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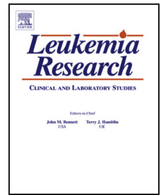

Isolated +15 in bone marrow: Disease-associated or a benign finding?

Rashmi Shivani Goswami, Cynthia S. Liang[1], Carlos E. Bueso-Ramos, Shimin Hu, Maitrayee Goswami, C. Cameron Yin, Gary Lu, L. Jeffrey Medeiros, Guilin Tang*

Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA

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ABSTRACT

It has been controversial if trisomy 15 (+15) as an isolated clonal cytogenetic abnormality in bone marrow (BM) is disease-associated or a benign finding. To answer this question, we retrospectively reviewed our cytogenetic archives and identified 31 patients with isolated +15. Four patients presented with acute myeloid leukemia (AML), +15 was the major clone (56–95% of interphases) in BM and the clonal size of +15 was correlated with blast burden and disease status. For the remaining 27 patients, +15 was a minor clone (3–24% of interphases) in BM. Eighteen patients had a history of cytotoxic therapies and developed +15 after a median latency interval of 34 months. Six patients had BM involvement by lymphoma or myeloma, and +15 was exclusively detected in myeloid and erythroid cells, not in lymphoma or myeloma cells. With a median follow-up of 28 months, none of these 27 patients had clinical or morphological evidence of myelodysplastic syndromes. We conclude that +15 can be associated with AML, but more often isolated +15 presents as a minor clone in BM, and may not be disease associated. Clinical follow-up rather than an immediate therapeutic intervention seems most appropriate for non-leukemic patients with isolated +15.

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1. Introduction

Trisomy 15 (+15) as a sole abnormality is very uncommon, detected in ~0.2% of patients suspected of having hematological disorders [1]. +15 is commonly detected in elderly patients and its occurrence has been frequently associated with loss of chromosome Y (−Y) [1–6]. +15 has been reported in bone marrow (BM) with various types of hematological diseases, such as acute myeloid leukemia (AML), myelodysplastic syndromes (MDS), aplastic anemia, and lymphoid neoplasms [1,4–9]. In some of the reported cases, +15 emerged following cytotoxic therapies, raising the concern of therapy-related myeloid neoplasms (t-MN). However, two studies have shown that +15 does not appear to be associated with any intrinsic bone marrow disease [2] and the authors have argued that +15 might be an aging effect, similar to −Y [5].

In this study, we retrospectively reviewed 31 patients with isolated +15 observed in the past 12 years in our institution. With the largest series of patients reported and a long length (median of 28 months) of follow-up, we sought to determine if +15 is disease related or a benign finding in bone marrow.

2. Materials and methods

2.1. Patients

We searched the Clinical Cytogenetics Laboratory database at The University of Texas MD Anderson Cancer Center during 2003 to 2014 for +15 as the sole clonal abnormality or in combination with acquired −Y. A detailed chart review was conducted in all patients. All samples were collected following institutional guidelines with informed consent in accordance with the Declaration of Helsinki.

2.2. Laboratory data and bone marrow assessments

Complete blood cell counts (CBC) at the time of +15 detection and during follow-up were reviewed. Peripheral blood (PB) smears, BM aspirate smears and trephine biopsy specimens were evaluated for morphologic evidence of dysplasia. BM cellularity and the percentage of blasts in PB and BM were also assessed. Involvement of BM by primary cancer was evaluated by morphology, immunohistochemistry and/or flow cytometry immunophenotyping analysis.

2.3. Conventional chromosomal analysis

Conventional chromosomal analysis was performed on G-banded metaphase cells prepared from unstimulated 24 and 48 h cultures, or unstimulated 24 h and mitogens stimulated 72 h BM aspirate cultures using standard techniques. Mitogens included 12-O-tetradecanoylphorbol-13-acetate, interleukin 4, lipopolysaccharide, and oligonucleotides. Twenty metaphases were analyzed and the results were

* Corresponding author at: Department of Hematopathology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030-4009, USA. Tel.: +1 713 792 5870; fax: +1 713 563 3166.
E-mail address: gtang@mdanderson.org (G. Tang).

[1] This author conducted this project as summer intern at MD Anderson Cancer Center.

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reported using the International System for Human Cytogenetic Nomenclature (ISCN 2013) [10].

2.4. Fluorescence in situ hybridization (FISH) or combined morphologic and FISH analysis

FISH was performed in all cases with CEP15 probe (15p11.2, spectrum green, Abbott Molecular) using standard method on cultured cells or direct smear. Combined morphologic and FISH analysis was performed on a subset of cases with the methods described previously [11] with minor modifications. In brief, morphologic evaluation and image capture were performed on BM aspirate smears with Wright-Giemsa stain (100×); smears were then destained using 1% acid alcohol, followed by protease II (Abbott Molecular) treatment and hybridization with CEP15 probe. Two hundred nuclei were counted and percentage of +15 cells was calculated. The target cell populations were captured under fluorescent microscope. The positive cutoff for +15 established in our lab is 3%.

3. Results

3.1. Patients

Trisomy 15 as a clonal abnormality presents in ~1% of patients by conventional cytogenetic tests at our institute (~11,000 conventional cytogenetic tests in ~4500 patients per year, with >95% specimen of BM and PB). Trisomy 15 is mostly associated with a complex karyotype (92% of cases), and is rare as an isolated abnormality (~5% of all cases with +15; <0.1% of all cases having conventional cytogenetics). We identified 31 patients with +15 (with or without −Y) as the sole clonal cytogenetic abnormality at our institution in the past 12 years and formed the study group. There were 22 male and 9 female patients, with a median age of 68 years. Among these patients, 18 patients received various cytotoxic therapies for their prior malignancies, which included AML (n = 4), chronic lymphocytic leukemia (n = 3), follicular lymphoma (n = 3), diffuse large B-cell lymphoma (n = 3), plasma cell neoplasms (n = 2), marginal zone lymphoma (n = 1), mantle cell lymphoma (n = 1), and breast cancer (n = 1) (Table 1). Of the remaining 13 patients, four patients were diagnosed with *de novo* AML, one patient with myeloproliferative neoplasm (MPN), three patients with cytopenia for MDS evaluation, and five patients with lymphoma/myeloma (Table 2). Of note, two patients (cases 13, 17) were included in our previous study [12].

3.2. Laboratory data and morphological findings

Of the 18 patients (cases 1–18) with a history of cytotoxic therapies, at the time +15 was detected, the median of white blood cell count (WBC) was 3.8×10^9/L (range: $3.2–8.4 \times 10^9$/L); hemoglobin level 12.9 g/dL (range: 9.7–15.1 g/dL), and platelet count 129×10^9/L (range: $83–242 \times 10^9$/L). No circulating blasts were present in any of the patients. The median of BM cellularity was 40% (range: 10–60%). The BM blasts were less than 5% (0–3%). Case #8 showed mild dysmegakaryopoiesis (small and hypolobated megakaryocytes); and the remaining cases showed no morphologic evidence of dysplasia. Two patients (cases 7 and 17) had positive BM infiltrate by lymphoma/myeloma.

Four patients (cases 19–22) presented as AML, with one case of AML without maturation (AML-M1) (case 21) and three cases of AML with maturation (AML-M2) (cases 19, 20 and 22). Patient 19 had *DNMT3A* and *IDH2* mutation, and patients 21 and 22 had *FLT3-ITD* mutation. No case had *NPM1* mutation. Patient 20 had no molecular mutation analysis.

One patient (case 23) showed PB and BM features consistent with a myeloproliferative neoplasm, best classified as chronic neutrophilic leukemia. Three patients (cases 24–26) presented with cytopenia, the PB and BM showed no diagnostic features of MDS. Five patients (cases 27–31) underwent BM biopsy for lymphoid/plasma cell neoplasms, 4 (cases 27–30) had a positive BM

Table 1
Demographic, clinical, and cytogenetic features of 18 patients with prior cytotoxic therapies.

Case	Sex	Age (Y)	Primary disease	Cytotoxic therapies	Inter. (mon)	Abnormal clone*	FISH	Detectable times	Dis-appear	Lasted (mon)	FU⁺ (mon)	Out-come
1	M	69	ALL IR	Chem#1	12	47,XY,+15[2]	5%	2	Yes	10	9	ACR
2	M	70	AML IR	Chem#2	14	45,X,−Y[2]/46,X,−Y,+15[5]	13%	6	No	66	67	ACR
3	F	63	AML IR	Chem#3, SCT	54	47,XX,+15[2]	5%	2	Yes	24	25	ACR
4	F	60	AML IR	Chem#3	8	47,XX,+15[2]	3%	1	Yes	3	7	ACR
5	M	73	CLL	Chem#4	17	47,XY,+15[2]	5%	4	No	36	41	Died
6	M	65	CLL	Chem#4, SCT	53	47,XY,+15[6]	17%	1	Yes	5	24	Died
7	M	72	CLL	Chem#4	6	47,XY,+15[2]	13%	1	NA	NA	3	AWD
8	M	76	FL	Chem#5	141	45,X,−Y[3]/47,XY,+15[4]	10%	1	NA	NA	15	AWD
9	M	67	FL	Chem#5	83	46,X,−Y,+15[4]	10%	1	NA	NA	5	AWD
10	M	71	FL	Chem#5, SCT	190	46,X,−Y,+15[3]	4%	1	NA	NA	8	ACR
11	M	75	MCL	Chem#5	7	45,X,−Y[6]/46,X,−Y,+15[4]	11%	1	NA	NA	10	Died
12	M	61	DLBCL	Chem#5, #1	25	47,XY,+15[2]	4%	1	Yes	4	46	ACR
13	M	61	DLBCL	Chem#5, SCT	79	46,X,−Y,+15[4]	11%	6	Yes	125	149	Died
14	M	52	DLBCL	Chem#1	62	47,XY,+15[2]	8%	2	Yes	24	31	ACR
15	M	65	MZL	Chem#6	35	46,X,−Y,+15[8]	23%	2	No	92	116	ACR
16	F	67	Plasmacytoma	Chem#7, R, SCT	9	47,XX,+15[5]	15%	3	No	21	30	Died
17	F	59	Myeloma	Chem#7, SCT	36	47,XX,+15[2]	24%	2	No	16	35	Died
18	F	65	Breast cancer	Chem#8, R	33	47,XX,+15[5]	20%	2	No	2	2	ACR

ACR, Alive in complete remission; AML: acute myeloid leukemia; AWD, alive with disease; ALL: acute lymphoblastic leukemia; Chem#1: hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with high dose methotrexate and cytarabine); Chem#2: FLAG (fludarabine, cytarabine, G-CSF); Chem#3: cytarabine, idarubicin; Chem#4: FCR (fludarabine, cyclophosphamide, rituximab); Chem#5: R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone); Chem#6: R-FND (rituximab, fludarabine, novantrone, decadron); Chem#7: thalidomide, dexamethasone, Velcade; Chem#8: docetaxel, adriamycin, cyclophosphamide; CLL: chronic lymphocytic leukemia; DLBCL: diffuse large B cell lymphoma; F: female; FL: follicular lymphoma; Inter: interval from the initiation of cytotoxic therapy to the detection of trisomy 15; IR: in remission; M: male; MCL: mantle cell lymphoma; mon: months; MZL: marginal zone lymphoma; NA: no answer; R: radiation therapy; SCT: stem cell transplant.

* 20 metaphases were analyzed. The normal diploid clone was not listed here.

⁺Follow-up time after trisomy 15 was detected.

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