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ATYPICAL CHRONIC MYELOID LEUKEMIA BCR-ABL 1 NEGATIVE: A CASE REPORT AND LITERATURE REVIEW

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ABSTRACT
Atypical chronic myeloid leukemia BCR-ABL negative is rare myelodysplastic syndrome/myeloproliferative neoplasm for which there is no current standard of therapy. Patients with aCML had pronounced immature granulocytosis and granulocytotic dysplasia in their blood smears. We admitted a 60-year-old man with splenomegaly, hyperleukocytosis, anemia, and thrombocytopenia; after cytology, cytogenetic, and molecular biology analyses of bone marrow, we diagnosed aCML using 2016 World Health Organization classification. Chemotherapy was used to treat the patient at first, but the patient's anemia worsened. This prompted a modification in treatment.

Key words: aCML, BCR-ABL 1 negative, neoplasm

INTRODUCTION
Atypical chronic leukemia (aCML) is a subtype of myelodysplastic syndrome/myeloproliferative neoplasm (MDS/MPN) with an incidence rate of 1 in 100.000 or fewer[1]. Patients with leukocytosis, splenomegaly, frequent anemia, and fluctuating platelet counts present in the hematology consultation in their seventh or eighth decade of life. The presence of circulation myeloid precursors and apparent dysgranulopoiesis are morphologic criteria for aCML, but cytogenetic and molecular tests for Ph1 and the BCR-ABL A fusion gene are negative. Overall, aCML has a dismal prognosis: the median survival time is less than two years, with a 20-40% likelihood of progressing to acute myeloid leukemia[2]. The difficulties with aCML stem from it diverse clinical and genetic features, high rate of transition to acute myeloid leukemia, and historically poor prognosis. We provide, in this report, our experience with a patient who was diagnosed with aCML after developing dermohypodermitis.

OBSERVATION
We describe previously healthy case of a 60-year-old man who has an unremarkable medical past history. His family history also was negative for hematological disease. The patient had been experiencing increased weariness for the past two months and had presented an inflammatory skin lesion on the left temple. Our clinical examination showed a Pallor and moderate splenomegaly, but no tumor syndrome. We started instrumental and laboratory tests,

hemoglobin was 93 g/L (reference range: 130-180g/L), WBC was 56.8 10^9/L (reference range: 4-10 10^9/L), platelets were 112 10^9/L (reference range: 120-400 10^9). Laboratory manual differential count showed 60% neutrophils, 16 % metamyelocytes, 8% myelocytes, 2 % promyelocyte, 1% blasts, 3 % monocytes, 1% basophilic granulocytes, 2% eosinophilic granulocytes, and 7% lymphocytes, with dysgranulopoisesis revealing abnormal nuclear segmentation: hypolobation nuclear, hypersegmentation nuclear, Pseudo Pelger-Huet and hypogranular granulocytes (figure1). Then a Bone Marrow Aspirate (BMA) was performed; the morphology of BMA revealed a hypercellular marrow with myeloid hyperplasia of up to 73%, including myeloblasts 3%, promyelocytes 5%, myelocytes 12%, metamyelocytes 20%, neutrophilic granulocytes 28%, eosinophils 5%, basophiles 0%, and 4% monocytes. A normal karyotype of 46, XY was discovered during cytogenetic investigation. BCR/ABL fusion gene negative Molecular biology analysis histopathological examination of a skin lesion on the left temple revealed polymorphic dermohypodermitis with CD3 and CD20 immunohistochemistry complements that were negative. The patient was diagnosed with aCML and given hydroxurea (2 capsules of 500 mg/j x 21 days). The progression was characterized by a decrease in white blood cell count (from 57 to 24 G/L) and a moderate drop in spleen size. However, the patient's anemia worsened (from 9.5 g/L to 8 g/dl), prompting a change in treatment, with azacytidine 75 mg/m2/j given every 1 to 7 every 1 to 7 days; every 28 days. HLA typing is also being done to find possible hematopoietic stem cell transplant donors (HSCT).

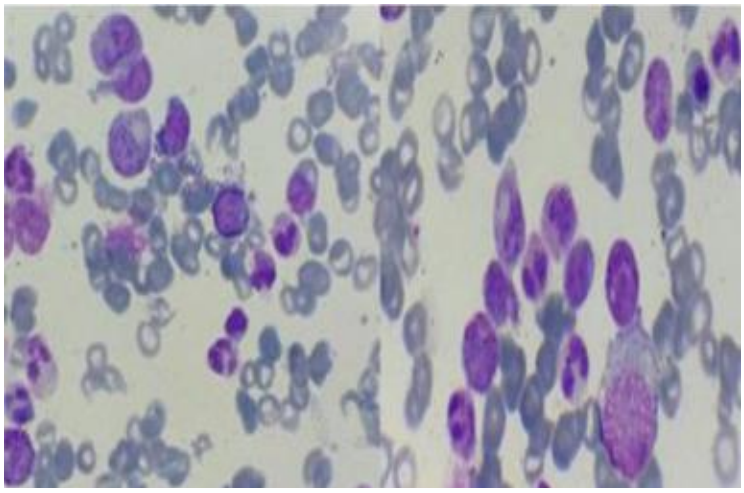

Figure 1: Bonne marrow smear

DISCUSSION

Atypical chronic myeloid leukemia (aCML) is a clonal hematopoietic disorder with both dysplastic and proliferative features, such as persistent granulocytosis with left shift, bone marrow hypercellularity with dysplastic hematopoiesis, and myeloid preponderance. It is a disorder of older adults with no apparent sex predominance [2]. Acute myeloid leukemia is an uncommon myeloid neoplasm that affects 1-2 people out of every 100 people with Philadelphia-positive CML. Anemia, thrombocytopenia, and splenomegaly are among the clinical symptoms, which are comparable to those of myeloproliferative syndrome. aCML etiology and pathogenesis are unknown. The 2016 WHO diagnostic criteria for aCML are based on the following factors: 1) Peripheral blood leukocytosis (WBC 13 10^9), caused by a 10% increase in neutrophils and their progenitors, 2) Dysgranulopoiesis (abnormal chromatin clumping).3) Basophils make up less than 2% of leukocytes; absolute basophilia is absent or limited. 4) Monocytes make up less than 10% of leukocytes; absolute monocytosisos absent or low. 5) Hypercellular BM with granulocytic proliferation and dysplasia in the erythroid and

megakaryocytic lineages, with or without dysplasia. 6) Blasts in the blood and BM of 20%; 7) No BCR-ABL fusion gene or Philadelphia chromosome. 8) No PDGFR, PDGFRB, FGFR1 rearrangement, or JAK2 rearrangement [3]. The diagnostic criteria for aCML are met in this patient. He has mild splenomegaly and normal chromosomes, a negative BCR-ABL fusion gene, $1.0x10^9$/L peripheral blood monocytes, 30% myeloid precursor in the peripheral blood, and 60% neutrophils, so chronic myeloid leukemia (CML), chronic myelomonocytic leukemia (CMML), and chronic neutrophilic leukemia (CNL) can all be ruled out. So, the aCML diagnosis was right.

In aCML patients, no specific chromosomal abnormalities were discovered to be associated with illness symptoms. Trisomy 8 and del(20q) are the most common karyotypic variations identified in aCML, however anomalies involving additional chromosomes such as 12,13, 14, 17,19, and 21 have also been recorded [4]. Many gene mutations have been discovered in aCML, including NRAS/KRAS (33% of patients), TET2 (33% of patients, CBL (10% of patients), E2H2 (13% of patients), and SETBP1 (25% of patients), among others[5]. In this exemple, the patient's chromosomes are normal. The syndrome of aberrant chromatin clumping, which has long been recognized as indicating as hematologic malignancy with both myelodysplastic and myeloproliferative characteristics is, in most cases, just a morphologic variant of aCML; the chance of leukemic transition is roughly 30% [6]. The majority of patients die of BM failure.

When treated with conventional chemotherapy, atypical CML patients have a dismal prognosis, with a median survival of only 24 to 25 months [7]. Age (>65 years), anemia (hemoglobin 10g/dl), and white blood cell count (WBC >50 10^9/L) are three independent variables in aCML, according to a retrospective analysis at MD Anderson Cancer Center [7]. Only a small percentage of patients are candidates for AML induction chemotherapy followed by allogeneic stem cell transplantation, yet it is the only treatment option that offers a cure. Koldehoff et al. [8]. found that allogeneic hematopoietic stem cell transplantation (HSCT) improved the diagnosis of aCML patients. Our candidate included hydroxyurea, which is converted to a free radical at the active site of ribonucleotide reductase's M2 protein subunit, inactivating the enzyme and selectively inhibiting DNA synthesis, resulting in cell death in S phase and synchronization of the fraction of cells that survive [9]. Our patient's anemia has worsened, prompting at therapeutic adjustment. 5-Azacytidine, in particular, has been proven to delay the time to disease progression in all subtypes of MDS and is the only medicine in this group that has been approved by the US food and Drug Administration (FDA) for all MDS subtypes[10].

CONCLUSION

In conclusion, aCML is difficult to distinguish from other MPS subtypes (CML, CNL, and CMML), making clinical diagnosis problematic. The absence of BCR-ABL1 translocation and the existence of granulocytic proliferation with significant dysgranulopoiesis are the diagnostic hallmarks of aCML. Azacytidine's ability in improving overall survival in high-risk MDS patients makes it worthwhile to investigate in aCML cases. Stem cell transplantation is the only known cure for aCML, however it comes with a substantial risk of toxicity and morbidity.

Declaration of interest

None

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