disease caused by the severe acute respiratory syndrome virus (SARS-CoV-2) (Lu et al. 2020). It presents, among other clinical signs, with cytopenias or leukocytosis and coagulopathy, laboratory findings that are also observed in about 80% of patients with acute promyelocytic leukemia (APL). APL is a rare hematological neoplasm characterized by the translocation t(15;17)(q22;q11-21) and fusion of the *PML-RARα* gene (Rowley et al. 1977). The initial clinical picture is severe; however, if diagnosed early and treatment is immediately established, and high cure rates can be achieved (Kamath et al. 2019). Here we present a report of a patient for whom the initial diagnostic impression was COVID-19 on account of clinical signs of severe acute respiratory syndrome presented in the midst of the pandemic caused by SARS-CoV-2. We describe the laboratory investigations that were essential to identify the concomitant diagnosis of APL masked by COVID-19 symptoms.

Case report: A 27-year-old man presented with fever, unexplained asthenia, ecchymosis, epistaxis, mild gingival hemorrhage, anosmia, skin pallor, cough, dyspnea, and 90% oxygen saturation. He underwent testing for SARS-CoV-2 using RT-PCR froma nasopharyngeal swab in June 2020, the result of which demonstrated the presence of SARS-CoV-2 RNA. Laboratory investigation of coagulation times revealed severe coagulopathy. Analysis of inflammation markers (C-reactive protein, procalcitonin, and ferritin) showed marked increases in all markers, confirming a systemic inflammatory syndrome. His complete blood count revealed significant anemia, leukopenia, thrombocytopenia, and left shift toward promyelocytes. The results of laboratory tests areshown in Table I.

Based on the analysis of the initial laboratory results, venous thromboembolism prophylaxis was started using low molecular weight heparin, corticosteroid, and empiricalantimicrobial treatment with cefepime, vancomycin, and liposomal amphotericin B. Then, due to the increase in promyelocytes observed in the blood counts performed afterthe diagnosis of COVID-19, the patient was evaluated by the infectious disease and hematology teams, who decided to perform a bone marrow biopsy to

Table I. Laboratory parameters with reference values adjusted for sex.

Parameter	Patient	Normal range
Hb (g/dL)	5.3	12.0–16.0
WBC (mm³)	2,300	4,000–11,000
Platelet (mm³)	14,000	150,000–450,000
PT (seconds)	21.4	9.3 – 13.3
aPTT (seconds)	53.2	25.4 – 36.9
Fibrinogen(mg/dL)	72.0	180.0–350.0
D-dimer (ng/mL)	28.000	< 500.0
LDH (U/L)	629.00	120.0–246.0
Creatinine (mg/dL)	0.59	0.60–1.10
Urea (mg/dL)	32.0	15.0–45.0
ALP (U/L)	80.0	35.0–104.0
GGT (U/L)	96.0	< 38.0
AST (U/L)	95.0	< 40.0
ALT (U/L)	73.0	10.0–49.0
CRP (mg/dL)	28.30	< 1.0
PCT (ng/dL)	13.7	< 0.1
Ferritin (ng/dL)	739.0	22.0–322.0

Hb: hemoglobin; WBC: white blood cell; PT: prothrombin time; aPTT: activated partial thromboplastin time; ALP: alkaline phosphatase; GGT: gamma glutamyl transferase; AST: aspartate aminotransferase; ALT: alanine transferase; CRP: c-reactive protein; PCT: procalcitonin.

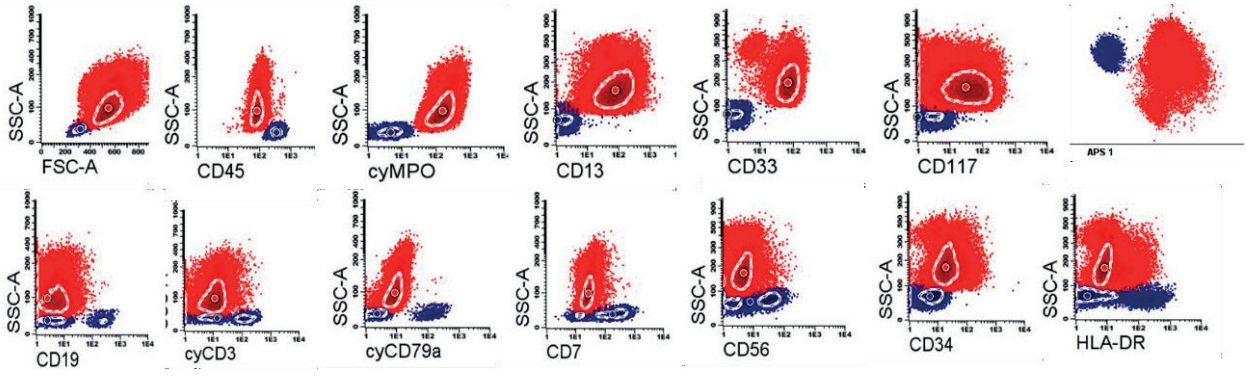

Figure 1. Result of the analysis by flow cytometry. The cells stained in red indicate the "blasts" of acute promyelocytic leukemia and the cells stained in blue indicate the residuallymphocytes. Immunophenotyping was performed using a panel of monoclonal antibodies standardized by the EuroFlow group. The acquisition of the events was performed in the flow cytometer FACS Canto II (Becton Dickinson-BD) and the data were analyzed using the Infinicyt™ software.

investigate the possibility of acute leukemia associated with COVID-19. The bone marrow was sent for immunophenotyping by flow cytometry and to assay for molecular rearrangement *PML-RARα*, due to the suspicion of acute promyelocytic leukemia.

Immunophenotyping by multiparametric flow cytometry revealed a profile compatible with APL, with the presence of 73.8% blasts with elevated SSC (side scatter) and FSC (forward scatter), heterogeneous expression of the CD13 antigen, and homogeneous expression of the CD33 antigen, in association with intracytoplasmic myeloperoxidase (MPO), CD117 and CD45 antigens. Antigens CD34 and HLA-DR, as well as antigens of T lymphoid lineage (CD3 and CD7), lineage B (CD19 and CD79a) and NK cells (CD56) were negative (Fig. 1). The presence of the *PML-RARα* fusion gene was confirmed by RT-PCR, thereby confirming the diagnosis of APL, as recommended by the WHO (Swerdlow et al. 2017).

Immediately after confirming the diagnosis of APL, the patient was requested to be transferred to the oncology hospital to begin therapy with all-trans-retinoic acid. However, after three days of hospitalization in the emergency care unit, the patient developed severe respiratory failure and successive cardiac arrests, after which he died.

The importance of reporting this case is that it is difficult to rule out the hematological neoplasms underlying COVID-19. Even mild cases of COVID-19 can exacerbate the severity of hematological neoplasms, increasing the mortality rate among patients with coincident hematological neoplasms and COVID-19 (Passamonti et al. 2020). In the specific case of APL, which usually presents with coagulopathy, thrombocytopenia, and hyperfibrinolysis, the diagnosis and management of this neoplasiawas extremely challenging in this patient diagnosed with COVID-19, which is also related to thrombotic events (Bikdeli et al. 2020).

In conclusion, hematological neoplasms can present complex and diverse clinicalmanifestations, representing a great challenge for clinical diagnosis. Multidisciplinary assessment and meticulous differential diagnosis, especially including neoplasms whose clinical spectrum is similar to those of COVID-19, is crucial during the pandemic period.

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R.P.S and M.M.F.S. contributed equally to the study. R.P.S and M.M.F.S. were involved in design and data interpretation. R.P.S. wrote the manuscript. S.R.P.F. conducted critical revision of the manuscript. All authors reviewed and commented on the manuscript and approved the final version. Written informed consent to publication was obtained.