in vivo *26*: 71-74 (2012)

A Novel der(16)t(3;16)(p25;q24) in a Patient with Ovarian Cancer

KANG-WOO MIN[1,2], YONG-SUK MOON[1], CHI-HUM CHO[3] and HONG-TAE KIM[1]

[1]*Department of Anatomy, School of Medicine, Catholic University of Daegu, Daegu, Korea;*
[2]*Jeilmadi Hospital, Pohang, Gyungbuk, Korea;*
[3]*Department of Obstetrics and Gynecology, School of Medicine, Keimyung University, Daegu, Korea*

Abstract. *Background: Non-random simple chromosomal aberrations in various malignancies provide important insights into the molecular pathogenesis of human cancer. Although extensive data exist on recurring chromosomal abnormalities in hematological cancer, data on individual solid tumor types remain limited. Here we present the case of a patient with ovarian cancer with a specific chromosomal abnormality. Case Report: Cytogenetic analysis utilized a G-banding technique, which was performed with direct culture of the surgically removed cancer cells from a 23-year-old woman with grade II ovarian serous cystadenocarcinoma. The patient had no family history of ovarian cancer. Results: We report a novel der(16)t(3;16)(p25;q24) accompanied by terminal deletion of 3p25 as the simple chromosomal aberration in this case. Conclusion: To the best of our knowledge, no such translocation has been previously reported. The present study supports the possible role of both del(3)(p25) and the translocation t(3;16)(p25;q24) in ovarian cancer; nevertheless, the significance of these chromosomal changes in the development of ovarian cancer remains unknown. The significance of this finding and its role in the pathogenesis of ovarian cancer requires further clarification.*

Cytogenetic work-up has the potential of providing improved diagnostic and prognostic tools. Cytogenetic data also provide key background information for the recognition and identification of genes involved in cancer and their subsequent application in therapeutic development (1). The mechanisms underlying chromosomal aberrations in tumor cells are still obscure. Variable recurrent simple chromosomal aberrations have been reported for different types of cancer, including leukemia, lymphoma, and solid tumor. These single chromosomal changes might be primary events implicated in the initiation of the neoplastic process (2).

Ovarian cancer is the leading cause of death in women with gynecological malignancies. The genetic mechanisms underlying the initiation and progression of ovarian cancer have not been well defined. More than 400 ovarian carcinomas with karyotypically characterized chromosomal abnormalities have been reported. Most of these are characterized by highly complex karyotypes with polyploidy and variable structural chromosomal changes (3). However, some non-random structural chromosomal aberrations have been found in ovarian cancer with common chromosomal breakpoints. The most prevalent structural rearrangements are deletions and unbalanced translocations primarily involving 1p, 1q, 3p, 3q, 6q, 7p, 10q, 11p, and 19q (2, 4-9). Here, we report an unbalanced der(16)t(3;16)(p25;q24) as the simple chromosomal aberration in a patient with ovarian serous cystadenocarcinoma. To the best of our knowledge, no such translocation has been previously reported.

Case Report

A 23-year-old Korean woman with an ovarian mass underwent bilateral salphingo-oophorectomy, partial omentectomy, and pelvic tissue biopsy for sporadic ovarian cancer. The patient had no family history of ovarian cancer and no prior treatment before surgery.

Grossly, the right ovary presented a pale yellow papillary surface and was conglomerated with the right fallopian tube. The cut surface of the right adnexa showed central multicystic and mucoid ovarian tissue surrounded by papillary tumor tissue. The external surface and cut surface of the left ovary and fallopian tube were similar to those of the right side. Microscopically, sections of both ovaries and fallopian tubes showed stromal invasion of atypical,

Correspondence to: Hong-Tae Kim, MD, Ph.D., Associate Professor, Department of Anatomy, School of Medicine, Catholic University of Daegu, 3056-6 Daemyung 4-Dong, Nam-gu, Daegu, 705-718 Korea. Tel: +82 536504479, Fax: +82 536214106, e-mail: htaekim@cu.ac.kr

Key Words: Ovarian cancer, simple chromosomal aberration, der(16)t(3;16), translocation.

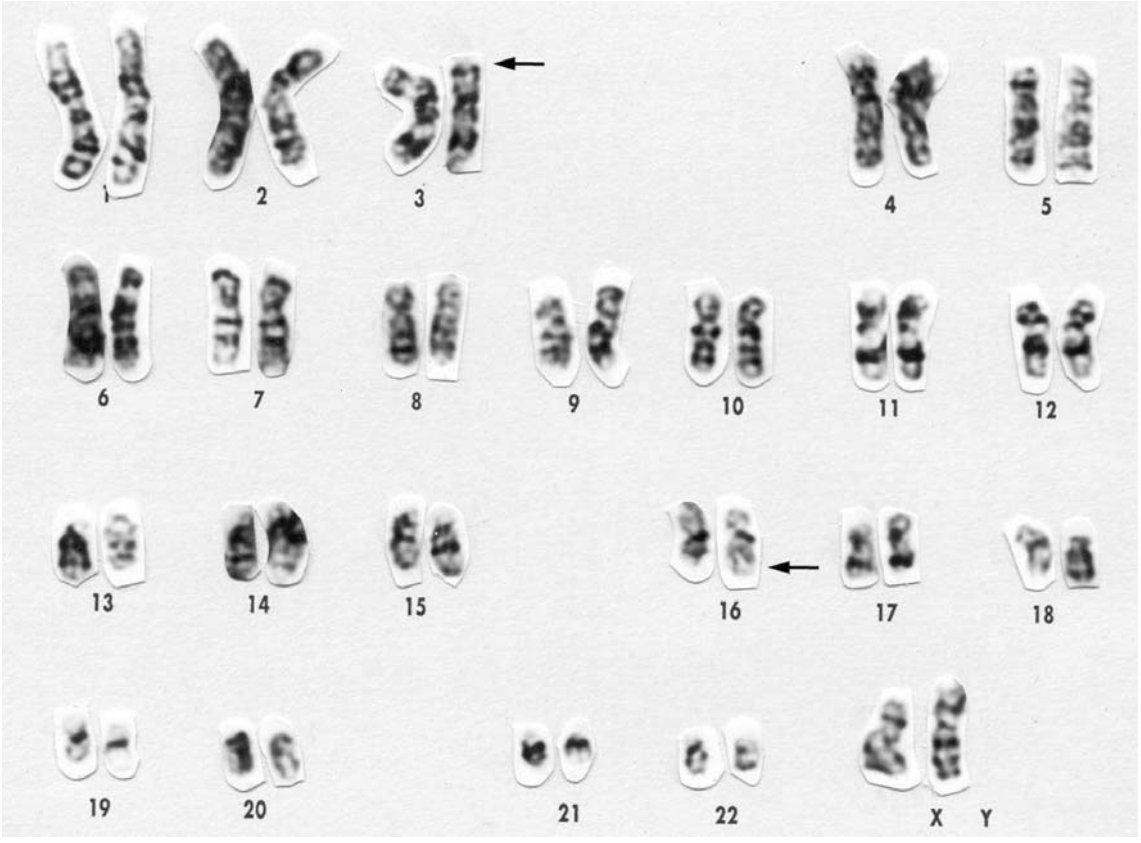

Figure 1. *Karyotype for G-banded metaphase showing 46,XX, der(16)t(3;16)(p25;q24). Arrows indicate clonal structural aberrations.*

glandular, papillary epithelium. Sections of the right pelvic, left paracolic, and uterine surface tissue exhibited infiltration by anaplastic tumor cells. The pathology report identified a well-differentiated serous papillary cystadenocarcinoma, grade II. Clinically, the patient was classified as stage IIIC.

Cytogenetic analysis. Cytogenetic analysis utilized a G-banding technique, which was performed with direct culture of cancer cells. The surgically removed tumor sample from the right ovary was disaggregated mechanically and enzymatically with collagenase type 2 (Sigma-Aldrich, St. Louis, MO, USA). The resulting cell clumps were seeded in plastic flasks and left to attach and grow in F12 medium (Invitrogen, Grand Island, NY, USA) supplemented with 10% fetal calf serum. Primary cultures were monitored for mitotic activity and harvested after 7 days. The prepared slides were trypsinized and stained with Wright stain for G-banding. Results of the cytogenetic analysis were described according to the International System for Human Cytogenetic Nomenclature (ISCN 2009) (10).

Cytogenetic analysis of the tumor cells revealed a simple karyotype: 46,XX, der(16)t(3;16)(p25;q24) (Figure 1). All 28 investigated metaphases suggested that the derivative chromosome resulted from a translocation of a deleted segment of the short arm of chromosome 3 (3p25) to the long arm of chromosome 16. Thus, the translocation t(3;16)(p25;q24) was defined (Figure 2).

Discussion

The identification of chromosomal abnormalities is a useful strategy for recognizing and identifying genes involved in carcinogenesis. Detecting recurrent chromosomal changes in solid tumors is extremely difficult. In some tumors, a specific recurrent chromosomal change may be the only alteration present. Many cases, however, display additional structural or numeric chromosomal changes that may be responsible for, or at least are associated with, disease progression (1, 11). The complexity of the karyotypes obtained from advanced tumors has obscured the initiating events in the pathogenesis of these tumors. Simple chromosomal changes may be primary events implicated in the initiation of the neoplastic process. Currently, more than 400 karyotypes have been published for ovarian carcinomas. The cytogenetic aberrations are non-random and complex. However, no pathognomonic rearrangements have

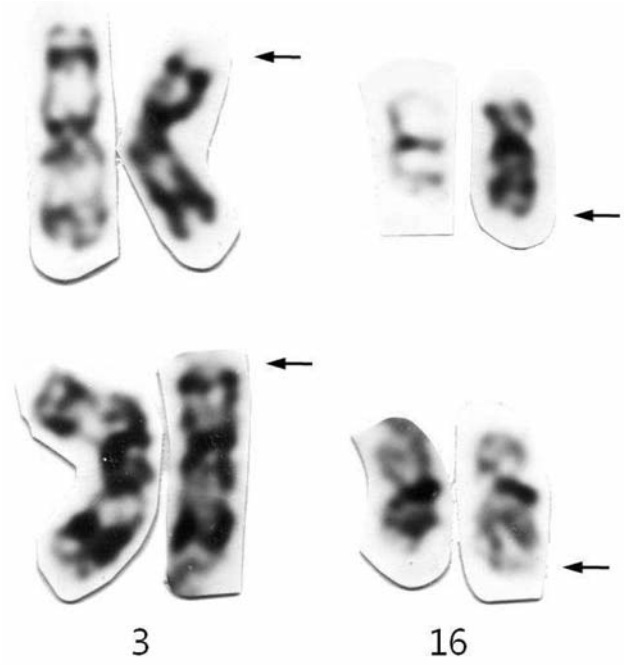

Figure 2. *Partial karyotype from two different metaphases showing der(16)t(3;16)(p25;q24).*

yet been identified (3, 12). Simple chromosomal changes are recurrently found in well-differentiated and borderline ovarian carcinomas, whereas complex abnormalities, most of them chromosome losses, deletions, and unbalanced translocations, are the typical findings in moderately and poorly differentiated carcinomas (13). In advanced ovarian cancer, the presence of a simple chromosomal abnormality is rare. Few recurrent simple chromosomal changes have been reported in advanced ovarian cancer, including rearrangements involving chromosomes 9, 11, and X (2).

This report presents a conventional cytogenetic study of an ovarian cancer patient with a novel finding of a rare t(3;16) accompanied by terminal deletion of 3p25 as the simple chromosomal changes. Despite the notion that carcinomas accumulate genetic abnormalities as they progress, in the present case, advanced ovarian cancer did not harbor complex chromosomal abnormalities. To the best of our knowledge, this is the first example of an ovarian cancer carrying such a translocation and deletion (3, 12). These simple anomalies are considered to be early events in clonal evolution, suggesting potential biological roles in carcinogenesis. Chromosomal breakpoints can deregulate gene expression or alter gene structures, resulting in a quantitatively or qualitatively altered gene product. Some chromosomal abnormalities may be involved in the genesis of cancer, whereas other chromosomal aberrations may be used to stratify patients into prognostic groups and therapeutic schemes.

In ovarian cancer, few chromosomal changes involving 3p25 with complex karyotypes have been reported previously (14, 15). The terminal deletion del(3)(p25) has not been reported (3, 12). However, loss of 3p25 has been described in other solid tumors, including breast cancer (16) and renal cell carcinoma (17). The deletion of 3p can inactivate the Von Hippel-Lindau gene, a tumor suppressor gene associated with renal cell carcinoma (18). Some chromosomal abnormalities may be responsible for the initiation or progression of a malignant disease. The involvement of chromosomal region 3p25 in this case might facilitate the identification of candidate genes implicated in this malignant disease.

In addition, no translocation involving 16q24 has been reported previously for ovarian cancer, although a preferential involvement of chromosome 16 as add(16)(q24) in ovarian cancer cases with complex karyotypes was reported (14, 19, 20). Loss of heterozygosity has been demonstrated frequently at defined regions of chromosome 16, including 16q24. The frequency of loss of heterozygosity at 16q24.3 is significantly higher in advanced-stage tumors than lower stage tumors (21). The presence of frequent chromosomal rearrangements at 16q24 suggests that this chromosome region harbors one or more factors important for the progression of ovarian cancer. The present study supports the possible role of both del(3)(p25) and the translocation t(3;16)(p25;q24) in ovarian cancer; nevertheless, the significance of these chromosomal changes in the development of ovarian cancer remains unknown. The significance of this finding and its role in the pathogenesis of ovarian cancer requires further clarification.

References

1 Sandberg AA and Meloni-Ehrig A: Cytogenetics and genetics for human cancer: Methods and accomplishments. Can Genet Cytogenet *203*: 102-126, 2010.

2 Panani AD, Aravidis C, Kosamaidou Z, Rodolakis A and Antsaklis A: Simple structural chromosomal abnormalities in advanced stage of ovarian cancer. In Vivo *23*: 425-428, 2009.

3 Mitelman F, Johansson B and Mertens F: Mitelman database of chromosome aberrations in cancer. Available at http://cgap.nci.nih.gov/Chromosomes/Mitelman 2011.

4 Panani AD: Preferential involvement of chromosome 11 as add(11)(p15) in ovarian cancer: Is it a common cytogenetic abnormality in cancer? Cancer Lett *258*: 262-267, 2007.

5 Panani AD and Roussos C: Non-random structural chromosomal changes in ovarian cancer: i(5p) a novel recurrent abnormality. Cancer Lett *235*: 130-135, 2006.

6 Bernardini M, Weberpals J and Squire JA: The use of cytogentics in understanding ovarian cancer. Biomed Pharmacother *58*: 17-23, 2004.

7 Sham JS, Tang TC, Fang Y, Sun L, Qin LX, Wu QL, Xie D and Guan XY: Recurrent chromosome alterations in primary ovarian carcinoma in Chinese women. Cancer Genet Cytogenet *133*: 39-44, 2002.

8 Taetle R, Aickin M, Panda L, Emerson J, Roe D, Thompson F, Davis J, Trent J and Alberts DS: Chromosome abnormalities in ovarian adenocarcinoma: II. Prognostic impact of nonrandom chromosome abnormalities in 244 cases. Genes Chromosomes Cancer *25*: 46-52, 1999.

9 Taetle R, Aickin M, Yang JM, Panda L, Emerson J, Roe D, Adair L, Thompson F, Liu Y, Wisner L, Davis JR, Trent J and Alberts DS: Chromosome abnormalities in ovarian adenocarcinoma: I. Nonrandom chromosome abnormalities from 244 cases. Genes Chromosomes Cancer *25*: 290-300, 1999.

10 Shaffer LG, Slovak ML and Campbell LJ: ISCN 2009: An International System for Human Cytogenetic Nomenclature (2005). Basel: S. Karger, 2009.

11 Ye CJ, Liu G, Bremer SW and Heng HH: The dynamics of cancer chromosomes and genomes. Cytogenet Genome Res *118*: 237-246, 2007.

12 Atlas of Genetics and Cytogenetics in Oncology and Haematology. URL http://AtlasGeneticsOncology.org/ 2011.

13 Micci F and Heim S: Tumors of the female genital organs. In: Cancer Cytogenetics–Chromosomal and Molecular Genetic Aberrations of Tumor Cells. Heim S and Mitelman F, (3rd eds.) NJ: Wiley-Blackwell, pp. 519-575, 2009.

14 Thompson FH, Emerson J, Alberts D, Liu Y, Guan XY, Burgess A, Fox S, Taetle R, Weinstein R and Makar R: Clonal chromosome abnormalities in 54 cases of ovarian carcinoma. Cancer Genet Cytogent *73*: 33-45, 1994.

15 Bullerdiek J, Bartnitzke S, Kahr E and Schloot W: Further evidence for nonrandom chromosome changes in carcinoma cell – a report of 28 cases. Cancer Genet Cytogenet *16*: 33-43, 1985.

16 Ferti AD, Stamouli MJ, Panani AD, Raptis SA and Young BD: Molecular cytogentic analysis of breast cancer; a combined multicolor fluorescence *in situ* hybridization and G-banding study of uncultured tumor cells. Cancer Genet Cytogenet *149*: 28-37, 2004.

17 Andrei A, Kost-Alimova M, Liu J, Li C, Bergerheim U, Imreh S, Klein G and Zabarovsky ER: Combined LOH/CGH analysis proves the existence of interstitial 3p deletions in renal cell carcinoma. Oncogene *19*: 1392-1399, 2000.

18 Sükösd F, Kuroda N, Beothe T, Kaur AP and Kovacs G: Deletion of chromosome 3p14.2-p25 involving the *VHL* and *FHIT* genes in conventional renal cell carcinoma. Cancer Res *63*: 455-457, 2003.

19 Micci F, Weimer J, Haugom L, Skotheim RI, Grunewald R, Abeler VM, Silins I, Lothe RA, Trope CG, Arnold N and Heim S: Reverse painting of microdissected chromosome 19 markers in ovarian carcinoma identifies a complex rearrangement map. Genes Chromosomes Cancer *48*: 184-193, 2009.

20 Kiechle-Schwarz M, Bauknecht T, Schmidt J, Walz L and Pfleiderer A: Recurrent cytogenetic aberrations in human ovarian carcinoma. Cancer Detect Prev *19*: 234-243, 1995.

21 Launonen V, Mannermaa A, Stenback F, Kosma VM, Puistola U, Huusko P, Anttila M, Bloiqu R, Saarikoski S, Kauppila A and Wingvist R: Loss of heterozygosity at chromosomes 3, 6, 8, 11, 16, and 17 in ovarian cancer: correlation to clinicopathological variables. Cancer Genet Cytogenet *122*: 49-54, 2000.

Received August 7, 2011
Revised September 30, 2011
Accepted October 3, 2011