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Clinical significance of acquired loss of the X chromosome in bone marrow

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ABSTRACT

Acquired loss of the X chromosome (-X) as a sole abnormality is detected rarely in bone marrow (BM) and its clinical importance remains largely unknown. We studied 38 patients with isolated -X in BM. All patients were women, with a median age of 71 years. At the time of -X detection, BM was positive for myeloid neoplasm in 14 patients, lymphoma/myeloma in 10 patients, and was normal in 14 patients. -X was detected as a major clone in 15 patients (11 of them had myeloid neoplasm) and a minor clone in 23 patients. Combined morphologic and FISH analysis was performed in 16 cases, -X was detected in myeloid/erythroid cells in all 16 patients and in lymphocytes in 15 patients. With a median of 23 months follow-up, none of the patients with a negative BM or BM with involvement by lymphoid neoplasms developed a secondary myeloid neoplasm. We conclude that isolated -X is a rare finding in BM. In majority of patients, -X presents as a minor clone and is likely to be an aging effect or a benign finding; whereas when -X presents as a major clone in BM, it is often disease associated.

1. Introduction

Numerical abnormalities of the sex chromosomes (chromosomes X and Y) are the most common types of constitutional chromosomal aneuploidy, with a frequency of 1 in 500 live births. This may be due to the fact that such abnormalities of sex chromosomes have less severe clinical consequences and are therefore more compatible with life. Potential reasons for these less severe clinical consequences include inactivation of one copy of X chromosome in female and the small number of genes on the Y chromosome in male [1].

Acquired loss of the Y chromosome (-Y) is a relatively common finding in bone marrow (BM) in elderly men and is often considered as an aging effect or a benign finding [1–3]. Acquired loss of the X chromosome (-X) has been mostly reported in older women (>65 years) in phytohemagglutinin (PHA) stimulated peripheral blood (PB) T lymphocytes [1,4,5]. However, the clinical impact of -X as a sole chromosomal abnormality in BM has been assessed rarely. So far, only a few cases with isolated -X in BM have been reported in patients who had acute lymphoblastic leukemia (ALL) [6], myelodysplastic syndromes (MDS) [7], acute myeloid leukemia (AML) [8] and chronic lymphocytic leukemia [9]. Due to its rarity, the clinical importance of isolated -X in BM is largely unknown.

In this study, we reviewed 38 patients with acquired isolated -X in BM in the past 15 years in our institution. With a median of 23 months of clinical follow-up and applying combined morphologic-fluorescence *in situ* hybridization (FISH) analysis, we sought to determine if -X is a disease-related clonal abnormality or an aging/benign change in BM.

2. Materials and methods

2.1. Patients

We searched the Clinical Cytogenetics Laboratory database at The University of Texas MD Anderson Cancer Center during 2000 to July 2015 for cases with -X as a sole abnormality in BM. Patients with -X as a constitutional abnormality (Turner syndrome) or a prior history of allogeneic stem cell transplant (SCT) before -X detection were excluded from this study. Detailed chart review was performed on all patients. All clinical and laboratory information were collected and reviewed following institutional guidelines with informed consent in accordance with the Declaration of Helsinki.

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2.2. Laboratory data and bone marrow assessment

Complete blood cell counts (CBC) at the first time of -X detection and during the follow-up were reviewed. PB smears, BM aspirate smears and trephine biopsy specimens were evaluated for BM cellularity, percentage of blasts, dysplasia, and involvement by primary cancer. Flow cytometry immunophenotyping and/or immunohistochemistry analysis were performed to evaluate the involvement by primary cancer.

2.3. Conventional chromosomal analysis

Conventional chromosomal analysis (karyotyping) was performed on G-banded metaphase cells prepared from unstimulated 24 h and 48 h BM aspirate cultures (for myeloid neoplasms), or unstimulated 24 h and mitogens stimulated 72 h BM aspirate cultures (for lymphoid neoplasms) using standard techniques. Mitogens included lipopolysaccharide, oligonucleotides, or 12-*O*-tetradecanoylphorbol-13-acetate. Cases with three or more metaphases showing -X were considered as clonal abnormality. Twenty metaphases were analyzed and the results were reported using the International System for Human Cytogenetic Nomenclature (ISCN 2013) [10]. Clone of -X in ≥55% of cells was defined as major clone, while in ≤50% of cells as a minor clone.

2.4. Combined morphologic and FISH analysis

Combined morphologic and FISH analysis was performed on a subset of cases using methods described previously with minor modifications [11]. In brief, morphologic evaluation and image capture were performed on BM aspirate smears with Wright-Giemsa stain (×100); smears were then de-stained using 1% acid alcohol, followed by protease II (Abbott Molecular) treatment and hybridization with XY (DXZ1,DYZ1) dual color probe (Abbott Molecular). The target cell populations were captured under fluorescent microscope. Four hundred nuclei were counted and percentage of X/XX cells was calculated.

3. Results

3.1. Patients and clinical information

A total of ~150,000 cases with chromosomal analysis were performed in our institution during a 15-year time frame, a loss of X chromosome (-X) was detected in 3174 cases, representing ~2% of all patients tested. However, only 52 (1.6%) cases showed -X as the sole abnormality; all the other patients (98.4%) had one or more additional chromosomal abnormalities. Among these 52 patients, 12 patients received allogeneic SCT as a treatment for their lymphoid or myeloid neoplasms, 9 of them were sex-mismatched SCT. Isolated -X was detected after SCT. However, we do not have detailed information about donors and we do not know whether the -X clone was derived from donor cells or receipt cells. Besides, a constitutional abnormality (Turner syndrome) could not be excluded in the other two patients. Therefore, these 14 patients were not included in our study. The remaining 38 patients constituted the study group.

All 38 patients were women with a median age of 71 years (range, 40–85 years), of whom 36 (95%) patients were older than 50 years. Nine patients had a primary diagnosis of a myeloid neoplasm, 21 had various lymphoid neoplasms, 5 had two types of malignancies, 2 had systemic mastocytosis, and 1 patient had cytopenia. Fourteen patients had received various cytotoxic therapies for their malignant neoplasms before -X detection, with a median interval of 20 months (range, 1–173 months) from the initiation of cytotoxic therapies to the detection of -X (Table 1).

3.2. Pathological findings in peripheral blood and bone marrow

At the time of -X detection, the BM was positive for myeloid neoplasms in 14 patients (1 patient had concurrent peripheral T cell lymphoma); all patients except case 13 had an abnormal blood count. The BM was involved by lymphoma/myeloma in 11 patients, 3 with minimal (5–10%) involvement (cases 10, 24, 26) and 8 (cases 17–23, 25) with 20–95% of lymphoma/myeloma cells. Mild dysplasia was observed in 2 patients, case 15 had AML in remission but with leukopenia and case 16 had monoclonal B lymphocytosis and anemia. The BM was negative for dysplasia or primary cancer involvement in 12 patients (cases 27–38) (Table 1).

3.3. Conventional cytogenetic analysis

Prior to detection of -X, 12 patients had a karyotype available: 6 (cases 1, 3, 12, 14, 25, and 36) had a normal female diploid karyotype and the other 6 had chromosomal abnormalities other than -X, including del(11)(q23) in case 9, t(8;16)(p11.2;p13.3) in case 15, complex karyotype in cases 19, 22, and 34, and t(9;22)(q34;q11.2) in case 27

At the time of -X detection, the number of metaphases showing a karyotype of 45,X,-X ranged from 3 (15%, 3/20) to 20 (100%, 20/20), with a median of 6 (30%, 6/20). -X presented as a major clone in 15 patients, 11 of them (73%) with myeloid neoplasms, 1 (7%) with mild dysplasia, 1 (7%) with CLL, and 2 (13%) with a morphologically negative BM. The median number of metaphases with -X was 20 (100%) in patients with myeloid neoplasms, which was significantly higher than 5 (25%) in patients with a negative BM and 4 (20%) in patients with BM involvement by lymphoma/myeloma (Table 1).

3.4. Combined morphologic and FISH analysis

Combined morphological and FISH studies were performed in 16 patients, including 7 with AML, MDS, or chronic myelomonocytic leukemia (CMML); 3 with chronic lymphocytic leukemia (CLL) (lymphocytes were 28%, 74% and 95% in cases 17, 18, 19); 2 with myeloma (plasma cells were 10% in case 24 and 21% in case 25); 1 with dysplasia; and 3 patients with negative BM (Table 2). The percentage of nuclei with -X detected by interphase FISH was slightly lower but correlated proportionally with the percentage of metaphases with -X (median: 85% *vs.* 65%, r = 0.958). Loss of X was detected in myeloid derived lineages in all patients, but in a significantly higher percentage of cells in patients with myeloid neoplasms compared with patients who had a negative BM or BM involved by lymphoma/myeloma ($P < 0.001$). -X was also detected in lymphocytes in all patients except case 31, a 40-year-old woman with untreated diffuse large B cell lymphoma (DLBCL) who did not have BM involvement. The overall percentage (0–85%) of lymphocytes with -X was lower than in myeloid derived cells, with the major discordance observed in patients with myeloid neoplasms (case 1–7). On the other hand, -X was detected at a similar frequency in myeloid derived cells and lymphocytes in patients with lymphoid neoplasms or patients with a negative BM (Table 2, Fig. 1).

3.5. Follow-up and outcome

The median follow-up interval was 23 months (range, 1–161 months) after detection of -X. Twenty-one patients underwent at least one conventional chromosomal analysis during follow up (median 2, range 1–7). -X was persistent in 15 patients and became undetectable in 6 patients during the follow-up. The median time that -X was detected was 12 months (range 1–125).