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CORRESPONDENCE

Germline CEBPA Mutation as a Rare Cause of Chronic Neutropenia

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Abbreviations

ANC	Absolute neutrophil count
CBC	Complete blood count
CEBPA	CCAAT/enhancer-binding protein-α
G-CSF	Granulocyte-colony stimulating factor
AML	Acute myeloid leukemia

Neutropenia is generally defined as an absolute neutrophil count (ANC) of < 1500/mm^3 and it can occur as a consequence of a wide variety of situations such as decreased bone marrow production or sequestration of neutrophils [1]. However, even in healthy individuals, ANC can be as low as 1000/mm^3, especially when the cell count is performed early in the day. Periodic monitoring of CBC parameters is needed for patients with an ANC of 1000–1500/mm3; a detailed evaluation is generally performed in the setting of ANCs lower than 500–1000/mm^3 [2]. Neutropenia is classified as mild (1000–1500/mm^3), moderate (500–1000/mm^3) or severe (< 500/mm^3) [3].

Neutropenia is considered chronic if the condition persists more than 3 months. While there are so many causes for chronic neutropenia, most common diagnosis in both children and adults is autoimmune or idiopathic neutropenia. Intrinsic neutropenias are caused by abnormalities in the function of hematopoietic progenitor cells to produce mature neutrophils and they can be either acquired or congenital [2]. There are several gene mutations described as causes of congenital neutropenia and they include but not limited to mutation of *ELA2*, *HAX1*, *WAS, SLC37A4* [4].

In this case, we present an otherwise healthy patient with chronic neutropenia and germline CCAAT/enhancer-binding protein-α (CEBPA) mutation. To the best of our knowledge, this is the first case describing germline CEBPA mutation as a cause of chronic neutropenia.

A 28-year-old female patient was referred to our hematology department in 2021 due to a chronic neutropenia, which was persisting for 11 years with no recurrent febrile infections. The onset of neutropenia occurred when she was getting evaluated for irrelevant complaints (muscle cramps) in 2010. Her CBC at that time revealed a leukocyte count of 2500 /mm^3 with severe neutropenia and she was referred to a hematologist. She had received Granulocyte-Colony Stimulating Factor (G-CSF) injections multiple times and responded well to the therapy. In multiple instances in the past, her ANC values obtained after discontinuation of G-CSF injection showed recurrence of neutropenia.

On admission, she had no complaints other than muscle cramps, followed by fatigue and recurrent oral ulcerations for the last 2 years. A focused family history was obtained and was significant for her father who had deceased because of acute myeloid leukemia (AML) in 2011, his cytogenetics or molecular reports were not available. The patient had no environmental or medical allergies, denied taking any medication or supplements and had undergone no surgical operations in the past. Physical examination was insignificant and revealed no organomegaly. Her complete blood count at the admission showed a low overall leukocyte count of 3270/mm^3, an ANC of 800/mm^3

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(moderate neutropenia) and a normal reticulocyte count. Serum levels of vitamin B12 and B9 were normal. Serologic tests were done to rule out concomitant infections with Brucella, parvovirus B-19, hepatitis B and C viruses, human immunodeficiency virus, human herpes virus-6 and human herpes virus-8 and all resulted negative. Her autoimmune antibodies (rheumatoid factor, anti-nuclear antibodies and extractable nuclear antigen antibodies) were negative. There were no atypical cells or any other abnormal findings on the morphologic examination of peripheral blood smear. Bone marrow biopsy showed a normocellular bone marrow with trilinage hematopoiesis with no infiltrations or reticuline fibrosis. In the bone marrow aspirates and imprints, there was no sign of dysplasia; no blast increase was observed. Flow cytometric analysis was unremarkable, there was no dysplastic myeloid or clonal large-granular lymphocyte population detectable; no significant finding was detected in the myelodysplastic syndrome-fluorescence in situ hybridization (FISH) panel. In cytogenetic analysis, no abnormal karyotype was detected. Next generation sequencing analysis (NGS) revealed a c.903 C > A variant in CEBPA gene with a variant fraction of 50.3%. After the detection of CEBPA mutation, patient's close relatives were advised to undergo genetic testing and one of her paternal uncles was positive for same CEBPA mutation. Table 1. shows our flow cytometry, FISH and NGS panels and Table 2. shows laboratory course of the patient.

Management of chronic neutropenia has more than one aspect including prevention and management of infections, with antimicrobial therapy and administration of G-CSF, for instance. Hematopoietic stem cell transplantation is also an option; it should be into account that long-term use of G-CSF therapy appears to increase the risk of leukemia in patients with congenital neutropenia [5]. Our patient had received only G-CSF therapy for a short period in an another center. She needs no therapy currently, oral ulcers resolved spontaneously, did not require treatment and is also followed closely in terms of leukemic transformation (Fig. 1).

CEBPA gene is located in the chromosome 19q13.1 band and encodes a transcription factor involved in the cell cycle regulation [6]. CEBPA variants are frequently encountered in malignancies such as non-small cell lung cancer, breast cancers and colorectal adenocarcinomas and are reported to be seen in 1.09% of myelodysplastic syndromes [7]. Acquired somatic CEBPA mutation is a well-known cause of sporadic AML [8]. However, germline CEBPA mutation was first described as a cause of 'familial AML' in 2004 [9] and is a very rare entity with only 26 reported families in the literature so far [10]. Familial cases of AML with germline-mutated

Table 1 Flow cytometry, FISH and NGS panels

Myeloid next generation sequencing panel
CEBPA, CSF3R, FLT3, MPL, UZAF1, CBL, NRAS, ABL1, JAK2, HRAS, SF3B1, ZRSR2, NPM1,IDH1, DNMT3A, IDH2, TET2, BRAF, PTPN11, RUNX1, ETV6, ASXL1, SETBP1, WT1, KIT, SRSF2, KRAS, CALR, TP53, EZH2
Myelodysplastic Syndrome fluorescence in situ hybridization panel
del 5q31, del 7q31, del 20q, monosomy 7/ trisomy 7, monosomy 8/ trisomy 8
Acute leukemia flow cytometry panel
CD1a (Thymocyte), CD2 (Early T cell), CD3 (T Lymphocyte), CD3 + CD4 + (T helper), CD3 + CD8 + (Cytotoxic/suppressor T cell), CD4 (T Helper, monocyte), CD5 (T and B lymphocyte subgroup), CD7 (Early T lymphocyte), CD8 (Cytotoxic/suppressor T lymphocyte), CD10 (cALLA), CD13 (Myeloid), CD14 (Monocyte, macrophage), CD15 (Granulocyte), CD19 (B lymphocyte), CD20 (B lymphocyte), CD22 (B lymphocyte), CD24 (B lymphocyte, granulocyte), CD33 (Myeloid), CD34 (Stem cell), CD38 (Activation marker), CD41 (Thrombocyte, megakaryocyte), CD45 (Pan-leukocyte antigen), CD56 (Natural killer), CD16?56? (Natural killer), CD64 (Monocyte, macrophage, granulocyte activated with G-CSF), CD117(c-kit), HLA DR (Activation marker), Glycophorin-A (Erythroid), Cytoplasmic CD3, Cytoplasmic CD79 + , MPO (Myeloperoxidase), TdT (Terminal deoxynucleotidyl transferase)

Table 2 Follow-up of the patient: laboratory course

Follow-up (months)	First admission (Not our clinic)	0 (First in our clinic)	3	6
Total Leukocyte (/mm^3) Count	2500	3270	2350	2540
ANC (/mm^3)	760	800	380	440
Erythrocyte (RBC) (10^6/microliters) Count	4.94	4.84	4.98	4.98
Hemoglobin (g/dL)	13.8	13.1	14	14
Platelet (/mm^3) Count	255,000	281,000	263,000	277,000

ANC: Absolute neutrophil count, RBC: Red blood cells

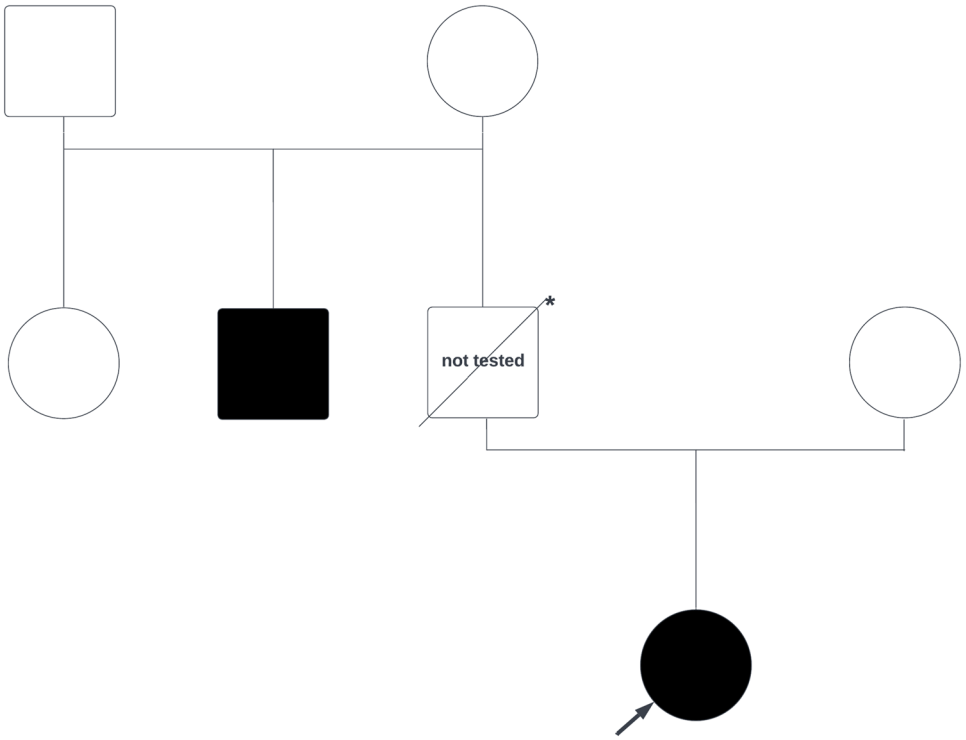

Fig. 1 Family tree of patient: c.903 C > A variant in (CCAAT/enhancer-binding protein-α) (CEBPA) gene

CEBPA has been included in the 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia [11].

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Data Availability Data are included in this published article and its additional file.

Declarations

Conflict of interest The authors declare that they have no competing interests.

Ethical Approval Informed consent was obtained from our patient to publish the presentation.

Consent for Publication Written informed consent was obtained from the patients for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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