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CASE REPORT

t(1;3)(p36;p21): presentation of a patient with MDS/AML (M2) and review of the literature

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ABSTRACT

t(1;3)(p36;p21) is a recurrent reciprocal translocation found in a subset of myelodysplastic syndrome (MDS)/acute myelogenous leukemia (AML) characterized by trilineage dysplasia, especially dysmegakaryopoiesis and poor prognosis. In the literature, some authors have suggested that this recurrent translocation is closely associated with prior chemotherapy including alkylating agents in various hematologic malignancies. We identified a recurring translocation, t(1;3)(p36;p21), in our patient with MDS/AML(M2), although she had not been given any kind of treatment previously.

Key words: Myelodysplastic syndrome (MDS), acute myelogenous leukemia (AML), translocation, chromosome 1, chromosome 3.

ÖZET

t(1;3)(p36;p21) bulgulu bir MDS/AML(M2) olgu sunumu ve literatür incelemesi

(1;3)(p36;p21) sitogenetik bulgusu, Myelodisplastik Sendrom (MDS)/Akut Myeloid Lösemi (AML) olgularının özellikle dismegakaryopoez ve kötü prognoz ile seyreden bir kısmında gözlenen tekrarlayan bir resiprokal translokasyondur.Bazı yazarlar bu translokasyonun değişik hematolojik kanserlerde alkilleyici ajanlarla yapılan kemoterapiyle sıkı bir ilişkisi olduğunu ileri sürmüşlerdir. Bu çalışmada, daha önce kemoterapi uygulanmamış t(1;3)(p36;p21) bulgulu bir MDS/AML(M2) olgusu sunulmaktadır.

Anahtar sözcükler: Myelodisplastik Sendrom (MDS), Akut Myeloid Lösemi (AML), translokasyon, 1. kromozom, 3. kromozom

INTRODUCTION

Recurrent chromosomal rearrangements are a common theme in the cytogenetics of leukemia and cancer. Often, these rearrangements have prognostic and diagnostic significance. Myelodysplastic syndromes (MDS) comprise a group of hematopoietic neoplasms which manifest as pancytopenias in patients. These cytopenias are frequently associated with hyperplastic marrow with trilineage dysplasia (dyserythropoiesis, dysgranulopoiesis and dysmegakaryocytopoiesis), with variable progression to acute leukemia [1,2]. MDS are associated with a high risk of progression to acute myelogenous leukemia (AML). Cytogenetic analysis is used as an effective tool at diagnosis in MDS, for predicting survival and progression to AML [1,3].

Recently, some authors reported recurrent translocations of t(1;3)(p36;p21) in some patients with various hematologic malignancies. Since most of the patients had a history of chemotherapy before the translocation was detected, they proposed this finding as a cytogenetic abnormality which was associated with therapy-related (t-) leukemias [4-6]. We report here an MDS/AML(M2) case with t(1;3)(p36;p21) without prior chemotherapy.

CASE REPORT

The patient was a 35-year-old female who came to our clinic with headache, leg pain and back pain in May 2002. Her own and family history were unremarkable and she had not taken any medication. She was a secretary with no history of environmental or occupational genotoxic exposure. In her first physical examination no abnormality was found. Hematologic examination results showed 8.4 g/dl hemoglobin, 24% hematocrit, a platelet count of $89x10^9$/L and white blood cell count (WBC) of $24x10^9$/L with 4% blasts, 2% eosinophils, 50% neutrophils, 40% lymphocytes and 4% monocytes. Bone marrow (BM) showed hypogranulation and nuclear abnormalities in myeloid and erythroid precursors [MDS (RAEB-2) according to WHO classification[7]]. The patient was accepted to be in the high-risk group based on IPSS. The bone marrow examination was repeated after a month, which revealed 22% blast cells. Acute leukemia with blastic transformation was diagnosed. A regimen with anthracycline 30 mg/m^2/day for three days and cytosine/arabinoside 100 mg/m^2/day for seven days was commenced, but no remission occurred.

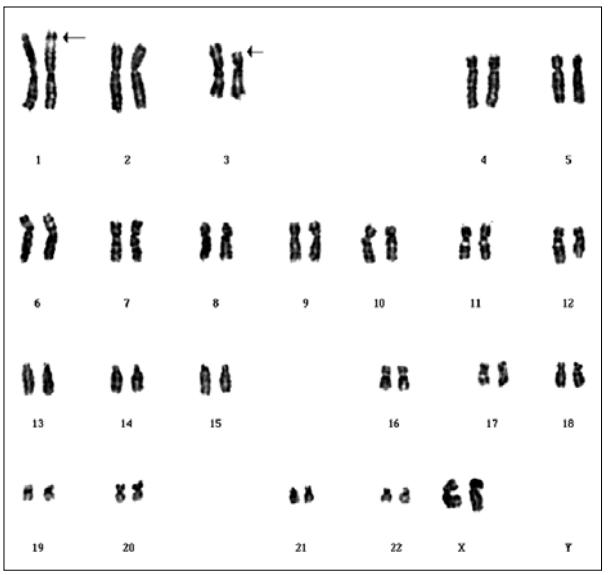

Figure: ???????????

The patient underwent allogeneic bone marrow transplantation (BMT) in January 2003. Two weeks after BMT, the general status of the patient progressively worsened and multiorgan failure developed. The patient died on the 24th day of the transplantation.

CYTOGENETICS

Cytogenetic studies were performed at diagnosis on unstimulated bone marrow cells cultured for 24 hours. Metaphase chromosomes were G-banded by conventional GTL-banding technique and a total of 21 metaphases were analyzed. The karyotype was reported according to the ISCN 1995 [8].

Chromosome analysis of the bone marrow cells at the time of diagnosis revealed 44~46,X X,t(1;3)(p36;p21)[21],-21[3],+mar1[3],+mar2[2] [cp21]. There were also nonclonal abnormalities in 7 out of the 21 cells. An exemplary karyotype is seen in Figure 1.

DISCUSSION

To date, t(1;3)(p36;p21) finding has been observed in 13 patients with different hematological malignancies, as follows: 2 chronic myelogenous leukemia (CML) (1 of accelerated phase), 1

MDS(RAEB), 2 t-MDS, 2 M3-acute nonlymphocytic leukemia (ANLL), 2 acute lymphocytic leukemia (ALL), 1 t-ALL, and 3 non-Hodgkin lymphomas (NHL)(2 follicular and 1 diffuse large cell) [9,6].

Five of these patients had a previous treatment and three of them had alkylating agents in their chemotherapy. Based on these findings, Sato et al.[6] suggested that this chromosomal abnormality could be related to prior exposure to mutagens including alkylating agents.

Thus far, seven cases out of a total number of 13 with t(1;3)(p36;p21) have been reported as not having received any kind of treatment before the detection of the cytogenetic abnormality, and the same condition also applies in our case. Therefore, it seems reasonable to reconsider the conclusion about the relation of the t(1;3)(p36;p21) finding with chemotherapy or mutagen exposure [9].

Although t(1;3)(p36;p21) is quite rare, having been seen in only 14 cases including ours so far, 1p36 and 3p21 breakpoints are involved in different chromosomal abnormalities in various hematological and solid malignancies[9]. This view implies that these chromosomal regions could harbor genes that play important roles in carcinogenesis. It is speculated that molecular biological events may be different from case to case, since t(1;3)(p36;p21) translocations are found in various hematologic malignancies [6].

In their eight-cased series, Sato et al.[6] reported that karyotypes in all cases were complex, and the t(1;3)(p36;p21) existed together with some other cancer-related chromosomal abnormalities.

Our case also had a complex karyotype with clonal -21 and two different marker chromosomes in addition to t(1;3)(p36;p21). Monosomy 21 mosaicism can appear as the sole cytogenetic abnormality in hematological malignancies, but it is rare [10]. Among the few reports with -21 as a sole abnormality in hematological malignancies, there is one with MDS [2]. -21 is also seen in complex karyotypes with various kinds of malignancies. There are 17 reported cases with -21 in complex karyotypes with MDS and 73 cases with AML(M2) [11]. De Souza Fernandez and colleagues[2] reported gain of ploidy and -21 in one case during the progression from MDS to AML, and they suggested that these cytogenetic findings could play a role in the evolution from MDS to AML. When we performed cytogenetic analysis, our patient had already progressed from MDS to AML(M2). Therefore, we do not know if -21 was present before the evolution from MDS to AML.

We have not met any other case in the literature with -21 with t(1;3)(p36;p21), but some cases have been reported with -21 with various 3p abnormalities, which include 3p21 breakpoint in complex karyotypes with AML(M2). There have also been two cases who had add(1)(p?) and -21 in complex karyotypes, one with MDS, and the other with AML(M2) [12,13].

Chromosomal band 1p36 is a recurring breakpoint involved in various rearrangements in hematologic malignancies as well as in solid tumors. Among translocations involving band 1p36, the most frequent is t(1;3)(p36;q21), which is associated with MDS/AML characterized by trilineage dysplasia (especially dysmegakaryopoiesis) and poor prognosis [13-17]. Recently, the MEL1 [18-20] and RPN1 [17] genes, respectively located near the 1p36 and 3q21 breakpoints, were reported to be expressed exclusively in patients with this translocation. However, in the remaining chromosomal abnormalities involving band 1p36, the identity of the genes involved remains to be clarified [6].

Shi and colleagues[16,21] reported that band 3p21 was a recurrent breakpoint in therapy-related (t-) MDS/AML, and AF3p21 was identified at 3p21 as a new partner gene for MLL in a t-AML case with t(3;11)(p21;q23). It is also known that frequent deletion or allelic loss of band 3p21 occurs in various cancers [14,22]. Although several cancer-related genes have been located to 3p21, no gene has yet been shown to be related with MDS or other hematological malignancies.

Survival in the patients with t(1;3)(p36;p21) varies widely, from 25 days to 16 yrs+ [9]. Our patient survived nine months after the diagnosis and the detection of t(1;3)(p36;p21).

Although it is rare, t(1;3)(p36;p21) is a recurrent chromosomal abnormality found in various hematological malignancies; therefore, further cytogenetic and molecular studies should be performed in order to understand the role of this abnormality in carcinogenesis.

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