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Case Report

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Description of an Institutional Cohort of Myeloid Neoplasms Carrying ETV6-Locus Deletions or ETV6 Rearrangements

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Keywords
ETV6 · MDS · MPN · Acute myeloid leukemia

Abstract
The gene encoding for transcription factor ETV6 presents recurrent lesions in hematologic neoplasms, most notably the ETV6-RUNX1 rearrangement in childhood B-ALL. The role of ETV6 for normal hematopoiesis is unknown, but loss of its function probably participates in oncogenic procedures. In myeloid neoplasms, ETV6-locus (12p13) deletions are rare but recurrent; ETV6 translocations are even rarer, but those reported seem to have phenotype-defining consequences. We herein describe the genetic and hematologic profile of myeloid neoplasms with ETV6 deletions (10 cases), or translocations (4 cases) diagnosed in the last 10 years in our institution. We find complex caryotype to be the most prevalent cytogenetics among patients with 12p13 deletion (8/10 patients), with most frequent coexisting anomalies being monosomy 7 or deletion 7q32 (5/10), monosomy 5 or del5q14-15 (5/10), and deletion/inversion of chromosome 20 (5/10), and most frequent point mutation being TP53 mutation (6/10 patients). Mechanisms of synergy of these lesions are unknown. We describe the entire genetic profile and hematologic phenotype of cases with extremely rare ETV6 translocations, confirming the biphenotypic T/myeloid nature of acute leukemia associated to ETV6-NCOA2 rearrangement, the association of t (1;12) (p36; p13) and of the CHIC2-ETV6 fusion with MDS/AML, and the association of the ETV6-ACSL6 rearrangement with myeloproliferative neoplasm with eosinophilia. Mutation of the intact ETV6 allele was present in two cases and seems to be subclonal to the chromosomal lesions. Decoding the mechanisms of disease related to ETV6 haploinsufficiency or rearrangements is important for the understanding of pathogenesis of myeloid neoplasms and fundamental research must be guided by observational cues.

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Introduction

ETV6 is an ETS-family transcription factor with a helix-loop-helix domain encoded by the N-terminal exons and mediating the homodimerization indispensable for the protein's function, and an ETS domain, encoded by exons 6–8, responsible for DNA-binding to ETS-binding site-bearing promoters [1]. The targets of ETV6 are largely uncharacterized, but ETV6 −/− is a lethal genotype for mice during embryonic life, the protein being indispensable for angiogenesis and other

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lineages within the yolk sac [2]. Regarding hematopoiesis, hematopoietic lineages in the yolk sac and fetal liver develop non-disrupted in ETV6-deficient mice. However, Cre-mediated excision of ETV6 in adult mice induces depletion of bone marrow hematopoietic stem cells, but when deletion is performed on progenitors after lineage commitment, it is of no consequence except for impaired megacaryocyte maturation [3, 4], a trait reminiscent of the thrombopenia present in carriers of germline ETV6 missense mutations [5]. Acquired ETV6 point mutations, deletions (12p13 band), and translocations have been recurrently described in hematologic neoplasms, although much rarer than other recurrent chromosomal abnormalities or gene mutations. Deletions of the ETV6 locus on 12p13 are more frequent than translocations and are reported at incidence ranging from 3% to 11% in AML/MDS [6, 7]. One work has reported 12p13 deletions, always heterozygous, as preferably present within complex caryotypes [8], while another study shows frequent co-occurrence with monosomy 7 [9]. Other than the translocations of the WHO-recognized entities B-ALL with ETV6-RUNX1 and myeloid neoplasm with eosinophilia with ETV6-PDGFRβ translocation, several ETV6 translocations with different partners have been reported [10]. Some (ETV6-ABL1, ETV6-FLT3, ETV-JAK2, and others) are accompanied by eosinophilia [11–13], a trait possibly related to the activity of the kinase fused to ETV6 being potentiated by the homodimerization which the ETV6 fusion facilitates, or to activation of genes adjacent to the translocation or to other mechanisms [10]. ETV6 translocations are very rare; in one study translocations other than ETV6-PDGFRβ were seen in 3% of myeloid neoplasms [14].

Case Series Presentation

We herein describe the genetic and hematologic profile of myeloid neoplasms with 12p13 deletions or ETV6 translocations diagnosed in our institution from January 1, 2011, to December 31, 2021, to define the context – and therefore contribute to the understanding of the pathogenicity of – ETV6-locus lesions in myeloid neoplasms. We identified 10 cases with ETV6 deletions and 4 cases with ETV6 translocations among patients with myeloid neoplasms diagnosed in this time interval (Table 1).

Eight out of ten (8/10) patients with ETV6-locus deletions had complex caryotypes or at least three genetic lesions on high-resolution array-based CGH (comparative genomic hybridization). Two patients had, each, only one anomaly additional to the 12p13 deletion: one an inversion of chromosome 20 on caryotyping and the other one a CN-LOH 11p15 on array CGH. Considering all the coexistent chromosomal lesions, the most frequent ones were monosomy 7 or deletion 7q32 (5/10 patients), monosomy 5 or del5q14-15 (5/10 patients), and deletion 20/20q11-12 or inversion of the chromosome 20 (5/10 patients). Regarding coexistent mutations on NGS panels, the most common ones were TP53 mutation at various codons in 6 patients and TET2 mutation at various codons in 3 patients, whereas ETV6 itself was mutated in only one case.

The diagnosis of cases with ETV6-locus deletions was AML/MDS-IB2 in 8/10 patients (AML subtypes shown in Table 1, with no cases of secondary or therapy-related AML), MP-CMML in one patient and MDS/MPN-U in another. Myeloproliferative features were present in 4/10 patients, with: MDS/MPN-U with prominent eosinophilia in patient 6, megacaryocytic hyperplasia with fibrosis in patients 8 and 10, and MP-CMML in patient 11. The presence of myeloproliferative features in these four patients could be accounted for by genetics only in patient 6, who carried multiple RAS-pathway mutations [15], and in patient 11, who showed a typical mutational signature of proliferative CMML, with a classical combination of epigenetically targeted and Ras-pathway gene mutations [16]. The genetic lesion causing the eosinophilia of patient 6 was not evident, having ruled out, by FISH, the fusion transcripts of PDGFRα, PDGFRβ, and band 8p11, as well as the PCM1-JAK2 fusion, and, by NGS, the presence of JAK2exon13indel; it is noteworthy that this patient had a "second hit" in ETV6 by a missense point mutation at an allele frequency of 14%, probably abolishing completely ETV6 function in a subclone of the disease [6].

Regarding the four patients with ETV6 translocations, patient 1 presented a t (8;12) (q13; p12-13) rearrangement, with a phenotype of T-lymphoblastic lymphoma in lymph nodes and with 10% peripheral blood blasts with phenotype of acute undifferentiated leukemia CD34+ CD33+ CD2dim, and manifested significant eosinophilia. Bone marrow showed fibrosis with no apparent leukemic infiltration. This patient, who relapsed quickly to AML-type treatment, carried, both at diagnosis and at relapse, the additional anomaly t (8;21) (p21; p13), not sequenced further, with a different breakpoint that the well-described RUNX1-RUNXT1 translocation. Array CGH and NGS were not performed.

Patient 2, presenting AML-NOS with moderate marrow fibrosis, carried a t (4;12) (q12; p13) rearrangement, which was sequenced and found to correspond to a CHIC2-ETV6 fusion gene. There was no other caryotypic abnormality (array CGH not performed), while a limited NGS panel for ASXL1, CEBPA, IDH1/2, KIT, NPM1, RUNX1, TP53, showed no mutations.

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Table 1. Age at diagnosis, genetic profile, diagnosis revised according to the 5th WHO classification (2022), and, presence or not of eosinophilia, in myeloid neoplasms diagnosed in our institution carrying ETV6 translocations or deletions (whether deletion of the locus is complete vs. indeterminate if complete – due to array CGH not having been carried out – is shown in the third column)

Patient	Age, years	ETV6 lesion	Caryotype	CGH array	NGS mutations	FISH positivity (ETV6 break-apart probe)	Sequencing of fusion	Diagnosis	Eosinophilia
1	54	Translocation	46, XY, t (8;12)(q13; p12-13)[6]/ 46, idem, t (8;21)(p21;p13)[14]/ 46, XY[1]	N.D.	N.D.	85%	N.D.	T-LBL/acute undifferentiated leukemia	2.3 G/L
2	58	Translocation	46, XY, t (4;12)(q12;p13)[20]	N.D.	None on a limited panel	94%	ETV6-CHIC2	AML NOS M1 (with fibrosis)	No
3	75	Translocation	46, XX, der(1)? inv(1)(q22q36) t(1;12)(p36;p13), der(12)(t(1;12)[15]/46, XX [5]	N.D.	FLT3 D835Y 8%	Positive, not quantified	N.D.	AML NOS M2	No
4	57	Translocation	46, XX, t(5;12) (q31;p13) [19]/ 46,XX [1]	N.D.	ETV6 V66Gfs*2 24%, NPM1 W288Cfs*12 25%, WT1 R369Gfs*16 20%	38%	ETV6-ACSL6	AML with NPM1 mutation	7.6 G/L
5	52	Deletion (total/ partial?)	46, XX, del(12)(p11.2p13), ?inv(20)(p11.2q13.1)[17] / 46, XX[3]	N.D.	N.D.	N.D.	N/A	AML-MR	No
6	75	Deletion (total/ partial?)	46, XY, del (12)(p12p13) [12] 48, idem, +8, +15 [6]/ 46, XY [2]	N.D.	ASXL1 p.G646Wfs*12 33%, CBL Y371N 9%, CEBPA L246Gfs*73 4%, ETV6 Y391C 14%, KRAS G12A 8%, NRAS G13V 4%, NRAS Q61K 16%, PTPN11 G503A 2%, STAG2 E721* 4%	60%	N/A	MDS/MPN-U	8.1 G/L
7	64	Deletion (complete)	45,XY,add(1)(p10),add(2)(q31), -3, del(5)(q?14q33),add(7)(q22), der(7)del(7)(p11.2),add(7)(q? 33),add(8)(q24),-9,-10,-12,-17, der(?)t(?;1)(?;p21),+mar[19]/ 46,XY[1]	N.D.	TP53 R248Q 94% (constitutional and acquired)	N.D.	N/A	AML-MR	No

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Table 1 (continued)

Patient	Age, years	ETV6 lesion	Caryotype	CGH array	NGS mutations	FISH positivity (ETV6 break-apart probe)	Sequencing of fusion	Diagnosis	Eosinophilia
8	50	Deletion (complete)	45,XY,del(5)(q14.1q33.1),-7,-7,add(8)(p11.22),-12,+2mar[3]/45,idem,+7,-20,-22,+mar[9]/46,XY[8]	del5q14-, -7, del8p11, del12p13, del12p12, del12q21, del12q23, +20, del20q11, del20q12, +22	TP53 c.783-1G>A 22%, TP53 E286*25%	N.D.	N/A	MDS-biTP53 (with fibrosis)	No
9	75	Deletion (complete)	N.D.	del7q11, del7q21, del7q31, del5q14, del12p12, del12q21, del20q12, del10q23, del15q12	TET2 R544* 46%, TP53 H179R 46%	N.D.	N/A	MDS-IB2	No
10	73	Deletion (complete)	47, X, -Y, -3, add(5)(q11), add(7)(q?31), +8, -12,- 21, +4mar [10]	del7q32, del5q11, +8, del12p13, CN-LOH 17p13, del3p26, del4q34, gain 5q11, gain 12p13, gain 12q13, del12q21, del12q23, gain Yq11, delYq11	TP53 V216M 90%, U2AF1 Q157R 43%	N.D.	N/A	AML-MR (with fibrosis)	No
11	71	Deletion (complete)	46, XY [20]	CN-LOH 11p15, del12p13	ASXL1 P920Tfs*4 43%, DNMT3A R882H 46%, NRAS G12S 43%, SETBP1 G872R 45%, SRSF2 P95H 45%, TET2 Q976Tfs*29 40%, TET2 P980L 41%	N.D.	N/A	MP-CMML-1	No

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Table 1 (continued)

Patient	Age, years	ETV6 lesion	Caryotype	CGH array	NGS mutations	FISH positivity (ETV6 break-apart probe)	Sequencing of fusion	Diagnosis	Eosinophilia
12	65	Deletion (complete)	N D.	del11q23, del12p13, del12q12, delXp22, delXp11, delXq12, delXq21	FLT3-ITD low 14.3%, RUNX1 R107C 35%	N.D.	N/A	AML-MR	No
13	65	Deletion (complete)	44, XY,add(2)(p12),-5,add(11)(q21-22),-13,-17,-18, −20,+4mar[19]/ 46,XY[1]	21 anomalies, including del12p13	TP53 V272M 53%	N.D.	N/A	AML-MR	No
14	73	Deletion (complete)	N.D.	-7, del5q15, del12p13, del20q11, del17p13	TET2 Q734* 20%, TP53 R280G 24%	N.D.	N/A	MDS-biTP53	No

Variant allele frequencies are shown in percentages for point mutations. Patient 7 had a Li-Fraumeni syndrome with presence of a germline TP53 mutation, and an identical mutation was acquired in the other allele at AML presentation. In the array results, deletions and gains are shown at band resolution. N.D., not done.

Patient 3 presented with AML-NOS and carried a t (1; 12) (p36; p13) translocation, in a complex rearrangement provoking simultaneously inversion of chromosome 1 and a derivative chromosome 12. The ETV6 rearrangement was confirmed by FISH, whereas an extended NGS panel showed only an FLT3-TKD mutation of low allele burden.

Patient 4 presented with AML with NPM1 mutation, with myeloproliferative features (neutrophilia) and prominent eosinophilia and carried a t (5;12) (q31; p13) translocation, corresponding not to an ETV6-PDGFRβ transcript, but to an ETV6-ACSL6 rearrangement, as we proved by RNA sequencing by NGS. Array-CGH was not performed, while an extended DNA NGS panel showed a WT1 mutation and an uncharacterized ETV6 mutation in the homodimerization domain – all point mutations, including NPM1, being probably subclonal if one compares their allele burdens to the proportion of metaphases with the translocation. This patient presented heart failure during induction with anthracycline and cytarabine, a complication for which a role of the prominent eosinophilia could not be ruled out.

Discussion

Our case series confirms that ETV6-locus deletions usually present in myeloid neoplasms with complex caryotypes. We show that most frequent anomalies coexisting with ETV6 deletions are monosomy 7 or deletion 7q32 (5/10 patients), monosomy 5 or del5q14-15 (5/10 patients), and deletion/inversion of chromosome 20 (5/10 patients), while most frequent point mutation is TP53 mutation; the mechanisms of synergy of these alterations are unknown.

Concerning the rare event of ETV6 translocations, only two of our four cases manifested eosinophilia, showing that eosinophilia is not a steady finding with ETV6 fusions, but appears in a subset of cases due to specific pathophysiologic consequences of the rearrangement present or even to other lesions. This is the third time overall, to our knowledge, that the t (8;12) (q13; p12-13) translocation of patient 1 is reported, with previous reports having sequenced it down to an ETV6-NCOA2 fusion gene, associated with T-ALL or biphenotypic T-ALL/AML [17, 18]. These previous reports of the ETV6-NCOA2 fusion gene did not report eosinophilia, which could therefore be associated to the additional t (8;21) rearrangement present in patient 1 or to undetected genetic alterations. Less than ten cases of the rearrangement CHIC2-ETV6 of patient 2 have so far been reported, showing an out-of-frame rearrangement of the two genes, with the cases reported corresponding to AML or MDS-IB, with the conjecture that increased expression of

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the gene GSX2, a HOX-similar gene, adjacent to the breakpoint, could be central to leukemogenesis [19–21]. The translocation t (1;12) (p36; p13) of patient 3 has previously been reported once, to the best of our knowledge, with sequencing showing an ETV6-MDS2 fusion gene lacking critical functional domains of ETV6 (downstream of exon 2) and suggesting loss of function of the translocated ETV6 allele in the corresponding AML case [22]. Patient 4 case is one of less than 20 in the literature of an ETV6-ACSL6 fusion, with all cases presenting myeloproliferative neoplasm with eosinophilia, a trait that could be related to aberrant induction, from the ETV6 5′ region, of the IL-3 gene located not far from the 5q31 breakpoint [23–25]; ACSL6 itself codes under normal circumstances for an acyl-CoA synthetase [26]. In our patient, it is plausible to hypothesize that the NPM1 mutation had been a late subclonal event leading to transformation of the myeloproliferative neoplasm. In summary, our series confirms the biphenotypic T/AML nature of acute leukemia associated to ETV6-NCOA2 rearrangement, the association of the t (1;12) (p36; p13) translocation and of the CHIC2-ETV6 fusion with MDS/AML, and the association of the ETV6-ACSL6 rearrangement with myeloproliferative neoplasm with prominent eosinophilia.

Mutation of the non-deleted/non-rearranged ETV6 allele was present in two cases of our series and seemed subclonal, if one compares the allele burden of the ETV6 point mutation to the percentage of metaphases/nuclei with ETV6 deletion or translocation. In the literature, biallelic hits on ETV6 in myeloid disease are not frequently encountered, with haploinsufficiency being the rule [20], whereas in the case of B-ALL with ETV6-RUNX1, deletions of the ETV6 locus are sometimes described in the non-rearranged allele [27, 28]. Decoding the mechanisms of disease related to ETV6 haploinsufficiency or rearrangements is important for the understanding of the pathogenesis of myeloid and lymphoid neoplasms and fundamental research must be guided by cues of clinical observation.

Statement of Ethics

This retrospective study protocol was reviewed and approved by the Ethics Committee of the Canton de Vaud (CER-VD), approval number 2022-00792. Specific written informed consent of the patients was not required, according to the decision of the CER-VD. However, use of patient data, including genetics, was authorized by the CER-VD for patients having given informed consent for use of their clinical and laboratory data (obtained for diagnostic and follow-up purposes) for research (that is, patients having signed the "general consent form for research" of our institution). For patients deceased before the start of this study and not having had the occasion to sign either consent or refusal of our "general consent form for research," the CER-VD granted exemption (ref. number 2022-00792) from written consent and allowed use of their data.

Conflict of Interest Statement

The authors have no relevant conflicts of interest to declare.

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Author Contributions

V.P. collected clinical data, evaluated the correlation of genetics results with clinical data, and wrote the manuscript. J.S. and I.S. interpreted and collected data of genetics analyses. S.B. collected clinical data and reviewed the manuscript.

Data Availability Statement

Additional clinical and laboratory data to those available in Table 1 are available upon request. Data are not publicly available due to ethical reasons. Further inquiries can be directed to the corresponding author.

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