

## Triplication of 1q in a Patient with Myelodysplastic Syndrome

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Triplication of 1q is a very rare chromosomal abnormality in hematologic malignancies, and it has been related to Fanconi anemia. The clinical significance of this abnormality is unknown. We report here on a 55-year-old female patient who had myelodysplastic syndrome (refractory anemia with excess blasts) with triplication of 1q and trisomy 8 as the clonal cytogenetic abnormalities, as determined by bone marrow cytogenetic analysis. However, there were no clinical manifestations of Fanconi anemia or any chromosomal instability according to the peripheral blood chromosomal breakage testing. The patient developed early gastric carcinoma (poorly differentiated adenocarcinoma with a signet ring cell component) eight months later. She continuously had pancytopenia with dysplastic features, but this showed no evidence of evolving to leukemia or any relapse of the gastric carcinoma over a 2 year follow up. (*Korean J Hematol* 2006;41:56-60.)

**Key Words:** Triplication of 1q, Myelodysplastic syndrome, Fanconi anemia

### INTRODUCTION

The myelodysplastic syndromes (MDS) are a group of clonal hematopoietic stem cell diseases characterized by dysplasia and ineffective hematopoiesis in one or more of the major myeloid cell lines. Clonal chromosomal aberrations are found in 30~50% of primary MDS cases, but no specific cytogenetic abnormality has been associated with a particular subtype of MDS. The chromosomal abnormalities are characterized by a predominance of partial/total chromosomal losses or gains and the rarity of translocation. The most common abnormalities include -5/del(5q), -7/del(7q), del

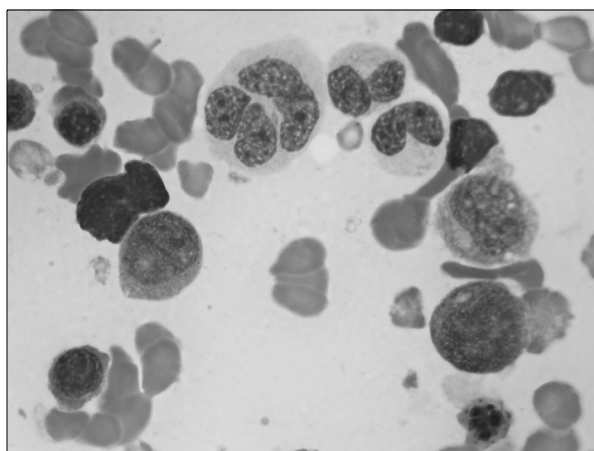
(11q), del(12p), del(20q), -Y and +8.<sup>1)</sup> Trisomy of 1q has been associated with various myeloid malignancies, such as polycythemia vera (PV), myelofibrosis (MF), essential thrombocythemia (ET), acute myeloid leukemia (AML) and MDS.<sup>2-5)</sup> In contrast, tetrasomy of 1q which results from triplication of 1q, is a very rare cytogenetic abnormality that seems to be related to Fanconi anemia (FA) and MDS.<sup>6,7)</sup> According to published literature, only nine cases with triplication of 1q have been reported and three of these were FA patients.<sup>3,7-14)</sup> We report here on a case of triplication of 1q in a patient with MDS and adenocarcinoma of stomach.

접수 : 2006년 1월 30일, 수정 : 2006년 3월 3일  
승인 : 2006년 3월 10일  
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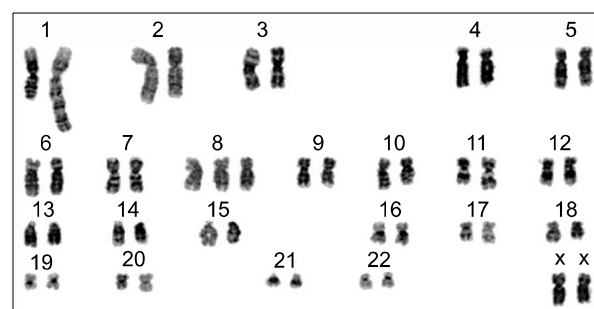
### CASE REPORT

A 55-years-old female was admitted for the evaluation of pancytopenia in October 2003. She had suffered from a fever and sore throat for a week. A complete blood cell count (CBC) revealed hemoglobin 7.9g/dL, platelet  $36 \times 10^9/L$ , white blood cells  $2.0 \times 10^9/L$  with segmented neutrophils 28%, band form neutrophils 16%, metamyelocytes 2%, lymphocytes 38%, atypical lymphocytes 7%, monocytes 9%. Peripheral blood films showed marked anisocytosis, poikilocytosis with elliptocytes and tear drop cells, hypogranulation and bizarre hypersegmentation. Bone marrow was normocellular and revealed dyserythropoietic and dysgranulopoietic features such as megaloblastic change, hypogranulation and large bizarre hypersegmented neutrophils. Blasts were rarely seen (0.5%). These findings were compatible with a diagnosis of refractory cytopenia with multilineage dysplasia, in accordance with the World Health Organization (WHO) classification.<sup>1)</sup> Cytogenetic study was not performed. Eight months later (in June 2004), she was diagnosed as having early gastric adenocarcinoma which was poorly differentiated with a signet ring cell component, and

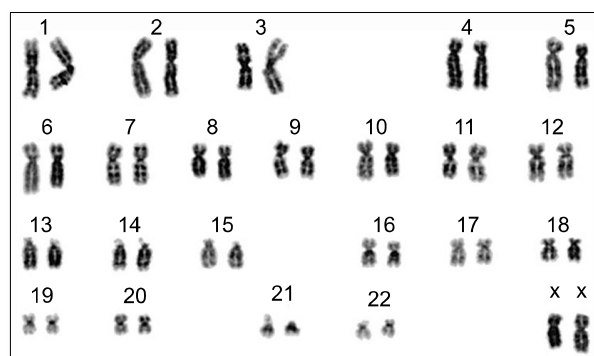


**Fig. 1.** The bone marrow aspirate showed dysplastic features and increase of blasts (Wright stain,  $\times 1,000$ ).

she was treated by subtotal gastrectomy. At this time, peripheral blood films continuously revealed dysplastic features and some blasts (1%). Bone marrow aspirates showed hypocellularity with increased blasts (9.0%) and dysplasia consistent with refractory anemia with excess blasts (Fig. 1). Cytogenetic analysis of bone marrow was performed using 24-hour unstimulated cultures and karyotypes are described according to the International System for Human Cytogenetics Nomenclature (ISCN) 2005. Triplication of 1q was examined all metaphases, and a secondary trisomy 8 abnormality was observed in 47.5% of the metaphases. Her karyotype was 46,XX, trp(1)(q21q32)[21]/47, idem, +8[19] (Fig. 2). A chromosome breakage study of peripheral blood was performed on 72-hour PHA stimulated culture with and without mitomycin-C, as previously



**Fig. 2.** The representative karyotype of bone marrow shows 47,XX, trp(1)(q21q32), +8.



**Fig. 3.** The karyotype of peripheral blood shows normal female karyotype.

described,<sup>15)</sup> and revealed a normal karyotype with no chromosomal instability (Fig. 3). Thus, allowing a constitutional anomaly of bone marrow to be excluded. FISH was performed using an FDA approved CEP 8 probe kit (Vysis, Downers Grove, IL) and 43.0% of interphase cells (215 cells per 500 cells) revealed trisomy 8. The patient received supportive care without chemotherapy. She continuously had pancytopenia with dysplastic features over a 2 year follow up, but there was no evidence of evolution to leukemia or relapse of gastric carcinoma. She had no known family history of malignancy or of a hematologic disorder.

## DISCUSSION

Although it is known that chromosome 1 is often involved in various malignant diseases, partial or total trisomy of the long arm of chromosome 1 appears to represent a nonrandom chromosomal anomaly in myeloid disorders.<sup>16,17)</sup> Moreover, it is remarkable that trisomy of 1q shows a higher frequency in postpolycythemic myelofibrosis,<sup>2)</sup> Korean and Japanese patients with MDS,<sup>4)</sup> and FA with or without hematologic malignancy.<sup>5,6)</sup> These anomalies mainly result from various unbalanced translocations, but some result from tandem duplication. Tetrasomy of 1q,

**Table 1.** Clinical and cytogenetic findings of the reported cases with triplication 1q

No. Case	Age/ Sex	Hematologic diagnosis	Cytogenetic abnormalities	Follow-up	Reference No.
1	55/M	MDS (RAEB), transformed from ET	trp(1)(q21q32)[16]/dup(1)(q21q32)[4]	Died 2 yrs later due to transformation to AML	[3]
2	38/M	FA, MDS (RA)	trp(1)(q12q32),add(11)(p15),add(21)(q22)	Died of secondary infection	[7]
3	52/M	MDS	trp(1)(q21q32)[32]/trp(1)(q21q32),+8[8]	Alive for 8 yrs	[8]
4	14/M	ALL	14q+ [8]/14q+,trp(1)(q11q21)[19]	Died 4 months later	[9]
5	17/M	FA	trp(1)(q12q32)[32]	Died at age 17 due to sepsis	[10]
6	21/M	FA, MDS (RAEB)	trp(1)(q32q44),+mar	Died 10 months later due to transformation to AML	[11]
7	ND	ALL	53,XX,+X,+6,+10,+17,+18,+21,+21[3]/53,idem,trp(1)(q21q42::q21q32::q21qter)[2]/53,idem,trp(1),?i(14)(q10)[2]	ND	[12]
8	ND	MM	47~48,X,-Y,trp(1)(q21q32),der(1)?t(1;10)(p22;p11.2)trp(1),+add(3p),-6,del(7p),+del(7q),add(8?q),+del(9p),add(12p),+der(12)add(12q),-13,-13,der(14)t(6;14),+add(19?q)[cp6]	ND	[13]
9	ND	B-cell lymphoma, NOS	47,XY,+X[3]/50,XY,+X,+X,trp(1)(q21q32),add(1p),+2,add(2p),+der(3;4),add(6p),+12,der(14;15)t(14;?),+18,i(21q),add(22p),+mar[cp16]	ND	[14]
10	55/F	MDS (RAEB)	trp(1)(q21q32)[21]/tri(1)(q21q32),+8[19]	Alive over 2 yrs	This case

Abbreviations: M, male; F, female; MDS, myelodysplastic syndrome; RA, refractory anemia; RAEB, refractory anemia with excess blasts; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; FA, Fanconi anemia; MM, Multiple myeloma; NOS, not otherwise specified; ND, not described.

which results from tandem triplication of 1q, is a rare cytogenetic abnormality, only nine previous reports have been issued (Table 1). By reviewing published cases, triplication of 1q has been related to MDS with or without FA and B cell neoplasm. Of the nine published cases and the present case, five cases were MDS. Three were associated with FA and two of them developed MDS. Four of five MDS patients and one FA patient without a hematologic malignancy had a common triplicated region between q21 and q32. FA is often considered a pre-leukemic state, because it frequently evolves toward MDS or AML, and clonal chromosomal abnormalities occasionally precede the onset of overt leukemia.<sup>10)</sup> Other four cases are diagnosed as variable B cell neoplasm. Triplication of 1q is a part of very complex composite karyotype in B cell neoplasm, whereas it is primary cytogenetic abnormality in MDS or FA. One patient was diagnosed as having acute lymphocytic leukemia (ALL) and this patient had a different triplicated region. Thus, triplication of 1q in MDS is seemed to be associated with different triplicated region than other diseases.<sup>3,7-14)</sup>

Triplication of chromosome 1 may be induced by several mechanisms, and one of these, tandem triplication, was observed in our patient. According to Knuutila,<sup>3)</sup> all karyotypes recovered from erythroid and granulocyte-monocyte colonies showed a duplication abnormality in chromosome 1, whereas the cells in direct bone marrow preparations showed triplication and duplication of 1q. This suggests that cells with triplication may evolve from a previous duplication and that the triplication is represent in karyotype of leukemic blasts which were unable to form colonies in vitro. The consequence of this is a genomic amplification of a specific chromosomal region. The long arm of chromosome 1 accommodates genes involved in the control of normal myeloid cell kinetics. Genes for interleukin-6 receptor (IL6RA, M20566) and myeloid cell leukemia sequence

(BCL2-related, stSG42485) are located at 1q21, myeloid cell nuclear differentiation antigen (MNDA, M81750, WI-7193) at 1q22, centromere protein F (mitosin, CENPR) at 1q32-q41, and tumor protein p53 binding protein 2 (TP53BP2) at 1q42.1-2. Since, in cases chromosome 1q multiplication, the copy numbers and perhaps the transcriptional activities of these genes are amplified, these may lead to a shift in the normal balance between proliferation and programmed cell death towards more pronounced cell proliferation.<sup>18)</sup> It is not clear which genes on chromosome 1q play a role in these phenotypes or how triplication of 1q (functional four copies of 1q) can predispose the development of MDS.

Papenhausen's case and ours have some common features, i.e., the same hematologic diagnosis as MDS, the development of adenocarcinoma, trisomy 8 as a clonal evolution of bone marrow cytogenetics, and a relatively stable clinical outcome. Although a high prevalence of malignancy is a feature of FA, neither revealed any other clinical features of FA or chromosomal instability.<sup>8)</sup>

By reviewing reported cases, triplication of 1q involving the q21-q32 region is suggested to be related to MDS with or without FA. The clinical significances of these abnormalities remain to be identified.

## 요 약

1번 염색체 장완의 triplication은 혈액종양에서 매우 드문 염색체 이상으로 판코니 빈혈과 관련이 있는 것으로 알려져 있으나 보고된 증례수가 적어 임상적 의미는 아직 명확하지 않다. 저자들은 골수형성이상증후군으로 진단받은 55세 여자 환자의 골수염색체 검사에서 1번 염색체 장완의 triplication을 관찰하여 보고하는 바이다. 본 증례에서는 판코니 빈혈의 임상적 증상은 없었고 말초혈액 염색체 절단분석법에서도 염색체 취약성은 관찰되지 않았다. 환자는 8개월 후 조기위암이 발생하였으며 2년 이상 경과추적 하는 동안 지속적으로 이형성소견과 함께 범혈구감소증을 보였으나 급성백혈병으로의 전환이나 위암의 재발은 관찰되지 않았다.

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