The relationship between expression of p53/bcl-2 and clinicopathological criteria in endometrioid adenocarcinomas of the endometrium

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Summary

Objective: Thirty patients with endometrioid adenocarcinomas of the endometrium who had undergone total abdominal hysterectomy and bilateral salpingo-oophorectomy were reviewed histopathologically.

Materials and Methods: Tissues were stained immunohistochemically with p53 and bcl-2, respectively. Ten cases were selected as grade 1, ten cases grade 2 and ten cases grade 3.

Results: We observed 14 cases (46.6%) of bcl-2 and four cases (13.3%) of p53 positivity; p53 expression showed an opposite correlation to bcl-2 staining, estrogen and progesterone.

Conclusion: We observed a decrease in bcl-2 reactivity and an increase in p53 positive staining as the histological differentiation worsened.

Key words: p53; bcl-2; Endometrioid adenocarcinomas; Endometrium.

Introduction

Recently many studies about the importance of genomic changes have been performed. Tumorigenesis is considered to result from many progressive gene alterations as activation of oncogenes and inactivation of tumor suppressor genes take place. One of these genes is the bcl-2 oncogene, which codes proteins blocking apoptosis in pathological conditions. Bcl-2 acts as an inhibitor of apoptosis; it may prolong the survival of genetically altered cells. As a tumor supressor gene, p53 induces apoptosis but a mutant p53 may inhibit it [1-3].

This study examined the relationship between bcl-2 and p53 in endometrioid adenocarcinomas of the endometrium.

Materials and Methods

Materials from 30 patients with squamous cell carcinomas of the cervix who had undergone total abdominal hysterectomy and bilateral salpingo-oophorectomy at Kayseri Obstetric Hospital and Medical Faculty of Gaziantep and Harran Universities were evaluated. All of the patients were aged 43-70 years; 50% were 50-60 years old. Ten cases were selected as grade 1, ten cases grade 2 and ten cases grade 3 (WHO histopathologic classification). The most hypercellular slides from each case (4-6 μm thick) were chosen from paraffin-embedded tumor tissues and stained immunohistochemically using an avidin-biotin peroxidase method for p53 expression and bcl-2. Tonsillar tissue for bcl-2 and p53, breast carcinoma tissue for estrogen and progesterone were used as positive control slides; and normal skin was used as a negative control slide to determine the specifity of the immunohistochemical staining. Expression of bcl-2 (clone 124) and p53 (DO 7, monoclonal) in each differentiation of the endometrioid carcinoma was assessed to find out if there were any expression differences. More than 5% nuclear and cytoplasmic staining of tumor cells was accepted as positive for p53 and bcl-2, respectively.

Results

We detected positive staining in 14 of 30 women (46.6%) for bcl-2 and four (13.3%) for p53 (Tables 1 and 2); p53 expression showed the opposite correlation to bcl-2 staining. We observed a decrease in bcl-2 reactivity and an increase in p53 positive staining as the histological differantiation worsened (Table 2). There was a strong

Table 1. — *Relationship between immunoreactivity and clinicopathological factors.*

Clinicopathological features	bcl-2 immunoreactivity	p value
Estrogen receptor		
Positive	12/19 (63.1%)	$p < 0.05$
Negative	2/11 (18.1%)	
Progesterone receptor		
Positive	12/19 (63.1%)	$p < 0.05$
Negative	2/11 (18.1%)	
p53		
Positive	1/4 (25.0%)	$p > 0.05$
Negative	13/26 (50.0%)	
Menopause status		
Premenopause	6/7 (85.7%)	$p < 0.05$
Postmenopause	8/23 (34.7%)	

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Table 2. — *Relationship between bcl-2/p53 reactivity and histological grade.*

Histological grade	bcl-2	p53
Low grade	9/10 (10.0%)	0/10 (0.0%)
Intermediate grade	4/10 (40.0%)	1/10 (10.0%)
High grade	1/10 (10.0%)	3/10 (30.0%)
p value	$p < 0.05$	$p > 0.05$

relationship between immunoreactivity of bcl-2 and progesterone/estrogen; intensive staining was observed in low grade tumors and premenopausal women with endometrioid adenocarcinomas of the endometrium (Table 1). For statistics, the chi-square test was used.

Discussion

Bcl-2 is a proto-oncogene that inhibits programed cell death, which is manifest morphologically as apopotosis. In the endometrium, bcl-2 expression assessed by immunohistochemistry varies during the menstrual cycle and is highly expressed in the proliferative phase, with down-regulation during the secretory phase [4]. Bcl-2 protein expresses high levels in simple hyperplasia but progressively diminishes in atypical hyperplasia and with decreasing differentiation in invasive endometrial adenocarcinoma [5-8]. Apoptosis is also increased in poorly differentiated endometrioid carcinoma compared with well differentiated endometrioid adenocarcinomas. Loss of bcl-2 expression has also been associated with negative progesterone receptor (PR) status which is a poor prognostic feature [5, 9].

The p53 gene is classified as a tumor suppressor gene. Mutations or over-expression of the p53 protein has been generally related to increased histologic grade in endometrial adenocarcinoma; p53 is confined to a subset of grade 3 endometrioid carcinomas. Mutations in p53 are found in approximately 10% of all endometrioid carcinomas, with most occurring in grade 3, and occasionally in grade 2 tumors. Overall, p53 mutations occur in approximately 50% of grade 3 tumors or they have not been identified in grade 1 tumors or endometrial hyperplasia [8, 10-15]. These results support p53 expression as a prognostic indicator.

Generally an inverse relationship between bcl-2 and p53 expression has been reported. High grade tumor reactivity for p53 has been reported to be strongly positive but for bcl-2 weakly positive [8, 11].

Expression of estrogen and progesterone receptor immunoreactivity has been found in the majority of endometrial carcinoma cases. Bcl-2 is closely related to positive staining of estrogen and progesterone receptors in endometrioid carcinoma cells and premenopausal status of the patient. Well to moderately differentiated endometrioid carcinomas usually express estrogen and progesterone receptors whereas poorly differentiated endometrioid carcinomas are usually negative for hormone receptors by immunohistochemistry [13].

This study examined the relationship between bcl-2/p53 and histological prognostic groups. As a result, our cases were consistent with the literature in that expression of bcl-2 inhibits apoptosis, but does not stimulate cell proliferation. Bcl-2 positive staining was accompanied by good prognostic parameters such as low histological grade and absence of mutant p53 reactivity. Bcl-2 positive tumors appear to have a better prognosis. However, before we can rely on the value of bcl-2 as a prognostic factor, further studies need to be undertaken on larger patient groups.

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