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CASE IMAGE

Sudden death of a SARS-CoV-2 patient with NPM1 + acute myeloid leukemia mimicking acute promyelocytic leukemia

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To the Editor,

NPM1-mutated de novo acute myeloid leukemia (AML) is a heterogeneous group of disorders, including forms with monocytic or myeloid morphology and immunophenotype and several different comutational patterns. Recently, a new subset was described: It shows an APL-like immunophenotype, with negativity for both CD34 and HLA-DR, in the absence of a PML-RARA translocation, with comutations in TET2 or IDH1/2.[1] This subset showed significantly longer relapse-free survival and overall survival, as confirmed in a further study by the same group concerning 239 patients.[2]

A 50-year-old man was admitted to our ER in September 2020 for fever and generalized bone pain, with a sudden onset while on vacation. Blood tests revealed severe neutropenia and moderate thrombocytopenia. A peripheral smear revealed 2% blasts with granules. Blood chemistry test showed increased levels of LDH and creatine kinase. Coagulation tests were normal, except for D-dimer's abnormally high value (35 200 ng/mL—normal range < 500 ng/mL). EKG and troponin test were normal. Nasopharyngeal swab with molecular (PCR) tests for SARS-CoV-2 gave negative results. In agreement with local protocol, a total body CT scan was performed and ruled out pulmonary or abdominal complications.

Bone marrow smear showed pathological hypergranular blasts similar to leukemic promyelocytes, but in the absence of Auer rods, and a minority of agranular, less differentiated blasts. Cytochemical stain for myeloperoxidase was intensely positive (Figure 1A,B).

A provisional diagnosis of acute promyelocytic leukemia (APL) was made, and all-trans retinoic acid (ATRA) and prednisone as prevention of differentiation syndrome were promptly instituted.

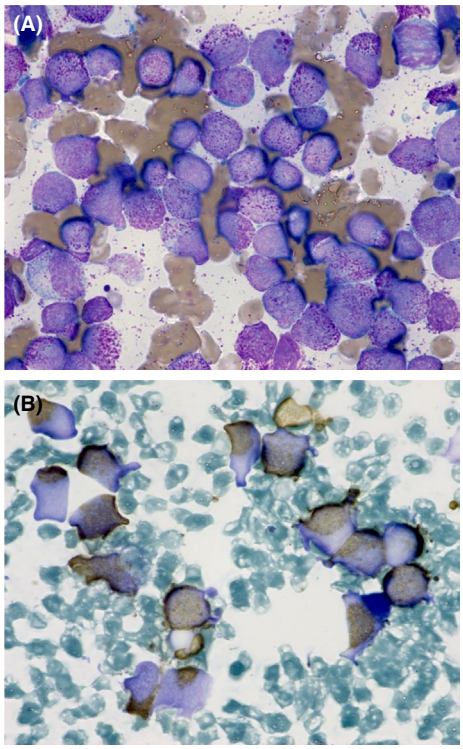

FIGURE 1 (100× magnification) (A) Hypercellular bone marrow aspirate shows diffuse infiltration by hypergranular promyelocyte-like blasts. A blast with large coalescent granules is visible near the middle-upper border, while a few hypo/agranular less differentiated blasts are scattered around the center of the microphotograph (May-Grünwald-Giemsa stain). (B) The cytochemical reaction for myeloperoxidase is intensely positive in the blast cell cytoplasms [Colour figure can be viewed at wileyonlinelibrary.com]

Sabrina Giammarco and Patrizia Chiusolo equally contributed to the study

Flow cytometry revealed abnormal myeloid blasts expressing myeloperoxidase, CD33, CD117, CD38, lacking CD34, CD45RA, and HLA-DR, compatible with an APL immunophenotype. Cytogenetics showed a normal 46 XY karyotype, and the absence of PML-RARα rearrangement was confirmed by FISH and PCR.

The patient continued on ATRA and prednisone, on the basis of a suspect translocation variant of APL. Suddenly, the patient reported back pain irradiated to lower limbs and treated with morphine sulfate 10 mg intravenously with pain control. In the absence of any blood count changes, a few hours later the patient lost consciousness. A cerebral CT scan revealed a massive subdural hematoma of the left side, involving frontal, parietal, and occipital areas, with a 12-mm midline shift. The patient underwent neurosurgery. Hemostasis was extremely difficult with diffuse bleeding, despite the infusion of fresh-frozen plasma. The patient died a few hours later with overt disseminated intravascular coagulopathy (DIC).

Molecular analysis for myeloid panel, including mutational screening for t(8;21), inv(16), cKit, FLT3, NPM1, was done, and it showed positivity for NPM1. Furthermore, next-generation sequencing, including 26 myeloid genes panel, revealed mutations of TET2 and IDH1 genes. An autopsy was granted, and unexpectedly, postmortem swabs were positive for SARS-CoV-2 in the nose, pharynx, and both lungs. This case image was approved by IRB.

Several studies have described morphological findings mimicking APL. An APL-like immune phenotype was common in the subpopulations of NPM1-AML with double negativity for CD34 and HLA-DR. It must take into account in differential diagnosis. Sudden death due to a major bleeding was unexpected in a young man, with no comorbidities, and with moderate thrombocytopenia and elevated D-dimer level, in the absence of overt DIC The SARS-CoV-2 infection possibly contributed to the general symptoms of our patient and played a significant role in the onset of overt DIC and intracranial bleeding, as previously reported.[3]

CONFLICT OF INTEREST

The authors have no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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