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Pr and Bcl-2 Expression in Endometrium Hyperplasia and Carcinoma

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Abstract **Original Research Article**

Introduction*:** Progesterone receptor and Bcl-2 expression were evaluated in endometrial hyperplasia and endometrial carcinoma in this study. ***Objective/aim: Bcl-2 expression in endometrial carcinoma is regulated in a hormone dependent manner. Bcl-2 expression and progesterone receptor are focal and less intense in atypical hyperplasia and carcinoma than proliferative endometrium and hyperplasia (without atypia). Bcl-2 expression is positively correlated with progesterone receptor in normal and hyperplastic endometrium and well differentiated carcinoma. ***Methods and material:*** We evaluated 10 simple, 10 complexes (without atypia), 1 complex (with atypia) hyperplasia and 25 endometrial adenocarcinoma at Ankara Training and Research Hospital. At these cases, we searched Bcl-2 expression and progesterone receptor and evaluated the correlation of these two markers. In endometrial hyperplasia Bcl-2 expression and progesterone receptor were higher than those seen in endometrial carcinoma. At an atypical hyperplasia case, the two markers were negative. ***Statistical analysis:*** For statistical analysis, MINITAB for Windows Ver. 13.0 statistical Package Program was used. Whether there was a relation between index values was researched by computing Spearman Rank Correlation Coefficient. Comparison of the ratios was conducted using Z-Test. $P<0.05$ and $P<0.01$ were considered significant. ***Results:*** In this study Bcl-2 expression was positively correlated with progesterone receptor in simple hyperplasia, complex hyperplasia and endometrial carcinoma. This result was consistent with literature. ***Conclusion:*** Bcl-2 and PR positivity was related to good prognosis in endometrial carcinoma. Also Bcl-2 and PR negativity requires being careful for endometrial carcinoma in endometrial hyperplasia case.

Keywords: Endometrial hyperplasia, Endometrial carcinoma, Bcl2, Progesterone receptor.

INTRODUCTION

Endometrial carcinoma is the most frequently seen malign tumour in female genital system. It remains the fourth most frequently seen cancers in the USA. Every year, with 33.000 endometrial carcinoma diagnoses, 4000 patients die of this disorder in the USA [1-4].

As well as developing on the basis of endometrial hyperplasia depending on excessive oestrogen stimulation, endometrial carcinoma may also develop de novo without oestrogen stimulation [5]. Recently, it has been shown that apoptosis and related proteins also play a significant role in the development of endometrial carcinoma. One of these is Bcl-2; an antiapoptotic protein [1, 5-11].

In endometrium, Bcl-2 expression is under hormonal control. Bcl-2 expression is intense in simple and complex endometrial hyperplasia without atypia and decreases in atypical complex hyperplasia and endometrial carcinoma [1, 10, 12, 13]. Moreover, existence of Bcl-2 expression in endometrial carcinoma is indicative of good prognosis and positively correlated with PR positivity [14].

PR expression is more intense in endometrial hyperplasia than in endometrial carcinomas. PR positive endometrial carcinomas have good prognosis while PR negative endometrial carcinomas show aggressive behaviour [10, 14]. In this study, PR positivity and Bcl-2 expression were researched in 10 simple, 10 complex (without atypia) endometrial hyperplasia, 1 complex (with atypia) hyperplasia and 25 endometrial adenocarcinoma cases at Pathology Department of Ankara Training and Research Hospital. Whether there was a correlation PR positivity and Bcl-2 expression was also researched.

MATERIAL & METHOD

The study involved 10 simple, 10 complex (without atypia) endometrial hyperplasia, 1 complex (with atypia) hyperplasia and 25 endometrial adenocarcinoma patients, who had applied to Pathology Department of Ankara Training and Research Hospital in 2002 and 2003. Patient consent forms of the participants for operations are available. Since the study was retrospective, ethical board approval and consent weren't sought.

All patients with simple and complex (with/without atypia) endometrial hyperplasia were Probe-C material. Among the samples of endometrial adenocarcinoma patients, 6 were hysterectomy materials while the other 19 were Probe-C materials [Table1].

Table-1: Distribution of cases included in the study

Case	P.C.	Hysterectomy	Total
Simple (without atypia) Endometrial hyperplasia	10	-	10
Complex (without atypia) Endometrial hyperplasia	10	-	10
Complex (atypical) Endometrial hyperplasia	1	-	1
Endometrial Adenocarcinoma	19	6	25
Total	40	6	46

All endometrial carcinomas were endometrioid adenocarcinoma. No histopathologic grade was given to Probe-c material, but among the 6 hysterectomy materials, 3 were evaluated as histopathologic grade 1, 2 as grade 2 and 1 as grade 2 (adenosquamous type) [Table 2].

Table-2 : Histopathological grade in hysterectomy specimen

Grade	Case number
Grade 1 (endometrioid adenocarinoma)	3
Grade 2 (endometrioid adenocarcinoma)	2
Grade 2 (endometrioid-adenosquamous type)	1
Total	6

Taking the suitable tissue samples from hysterectomy materials and probe-C materials, paraffin blocks were prepared out of these tissue samples. 5-micron sections were taken from the paraffin blocks of Probe-C and hysterectomy materials and were stained with Hematoxylin-Eozin (H.E.). Histomorphological evaluation was conducted on these sections. These evaluations were based on Kurman and Norris classification, conducted in 1986, whereas FIGO grade and stage were the basis for carcinomas [15]. Also, the sections prepared out of paraffin blocks were taken on polylysine lamina and PR and Bcl-2 were applied using immunohistochemical method. "Lab-vision (Klon SP2, epitope 412-526aa)" was used for PR and "DAKO, (Klon 124, subklas Ig GI, Kapa kod N1587)" was used for Bcl-2.

Cytoplasmic staining was conducted for Bcl-2 and nuclear staining was conducted for PR in endometrial gland epithelium cells. For Bcl-2, tonsil sections were used as positive control. Also, lymphocytes in endometrial stroma were removed as internal control. For PR, endometrial stromal and myometrial cells were used as positive control. Immunohistochemically evaluation was based on an index used by Makato Saegusa *et al*. [10]. For Bcl-2 and PR, staining percentage in endometrial glands was

1- less than 10%
2- 10-30%
3- 30-50%
4- more than 50%

And staining density was
0: Negative
+1: poor staining
+2: medium staining
+3: strong staining

(Positive control was accepted +3)

Staining index was found by multiplying staining percentage by staining density for both Bcl-2 and progesterone. Index was evaluated as
0: Staining negative
1-5: poor staining
6-8: medium staining
9-12: strong staining.

For statistical analysis, MINITAB for Windows Ver. 13.0 statistical Package Program was used. Whether there was a relation between index values was researched by computing Spearman Rank Correlation Coefficient. Comparison of the ratios was conducted using Z-Test. $P<0.05$ and $P<0.01$ were considered significant.

RESULTS

All 10 patients with simple endometrial hyperplasia (100%) showed positive reaction with Bcl-2 (7 strong (70%), 3 medium (30%) positive). All 10 patients with simple endometrial hyperplasia (100%)

were stained positive with PR (9 strong (90%), 1 medium (10%) positive). All 10 patients with complex endometrial hyperplasia (without atypia) (100%) showed positive reaction with Bcl-2 (4 strong (40%), 4 medium (40%), 2 poor (20%) positive). All 10 patients with complex endometrial hyperplasia (without atypia) (100%) were stained positive with PR (7 strong (70%), 2 medium (20%), 1 poor (10%) positive). 1 patient with complex endometrial hyperplasia (with atypia) was Bcl-2 and PR negative [Table3, Table4, Table5].

Table-3: Bcl-2 and PR positive case percent in endometrial hyperplasia and endometrial carcinoma

	Bcl-2 (%)	PR (%)
Simple endometrial hyperplasia (without atypia)	100	100
Complex endometrial hyperplasia (without atypia)	100	100
Endometrial carcinoma	56	64

Table-4: Distrubution of cases according to staining index with Bcl-2 and PR in simple (without atypia) endometrial hyperplasia

Staining index	Bcl-2 (%)	PR (%)
Strong positivity (9-12)	70	90
Moderate positivity.(6-8)	30	10
Weak positivity(0-5)	0	0
Negative	0	0

Table-5: Distrubution of cases according to staining index with Bcl-2 and PR in complex (without atypia) endometrial hyperplasia

Staining index	Bcl-2 (%)	PR (%)
Strong positivity (9-12)	40	70
Moderate positivity (6-8)	40	20
Weak positivity (0-5)	20	10
Negative	0	0

Among the 25 patients diagnosed endometrial carcinoma, 14 (56%) were positive with Bcl-2 (4 strong (16%), 4 medium (16%), 6 poor (24%) positive) and 11 (44%) were negative. While 16 patients diagnosed endometrial carcinoma (64%) were stained positive with PR (6 strong (24%), 4 medium (16%), 6 poor (24%) positive), no PR staining was seen in 9 (36%). [Table 6: Bcl-2 and PR in Endometrial carcinomas]

Table-6: Distrubution of cases according to staining index with Bcl-2 and PR in endometrial carcinoma

Staining index	Bcl-2 (%)	PR (%)
Strong positivity (9-12)	16	24
Moderate positivity (6-8)	16	16
Weak positivity (0-5)	24	24
Negative	44	36

The difference between Bcl-2 expression rate (%100) in simple and complex hyperplasia and Bcl-2 expression rate (%56) in endometrial carcinoma is significant without a need for any statistical check [Figure 1, 2, 3, 4].

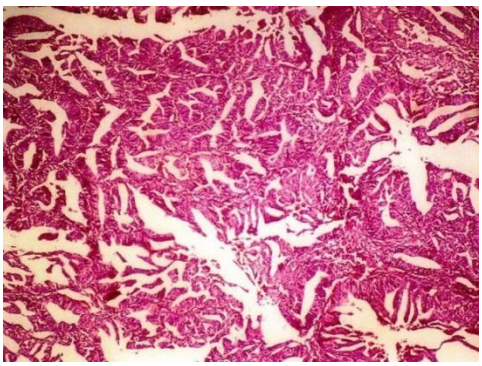

Fig-1: Well differentiated adenocarcinoma(endometrioid type), 100 X H&E

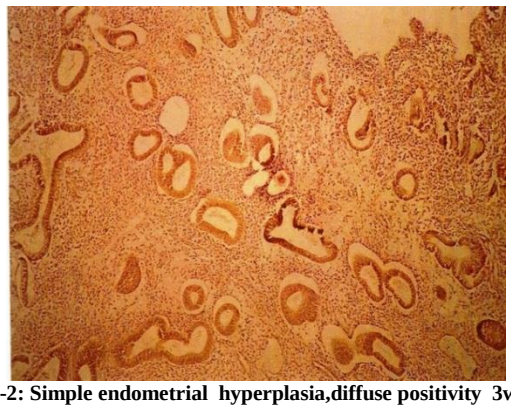

Fig-2: Simple endometrial hyperplasia,diffuse positivity 3with Bcl-2 in glandular epithelium , 100 X Bcl-2

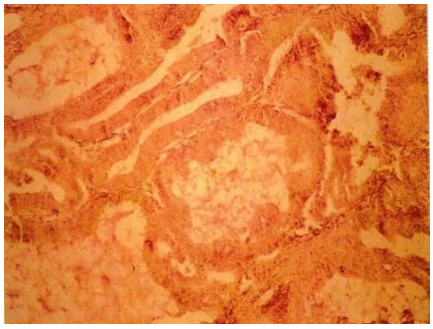

Fig-3: Complex (without atypia) endometrial hyperplasia, diffuse positivity with Bcl-2 , 100 X Bcl-2

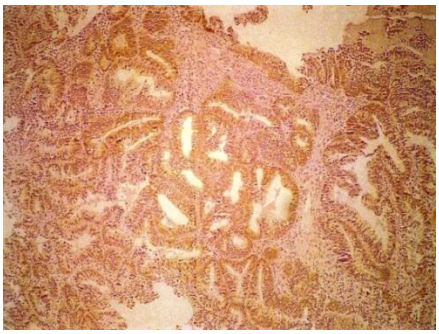

Fig-4: Endometrial carcinoma focal positive staining with Bcl-2, 100 X Bcl-2

The difference between PR positivity rate (%100) in simple and complex endometrial hyperplasia and PR positivity rate (%64) in endometrial carcinoma is significant without a need for any statistical check [Figure 5, 6, 7].

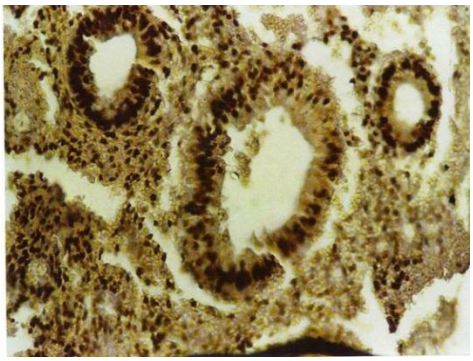

Fig-5 Simple endometrial hyperplasia, diffuse and strong positive staining with PR , 200 X PR

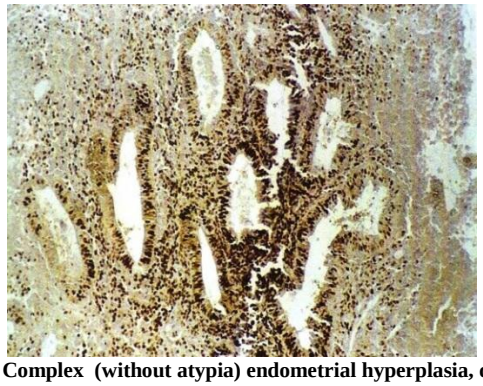

Fig-6: Complex (without atypia) endometrial hyperplasia, diffuse positive staining with PR , 100 X PR

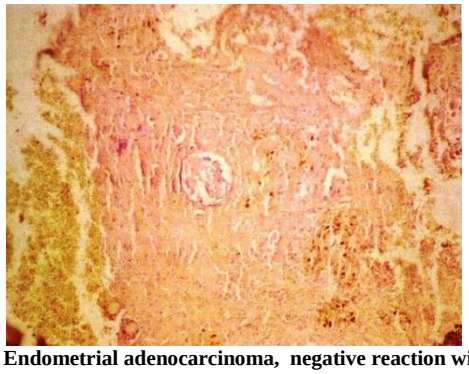

Fig-7: Endometrial adenocarcinoma, negative reaction with PR in glandular epithelium and positive reaction in stroma , 100 X PR

When compared with the PR positivity and Bcl-2 expression rates in endometrial carcinoma, those in simple and complex endometrial hyperplasia were found to be higher.

There is no difference between simple and complex endometrial hyperplasia in terms of both Bcl-2 expression and PR. Without a need for a statistical check, all simple and complex hyperplasia patients were stained positive. The difference between strong positivity rate and medium positivity rate for Bcl-2 expression in simple endometrial hyperplasia is statistically significant (P= 0.003) - (P<0.01). The difference between strong positivity rate and medium positivity rate for PR in simple endometrial hyperplasia is also statistically significant (P=0.004) - (P<0.01).

The difference between strong positivity rate and poor positivity rate for PR in complex endometrial hyperplasia (without atypia) is also statistically significant (P=0.007) - (P<0.01). The difference between strong positivity rate and poor positivity rate for Bcl-2 expression in complex endometrial hyperplasia (without atypia) is also statistically significant (P=0.003) - (P<0.01).

Statistically significant strong and medium level positive staining was seen in simple and complex endometrial hyperplasia (without atypia) for Bcl-2 and PR. When compared with Bcl-2 and PR staining rates in hyperplasia, those in endometrial carcinomas were significantly low; however, no statistically significant difference was found between strong, medium and poor level staining rates for Bcl-2 and PR in carcinomas.

In terms of the correlation between Bcl-2 and PR, there is a positive correlation between Bcl-2 and PR in simple endometrial hyperplasia (P=0.032)-(P<0.05), in complex endometrial hyperplasia (without atypia) (P=0.024)- (P<0.05) and in endometrial carcinoma (P=0.003)-(P<0.01).

DISCUSSION

Hyperestrogenism is one of the most important risk factors in endometrial carcinoma development [2, 15]. Accompanied by hyperestrogenism, endometrial carcinomas develop on the basis of hyperplasia, their grade and stages are generally low with good prognosis [16]. De novo developing endometrial carcinomas generally have high grade and stage with bad prognosis [16]. It has recently been shown that apoptosis and apoptosis-related proteins also have important roles in endometrial carcinoma development [1, 6, 8, 11, 13, 16, 17].

Of these proteins, Bcl-2 is localised in chromosome 18. By inhibiting apoptotic cell death, Bcl-2 expression prolongs cell life [16]. An increase is seen in Bcl-2 expression in such various tumour tissues as breast, thyroid and colon tumours. Bcl-2 expression is on the increase in endometrial carcinomas. Studies also show that Bcl-2 expression differentiates depending on aggressiveness and differentiation of tumour. When compared with low grade carcinomas, Bcl-2 expression in high grade carcinomas is rather low or doesn't exist. It is thought that Bcl-2 expression might be supressed during cancer progression. Therefore, Bcl-2 expression might be a significant marker for cancer progression and prognosis [18].

Bcl-2 expression is partly under hormonal control in endometrial epithelium. Bcl-2 is expressed in endometrium throughout proliferative phase. Proliferative phase is at the highest level at the end. Bcl-2 expression disappears at secretion phase [16].

Bcl-2 expression is regulated with oestrogen and progesterone levels. Bcl-2 expression is high in endometrial carcinomas, during which oestrogen is high [16]. ın endometrial hyperplasia, Bcl-2 is diffuse and intensely positive [16]. Bcl-2 expression in complex atypic hyperplasia and endometrial carcinoma is focal and less intense. Bcl-2 plays a role in simple and complex (without atypia) hyperplasia development but doesn't play a role in complex atypic hyperplasia and carcinoma development [16, 18].

Also, malign changes in endometrial tissue are together with decrease in hormone addiction and loss in ER and PR [14]. Survival tends to be good in ER and PR positive carcinomas. Aggressive behaviour occurs in ER and PR negative endometrial carcinomas [14].

Another important result is the close relation between PR positive and Bcl-2 positive carcinomas. Bcl-2 expression is under hormonal control while it shows positive correlation with PR existence in both endometrial hyperplasia and endometrial carcinomas [14]. PR and Bcl-2 positive endometrial carcinomas have good histologic appearance, are low histologic grade, show superficial myometrial invasion and have good clinical progress [14].

Bcl-2 regulation in normal endometrial tissue is hormone dependent. It was shown that PR positive malign endometrial cells expressing Bcl-2 have a phenotype that has a close relation with normal proliferative endometrium [14]. PR negative endometrial neoplasia show aggressive behaviour [14].

Efthimious Sivridis *et al*. found PR positivity for 164 endometrial carcinoma 32%. In this study, PR loss decreased significantly in non-endometrioid carcinomas. It is correlated with Bcl-2 expression loss and shows aggressive progress [14]. Liao *et al*. found PR positivity 92% in grade I tumours and 44% in grade 3 tumours [19]. As the grade increased, PR positivity rate decreased [19]. Ehrlich *et al*. found PR positivity 52,6% in 175 endometrial carcinomas [20].

In the literature, PR positivity varies between 92% and 32% in endometrial carcinomas, which is due to histologic type and grade. However, PR positivity is clearly higher in endometrial hyperplasia than carcinomas [14].

CONCLUSION

In our study, we found PR positivity 100% in simple and complex (without atypia) hyperplasia and 64% in endometrial adenocarcinomas. Patients with simple and complex (without atypia) hyperplasia were stained statistically significantly strong and medium positive. One atypic hyperplasia patient was negative to PR. Compared with the carcinomas, staining in the hyperplasia was significantly intense with no need for statistics and the results were in line with the literature.

Review of the studies about Bcl-2 shows that Linda B. *et al*. found Bcl-2 expression in endometrial carcinoma significantly lower than in endometrial hyperplasia (with/without atypia) [21]. In the studies of Hassan M. *et al*. the mean value of Bcl-2 positive cells was 9.70% in hyperplastic endometrium and 6,79% in endometrial carcinoma while it fell down to 3.10% in Grade 3 carcinoma [22].

Katsuji K. *et al*. found Bcl-2 expression in endometrial hyperplasia (without atypia) significantly higher than in atypic hyperplasia and endometrial carcinoma [23]. they didn't see any significant difference between grade 1, 2 and 3 in endometrial carcinoma in terms of Bcl-2 expression [23].

In another study, Hassan M. *et al.* found Bcl-2 reactivity %92 in simple hyperplasia and %100 in complex hyperplasia. They determined positivity 54% in Grade I carcinoma, 18% in Grade 2 and 57% in Grade 3; however, no significant relation was found in this study between Bcl-2 expression and histopathologic grade [24].

In the study of Taskin *et al*. Bcl-2 was positive in 42 of 57 endometrial carcinomas and in this study,

Bcl-2 expression was found related with stage and grade. Bcl-2 expression showed correlation with PR positivity [1].

In the study of Roman Miturski *et al*. Bcl-2 expression was found 40% in proliferative endometrium, 80% in simple hyperplasia and 80% in complex hyperplasia while it was 28% in endometrial carcinoma [5]. In this study, Bcl-2 expression was evaluated to play a role in simple and complex hyperplasia (without atypia) development, but not to play a role in carcinoma and atypic hyperplasia development [5]. Makoto S *et al*. found Bcl-2 expression 78,4% in tubular component and 50% in solid component of endometrial carcinoma while they also found PR positivity 86,4% in tubular component and 52,3% in solid component. In this study, a positive correlation was seen between PR existence and Bcl-2 expression [10].

CONCLUSION

In our study, Bcl-2 expression was positive in all the patients (100%) with simple and complex hyperplasia (without atypia). In the patients with simple and complex endometrial hyperplasia, statistically significant strong and medium staining existed for Bcl-2 and the results were consistent with the literature. Bcl-2 was negative in one patient with complex atypic hyperplasia. PR positivity was 56% in endometrial carcinoma. Compared with hyperplasia, expression existed in carcinomas in a small number of patients with no need for statistics and there was no significant difference between strong, medium and poor staining. Our results for Bcl-2 expression were consistent with the literature.

A positive correlation was determined between PR and Bcl-2 expression for both complex endometrial hyperplasia and carcinoma. Our results were consistent with the literature [10, 14]. Efthimious Sivridis *et al*. found a positive correlation between PR and Bcl-2 in 164 patients with endometrial carcinoma [14]. Makoto Saegusu *et al*. found a positive correlation between PR and Bcl-2 in both endometrial hyperplasia and endometrial carcinoma (tubular component) [10].

In our study we found a positive correlation between PR and Bcl-2. Our results were consistent with the literature.

Bcl-2 expression contributes to simple and complex hyperplasia development, but has no role in atypic hyperplasia and carcinoma development [5, 22]. It is thought that a fall in Bcl-2 expression in complex atypic hyperplasia and carcinoma decreases modification in cellular mechanism and this decreases Bcl-2 expression [16]. Endometrial carcinoma is a hormone dependent tumour. Also, a loss in steroid hormone receptors in endometrial carcinoma is accompanied with aggressive behaviour and deep myometrial invasion [14].

An important matter is that Bcl-2 expression in normal endometrial glands is related to ER and PR. Overian hormones of Bcl-2 expression are thought to be under the influence of oestrogen in particular [10, 14]. Progesterone synthesis provides oestrogen effect in hormone-sensitive cells [10, 25].

Bcl-2 expression is more complex in carcinomas and hyperplasia than in normal endometrial epithelium. Multiple regulator proteins play a role in Bcl-2 expression [10]. PR case was found to be more significant in terms of prognosis. There is a positive correlation between Bcl-2 expression and PR in both hyperplasia and carcinomas [10, 14].

Bcl-2expression is correlated with PR positivity. Consequently, while the fact that Bcl-2 and PR are positive together shows good prognosis in endometrial carcinomas, Bcl-2 negativity and PR negativity in hyperplasia patients may require caution in the future for carcinoma development [10, 14].

We think that as studies about apoptotic genes and steroid receptors advance, significant knowledge about prognosis and treatment will be acquired.

REFERENCES

1. Taskin M, Lallas T, Barber HR, Shevchuk MM. bcl-2 and p53 in endometrial adenocarcinoma. Mod Pathol 1997;10(7):728-34.
2. Ioffe OB, Papadimitriou J, Drachenberg CB. Correlation of proliferation indices, apoptosis, and related oncogene expression (bcl-2 and c-erbB-2) and p53 in proliferative, hyperplastic, and malignant endometrium. Hum Pathol. 1998;29(10):1150-9.
3. Kounelis S, Kapranos N, Kouri E, Coppola D, Papadaki H, Jones MW. Immunohistochemical profile of endometrial adenocarcinoma: a study of 61 cases and review of the literature. Mod Pathol. 2000;13(4):379-88.
4. GL. M. Diagnosis of premalignant endometrial disease. J Clin Pathol. 2002;55(5):326-31. PMCID: PMC1769645.
5. Miturski R, Semczuk A, Tomaszewski J, Jakowicki J. bcl-2 protein expression in endometrial carcinoma: the lack of correlation with p53. Cancer Lett. 1998 Nov 13;133(1):63-9.
6. Wang X, Huang Z, Di W, Lin Q. Comparison of D&C and hysterectomy pathologic findings in endometrial cancer patients. Arch Gynecol Obstet. 2005;272(2):136-41. Epub 2005 Jan 22.

7. Terzea D, IC, Vasilescu F, Andrei F, Dobrea C, Nicolae A, Georgescu A, Mircea F, Ceauşu M, Vişan A, Mihai M, Ardeleanu C. Quantification of apoptotic phenomenon on endometrial biopsies in postmenopausal patients under hormonal replacement therapy (HRT). Rom J Morphol Embryol. 2007;48(2):107-11.
8. Song JY, Kim J, Lee JK, Lee NW, Yeom BW, Kim SH, Lee KW. BAG-1 expression in normal endometrium, endometrial hyperplasia and endometrial cancer. Acta Obstet Gynecol Scand. 2008;87(8):862-7.
9. Zhang R, He Y, Zhang X, Xing B, Sheng Y, Lu H, Wei Z. Estrogen receptor-regulated microRNAs contribute to the BCL2/BAX imbalance in endometrial adenocarcinoma and precancerous lesions. Cancer Lett. 2012;314(2):155-65. Epub 2011 Sep 29.
10. Saegusa M, Kamaya Y, Isono M, Okayasu I. Bcl-2 expression is correlated with a low apoptotic index and associated with progesterone receptor immunoreactivity in endometrial carcinomas. J Pathol. 1996;180(3):275-83.
11. Vaskivuo TE, Stenback F, Karhumaa P, Risteli J, Dunkel L, Tapanainen JS. Apoptosis and apoptosis-related proteins in human endometrium. Mol Cell Endocrinol. 2000;165(1-2):75-83.
12. Lu PJ, Lu Q, Rughetti A, Taylor-Papadimitriou J. bcl-2 overexpression inhibits cell death and promotes the morphogenesis, but not tumorigenesis of human mammary epithelial cells. J Cell Biol. 1995;129(5):1363-78.
13. Moriyama T, Littel R, Debernardo R, Oliva E, Lynch MP, Rueda BR, Duska LR. BAG-1 expression in normal and neoplastic endometrium. Gynecol Oncol 2004;94(2):289-95.
14. Sivridis E, Giatromanol A, Koukourakis M, Anastasiadis P. Endometrial carcinoma: association of steroid hormone receptor expression with low angiogenesis and bcl-2 expression. Virchows Arch. 2001;438(5):470-7.
15. J R. Ackerman's Surgikal pathology. Vol 1-2 Sevent edition . USA 1989.
16. Niemann TH, Trgovac T, McGaughy VR, Vaccarello L. bcl-2 expression in endometrial hyperplasia and carcinoma. Gynecol Oncol 1996;63(3):318-22.
17. Pinheiro A, Antunes AJ, Andrade L1, De Brot L2, Pinto-Neto AM1, Costa-Paiva L1. Expression of hormone receptors, Bcl‐2, Cox‐2 and Ki67 in benign endometrial polyps and their association with obesity. Mol Med Rep 2014;9(6):2335-41. Epub 2014 Apr 9.
18. Dorjgochoo T, Xiang Y, Long J, Shi J, Deming S, Xu WH, Cai H, Cheng J, Cai Q, Zheng W, Shu XO. Association of genetic markers in the BCL-2 family of apoptosis-related genes with endometrial cancer risk in a Chinese population. PLoS One. 2013;8(4). PMCID: PMC3634058
19. Liao BS, TL, Leung BS, Yu WC, Potish RA, Prem KA. Cytoplasmic estrogen and progesterone receptors as prognostic parameters in primary endometrial carcinoma. Obstet Gynecol. 1986;67(4):463-7.
20. Ehrlich CE, Young P, Stehman FB, Sutton GP, Alford WM. Steroid receptors and clinical outcome in patients with adenocarcinoma of the endometrium. Am J Obstet Gynecol. 1988;158(4):796-807.
21. Mora LB, Diaz J, Cantor AB, Nicosia SV. Differential diagnosis of endometrial hyperplasia and carcinoma by computerized image cytometry of cell proliferation, apoptosis and Bcl-2 expression. Ann Clin Lab Sci. 1999;29(4):308-15.
22. Morsi HM, Leers M, Radespiel-Tröger M, Björklund V, Kabarity HE, Nap M, Jäger W. Apoptosis, bcl-2 expression, and proliferation in benign and malignant endometrial epithelium: An approach using multiparameter flow cytometry. Gynecol Oncol. 2000;77(1):11-7.
23. Kokawa K, Shikone T, Otani T, Nishiyama R, Ishii Y, Yagi S, Yamoto M. Apoptosis and the expression of Bax and Bcl-2 in hyperplasia and adenocarcinoma of the uterine endometrium. Hum Reprod. 2001;16(10):2211-8.
24. Morsi HM, Leers M, Jäger W, Björklund V, Radespiel-Tröger M, el Kabarity H, Nap M, Lang N. The patterns of expression of an apoptosis-related CK18 neoepitope, the bcl-2 proto-oncogene, and the Ki67 proliferation marker in normal, hyperplastic, and malignant endometrium. Int J Gynecol Pathol. 2000;19(2):118-26.
25. Press MF, Udove J, Greene GL. Progesterone receptor distribution in the human endometrium. Analysis using monoclonal antibodies to the human progesterone receptor. Am J Pathol. 1988;131(1):112-24.