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Original investigation

Polysomy 8 Syndrome: A Distinct Clinical Entity Comprising of Myelomonocytic/Monocytic Lineage Involvement in Acute Leukemia

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Abstract

Purpose: Cytogenetic abnormalities have been proven to be among the most valuable prognostic indicators in leukemia, allowing the stratification of patients in risk groups. We describe a patient diagnosed as AML-M5, with myeloid sarcoma and tetrasomy 8 as the sole chromosomal abnormality. We confirm that the presence of polysomy 8 in myeloid lineage malignancies is associated with a distinct clinical entity comprising of myelomonocytic/monocytic lineage involvement, poor prognosis and high incidence of myeloid sarcoma. In aim to obtain a detailed description of this clinical entity, literature of polysomy 8 cases has been reviewed.

Methods: Cytogenetic analysis was performed on bone marrow samples directly after aspiration and following 24 h short term culture. Fluorescence *in situ* hybridization (FISH) analyses were performed at complete remission stage on interphase nuclei from bone marrow.

Results: Cytogenetic analyses revealed tetrasomy 8 as the sole karyotipic change in all metaphases. The presence of tetrasomy was confirmed with *C-MYC* (8q24), *AML1/ETO (ETO*-8q21) and chromosome 8 centromeric probe cocktail.

Conclusion: Recognition of the polysomy 8 syndrome will allow for the development of a standardized approach to these patients; as well as stimulating further research into the biology of the disorder that will allow for the development of better therapeutic strategies.

Keywords: Tetrasomy 8, Acute Myeloid Leukemia, AML-M5, Myeloid Sarcoma, Polysomy 8 Syndrome, Cytogenetics

INTRODUCTION

Cytogenetic analysis of bone marrow cells reveals non-random chromosomal aberrations associated with distinct subsets of hematological malignancies. Thus karyotypes of patients provide powerful diagnostic/prognostic indicators for leukemia and lymphoma subgroups. The WHO 2008 classification of tumors of the hematopoietic system uses common genetic findings in addition to morphologic, clinical and immunophenotypic features to define distinct diagnoses (1). However, there is a lack of consensus as to the diagnostic and prognostic significance of rare non-random aberrations. Considering that cytogenetics provides the framework for the development of risk stratified therapeutic strategies (2), it is extremely important that recurrently reported, less frequent karyotypes with their associated clinical and cellular phenotypical/morphological features should be recognized to establish better standardized treatment approaches and patient management. Polysomy 8 is one of such rare karyotypic abnormalities that define a distinct biological subgroup of myeloid hematopathologies. It has been associated with myelomonocytic/monocytic lineage involvement, poor prognosis and high incidence of myeloid sarcoma. We describe a patient diagnosed as AML-M5, with myeloid sarcoma and tetrasomy 8 as the sole chromosomal abnormality.

Patient

59 years old male patient was admitted to an outpatient clinic with complaints of progressive fatigue and dyspnea on exertion. Blood count revealed pancytopenia and the patient was referred to our hematology department. At admission the differential blood count was as follows: Hb: 7 g/dl, Hct: 20.9%, WBC: 1900/µl, Neu: 700/µl, Ly: 1100/µl, Mo: 100/µl, Platelet: 81000/µl. Past medical history revealed a basal cell carcinoma at the left frontal region of the head which was radiated after excision, two years before admission. No other ongoing medication or chronic illness was recorded. Upon physical examination, neither lymphadenopathy nor organomegaly was detected. There was a guttate, hyperemic and squamated purple papular lesion,

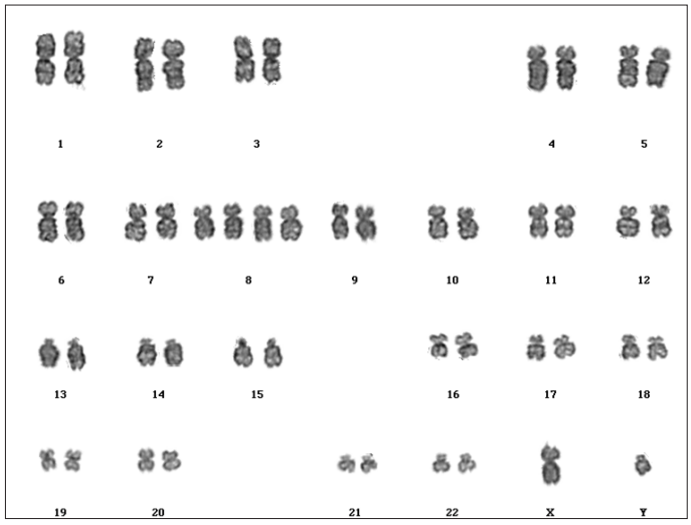

Figure 1. 48,XY,+8,+8 karyotype of pre-treatment bone marrow sample.

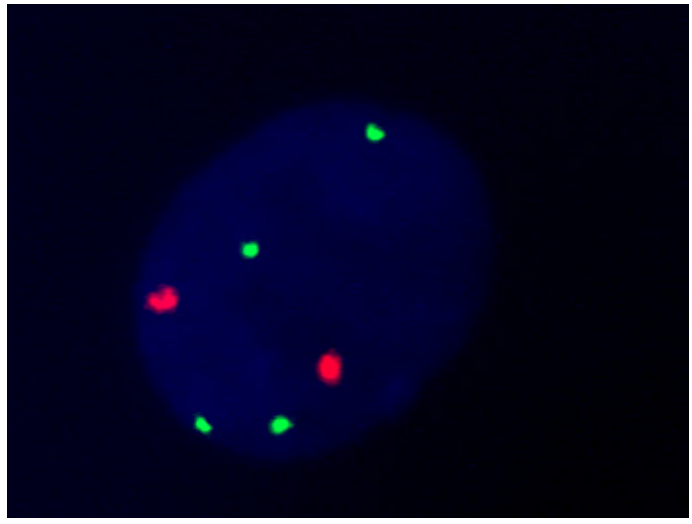

Figure 2. An interphase nucleus with four green (ETO/8q21.3) and two red (AML1/21q22.12) signals due to the presence of tetrasomy 8.

approximately 1 cm in diameter on the left frontal region of the forehead. Peripheral blood smear revealed 80% monoblasts. Bone marrow aspiration revealed an 80–90% blastic infiltration with suppressed erythropoiesis and megakaryopoiesis. Based on blast morphology, FAB M5 AML was diagnosed. Flow cytometric analysis of the blastic population was also consistent with a pure monoblastic cell population. The pathological evaluation of the skin lesion revealed a myeloid sarcoma. The patient was put on 7 + 3 induction regimen which included cytarabine (200 mg/m^2 × 2/7 days) and idarubicin (12 mg/m^2/day). After the first cycle of induction regimen, complete remission was achieved. But disease was relapsed after the second cycle of induction therapy. Allergenic bone marrow transplantation is recommended.

METHODS

Cytogenetics

Cytogenetic analysis was performed on bone marrow samples directly after aspiration and following 24 h short term culture (McCoy's 5A culture medium, 10% FBS) without mitotic stimulation. Harvesting of the cells and slide preparation were done according to standard methods. Chromosomes were banded with GTG technique. Twenty metaphase spreads were analyzed and karyotyped in accordance with ISCN 2013 (3).

Molecular Genetics

Fluorescence *in situ* hybridization (FISH) analyses were performed at complete remission stage on interphase nuclei from bone marrow culture as described above. The AML1/ETO translocation, dual fusion (Cytocell Ltd, Cambridge, UK), the chromosome 8 satellite enumeration (C-MYC/SE 8, KREATECH Diagnostics, The Netherlands), and the MLL break apart (Kreatech, Amsterdam, Netherlands) probes were used. At least 200 cells were analyzed for each probe cocktail.

RESULTS

All metaphases examined on the bone marrow sample obtained prior to treatment revealed tetrasomy 8 as the sole karyotipic change (Fig. 1). No metaphase with trisomy 8 was observed. Post-treatment bone marrow cytogenetic analysis during remission displayed normal karyotype.

FISH analysis with *AML1/ETO* revealed tetrasomic signals for ETO (8q21) in 5.5% of the cells analyzed (Fig. 2). The presence of tetrasomy was confirmed with *C-MYC* (8q24) and chromosome 8 centromeric probe cocktail. FISH analysis with *MLL* (11q23) break apart probe ruled out a cryptic MLL gene rearrangement (intact signals were observed).

DISCUSSION

Although trisomy 8 is one the most common chromosomal abnormalities observed in hematological malignancies (4), polysomy 8 is a rare, non-random numerical abnormality associated with myeloid malignancies such as acute myelod leukemia (AML), myelodysplastic syndromes (MDS) and rarely myeloproliferative disorders (MPDs) (4, 5). Tetrasomy 8 is the most common of the polysomies, first described in AML in 1987 (6). Since then it has been reported in 129 cases comprising of AML, MDS and MPDs as a sole anomaly or part of a complex karyotype. To date there are only two case where tetrasomy 8 was reported in patients with lymphoid lineage pathology (7, 8). Aside from these two cases, common characteristics of patients-irrespective of their clinical presentation-are: a predominant myelomonocytic/monocytic lineage involvement; poor prognosis (median survival 7 months) and a high incidence of extramedullary involvement (myeloid sarcoma), mainly as skin lesions. In 2005 Beyer et al. reported a slight male gender predominance; in addition to *MLL* gene rearrangements described in 19 of the 103 published cases (16%) (9). Our literature search provided 11 new patients with MLL

gene rearrangements, bringing the total to 30 cases out of 129 (23.2%) (9, 10–14). The high occurrence of MLL rearrangements possibly contributes to the adverse prognosis observed in patients with this genotype.

In most cases in which polysomy 8 was reported as the only karyotypic abnormality, cryptic MLL rearrangements-when investigated-were found to be rare (9). Our results are in line with the previously published cases in this respect.

Trisomy 8 was undetectable at diagnosis with conventional cytogenetics in 75% of all reported cases. In nearly all cases that were further examined with FISH, a concurrent trisomy 8 clone was also detected. It has been suggested that tetrasomy 8 occurred subsequent to trisomy 8 by serial clonal evolution from a normal karyotype to tetrasomy 8 (8, 13, 15–18). An alternative explanation would be the segregation lag of all four chromatids during mitosis and trisomy 8 resulting from the subsequent loss of one of the four chromosome 8 s' . In the patient presented here, conventional cytogenetics was performed at presentation and revealed tetrasomy 8 as a sole anomaly in all metaphases examined. FISH analysis was carried out on a post-treatment sample and tetrasomy 8 was detected in approximately 6% of the interphase nuclei; no trisomy 8 clones were observed.

The observation that the trisomy 8 clone is usually not detected by conventional cytogenetics has been proposed to be a result of the high proliferative capacity of the tetrasomy clone (19). This proliferative advantage of the tetrasomy clone is one of the features that is thought to contribute to the aggressive phenotype and poor prognosis. The involvement of the chromosome 8 in myeloid leukemias suggests that dosage sensitive, cell type specific genes are localized on chromosome 8. These genes located on chromosome 8-such as *c-MYC* in 8q24, MOS in 8q22, *ETO* in 8q21.3-may play a significant role in the biology of myeloid lineage disorders via increased gene dosage leading to over-expression (14). Interestingly the aggressive phenotype and poor prognosis associated with tetrasomy 8 is not limited to hematological malignancies. There have been two cases of Ewing sarcoma, where an *in vitro* proliferative advantage and aggressive behavior of the tetrasomy 8 clone has been reported (20, 21).

Numerical aberrations of chromosome 8 from trisomies to polysomies, have been describes in nearly all myeloid lineage disorders, corresponding predominantly to neoplasms with monocytic differentiation (17, 22, 23). Myelomonocytic/ monocytic lineage involvement is also a characteristic of polysomy 8 cases. It is tempting to speculate that in the absence of signals required for differentiation of the granulocytic lineages, the monocytic lineage is the default route of differentiation for the myeloblast. Thus, the gain of extra chromosome 8's may cause a block in the differentiation route of granulocytes, skewing cells towards a default myelomonocytic pathway.

Our patient was presented with myeloid sarcoma, another feature observed at a high incidence in patients with polysomy 8 (13, 23, 24). It is not clear how tetrasomy 8 can predispose to the development of an extramedullary disease. One explanation may be the gain or over-expression of genes such as *FAK*, *FGFR1*, *EXT1*, *ASAP1*, *ADAM9*, *HPT1*, *RHOBTB2*, and *SYCL* associated with cell adhesion, cell-cell contacts, migration and extracellular matrix interactions.

In conclusion, we believe there are significant number of cases reported to date to support the presence of a distinct clinical entity: polysomy 8 syndrome (25). The poor prognosis associated with this genotype calls for reconsidering therapeutic options such as considering these patients for allogenic bone marrow transplantation immediately after first remission. Cytogenetic abnormalities have been proven to be among the most valuable prognostic indicators in leukemia, allowing the stratification of patients in risk groups associated with different clinical outcomes. Recognition of the polysomy 8 syndrome will allow for the development of a standardized approach to these patients; as well as stimulating further research into the biology of the disorder that will allow for the development of better therapeutic strategies.

Ethics Committee Approval: All the work herein has been done as part of routine patient care and diagnostics. A separate ethics clearance was not taken.

Informed Consent: Informed consent was obtained from all individual participants included in the study

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – ZY, EY; Design - ZY, EY; Supervision - ZY; Resource - ZY, OGS, IA, OA; Materials –IA,OGS; Data Collection and/ or Processing - ZY, EY, MP, OGS, IA, OA; Analysis and/or Interpretation - ZY, EY, MP; Literature Search- ZY, EY, MP; Writing - ZY, EY; Critical Reviews – OA.

Conflict of Interest: No conflict of interest was declared by the authors.

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