Abstract. Background: Ovarian cancer represents the leading cause of death among patients with gynaecological cancer. The identification of chromosomal abnormalities is a useful strategy toward understanding tumourigenesis and specific chromosomal associations. Since single chromosomal changes might be primary events implicated in the initiation of the neoplastic process, the aim of the present study was to investigate the presence of simple structural chromosomal changes in ovarian cancer. Materials and Methods: Reviewing on ascetic effusions samples cytogenetically studied by direct culture of tumour cells and a G-banding technique, two ovarian cancer cases were found which presented simple structural chromosomal abnormalities. Results: The first case presented an abnormal clone of cells with an acquired pericentric inversion of chromosome 9, inv(9)(p11q13), as a sole anomaly. The second case presented simple chromosomal changes with involvement of the Xq23 chromosomal region, while a translocation t(X;11)(q23;q23) was also defined. Conclusions: The significance of the acquired pericentric inversion 9 in the development of the neoplastic process remains unknown. The chromosomal regions Xq23 and 11q23 need to be further investigated in association with clinical-pathological parameters in ovarian cancer. The documentation of more ovarian cancer cases with simple chromosomal abnormalities is considered of major importance facilitating the identification of candidate genes involved in the neoplastic process. Improving the molecular understanding of ovarian cancer development and progression could facilitate the detection of specific tumour subtypes.

Ovarian cancer represents the leading cause of death among patients with gynaecological cancer. Patients with ovarian cancer are usually diagnosed at advanced disease stage. Most of the ovarian cancer cases described in the literature are characterized by complex chromosomal changes with polyploidization and structural chromosomal changes resulting usually in uncompleted karyotypes. However, non-random structural chromosomal aberrations have been found in ovarian cancer with common chromosomal breakpoints. Moreover, clinical associations with chromosomal abnormalities have been described in ovarian cancer patients (1-11). Two advanced stage ovarian cancer cases cytogenetically studied and showing simple chromosomal changes are hereby presented.

Materials and Methods

We reviewed on ascetic cancerous effusions samples cytogenetically studied. Since single chromosomal changes might be primary events implicated in the initiation or progression of the neoplastic process, we focused on single or simple structural chromosomal changes. Among cases studied, only two cases with a diagnosis of ovarian cancer presented simple chromosomal abnormalities. Both patients had never received chemotherapy or radiotherapy prior to cytogenetic study. Cytogenetic analysis was performed by direct culture of cancerous cells and a G-banding technique. Cancerous cells derived from ascetic fluids were immediately put into direct culture in Mc Coys 5A medium supplemented with fetal calf serum and colchicine. The cell suspension was incubated for 90 minutes at 37°C, then exposed to hypotonic treatment and fixation. The preparations were processed by the trypsin-Giemsa banding technique. As many cells as possible were analyzed in each case and not fewer than 15. An abnormal clone was defined as two or more cells with the same structural anomaly. Chromosomal aberrations were designed according to the International System for Human Cytogenetic Nomenclature (ISCN 1995) (12).
Results

The first case presented metaphases with a normal karyotype, while an abnormal clone of cells with a pericentric inversion of chromosome 9, inv(9)(p11q13), as a sole anomaly was also detected (Figure 1). The second case presented simple chromosomal changes with involvement of the sex chromosome X. In this case 3 metaphases had loss of sex chromosome X, while 4 metaphases presented a deletion of its long arm with a breakpoint at the Xq23 chromosomal region. Two of the metaphases with del(X)(q23) presented an abnormal chromosome 11 with an extra material on its long arm, which probably arose from the deleted segment of the sex chromosome X. Thus a translocation t(X;11)(q23;q23) was defined (Figure 2).

Discussion

The detection of recurrent chromosomal changes in solid tumors is extremely difficult. The tumors display complex chromosomal changes with various numerical and structural aberrations, while the presence of simple chromosomal abnormalities is a rare finding (13-15). In ovarian cancer recurrent abnormalities have been identified but today no specific aberration has been established (16).

A total of 31 cases of cytogenetically studied ovarian cancer have been previously reported by the authors (4-6), while approximately 35 additional ovarian cancer cases have been studied but not successfully karyotyped (not published). None of all these cases presented simple chromosomal changes. In the present study simple chromosomal changes in two advanced stage ovarian cancer cases are described. The first case had an abnormal clone with a pericentric inversion of chromosome 9, inv(9)(p11q13), as a sole anomaly, while in the second case simple chromosomal changes of the sex chromosome X with involvement of the chromosomal region Xq23 were found. Despite the notion that cancers accumulate more genetic abnormalities as they progress, in the present cases advanced ovarian cancer did not harbor complex chromosomal abnormalities.

Over the past four decades it has become clear that acquired non-random chromosomal abnormalities are associated with specific malignant diseases. Acquired chromosomal changes occur during life and are present in a specific tissue, while constitutional chromosomal abnormalities are either inherited from the parents or occur de novo during gametogenesis and they are present in all tissues. Familial pericentric inversion of chromosome 9 inv(9)(p11q13) is the most frequent pericentric inversion in man, with an incidence of 1% in the general population (17). Since the chromosomal breakpoints are in repetitive sequences this pericentric inversion of chromosome 9 is considered clinically insignificant (18). To date an acquired pericentric inversion of chromosome 9 has been reported in only 3 cases of hematologic malignant diseases, the significance of which remains unknown (18, 19). Betz et al. (18) supposed that the breakpoints of the acquired inversion 9 seen in hematologic malignancy might have occurred in euchromatin distal to the repeat sequences involved in the familial pericentric inversion 9, potentially leading to disruption of a gene implicated in the pathogenesis of the neoplastic disorder. The case presented here is the first case of ovarian cancer with an acquired inversion of chromosome 9. Until additional cases of ovarian cancer or other cancers with acquired inversion 9 are reported, the significance of this abnormality in the development of the neoplastic process will remain unknown.

The second case presented simple chromosomal changes with either loss of the sex chromosome X or structural abnormalities involving the chromosomal region Xq23. In this case a translocation t(X;11)(q23;q23) was also defined. Deletion del(X)(q23) has been previously reported in 4 cases of ovarian cancer with complex karyotypes (16).

It is considered that some chromosomal abnormalities may be responsible for the initiation or progression of a malignant disease. Since single chromosomal changes might be primary events implicated in the initiation of the neoplastic process the involvement of the chromosomal region Xq23 in the case described here might facilitate the identification of candidate genes involved in this malignant disease. Furthermore, in this case a translocation t(X;11)(q23;q23) was also defined. A preferential involvement of chromosome 11 as add(11)(q23) in ovarian cancer cases with complex karyotypes has been previously reported (4, 6). Moreover, loss of heterozigosity (LOH) has been demonstrated frequently at defined regions of chromosome 11 including 11q23-q25. It has also been reported that the frequency of LOH at 11p15 and 11q23 is significantly higher in advanced-stage tumours than in lower-stage tumours, while LOH at 11p15 and 11q23 was found to be associated with an adverse disease course in ovarian cancer. The presence of LOH at 11q23 suggests that chromosome 11 contains several tumour suppressor genes involved in ovarian cancer (20-23). To the authors’ knowledge, abnormalities of chromosome 11 as add(11q23) have been described to date in 13 ovarian cancer cases (4, 6, 16, 24-26). A number of genes have been mapped on 11q23 that might be target genes for the development of ovarian cancer. Although, add(11)(q23) may result in loss of genetic material from chromosome 11q, alterations of specific genes involved by the translocation t(X;11)(q23;q23) could not be excluded. The documentation of more ovarian cancer cases with simple structural chromosomal abnormalities is considered of major importance facilitating the identification of candidate genes involved in the neoplastic process.
Tumorigenesis is a multistep process and chromosomal abnormalities have been shown to be implicated in the development or progression of tumours. Data of the present study support the possible role of both del(X)(q23) and the translocation t(X;11)(q23;q23) in ovarian cancer. The chromosomal regions Xq23 and 11q23 need to be further investigated in association with clinico-pathological parameters in ovarian cancer. Improving the molecular understanding of ovarian cancer development and progression could facilitate the detection of specific tumour subtypes, contributing also to novel strategies for the management of ovarian cancer patients.

Figure 1. *Karyotype from case No 1 showing a pericentric inversion of chromosome 9, inv(9)(p11q13).*

Figure 2. *Karyotype from case No 2 showing the translocation t(X;11)(q23;q23).*
References


