ORIGINAL ARTICLE

Comparison of cytogenetic and molecular features observed in endometrial cancers: known clinic and difficulties in treatment

Comparación de las características citogenéticas y moleculares observadas en los cánceres de endometrio: clínica conocida y dificultades en el tratamiento

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Abstract

Objective: *Understanding the relationship between genetic structure and the molecular changes involved in endometrial cancer (EC) provides an opportunity to personalize treatments and incorporate targeted therapies.* **Method:** *We compared cytogenetic and molecular features observed in tumoral and adjacent healthy tissue endometrium samples in EC patients.* **Results:** *Non-clonal chromosome aberrations (NCCAs) frequently in patients with EC, especially in 10,15,17,22, X chromosomes and were monitored in 73.7%, clonal chromosomal alterations were observed in 26.3% of the patients. Down POLE gene expression in 42.1%, up p53gene expression in 57.9%, PTEN down-regulation in 47.3%, down ARID1A gene expression in 42.1%, PIK3CA up-regulation was observed in 68% of patients.* **Conclusion:** *The up-regulation of tumor suppressor genes in our study shows that not only these genes are involved but also different pathways and factors play a role in tumorigenesis. Furthermore, an increased number of NCCAs shows an essential role in the development of ECs.*

Keywords: *Endometrial cancer. Genomics. Pathology. Prognostic factors. Targeted therapy.*

Resumen

Objetivo: *Comprender la relación entre la estructura genética y los cambios moleculares involucrados en el cáncer de endometrio brinda la oportunidad de personalizar los tratamientos e incorporar terapias dirigidas.* **Método:** *Comparamos las características citogenéticas y moleculares observadas en muestras de endometrio de tejido sano tumoral y adyacente en pacientes con cáncer de endometrio.* **Resultados:** *Las aberraciones cromosómicas no clonales (NCCA) son frecuentes en pacientes con cáncer de endometrio, especialmente en los cromosomas 10, 15, 17, 22, X y fueron monitoreadas en el 73,7%; se observaron alteraciones cromosómicas clonales en el 26,3% de las pacientes. Disminución de la expresión del gen POLE en el 42,1 %, aumento de la expresión del gen p53 en el 57,9%, disminución de la regulación de PTEN en el 47,3 %, disminución de la expresión del gen ARID1A en el 42,1%, aumento de la expresión de PIK3CA en el 68% de los pacientes.* **Conclusión:** *La regulación positiva de los genes supresores de tumores en nuestro estudio muestra que no solo estos genes están involucrados, sino que diferentes vías y factores juegan un papel en la tumorigénesis. Además, un mayor número de NCCA muestra un papel esencial en el desarrollo de cánceres de endometrio.*

Palabras clave: *Cáncer de endometrio. Genómica. Patología. Factores pronósticos. Terapia dirigida.*

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Introduction

Although cervical cancer is responsible for the highest incidences and deaths of gynecological cancers, endometrial cancers (EC) are still quite common[1]. PTEN is a tumor suppressor gene located in the 10q23.3 chromosome region. PTEN mutations are present in approximately 83% of ECs. Detection of up to 40% of complex hyperplasia suggests that PTEN mutations play a role in early pathogenesis[2]. POLE somatic mutations are found in < 10% of endometrial carcinomas[3]. In EC, p53 mutations are more common in high-grade tumors and it considered among late mutations in pathogenesis[3]. The ARID1A gene has been characterized as a tumor suppressor, and most mutations seen in human cases are frameshift or nonsense mutations. In particular, ARID1A is mutated in all endometrium-associated tumor types, including undifferentiated endometrial carcinomas[4,5]. Activating mutations and amplification of PIK3CA are common in cancer in general. However, the highest rates of PI3K pathway alterations were reported in endometrial malignancies[6].

Five-year survival rates for EC vary according to the stage at diagnosis. The 5-year survival rate in patients with tumors localized in the uterus is ≥ 95% but may decrease to 69% in patients with regional metastases and 17% in patients with distant metastatic disease[7].

Endometrioid and serous EC s were divided into four groups with distinct clinical, pathologic, and molecular features[3]:

– DNA polymerase epsilon (POLE) mutant [ultramutated].

– Microsatellite instability-high (MSI-H)/mismatch-repair deficient (MMR-D) [hypermutated].

– Copy-number low (CN-low) [endometrioid-like].

– Copy-number high (CN-high) [serous-like].

Chromosome breakpoints are a manifestation of chromosomal instability. It has been found that chromosomal deletions in cancer cells often contain tumor suppressor genes. Among the 30 most gene-rich bands, cancer breakpoints localize at 1p36, 1q21, 7q22, 8q24, 11p15, 11q13, 11q23, 12q13, 16p13, and 19p13 sensitive regions[8].

Understanding the relationship between genetic structure and the molecular changes involved in EC provides an opportunity to personalize treatments through facilitating diagnostic testing and incorporating targeted therapies. Therefore, in this study, we aimed to investigate the genetic features of EC s and give clinicians an opinion in this direction.

Method

In this study, endometrial tumoral and adjacent healthy tissue samples were surgically taken from 34 patients diagnosed with EC at University Hospital, Department of Obstetrics and Gynecology. Patient information was obtained from the hospital information system and patients. Tumor sizes and degrees of myometrial invasion were determined by MR imaging. All patients in our study did not receive any neoadjuvant chemotherapy. Primary cell cultures were made as explant cultures or as single-cell suspensions by enzymatic application. Chromosome analysis-prepared preparations were examined under Leica DM2500 optical microscope. Analyzed metaphases were evaluated according to ISCN 2013 (International System for Human Cytogenetic Nomenclature). Metaphases were photographed in an automated imaging (Cytovision) system. In this study, at least 20 metaphases from each patient were examined.

Thirty mg samples were taken from endometrial tissues with scalpel and homogenized by the RNeasy Micro Kit (50) (Qiagen, Germany) protocol, total RNA was isolated. The quantity of RNAs was checked with a spectrophotometer (NanoDrop ND-1000; NanoDrop Technologies, Wilmington, DE). For cDNA synthesis, a cDNA synthesis kit (WisentBioProducts, Canada) and 1μg total RNA were used. Obtained gene expression values were normalized using a housekeeping gene of beta2 microglobulin. Gene expression ratios were compared in tumoral and adjacent healthy tissue groups using REST (Relative Expression Software Tool). The investigated genes in the study are POLE, PTEN, TP53, PIK3CA, and ARID1A. A list of the primers used for the quantitative RT-PCR are presented in table 1.

Statistical analysis

Statistical Package for the Social Sciences (SPSS for Windows, Version 25.0, Chicago, IL, USA) program was used for statistical analysis. Results were presented as the median and interquartile range (25%-75%) for continuous (numeric) data; frequency and percentage for categorical variables. Fisher's exact test was used to

Table 1. List of the primers used for the quantitative RT-PCR

Genes	Primer sequences
POLE (Exon 9)	Forward primer: 5-CTTTTAACAACCAGAGGGAGGT -3 Reverse primer: 5-TTGCTCCCATTCCTGGACTAA-3
PIK3CA (Exon 21)	Forward primer: 5-CATTTGCTCCAAACTGACCA-3 Reverse primer: 5-GATTGGCATGCTGTCGAATA-3
PTEN (Exon 7)	Forward primer: 5-CAGTTTGTGGTCTGCCAGCT-3 Reverse primer: 5-ATCACCACACACAGGTAACG-3
TP53 (Exon 5)	Forward primer: 5-TTGCCAACTGGCCAAGACCT-3 Reverse primer: 5-ACCTCCGTCATGTGCTGTGA-3
ARID1A (Exon 14)	Forward primer: 5-TTCAGTTGGGATCCAGGATGC-3 Reverse primer: 5-ATACTGGGCTGATACCCAGG-3

Table 2. Characteristics of tumors detected in participants

Characteristics of tumors	n	%
Metastasis		
No	30	88.2
Yes	4	11.8
Grade		
1	9	26.5
2	16	47.1
3	9	26.5
Histopathology result		
Non-endometrioid	5	14.7
Endometrioid	29	85.3
Chromosomal abnormality	5	73.7
CCAs	14	26.3
NCCAs		
Myometrial invasion		
< ½	26	76.5
> ½	8	23.5

CCAs: clonal chromosomal alterations; NCCAs: non-clonal chromosome aberrations.

compare categorical variables. For the statistical significance level, $p < 0.05$ was considered sufficient.

Results

While the mean age of the participants was 60.3 ± 1.4 (30-84), the gravida and parity medians were found 3. USG endometrial thickness (mm) was found 16. When the characteristics of the tumors detected in the participants were examined, it was determined that the median tumor size was 4 cm and metastasized in 4 of them. When the laboratory findings of the participants were examined, it was determined that the median of CA 125 was 15.7. In our study, tumors were detected as Stage 1A in 69.7% and Stage 3C in 12.1% of the patients. Characteristics of tumors detected in participants are presented in table 2.

The karyotype analysis results of the participants by tumor type are shown in table 3. Regulation and abnormality situations are presented in table 4.

When the regulation status was compared according to the presence of chromosomal anomaly, no statistically significant difference was found (Table 5).

We analyzed the differential expression of a gene in the tissues affected by the disease, compared with non-affected tissues. In our results, all gene expression values show increases and decreases in pathological tissue compared to healthy tissue.

Discussion

Although we started by using explant and enzymatic methods to produce primary endometrium cancer cell culture, we continued our work with the enzymatic method because, by the explant method, the cell count was less and cultivated for a longer time. Metaphase was observed in only 19 of the 34 patients. This shows a slightly higher rate than the literature, with a success rate of 56%.

About 90% of solid tumors and 75% of hematopoietic cancers have either gained or lost chromosomes[9]. Aneuploidy occurs before or at the same time as malignant transformation[10]. Furthermore, aneuploidy is a feature of cancer caused by increased cell proliferation[11]. Studies on hematologic cancers concluded that the survival of cytopenic patients with non-clonal chromosome aberrations (NCCAs) is worse than cytopenic patients with clonal chromosomal alterations (CCAs) without hematologic malignancies, suggesting that follow-up should be considered for cytopenic patients with both CCAs and NCCAs[12].

Table 3. Karyotype analysis results according to the tumor type of the participants

Histopathology	Karyotype
Endometrioid	41~88, X, -X [5], -4[3], -11[3],19[4] [cp10]/46, XX[7] NCCAs [10]
Carcinosarcoma	46, XX, inv (9)(p11q13)[17] NCCAs[3]
Endometrioid	46, XX[8]/NCCAs[3]
Endometrioid	46, XX[1]/NCCAs[1]
Carcinosarcoma	46, XX[3]/NCCAs[2]
Endometrioid	46, XX[1]/NCCAs[2]
Endometrioid	46, XX[2]/NCCAs[2]
Endometrioid	46, XX[1]/NCCAs[1]
Endometrioid	46, XX[17]/NCCAs[6]
Endometrioid	44~78, XX,+9[2],+19[2],-20[3] [cp5]/46, XX[1] NCCAs[7]
Endometrioid	46, XX[9]/NCCAs[6]
Endometrioid	39~49, XX,-15[3],+16[2][cp5]/46, XX[8]NCCAs[4]
Serous	45, X,-X,[3],-16[3]/46, XX[8] NCCAs[4]
Endometrioid	40~44, X,-X[2]/46, XX[6] NCCAs[7]/46, XX[8]/NCCAs[7]
Endometrioid	46, XX[9]/NCCAs[3]
Endometrioid	46, XX[15]/NCCAs[5]
Endometrioid	46, XX[1]/NCCAs[1]
Endometrioid	46, XX[1]NCCAs[2]
Endometrioid	46, XX[3]/NCCAs[5]

NCCAs: non-clonal chromosome aberrations.

We observed NCCA losses frequently in patients with EC, especially in 10,15,17,22, X chromosomes. On the other hand, polyploidy anomalies were frequently encountered in these patients. CCAs were observed in 26.3% of the patients. NCCAs monitoring in 73.7% of the participants show that these abnormalities cannot be underestimated in cancer cases and play an important role in the development of ECs. At the same time, a decrease in cell differentiation (increased tumor grade) with the numerical anomaly is one of the other results of our study.

POLE mutation status has proven an independent prognostic factor for EC patients. Patients with somatic POLE mutations exhibited a favorable prognosis[13]. POLE low expression has been associated with a favorable prognosis in EC patients[14]. In our results, we observed down POLE gene expression in 42.1% of patients, and Type 1 EC was observed in 78% of these patients, which is associated with a favorable prognosis.

Several studies have shown that p53 overexpression in endometrioid adenocarcinomas of the uterus is significantly higher in serous papillary (75-90% of cases) than in endometrioid endometrial carcinomas (10-35% of cases)[15]. In patients with endometrial carcinoma, overexpression of p53 has been reported largely unfavorable prognostic marker[16]. Up p53gene expression in 57.9% of cases and tumor Grade 2–3 in 63% of these patients is another result of our research, which is related to weaker cell differentiation in these cases, as well as a poor prognosis.

While decreased expression of PTEN is associated with Grade 3, increased PTEN expression is known associated with Grades 1 and 2 endometrial carcinomas[17]. In addition, the association between PTEN expression and the stage of endometrioid endometrial adenocarcinomas has been demonstrated[18]. It has been suggested that since PTEN can increase the chemosensitivity of neoplastic cells, it is an important prognostic indicator of improved overall survival in patients with advanced endometrial carcinoma receiving postoperative chemotherapy[19]. Tumor grade was observed higher in PTEN down-regulated cases. Grade 2–3 was observed in 87% of the patients with down-regulation and down-regulation was observed in 47.3% of the participants.

Considering tumor development and progression, ARID1A loss is associated with deep myometrial invasion in endometrial carcinoma[20]. Studies have shown that ARID1A acts as a tumor suppressor and is involved in tumorigenesis, progression, and apoptosis through the regulation of cellular proliferation in many cancer types, including ECs[21]. Down ARID1A gene expression in 42.1% of patients and deep myometrial invasion was observed in 37.5% of these cases.

PIK3CA mRNA expression was found increased from normal control tissue to EC tissues and endometrioid to non-endometrioid histological type[22]. Furthermore, high PIK3CA mRNA expression is associated with poor prognosis and increased expression in metastases demonstrating the independence of PIK3CA mutational status[23]. We observed PIK3CA up-regulation in 68% of the participants and tumor Grade 2–3 as an indicator of poor prognosis in 66.6% of these patients.

Table 4. Karyotype analysis results, gene regulation and chromosome abnormality status of the participants

Karyotype	Missing or excess chromosome	*POLE 12q24.33*	*PTEN 10q23.31*	*TP53 17q13.1*	*ARIDA 3q26.32*	*PIK3CA 1p35.3*
41~88, X, -X [5], -4[3], -11[3],19[4] [cp10]/46, XX[7] NCCAs [10]	–1, –2, –3, –4, –5, –6, –7, –9, –10, –11, –13, –14, –16, –17, –19, –20, –21, –22, –X, +4, +21	10,014u	87,305u	59,466u	67,6,2u	81,346u
46, XX, inv (9) (p11q13)[17] NCCAs [3]	–6, –12, –17, –X	2,439d	1,312d	1,075u	3,202u	2,542u
46, XX [8]/NCCAs [3]	–10, –15 –22, +2	4,389u	7,454u	9,409u	14,611u	12,346u
46, XX [1]/NCCAs[1]	+8	3,565u	3,753u	4,011u	16,784u	33,498u
46, XX[3]/NCCAs [2]	–1, –8, –9, –10, 11, –12, –15, –17, –18, –21, –X	29,324u	114,405u	58,242u	60,506u	99,457u
46, XX[1]/NCCAs [2]	–2	4,275d	3,143d	2,167d	3,948d	2,556d
46, XX[2]/NCCAs [2]	–14, –X, +13	1,480d	2,864u	2,740u	1,486d	1,533u
46, XX[1]/NCCAs [1]	–7, –8, –9, –10, –13, –20, –X	1,202d	2,709u	2,369u	2,202u	3,173u
46, XX[17]/NCCAs [6]	–6, –8, –9, –10, –14	25,563d	11,096d	5,881d	13,187d	9,409d
44~78, XX,+9[2],+19[2],-20[3] [cp5]/46, XX[1] NCCAs [7]	–14, –16, –19, –20, –21, –22, +2, +5, +7, +8, +9, +11, +12, +13, +14, +18, +19	7,485u	2,852d	2,614d	9,911u	15,412u
46, XX[9]/NCCAs [6]	–3, –4, –15, –17, –22,-X, +8	7,857u	29,000u	18,430u	15,878u	17,101u
39~49, XX,-15[3],+16[2][cp5]/ 46, XX[8] NCCAs [4]	–1, –2, –3, –5, –6, –7, –10, –13, –15, –16, –18, –19, –X, +2, +4, +6, +10+19, +22	21,917u	316,926u	174,127u	179,644u	48,705u
45, X,-X,[3],-16[3]/46, XX[8] NCCAs [4]	–3, –5, –7, –14, –15, –16, –18, –19,-20, –X, +15, polyploidy	2,763d	2,045d	1,334d	1,671d	1,520d
40~44, X,-X[2]/46, XX[6] NCCAs [7]/ 46, XX[8]/NCCAs [7]	–3, –6, –7, –15, –16, –17, –18, –20, –22	98,633u	5,688u	7,130u	342,272u	303,594u
46, XX[9]/NCCAs [3]	–2, –5, –10, –11, –15, –17, –22	9,741u	2,654u	4,608u	2,547u	3,130u
46, XX[15]/NCCAs [5]	–2, –4, –5, –6, –15, –16, –17, –18, –19, –22	1,038u	4,931d	1,262d	2,315d	1,520d
46, XX[1]/NCCAs [1]	–7, –X	20,908d	53,520d	44,818d	39,698d	35,115d
46, XX[1]/NCCAs [2]	–19	4,395d	53,150d	16,178d	16,576d	24,488d
46, XX[3]/NCCAs [5]	–6, –9, –10, –11, –12, –15, –17, –18, –22	2,034u	4,147d	2,275d	1,166d	3,468d

NCCAs: non-clonal chromosome aberrations; u: up-regulation; d: down-regulation; Gene locations: *POLE-12q24.33, PTEN-10q23.31, TP53-17q13.1, PIK3CA-3q26.32, ARID1A-1p35.3*

Although the locations of the genes on the chromosomes are: POLE-12q24.33, PTEN-10q23.31, TP53-17q13.1, PIK3CA-3q26.32, and ARID1A-1p35.3, unfortunately, there is no statistical difference between the cytogenetic findings and the results that we obtained with quantitative reverse transcription polymerase chain reaction (RT PCR). The reason for this is sensitivities of the classical cytogenetic technique and the RT PCR technique is quite different from each other and insufficient to compare these methods, and the changes in gene expression don't depend only on the changes in the copy number of the genes. While large-scale chromosomal abnormalities (insertion/deletion) can be detected with classical cytogenetics, only gene-based examinations with RT PCR are possible. The small number of cells analyzed is an important factor and a major limitation of our study. At the same time, the inability to follow-up on the survival of the patients is another limitation of the study.

Table 5. Comparison of the regulation status according to the presence of a chromosomal abnormality

Gene	Chromosomal abnormality				χ2	p
	NCCAs		CCAs			
	n	%	n	%		
POLE						
Up-regulation	7	50.0	4	80.0	1.360	0.338
Down-regulation	7	50.0	1	20.0		
PTEN						
Up-regulation	7	50.0	3	60.0	0.148	1.000
Down-regulation	7	50.0	2	40.0		
TP53						
Up-regulation	8	57.1	3	60.0	0.012	1.000
Down-regulation	6	42.9	2	40.0		
ARIDA						
Up-regulation	7	50.0	4	80.0	1.452	0.338
Down-regulation	7	50.0	1	20.0		
PIC3CA						
Up-regulation	8	57.1	4	80.0	0.827	0.603
Down-regulation	6	42.9	1	20.0		

χ2: Fisher exact test.

Conclusions

We recommend surgeons and oncologists work with diagnostic methods such as chromosomal microarray and whole genome sequencing since they are more sensitive in the management of targeted therapies. Increased expression of POLE, TP53, and PIK3CA genes is known associated with decreased survival, poor prognosis, and metastasis. We believe that silencing with CRISPR/Cas9-mediated genome editing technology using primary tissue samples may be a potential strategy in the treatment of patients and will be the focus of future research. At the same time, the up-regulation of tumor suppressor genes such as PTEN, TP53, and ARID1A in our study shows that not only these genes are involved but also different pathways and factors play a role in tumorigenesis. The increased number of NCCAs shows that these abnormalities cannot be underestimated in cancer cases and play an important role in the development of ECs, which indicates the need for further research.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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