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THE ROLE OF BETA-CATENIN AND FOXP1 IN THE PATHOGENESIS OF POLYPOID ENDOMETRIOSIS

POLİPOİD ENDOMETRİOZİS PATOGENEZİNDE BETA-KATENİN VE FOXP1'İN ROLÜ

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ABSTRACT

Objective: To investigate whether beta-catenin and Forkhead box protein P1 (FOXP1) play a role in pathogenesis of polypoid endometriosis (PE).

Material and Method: Our study included fifteen cases of PE. Clinical findings were gathered from archived files of relevant clinics and pathology reports. All glass slides were re-examined for confirmation of the diagnosis and the detection of additional microscopic findings. An immunohistochemical examination was performed using anti beta-catenin and FOXP1 antibodies in fifteen cases of PE, and in a control group that contained nine cases of endometrial polyps (EP) and nine cases of conventional ovarian endometriosis (OE).

Result: Stromal nuclear beta-catenin expression was observed in six cases in PE, five cases in EP and one case in the OE group. Stromal FOXP1 staining in PE and EP was significantly reduced as compared to OE. Five PE and two EP cases showed stromal FOXP1 staining while all the OE cases showed stromal FOXP1 staining. The Stromal FOXP1 staining was statistically significant between PE vs OE (p=0.002) and EP vs OE (p=0.023) cases. There was no difference between PE and the control cases in terms of nuclear beta-catenin staining (p=0.69). There was no correlation between these two antibodies and histologic features.

Conclusion: The loss of stromal FOXP1 is another biological difference of PE and the overall similarity of expression of FOXP1 between PE and EP could be regarded as a contributing factor for polyp formation.

Keywords: Endometriosis, polyp, immunohistochemistry, FOXP1, beta-catenin

ÖZET

Amaç: Polipoid endometriozis (PE) patogenezinde Forkhead box protein P1 (FOXP1) ve beta-katenin'nin rolünün araştırılması.

Gereç ve Yöntem: Çalışmaya 15 PE olgusu dahil edilmiştir. Klinik bilgiler hastaların tıbbi kayıtlarından ve patoloji raporlarından elde edilmiştir. Tüm mikroskopik preperatlar tanının doğrulanması ve ek mikroskopik özelliklerin tanımlanması amacıyla tekrar değerlendirilmiştir. FOXP1 ve beta-katenin antikorları kullanılarak 15 PE ve kontrol grubu olarak dokuz endometrial polip (EP) ve dokuz ovarian endometriozis (OE) olgusuna immünhistokimyasal inceleme yapılmıştır.

Bulgular: Stromal nükleer beta-katenin boyanması altı PE, beş EP ve bir OE olgusunda gözlenmiştir. Stromal FOXP1 boyanması OE olgularına göre PE ve EP olgularında belirgin şekilde azalmış olup tüm OE olgularında stromal FOXP1 boyanması izlenirken beş PE ve iki EP olgusunda stromal FOXP1 boyanması saptanmıştır. PE ile OE ve EP ile OE olguları arasındaki stromal FOXP1 boyanması farkı anlamlıdır (sırasıyla p=0,002 ve p=0,023). Beta-katenin ile PE ve kontrol grubu olguları arasında anlamlı fark bulunmamıştır (p=0,69). Histolojik özelliklerle bu antikorların pozitifliği arasında ilişki yoktur.

Sonuç: PE olgularındaki FOXP1 kaybı PE ve konvansiyonel endometriosis arasındaki bir diğer biyolojik fark olarak tanımlanabilir. Ayrıca PE ve EP olgularındaki stromal FOXP1 boyanmasındaki benzerlik FOXP1'in polip oluşumunda rolü olduğunu düşündürmektedir.

Anahtar Kelimeler: Endometriozis, polip, immünhistokimya, FOXP1, beta-katenin

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INTRODUCTION

Endometriosis is a condition characterized by the presence of endometrial-like glands and stroma outside the uterine corpus. It usually affects women in reproductive age and its prevalence ranges between 5-10% (1-2). Polypoid endometriosis (PE) is a rare form of endometriosis which resembles endometrial polyps microscopically (3). It can form mass lesions that can be misdiagnosed as tumors clinically.

The forkhead box protein P1 (FOXP1) is a member of the forkhead box family of proteins that belongs to the P subfamily. It is a master regulator of embryonic stem cells pluripotency and acts as a tissue specific tumor suppressor or oncogene (4,5).

Beta-catenin is the key transcriptional factor of the canonical Wnt/beta-catenin pathway (6). Wnt signaling increases the stability of the beta-catenin and allows it to translocate to the nucleus where it acts as a transcriptional co-activator of the T cell factor/lymphoid enhancer factor (TCF/LEF) family of transcription factors (5).

As the transcription factor FOXP1 potentiates Wnt signaling via acetylation of beta-catenin which increases the transcription of beta-catenin target genes (5). In endometriosis, this interplay is evident in stromal cells as FOXP1 increases fibrosis in endometriotic lesions through the Wnt/beta-catenin pathway (7).

Pathogenesis of endometriosis is complex and not fully understood but the pathogenesis of PE is largely unknown and few case series were available (8,9,10). In this study we built upon our previous work and examined whether FOXP1 and beta-catenin played a role in the pathogenesis of PE (11).

MATERIALS and METHODS

The computer archives of the Pathology Department, Istanbul Faculty of Medicine, were searched for cases diagnosed as PE. Fifteen cases were identified between 2005 and 2019. Surgical procedures of the cases are as follows: four total abdominal hysterectomy, one unilateral or bilateral salphingo-oophorectomy, one salphingectomy, one cystectomy, one mass excision, two low anterior resection, three total abdominal hysterectomy with bilateral salphingo-oophorectomy, omentectomy and lymph node dissection, one total abdominal hysterectomy with bilateral salphingo-oophorectomy, omentectomy, lymph node dissection and low anterior resection, and one total abdominal hysterectomy with bilateral salphingo-oophorectomy, parametrial resection, nephroureterectomy. Glass slides were reexamined, and immunohistochemistry was performed on cases using monoclonal antibodies against FOXP1 (Cell Marque SP133, dilution: 1/200) and beta-catenin (Biocare, dilution: 1/250). Nine cases of ovarian endometriosis (OE) and nine cases of endometrial polyp (EP) cases were selected as control groups.

Stromal and glandular staining were evaluated as: extent, intensity and cellular compartment stained with FOXP1 and beta-catenin. Membranous staining for beta-catenin was accepted as normal (N) and nuclear beta-catenin staining was accepted as aberrant (A). The staining intensity for FOXP1 and aberrant beta-catenin were graded as 0: no staining, 1+: weak, 2+: moderate, 3+: strong.

The Chi-square test, Kruskal-Wallis test and Fischer Exact test were used for comparing the positivity of FOXP1 and beta-catenin nuclear positivity between groups. The P value less than 0.05 was considered statistically significant. The Statistical Package for Social Sciences (SPSS) version 27.0 was used for statistical analysis.

RESULTS

Clinical and demographic findings

Patient ages ranged from 29 to 58 (mean: 41.93, median: 40) years. Only seven of their presenting symptoms were known. These symptoms were menometrorrhagia, vaginal bleeding, rectal bleeding, and inguinal pain. Polypoid masses were usually multiple. In five cases the masses were found in multiple anatomic sites. In remaining ten cases the lesions were detected in only one anatomic site. The most common sites of involvement were the ovary and rectosigmoid colon. Details of the clinical findings of PE cases are presented in Table 1.

Pathologic features of PE, EP and OE cases

All PE cases consisted of glandular and stromal components. Most of the cases showed features consistent with proliferative and secretory phase endometrium. Two ovarian PE cases showed glandular proliferation consistent with atypical complex hyperplasia (borderline endometrioid tumor) and the International Federation of Gynecology and Obstetrics (FIGO) grade 1 endometrioid carcinoma arising within a polypoid lesion respectively. The stromal components of PE cases were typical for regular endometrial polyps. No features consistent with Müllerian adenosarcoma were observed. The most common feature was predecidual change. Six cases showed features of aggressive endometriosis, which had involvement of the colon and pelvic soft tissue. Extensive pelvic involvement led to hydroureter and hydronephrosis in one PE case (Figure 1).

EP cases showed varied morphological features. One of the cases showed atrophic glands. The rest of the cases showed glandular features consistent with proliferative phase. Four cases showed marked and two showed mild hypercellular stroma. Decidual change was observed in one case (Figure 1).

Table 1: Clinicopathologic features of PE cases.

Clinicopathologic features of PE cases	
Patient age	41.93±8.77 (min-max: 29-58)
Presenting symptom	Menometrorrhagia (1) Inguinal pain (1) Rectal bleeding (1) Vaginal bleeding (4)
Surgical procedure	Total abdominal hysterectomy (4) Unilateral or bilateral salphingo-oophorectomy (1) Salphingectomy (1) Cystectomy (1) Mass excision (1) Low anterior resections of the colon (2) Total abdominal hysterectomy with bilateral salphingo-oophorectomy, omentectomy and lymph node dissection (3) Total abdominal hysterectomy with bilateral salphingo-oophorectomy, omentectomy, lymph node dissection and low anterior resection (1) Total abdominal hysterectomy with bilateral salphingo-oophorectomy, parametrial resection, nephroureterectomy (1)
Location of the lesion*	Ovary (6) Salpinx (3) Uterinecorpus (2) Douglas pouch (2) Rectosigmoid colon (4) Cervix (1)
Number of the lesion (Solitary/multiple)	Solitary (10) Multiple (5)
Size of the lesion	Macroscopic (12) Microscopic (3)
Glandular features	Atrophic (1) Proliferative (5) Secretory (3) Cystic change (1) Focal hyperplasia without atypia (1) Focal complex hyperplasia with atypia (1) Nonspecific (3)
Stromal features	Hypercellular (3) Hypercellular with decidualization (2) Hypocellular (1) Decidualization (2) Myomatous (2) Nonspecific (5)
Growth direction of the polyp	Peritoneal cavity (6) Neolumen (5) Peritoneal cavity and neolumen (2) Intestinal lumen and neolumen (1) Vagina and neolumen (1)

PE: Polypoid endometriosis, *: Number of involved locations is greater than 15 because 5 cases have multiple PE lesions in different locations.

In OE cases tubal ciliated metaplasia and fibrosis were the most common features for glands and stroma respectively (Figure 1).

Polypoid endometriosis

Nuclear beta-catenin expression was not observed in the glandular component of the PE cases. For the stromal com-

ponent, six cases showed nuclear beta-catenin expression. Staining intensity for nuclear beta-catenin expression was weak for three cases and moderate for three cases. Staining extent in cases with nuclear expression ranged between 5% and 40% (mean 24.16±14.63) (Table 2) (Figure 1).

FOXP1 showed only nuclear staining for both compartments. Five cases showed no glandular staining. Of the remaining ten cases staining extent was between 5% and 90% (mean 22.5±27.30). Staining intensity was weak for nine cases and moderate for one case. Ten cases showed no stromal staining while four cases showed weak, and one case showed moderate nuclear staining. Staining extent for stromal FOXP1 was between 5% and 70% (mean 33±33.83) (Table 2) (Figure 1).

When nuclear expressions of both antigens were considered, only one of the six cases showing stromal nuclear beta-catenin expression had nuclear stromal FOXP1 expression. In that case both beta-catenin and FOXP1 expression were detected in the same area.

Endometrial polyps

Same as PE cases; nuclear beta-catenin staining was not observed in the glandular component. In the stromal component, nuclear beta-catenin staining was observed in five of the cases. Staining intensity for cases with nuclear beta-catenin expression was weak for two and moderate for three cases. Staining extent for nuclear beta-catenin expression was between 5% and 70% (mean 35±27.38) (Table 2) (Figure 1).

FOXP1 nuclear staining was observed in both the glandular and stromal components. Two cases showed no staining whereas the rest of the cases showed nuclear staining in glandular compartment. Six of the cases showed weak and one case showed moderate glandular FOXP1 staining. Staining extent was between 10% and 40% (mean 27.14±12.53). For the stromal component only two cases showed nuclear staining. Staining intensity was weak and moderate. Staining extent was 10% and 70% respectively (Table 2) (Figure 1).

Only one case showed both nuclear beta-catenin and FOXP1 staining.

Ovarian endometriosis

Nuclear beta-catenin staining was not observed in glandular cells of the OE cases. For stromal cells, only one case showed nuclear staining. Staining extent was 50% and intensity was moderate for the case with nuclear beta-catenin staining (Figure 1).

Glandular and stromal nuclear FOXP1 staining was observed in eight OE cases. One OE case showed only stromal FOXP1 staining. Staining extent was between 5% and 30% (mean 15.62±9.79) in glandular component. Nuclear staining was observed in stromal cells of all OE cases. Staining extent was between 60% and 90% (mean 84.44±10.13). Staining intensity was moderate for all OE cases (Table 2) (Figure 1).

Only one case showed both nuclear beta-catenin and FOXP1 staining.

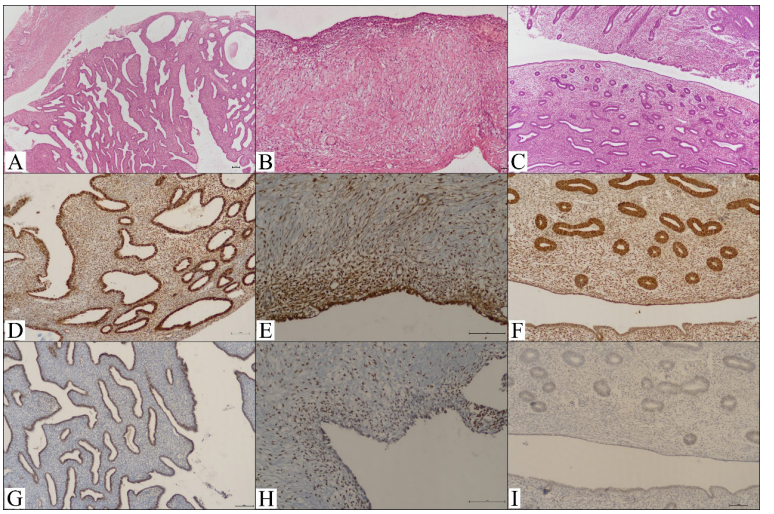

Figure 1: A: Polypoid endometriosis in fallopian tube. HE x40. B: Ovarian endometriosis. Attenuated endometriosis epithelium and stroma is visible at the top. HE x100. C: Endometrial polyp. HE x40. D: Weak and moderate nuclear beta-catenin staining of the stromal cells of polypoid endometriosis. Beta-catenin IHC x100. E: Moderate nuclear staining of the stromal cells of ovarian endometriosis. Beta-catenin IHC x200. F: Beta-catenin staining in endometrial polyp. Both nuclear and cytoplasmic staining is observed. Beta-catenin IHC x100. G: FOXP1 staining in polypoid endometriosis. While stromal cells didn't show FOXP1 expression, there is nuclear FOXP1 staining in glands. FOXP1 IHC x100. H: FOXP1 staining in ovarian endometriosis. Most of the stromal cells show moderate FOXP1 expression. FOXP1 IHC x200. I: FOXP1 staining in endometrial polyp. Weak staining was observed in glands, endothelial cells and inflammatory cells. Staining with FOXP1 was not observed in stromal cells. FOXP1 IHC x100.

Table 2: Beta-catenin and FOXP1 staining of the polypoid endometriosis, ovarian endometriosis and endometrial polyp cases.

Beta-catenin expression of the polypoid endometriosis, ovarian endometriosis and endometrial polyp cases

	Epithelial	Stromal		Epithelial	Stromal		Epithelial	Stromal
PE#1	N	5%,1+	**OE#1**	N	N	**EP#1**	N	40%,2+
PE#2	N	N	**OE#2**	N	N	**EP#2**	N	N
PE#3	N	N	**OE#3**	N	N	**EP#3**	N	50%,2+
PE#4	N	40%,1+	**OE#4**	N	N	**EP#4**	N	N
PE#5	N	N	**OE#5**	N	N	**EP#5**	N	70%,1+
PE#6	N	N	**OE#6**	N	50%,2+	**EP#6**	N	5%,1+
PE#7	N	15%,2+	**OE#7**	N	N	**EP#7**	N	10%,2+
PE#8	N	N	**OE#8**	N	N	**EP#8**	N	N
PE#9	N	30%,2+	**OE#9**	N	N	**EP#9**	N	N
PE#10	N	15%,2+						
PE#11	N	N						
PE#12	N	40%,1+						
PE#13	N	N						
PE#14	N	N						
PE#15	N	N						

Only aberrant (nuclear) staining extent and intensity were considered significant. 0: Negative, 1+: Weak, 2+: Moderate, 3+:S trong, PE: Polypoid endometriosis, OE: Ovarian endometriosis, EP: Endometrial polyp, N: Normal.

FOXP1 expression of the polypoid endometriosis, ovarian endometriosis and endometrial polyp cases

	Epithelial*	Stromal**		Epithelial*	Stromal**		Epithelial*	Stromal**
PE#1	10%,1+	0	**OE#1**	30%,1+	90%,2+	**EP#1**	30%,1+	0
PE#2	10%,1+	0	**OE#2**	30%,1+	90%,2+	**EP#2**	0	10%,1+
PE#3	5%,1+	0	**OE#3**	10%,1+	80%,2+	**EP#3**	10%,1+	0
PE#4	5%,1+	0	**OE#4**	20%,1+	80%,2+	**EP#4**	30%,1+	0
PE#5	10%,1+	10%,1+	**OE#5**	10%,1+	90%,2+	**EP#5**	30%,1+	0
PE#6	0	0	**OE#6**	10%,1+	90%,2+	**EP#6**	0	0
PE#7	10%,1+	0	**OE#7**	10%,1+	90%,2+	**EP#7**	10%,1+	70%,2+
PE#8	0	0	**OE#8**	5%,1+	60%,2+	**EP#8**	40%,2+	0
PE#9	90%,2+	5%,1+	**OE#9**	0	90%,2+	**EP#9**	40%,1+	0
PE#10	40%,1+	0						
PE#11	5%,1+	10%,1+						
PE#12	0	0						
PE#13	0	0						
PE#14	0	70%,1+						
PE#15	40%,1+	70%,2+						

*: Epithelial staining values: 0: Negative, 1+: Weak, 2+: Moderate, 3+: Strong, **: Stromal staining intensity values: 0: Negative, 1+: Weak, 2+: Moderate, 3+: Strong, PE: Polypoid endometriosis, OE: Ovarian endometriosis, EP: Endometrial polyp.

Correlation between histologic features and beta-catenin/ FOXP1 expression

Nuclear beta-catenin staining was observed in three out of six PE cases with aggressive features and three out of five cases with multiple lesions. The PE cases with atypical complex hyperplasia (borderline endometrioid tumor) and endometrioid carcinoma (FIGO Grade I) showed no stromal staining with beta-catenin.

Three cases with >10% glandular FOXP1 staining showed no specific histologic features. Stromal FOXP1 staining was not observed in PE cases with multiple lesions. Only one PE case with aggressive features showed stromal FOXP1 staining, and it was weak and focal (10%). Two cases with glandular proliferations consistent with atypical complex hyperplasia (borderline endometrioid tumor) and endometrioid carcinoma (FIGO Grade I) showed weak and focal (10%) and no FOXP1 staining, respectively. Two cases with extensive (70%) stromal FOXP1 showed proliferative phase glandular features but had no specific stromal features.

For control cases, EPs did not show any specific histologic features with regards to beta-catenin or FOXP1 staining. In OEs stromal sclerosis was a prominent feature in terms of FOXP1 expression.

Statistical analysis

Both beta-catenin and FOXP1 positivity, regardless of extent and intensity, compared as PE vs EP vs OE, PE vs control cases (EP and OE), PE vs EP, PE vs OE and EP vs OE. Beta-catenin staining was analyzed only for stromal components of the PE, EP and OE cases because nuclear staining was not detected in any of the glandular components.

Stromal FOXP1 staining was statistically significant between PE vs EP vs OE (p=0.007), PE vs OE (p=0.002) and EP vs OE (p=0.023) while there was no statistical difference between PE vs EP (p=0.66) and PE vs control group (EP+OE) (p=0.119).

Glandular FOXP1 staining showed no statistical difference between PE vs EP vs OE (p=0.66), PE and control group (EP+OE) (p=0.41), PE vs EP (p=0.66), PE vs OE (p=0.35) and EP vs OE (p=1).

There was no statistically significant beta-catenin staining difference between PE vs EP vs OE (p=0.26), PE and control group (EP+OE) (p=0.69), PE vs EP (p=0.67), PE vs OE (p=0.19) and EP vs OE (p=0.13) found.

DISCUSSION

PE is an uncommon type of endometriosis. With its polyp-like structure it raises the question of which common features it shares with endometrial polyps and with conventional endometriosis. In this study we tried to answer this question on the aspect of beta-catenin and FOXP1 expression.

Many factors contribute to the survival and progression of the ectopic endometrial tissues. Wnt pathway is one of these factors where beta-catenin is the central molecule (8). This molecule is normally located at cell membrane, and it is bound to E-cadherin but when it is uncoupled, beta-catenin is degraded upon phosphorylation by GSK3beta. Stabilization of beta-catenin allows translocation to the nucleus and interacts with TCF-LEF family of transcription factors. It has been shown that the Wnt pathway is activated in endometriosis (12-15). The Wnt pathway is also an oncogenic pathway that is active in different tumors and a potential target in endometrial polyp pathogenesis (16,17). In our study nuclear beta-catenin staining was observed more frequently in PE and EP cases as compared to OE cases but the difference was not statistically significant. We concluded that beta-catenin is not a meaningful contributor to PE pathogenesis.

The FOXP family of proteins are multifunctional transcription factors. They act as both tumor suppressors and oncogenes depending on the neoplasm (18). Two aspects of FOXP1 make it a potential target for PE pathogenesis. First, FOXP1 expression is associated with fibrosis and stromal cell proliferation in endometriosis which is important as stromal cells are the main reason of polyp formation. Second, its organ specific function on cell proliferation is demonstrated in different neoplasms (7,18,19). In our study, OE cases showed results in line with the first the aspect of FOXP1. Fibrosis was the prominent feature of these cases. In PE cases the FOXP1 expression is greatly reduced. When combined with the similar FOXP1 expression of EP cases we assumed that FOXP1 expression was not required for polyp formation. In contrast, the loss of FOXP1 expression in stromal cells in PE and EP cases could be causing stromal cell overgrowth in both groups. We based this assumption on FOXP1's tumor suppressor/oncogenic properties. The reports in literature pointed out that FOXP1 acts as a tumor suppressor in endometrioid carcinoma (20,21). In our PE cohort, the case with endometrioid carcinoma showed no expression of FOXP1 in either the stromal or glandular component. Although PE is not considered a neoplastic entity, the loss of FOXP1's tumor suppressor function could be a contributing factor in polyp formation in PE.

The above-mentioned markers are also interlinked. FOXP1, through acetylation enhances the beta-catenin's transcriptional activity (5). Also, FOXP1's fibrotic activity is reported to be through the Wnt pathway (7). This association was encountered in one PE case. Other than that, we did not find any correlation with nuclear beta-catenin and FOXP1 expression with immunohistochemistry. But there was a similarity between PE and EP cases in their FOXP1 and beta-catenin expression. This raises the question as to whether this immune profile has a role in polyp formation. Endometrial polyp pathogenesis was not investigated in this regard, and this will be an interesting topic for a future study.

CONCLUSION

We investigated FOXP1 and beta-catenin expression in PE and their roles in PE pathogenesis. Significant reduction of FOXP1 in PE and EP stromal cells indicated that FOXP1 could play a role in polyp formation in PE.

Ethics Committee Approval: This is a retrospective archive study that does not include live animals or humans. Therefor ethics approval was not sought.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- E.Y., S.Ö, A.Y.A.; Data Acquisition- A.Y.A., C.Y., H.S.; Data Analysis/Interpretation- A.Y.A., A.B.; Drafting Manuscript- A.Y.A., A.B.; Critical Revision of Manuscript- E.Y., S.Ö., C.Y., H.S.; Final Approval and Accountability- A.Y.A., E.Y., A.B., C.Y., H.S., S.Ö.

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