Case Report
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A Case Report of Concurrent *IDH1* and *NPM1* Mutations in a Novel t(X;2)(q28;p22) Translocation in Acute Myeloid Leukaemia without Maturation (AML-M1)

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Abstract

Acute myeloid leukaemia (AML) is one of the fatal haematological malignancies as a consequence of its genetic heterogeneity. At present, the prediction of the clinical response to treatment for AML is based not only on detection of cytogenetic aberrations but also by analysing certain molecular genetic alterations. There are limited in sights into the contribution, disease progression, treatment outcome, and characterisation with respect to the uncommon chromosomal abnormalities leading to AML. Here, we describe the clinical, morphological, cytogenetic, and mutational findings of a 52-year-old female patient with AML without maturation (AML-M1). Conventional karyotyping and spectral karyotyping (SKY) were done on metaphase chromosomes from bone marrow cells at the time of diagnosis. A mutation analysis was performed on the hotspot regions of various genes, including *FLT3, CEBPA, NPM1, RAS, c-KIT, IDH1* and *IDH2*. Cytogenetic and mutation analyses revealed a novel translocation, t(X;2)(q28;p22), with both *NPM1* and *IDH1* mutations. To the best of our knowledge, the presence of both NPM1 and IDH1 mutations in t(X;2)(q28;p22) is a novel finding in AML.

Keywords: *acute myeloid leukaemia, isocitrate dehydrogenase 1, nucleophosmin 1, chromosomal translocation, spectral karyotyping*

Introduction

Acute myeloid leukemia (AML) is a heterogeneous disease with a poor outcome. Approximately 50–60% *de novo cases* of AML are associated with cytogenetic abnormalities, such as translocations, inversions, deletions, duplications, and monosomies (1). Because of its pivotal role in the prognostic stratification in AML, cytogenetic characterisation is essential for proper subclassification, according to the World Health Organization (WHO) (2). Among the different structural chromosomal abnormalities in leukaemia, translocations have been the focus of research since the first recurrent translocation t(8;21) was identified by JD Rowley in 1973. Identification of specific chromosomal translocations is extremely important in diagnosing and predicting treatment outcomes in AML (3). Structural chromosomal abnormalities such as inversions and translocations can generate oncogenic-capable genome segments by bringing together two structurally and functionally distinct genome segments (4). In AML pathogenesis, besides chromosomal abnormalities, mutations in genes also playa pivotal role. Mutation analysis of leukaemia-relevant genes, along with cytogenetic analysis, is beneficial for clinicians in deciding on treatment options, prognosis stratification and minimal residual disease (MRD) monitoring (5). Isocitrate dehydrogenase *1(IDH1)* mutations, which result in alterations in the DNA methylation pattern, are some of the most common methylation-associated mutations in AML and are significantly associated with nucleophosmin1 (NPM1) mutations. Translocations involving sex chromosome X and autosomes are infrequent in AML. Chromosomal translocations involving the Xq and 2p regions have been reported only once in AML, which was a case of AML, not otherwise specified (AML, NOS); this has not yet been reported in AML-M1 (6). Here, we report a novel chromosomal rearrangement t(X;2)(q28;p23) in AML-M1, harbouring mutations in both the *NPM1* and the *IDH1* genes.

Case Report

The patient was a 52-year-old female who presented with a history of a sore throat of two weeks duration. On examination, she had bilateral tonsillar enlargement with ulceration. There was no history of fever or bleeding. Initial investigations revealed haemoglobinof 7.5g/dL, white blood cellcount of 18 000/mm^3, platelet count of 54,000/mm^3 and serum lactate dehydrogenase (LDH) of 738 IU/L. The peripheral smear showed 80% blasts, and bone marrow aspiration was suggestive of AML (AML-M1 FAB subtype), with 90% blasts. The patient was started on induction chemotherapy with a 7/3 regimen (cytosine arabinoside 100mg/m^2 for 7 days and daunorubicin 50mg/m^2 for 3 days). She developed pneumonitis as a complication of post-chemotherapy neutropenia, and a sputum culture grew multidrug-resistant Acinetobacter species. Despite broad-spectrum antibiotics and anti-fungal therapy, she succumbed to complications of neutropenic sepsis on day 9 post-chemotherapy.

Bone marrow aspirate withdrawn at the time of disease diagnosis was used for classical cytogenetic analysis after short-term culture, after receiving official institutional approval. Harvesting and GTG banding were performed as per the standard procedure (7). Karyotypes were described according to the International System for Human Cytogenetic Nomenclature (ISCN) 2013 (8). Twenty metaphases were karyotyped using Cytovision software (Cytovision, USA). Cytogenetic investigation of bone marrow cells showed 46,X,t(X;2)(q28;p23)[16]/46,XX[4] (Figure 1). Spectral karyotyping (SKY), which helps in the differential display of all pairs of human chromosomes, was performed to confirm the chromosomal translocation. A 22 x 22 mm region of the metaphase preparation on one of the GTG slides was hybridised with a SKY probe mixture (ASI, MigdalHa'Emek, Israel). The result was analysed using the SKY system according to the manufacturer's instructions. SKY confirmed t(X;2)(q28;p23) translocation (Figure 2). Determination of mutations in various genes, including *FLT3/ITD, FLT3/D835, CEBPA, NPM1, RAS, c-KIT, IDH1* and *IDH2*, was performed as described previously (9). We found that there were concurrent *NPM1* and *IDH1* mutations in this patient. The patient showed the most common *NPM1* type A(c.860-863dupTCTG) and *IDH1* R132 (c.394C>T; p.R132C) mutations (Figures 3a and 3b).

Figure 1: G-banded karyotype of the bone marrow cells showing 46,X,t(X;2)(q28;p23).

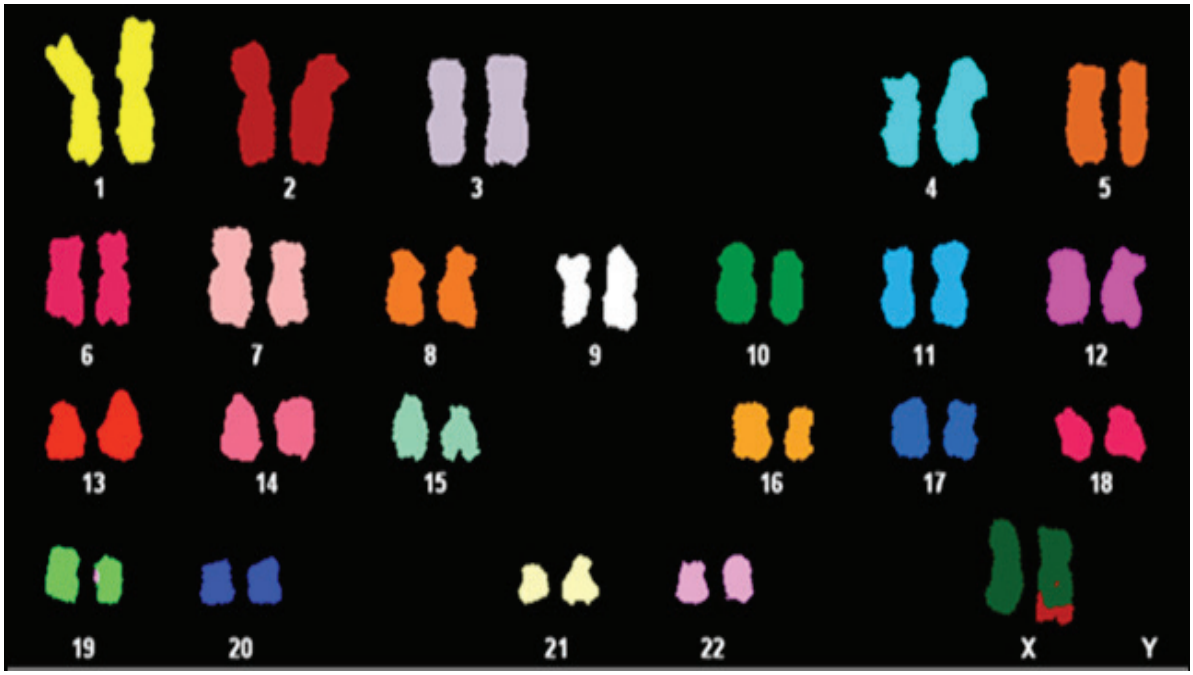

Figure 2: Spectral karyotyping (SKY) of the metaphase spread showing der(X)t(Xq;2p).

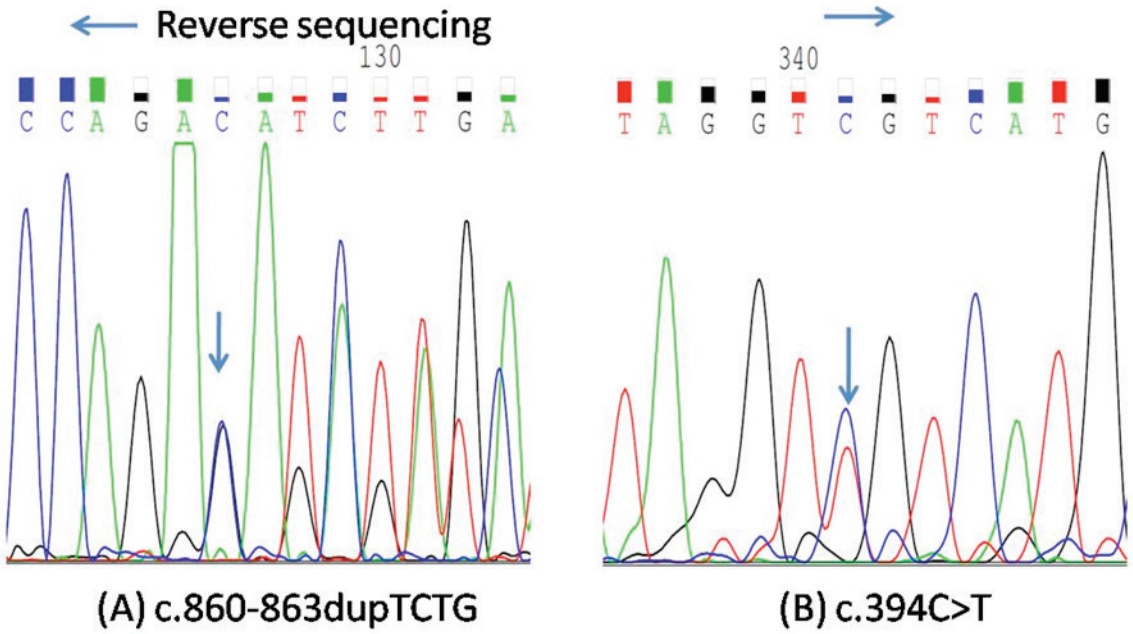

Figure 3: Electropherograms of *NPM1* and *IDH1* mutations; (A) *NPM1* c.860-863dupTCTG, (B) *IDH1* c.394C>T.

Discussion

We identified a novel chromosomal translocation t(X;2)(q28;p23) in AML-M1. Interestingly, a mutation analysis of the commonly mutated candidate genes in AML revealed the presence of mutations in both *NPM1* and *IDH1*, which are usually mutated in normal-karyotype AML (NK-AML).To the best of our knowledge, this is the first case report of a novel translocation harbouring mutations in both of these genes.

Translocations involving chromosomes X and 2 are very rare in AML and have not yet been reported in AML-M1. So far in the literature, eight t(X;2) translocationshave been described in AML (two in AML-M2, one in AML-M4 and five in AML, NOS) (6). Among these, in six reported cases, both the p and q arms of chromosomes X and 2 were involved in the exchange of the genetic materials. Translocation involving Xq and 2p were reported only once in AML in the literature, in a case of AML, NOS with 46,Y,t(X;2)(q13;p21) (6).

The gene-expression patterns of the X chromosome-involved translocations are distinct from autosomal chromosomal translocations. As a result of translocation between an autosome and the X chromosome, there might be a chance of reactivation of the inactivated X-linked gene or silencing of the autosomal gene by the X-chromosome inactivation centre (XIC)(4). Chromosome band Xq28 harbours several genes that play important roles in carcinogenesis, such as a transcription corepressor, *MECP2* (methyl CpG-binding protein 2), in colorectal adenocarcinomas, and a tumour suppressor, *RPL10* (ribosomal protein L10), in prostate adenocarcinomas (4). Very few cancer-causing genes are seen in the 2p22 region. Among these, *BIRC6* (baculoviral IAP repeat-containing 6) in the colon cancer and tumour-suppressor genes, such as eukaryotic translation initiation factor 2-alpha kinase 2 (*EIF2AK2*) and DNA mismatch repair protein mutS homolog 2 (*MSH2*), are the most-studied genes.

IDH1 mutations were significantly more frequent in normal-karyotype AMLs than in those with chromosomal aberrations. In the aberrant karyotypes, there was a higher frequency in trisomy 8. Among the common mutations in AML, *IDH1* mutations were significantly more frequent in cases with *NPM1* mutations. Studies show that IDH1 mutations are associated with a favourable prognosis in AML patients with *NPM1* mutations (10). Approximately 15% of AML patients with *NPM1* mutations harbour non-recurrent chromosomal abnormalities (eg:+8,+21,-Y,del[9q]). Several findings suggested that these chromosomal aberrations or additional mutations were secondary events because of the retention of the *NPM1* mutation during clonal evolution (11).

In the present case, the patient showed a t(X;2)(q28;p23) translocation with *NPM1* and *IDH1* mutation. Despite the favourable prognosis of the *NPM1* with *IDH1* mutations in AML, the patient passed away on day 9 post-chemotherapy. The unfavourable prognosis for this patient might be due to the activation or inactivation of genes involved in the translocation. In the future, molecular characterisation of these types of cytogenetic abnormalities would provide insights into the heterogeneity of genomic rearrangement that further leads to tumourigenesis and would thereby add information to the prognosis, which will help in improved patient management.

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Conflict of Interest

None

Authors' Contributions

Conception and design: SR
Analysis and interpretation of the data: SR, SS, SV
Drafting of the article: SR, SS, SV, SP
Critical revision of the article for the important intellectual content: SR, HS
Final approval of the article and provision of study materials or patient: SP, HS

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