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ORIGINAL ARTICLE

Acute myeloid leukemia due to germline *CEBPA* mutation in a Syrian family

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Abstract

Background: Familial cases of adult acute myeloid leukemia (AML) with germline-mutated CCAAT/enhancer-binding protein-α (*CEBPA*) gene are a rare entity classified in World Health Organization (WHO) classification 2016. Most families reported in the literature show an autosomal dominant inheritance pattern consistent with a single-gene mutation.

Methods: Here we studied a Syrian family with four individuals suffering from AML for *CEBPA* gene mutations by Sanger sequencing.

Results: The father, his three affected, and one yet unaffected child had the same mutation in the N-terminal region of *CEBPA* (c.198dupC), resulting in termination at Tyr67Leufs*41. All affected family members had a good primary response to chemotherapy and achieved complete remission.

Conclusion: Overall, another AML family with *CEBPA* gene mutation is added to the literature, presenting with yet unreported FAB subtype M5 and absence of CD7 expression in some family members.

KEYWORDS
acute myeloid leukemia (AML), *CEBPA* gene, familial, germline, prognosis

1 | INTRODUCTION

Adult acute myeloid leukemia (AML—OMIM #601626), in general, can be classified into several subgroups according to World Health Organization (WHO 2016 classification of hematologic cancers) (Arber et al., 2016) and the European LeukaemiaNet (ELN) (Döhner et al., 2017). A rare such entity is hereditary AML due to germline-mutated CCAAT/enhancer-binding protein-α (*CEBPA*—OMIM *116897) gene (Arber et al., 2016). Most of the families reported in the literature demonstrate an autosomal dominant pattern of inheritance, and patients are affected by the malignancy at a younger age than other AML entities (Owen et al., 2008); according to Hackl et al. (2017), AML, in general, has a median age of onset of ~67 years while familial CEBPA-mutated AML affects corresponding family members between 2 and 50 years (Tawana et al., 2017), as is typical for familial cancer syndromes (Rahner & Steinke, 2008).

CEBPA gene, located in 19q13.11 and having no introns, encodes a transcription factor involved in hematopoiesis as it controls (among others) proliferation and differentiation of myeloid progenitor cells (Gao et al., 2019). The encoded protein is homodimeric or heterodimeric with products of *CEBPB* (OMIM * 189965) and *CEBPG* genes (OMIM * 138972), and several isoforms of CEBPA protein are known (for more details, see https://www.genecards.org/cgi-bin/carddisp.pl?gene=CEBPA). Mutations are most commonly found in the N-terminal part as frameshift or nonsense mutations (Owen et al., 2008; Gao et al., 2019).

In sporadic and familial AML, the *CEBPA* gene is affected by a single (*CEBPA*sm) or double (*CEBPA*dm) mutations. In familial AML, these are typically one germline and an acquired one. However, *CEBPA* gene mutations are also observed in 10–15% of "common" AML cases, mostly in the context of a normal karyotype, and are associated with a favorable outcome (Pabst et al., 2001; Renneville et al., 2009; Green et al., 2010; Dufour et al., 2010). Interestingly, in families carrying *CEBPA* mutations, the germline mutation is predominantly N-terminal, whereas the acquired one is C-terminal (exceptions are, e.g., reported in [Tawana et al., 2017]), suggesting a potential role in leukemia predisposition for the N-terminal mutations only (Carmichael et al., 2010). Such cases of "familial AML" bear considerable clinical similarities to sporadic AMLs with *CEBPA* mutations, but disease progression may differ significantly due to the persistence of germline lesions postchemotherapy and the potential for completely new, independent episodes of the disease (Tawana et al., 2017).

Here, we report the clinical and biological features of four members of a Syrian family suffering from AML due to a germline mutation in the *CEBPA* gene.

2 | MATERIAL AND METHODS

2.1 | Editorial policies and ethical considerations

The father of the studied family agreed with the scientific evaluation and the study was approved by the ethical committee of the Atomic Energy Commission, Damascus, Syria.

2.2 | Clinical information

Here a nonconsanguineous Syrian family is reported: among the parents and their six children (four boys and two girls, see Figure 1), overall four are affected by AML. The father and three of his children were diagnosed with the malignancy, whereas the mother and the remaining of family members were unaffected and are yet clinically healthy. Age of onset of AML was in the father (I-1) 37 years, in son 1 (II-1) 8 years, son 2 (II-2) 2.8 years, and daughter 5 (II-5) 2.5 years.

The father was given standard treatment for AML including 3 + 7 induction chemotherapy (Daunorubicin 60 mg/m^2 for 3 days and Cytarabine 200 mg/m^2 for 7 days), and his affected children were treated by ELAM02 induction chemotherapy (Aracytine 200 mg/m^2 for 5 days and Mithoxantrone 12 mg/m^2 for 3 days). Bone marrow (BM) examination on day 20 postinduction was consistent with the achievement of complete remission (CR) for the father and his affected children. CR is still present for family members I-1 and II-5. Patient II-2 had one relapse which could be brought to CR again, whereas patient II-1 relapsed 7 years after diagnosis and died (see Table 1).

Interestingly, no CD7 expression was detectable for I-1 and II-2; also, family members showed different FAB subtypes during their causes of AML: The father (I-1) had FAB subtype M2, the eldest boy (II-1), and the youngest affected daughter had FAB subtype M5, whereas the second boy (II-2) had FAB subtype M4.

2.3 | Chromosome analysis and fluorescence in situ hybridization (FISH) analysis

Chromosome analysis using GTG-banding was performed on bone marrow (BM) samples prior to chemotherapy and postchemotherapy was performed according to standard protocols (Al-Achkar et al., 2007). Fluorescence in situ hybridization (FISH) using specific probes to detect translocations t(8;21), t(15;17), t(16;16), t(12;21), and deletion del(13q) were applied chromosome preparations of BM samples prior to chemotherapy and postchemotherapy as previously reported (Al-Achkar et al., 2007).

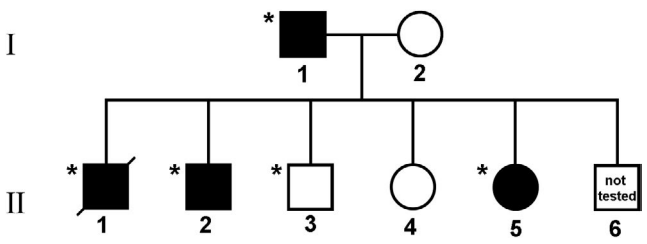

FIGURE 1 Pedigree of the reported family. Family members with asterisks are carriers of the familial *CEBPA* mutation

TABLE 1 Clinical features of the four affected family members of the presented family

	I–1	II–1	II–2	II–5
Gender	M	M	M	F
AML diagnosis	April 2014	April 2013	April 2010	December 2014
Age at AML diagnosis (years)	37	8	2.8	2.5
FAB subtypes	M2	M5	M4	M5
Immunophenotyping	$CD45^{dim}$, HLADr, MPO,CD33,CD34,CD11c,CD71,CD32,CD38,$CD15^{dim}$,CD13	$CD45^{dim}$, HLADr, MPO,CD33,CD4,CD34,CD11c,CD71,CD7,CD32 CD38, D64,CD14, $CD15^{dim}$,CD13	$CD45^{dim}$, HLADr, MPO,CD33,CD4,CD34,CD11c,CD71, CD32,CD38, CD117, $CD15^{dim}$,CD13	$CD45^{dim}$, HLADr, MPO,CD33,CD34,CD11c,CD7,CD32, CD117,CD14 CD38,CD64,$CD15^{dim}$,CD13
WBC count	36.8×10^9/L	31.3×10^9/L	25.4×10^9/L	57.6×10^9/L
Plt count $\times 10^9$/L	31×10^9/L	78×10^9/L	20×10^9/L	67×10^9/L
HgB, g/dL	11	10	10	6.6
LDH, U/L (normal value up to 420)	277	1303	1178	873
Blasts count in BM	80%	55%	85%	52%
Main clinical features	Purpura, bleeding gums, neck lymphadenopathies (2 × 1 cm)	Bruising's, several lymphadenopathies (2 × 1 cm)	Purpura, bleeding gums, hepatomegaly (3 cm), splenomegaly (2 cm), several lymphadenopathies (2 × 1 cm)	Bruising's, pallor, several lymphadenopathies (2 × 2 cm), hepatomegaly (2 cm)
Karyotype at AML diagnosis	Normal	Normal	Normal	Normal
Germline *CEBPA* mutation	c.198dupC (Tyr67Leufs*41)	c.198dupC (Tyr67Leufs*41)	c.198dupC (Tyr67Leufs*41)	c.198dupC (Tyr67Leufs*41)
Prior chemotherapy treatment protocol	3 + 7	ELAM02	ELAM02	ELAM02
CR, weeks	Yes	Yes	Yes	Yes
Time to get CR followed initial chemotherapy treatment	3 weeks	3 weeks	3 weeks	3 weeks
Relapse	No	Yes	Yes	No
Disease status at last follow-up	CR1	Relapse March 2020	CR2	CR1

(Continues)

TABLE 1 (Continued)

	I–1	II–1	II–2	II–5
Relapse parameters		Fever (39.5°C), vomiting, green diarrhea, abdominal pain, leukopenia (WBC 0.4 × 10^9/L), anemia (HgB 9.2 g/dL), thrombocytopenia (Plt 11× 10^9/L)	Splenomegaly (4 cm), several lymphadenopathies (left submandibular 0.5 × 0.5 cm), leukopenia (WBC 2.2 × 10^9/L), anemia (HgB 8.4 g/dL), thrombocytopenia (Plt 16× 10^9/L), LDH 533 U/L	
OS (months)	87+	89+	13+	79+
Death	n.a.	Yes	n.a.	n.a.
		April 2020		

2.4 | Molecular genetic analysis

Genomic DNA was isolated from peripheral blood (PB) samples after chemotherapy using QIAamp DNA Blood Mini Kit (Qiagen GMBH, Hilden, Germany). Germline mutation analyses were done using next-generation sequencing (NGS) by panel diagnostics in all family members apart from II-6, which was very young at the time of analyses; thus, no blood could be taken. The TrueSight Cancer panel (Illumina; FC-121–0202) was used.

3 | RESULTS

Father (I-1) and his affected children (II-1, II-2, and II-5) had normal results after karyotyping of bone marrow cells (results not shown). Also FISH revealed no evidence of cryptic translocations t(8;21), t(15;17), t(16;16), t(12;21), and/or a deletion del(13q).

However, germline mutation analyses by NGS identified a *CEBPA* gene mutation NM_004364.5:c.198dupC, p.(Tyr67Leufs*41) (described according to HGMD) and according to ACMG a class 5 mutation—see also http://ftp.ebi.ac.uk/pub/databases/lrgex/LRG_456.xml.

This mutation was present in all four affected family members, that is, I-1, II-1, II-2, and II-5, and besides also in the yet unaffected third son (II-3).

4 | DISCUSSION

A new familial AML with four affected and a yet unaffected member with the identical germline *CEBPA* mutation is reported. Other unaffected family members did not have this mutation (I-2, II-4) or were not tested (II-6). The identified c.198dupC mutation has previously been observed in a single case of nonfamilial AML (according to the COSMIC database for somatic samples from hematopoietic and lymphoid tissue, COSV57200711)—see also Dufour et al. (2012). As outlined before, *CEBPA* mutations can occur as acquired somatic and/or germline mutations (Gao et al., 2019). However, only 26 families with germline *CEBPA* mutations have been reported yet (reviewed in Brown et al., 2020). In systematically studied AML cases with normal karyotype, 8–13% of the cases had *CEBPA* gene mutations (Preudhomme et al., 2002; Pabst et al., 2008; Taskesen et al., 2011); among these, 7–11% have *CEBPA* germline mutations (Pabst et al., 2008; Taskesen et al., 2011). As the majority of the AML patients have two *CEBPA* mutations in trans, with both N-terminal and C-terminal frameshift mutations, this might also be suggested here for the reported family, even though it could not be verified. Even though no DNA was

available from the diseased bone marrow of the here presented family members, the fact that an N-terminal frameshift mutation was present here coincidences with other cases from the literature, for which such a germline mutation predisposes to acquire a somatic C-terminal *CEBPA* mutation on the other allele (Pabst et al., 2008; Tawana et al., 2015).

Also, another observation for the presented family is in concordance with the literature: familial AML with mutated *CEBPA* gene is inherited in an autosomal dominant way and displays complete or near-complete penetrance for development of AML and disease onset between 2 and 50 years of age (Owen et al., 2008, Renneville et al., 2009, Tawana et al., 2015). As four of six children of the mutated *CEBPA* gene carrier I-1 have inherited the same *CEBPA* mutation, it is inherited in an autosomal dominant way; the penetrance is yet four in five gene carriers, suggesting close supervision of blood values of family member II-3 (the family had genetic counseling and II-3 is being monitored with complete blood counts every 6 months), while no special care is necessary for II-4, as he is not a carrier of familial *CEBPA* mutation. Also, *CEBPA* mutation screening is indicated of II-6 as soon as possible.

Normally, the clinic-pathologic features of familial *CEBPA*-mutated AML cases, similar to those of sporadic AMLs with the majority displaying a normal karyotype, include FAB subtypes M1, M2, and, less frequently, M4 (with Auer rods seen in PB or BM blasts), and aberrant CD7 expression on blasts (Tawana et al., 2015). Thus, it is striking that here in overall four diseased family members, three different FAB subtypes were observed: the expected subtypes M2 and M4 (one time, each) and the yet in this familial AML-type unreported subtype M5—being present in father I-1 and daughter (II-5). Also, the normally in AML with mutated *CEBPA* gene present CD7 expression was not detectable in family members I-1 and II-1; the underlying mechanisms for both phenomena are yet not understood. Nonetheless and irrespective of the FAB subtype, the clinical outcome was comparatively positive in the reported family. This is also in concordance with literature data; here a favorable prognosis with an overall survival rate of 50–65% compared with 25–40% in normal karyotype AML without germline *CEBPA* mutation is given (Preudhomme et al., 2002; Fröhling et al., 2004; Bienz et al., 2005; Marcucci et al., 2008).

In conclusion, we describe here a novel case of a familial AML with four affected members and five of which had a germline mutation c.198dupC *CEBPA* being never observed in familial AML cases before. This family presents in individual I-1 a new clinical feature such as FAB subtype 5 without CD7 expression but still had a favorable outcome in all but one family member.

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CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

AW, SA, and WA performed banding cytogenetics and provided the clinical data; BA also provided clinical data and chemotherapy plan; AW, FA, and TL performed the molecular cytogenetic analyses; KM did molecular genetic analyses; AA performed immunophenotyping. AW and TL drafted the paper and all authors worked on the final version of the paper. All authors read and approved the final manuscript.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the patient's brother for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

DATA AVAILABILITY STATEMENT

All data necessary to understand the results and conclusions are provided in this article.

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