

Comparison of the distinctive pathological features of and p16 and c-Kit expression levels in benign and malignant endometrial polyps

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Received: 11.08.2015 • Accepted/Published Online: 26.03.2016 • Final Version: 20.12.2016

Background/aim: Histopathological examination is crucial for the effective management of endometrial polyps. Immunohistochemical markers such as p16 and c-Kit may facilitate the differential diagnoses of benign and malignant polyps. The aim of the present study was to explore the expression levels of c-Kit (CD117) and p16 in endometrial polyps of postmenopausal women.

Materials and methods: Twenty-five hysterectomy specimens with malignant endometrial polyps and hysterectomy or polypectomy specimens featuring 55 benign polyps were studied. The polyps were immunohistochemically stained for p16 and c-Kit, and differences in the expression levels of these proteins in the glandular and stromal components of benign polyps and the benign regions of the malignant polyps were assessed by using Fisher's exact test.

Results: The glandular components of malignant polyps exhibited significantly more intense p16 immunostaining than did benign polyps. Most immunoreactive cells were glandular cells exhibiting tubal metaplasia. The stromal components of either type of polyp did not differ in terms of p16 immunostaining. The extent of c-Kit immunostaining in benign and malignant polyps was similar.

Conclusion: The extensive tubal metaplasia in and the p16 immunoreactivity of the glandular components of malignant polyps may be useful to distinguish such polyps from benign polyps.

Key words: p16, c-Kit, endometrial polyp, tubal metaplasia

1. Introduction

An endometrial polyp is a common benign lesion extending from the endometrial surface. A polyp is composed of endometrial glands and (at least) a focally fibrous stroma with thick-walled vessels (1). The incidence of malignant polyps is low, but the risk increases after menopause. The incidence of malignancy confined to the polyps is 0.8%–8%, but 10%–34% of endometrial carcinomas in postmenopausal women are associated with endometrial polyps (1–3).

Although no consensus on polyp management has emerged, such management should be conservative when Doppler flowmetry data are normal and no atypical change is evident upon endometrial biopsy (4). It is not always possible to sample the polyp or to identify a malignancy via endometrial biopsy; this means that false-negative test results are not uncommon (5,6). Much effort has been devoted to the detection of polyps associated with a high risk of malignancy; timely diagnosis and treatment of

such polyps are essential. Risk factors include older age, menopausal status, abnormal uterine bleeding, diabetes, hypertension, and a polyp diameter of >1.5 cm (2,3,7–9). Few studies have sought to define immunohistochemical biomarkers that may distinguish polyps accompanying malignancies from benign polyps. Such studies have compared the immunohistochemical staining intensities of Ki-67, Bcl-2, COX2, the estrogen receptor, and the progesterone receptor in benign and malignant polyps (10,11).

p16 is a cyclin-dependent inhibitor of kinase-4, and p16 expression has been used in the differential diagnoses of polyps, hyperplasia, adenocarcinomas of the endometrium, malignant lesions arising from the transformation of benign lesions, and many other types of both malignant and benign lesions (12–16).

c-Kit is a protooncogene encoding the transmembrane tyrosine kinase receptor termed CD117. The expression levels of c-Kit in malignant and benign endometrial

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polyps, adenocarcinomas, and many other types of benign and malignant lesions have been examined immunohistochemically (17–20).

The aim of the present study was to evaluate p16 and c-Kit expression levels in the stromal and glandular epithelia of malignant and benign polyps.

2. Materials and methods

Twenty-five postmenopausal endometrial polyps that had become malignant and 55 postmenopausal benign endometrial polyps were examined. All polyps were collected from patients diagnosed by the pathology departments of the Zeynep Kamil Maternity and Pediatric Research and Training Hospital and the Fatih Sultan Mehmet Research and Training Hospital between 2004 and 2014. The ethics committees of both hospitals approved the present work. Complete hysterectomy and bilateral salpingo-oophorectomy specimens were available for all malignant cases. The hysterectomy specimens of 31 benign cases and polypectomy specimens (only) of the other 24 cases were also available.

Data on macroscopic specimen assessments and pathological and clinical findings were collected by chart review. All sample slides were reexamined by two pathologists under light microscopes.

An endometrial polyp was defined as a focal proliferation of the endometrium in polypoid form, combined with a sclerosing stroma and thickened wall vessels. A malignant polyp or a malignant region in an otherwise benign polyp was defined as an intraepithelial or invasive carcinoma replacing at least a portion of a polyp (21). Menopause was defined as amenorrhea >12 months in duration.

Diagnostic tissue blocks were excised from the benign and malignant (if present) portions of all polyps, and immunohistochemical staining for p16 and c-Kit (CD117) followed. We stained formalin-fixed paraffin-embedded tissue sections using a manual polymer detection system after epitope retrieval by heating in citrate buffer. The following prediluted (thus, ready-to-use) primary antibodies were employed: anti-p16 (INK 4; BioGenex) and CD117/c-Kit (Thermo Fisher Scientific).

p16 positivity was evidenced by brown staining of the nucleus and/or the cytoplasm. The extent of nuclear and cytoplasmic staining in each section was assessed in terms of cell percentage and categorized as follows: 1) negative: no staining; 2) + (focally positive): less than 5% of cells stained; 3) ++ (regionally positive): 5%–50% of cells stained; and 4) +++ (diffusely positive): more than 50% of cells stained (22).

For c-Kit, cells exhibiting either cytoplasmic or membranous staining were considered positive. Immunostaining data included the extent of staining

(focal: <10% of cells; intermediate: 10%–50%; diffuse: >50%) and staining intensity (1+ to 3+) (17).

SPSS 13.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The p16 and c-Kit immunostaining data from benign polyps and the benign portions of malignant polyps were compared using Fisher's exact test. $P < 0.05$ was considered to indicate statistical significance.

3. Results

Of the 80 endometrial polyps, 25 (31.25%) were malignant and 55 (68.75%) were benign. The mean patient ages were 60.8 years for those with malignant polyps and 58 years for those with benign polyps. Histopathologically, the tumors were as follows: 10 serous adenocarcinomas (40%), 9 endometrioid adenocarcinomas (36%), 4 clear cell carcinomas (16%), and 2 (8%) endometrial intraepithelial carcinomas (EICs). All malignancies were in postmenopausal women. The smallest and largest diameters of malignant polyps were 0.5 cm and 7 cm, respectively. The mean polyp diameter was 3.4 cm. For benign polyps, the smallest and largest diameters were 0.2 cm and 2.7 cm, respectively. The mean diameter of benign polyps was 1.4 cm (Table 1).

All malignancies had initially invaded the polyp tips, and all were restricted to the polyps with the exception of two cases of serous adenocarcinoma in which both the pedicles of the polyps and the deep myometrium had been invaded.

The endometrium proper was malignant (accompanied by polyp carcinoma) in only one case each of serous and clear cell carcinoma. In the former case, the tumor had metastasized to the uterine serosa and right pelvic lymph nodes. In the other case, the carcinoma was restricted to the uterus.

Endometrial samples of all malignant polyps were available. Endometrial curettage of 2 of the 25 malignant polyps yielded negative results (8%). However, malignancy was evident in the hysterectomy materials (8%).

p16 and c-Kit expression levels were evaluated in the stroma and glandular epithelia of the polyps. Upon glandular staining for p16, 21 of the 25 malignant polyps (84%) were immunopositive. Staining was generally focal or regional, thus rarely diffuse. Of the benign polyps, only 7 (13%) were positive for p16; this difference was significant ($P < 0.001$). Morphologically, the immunopositive glands were benign in appearance, but most were overlaid by cells exhibiting secretory tubal metaplasia. Some of these glands were cystic, dilated, and overlaid by simple epithelium. All staining was both cytoplasmic and membranous (Figures 1a–1d). Upon stromal staining for p16, 9 (36%) of the 25 malignant polyps were positive, as were 15 (27%) of the 55 benign polyps; however, this difference was not significant ($P = 0.44$) (Table 2)

Table 1. Histopathological features of malignant polyps (n = 25 cases).

Case	Age	Malignancy originating from endometrial polyp	Size of the polyp (cm)	Size of tumor (cm)
1	46	Adeno Ca	2.5	1.6
2	78	Adeno Ca	3	2
3	38	Adeno Ca	2	1 and 0.5
4	56	Serous Ca	3.5	3
5	75	EIC	5	0.5
6	69	Serous Ca, EIC	3	0.6 and 0.3
7	71	Clear cell Ca	5	4
8	58	Adeno Ca	7	6
9	70	Serous Ca	1.5	0.5
10	65	Clear cell Ca	6	5
11	46	Serous Ca	3	2.5
12	67	Clear cell Ca	3 and 0.5	0.3 and 0.2
13	74	Serous Ca	3	2.5
14	42	Adeno Ca	4	0.5
15	66	Serous Ca	3	2.5
16	64	Adeno Ca	3	2
17	49	Serous Ca	1.5	1
18	62	Adeno Ca	3	3
19	62	Serous Ca, EIC	2	1
20	61	Serous Ca, EIC	3.5	1
21	58	Adeno Ca	3	1
22	63	EIC	4	1.4
23	50	Serous Ca, EIC	2.5	0.8
24	71	Adeno Ca	4.5	1.5
25	59	Clear cell Ca	3.2	1.2

EIC: Endometrial intraepithelial carcinoma, Ca: carcinoma.

Upon glandular staining for c-Kit, 17 of the 25 malignant polyps (68%) were immunopositive to varying intensities (focal, intermediate, or diffuse); 33 of the 55 benign polyps (60%) were similarly immunopositive. Upon stromal staining, 17 malignant polyps (68%) were immunopositive to varying intensities, as were 44 of the benign polyps (80%). Neither the glandular nor stromal staining levels for c-Kit differed significantly between the two groups ($P = 0.62$ for glandular staining and $P = 0.26$ for stromal staining) (Table 3).

4. Discussion

The mean ages of patients with malignant and benign polyps were 60 and 58 years, respectively, compatible with literature data. Previously reported mean ages were 63.6 and 64.4 years for those with malignant polyps, and 56.5 and 61.7 years for those for benign polyps (11,23). However, Hui et al. reported that the mean age of patients with malignant polyps was 67 years. This may be because the cited authors included only patients with serous adenocarcinomas, which occur in patients older than those with endometrioid adenocarcinomas (24).

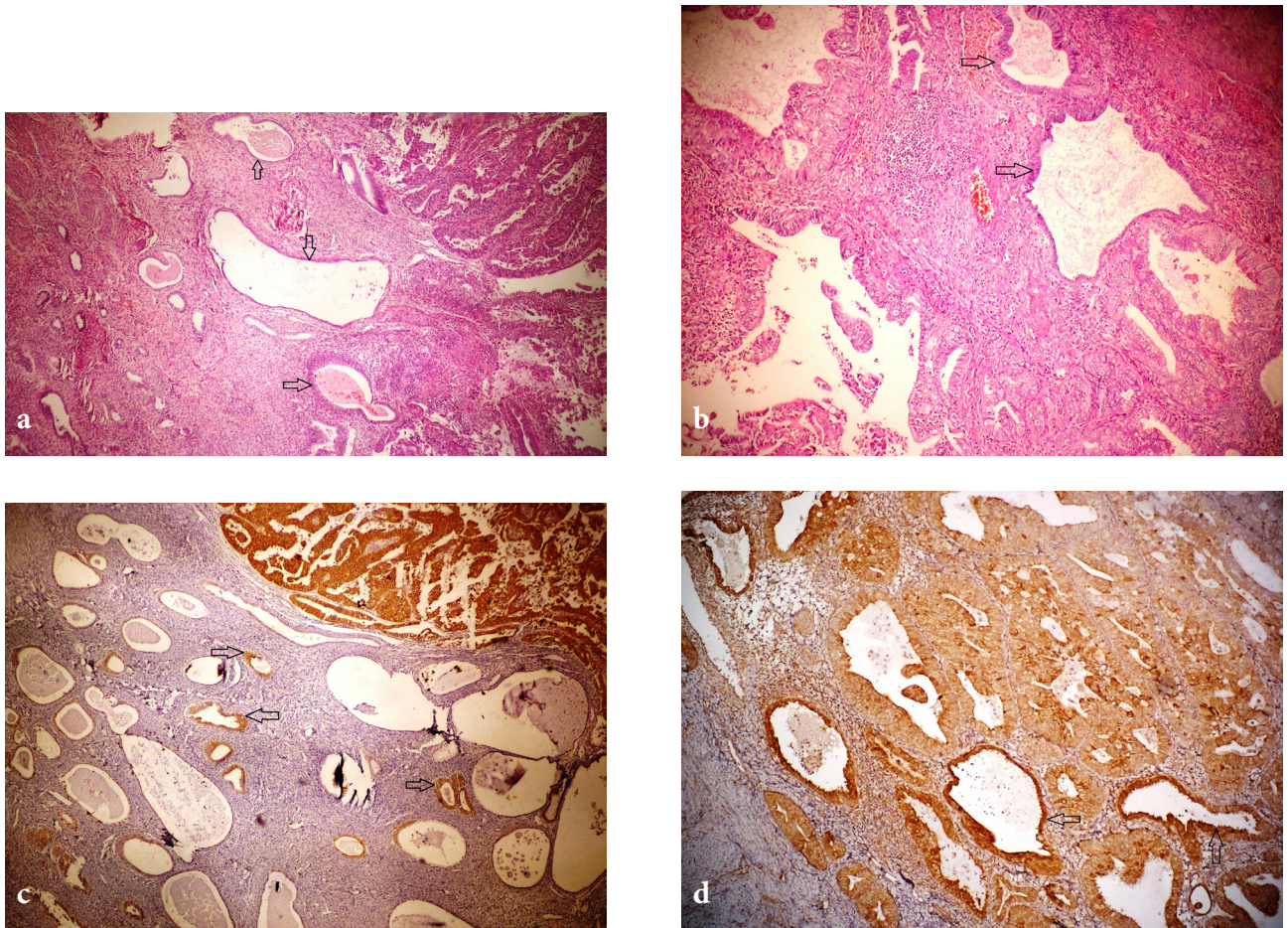


Figure 1. Malignancy originating from endometrial polyp. a, b) Hematoxylin and eosin staining: glands exhibiting tubal metaplasia (arrows) (original magnification: a, 100×, b, 200×). c, d) p16 immunostaining: epithelial staining intensities in individual glands are variable but more consistent in cells exhibiting tubal metaplasia (arrows) (original magnification: c, 100×, d, 200×).

Table 2. Immunohistochemical expression levels of p16 in benign and malignant polyps (intensity/distribution of staining).

		p16		
	Staining intensity	Malignant (n = 28)	Benign (n = 55)	p
Glandular	+	12 (48%)	5 (9%)	<0.001
	++	7 (28%)	2 (4%)	
	+++	2 (8%)	0	
	-	4 (16%)	48 (87%)	
Stromal	+	3 (12%)	9 (16%)	0.44
	++	4 (16%)	4 (7%)	
	+++	2 (2%)	2 (4%)	
	-	16 (64%)	40 (73%)	

Table 3. Immunohistochemical expression levels of c-Kit in benign and malignant polyps (intensity/distribution of staining).

	c-Kit			
	Staining intensity	Malignant (n = 25)	Benign (n = 55)	P
Glandular	+ / +	3 (12%)	16 (30%)	0.62
	++ / +	3 (12%)	10 (18%)	
	++ / ++	6 (24%)	5 (9%)	
	++ / +++	5 (20%)	2 (3%)	
	- / -	8 (32%)	22 (40%)	
Stromal	+ / +	5 (20%)	16 (30%)	0.26
	++ / +	3 (12%)	14 (26%)	
	++ / ++	4 (16%)	10 (18%)	
	++ / +++	5 (20%)	4 (6%)	
	- / -	8 (32%)	11 (20%)	

All malignant polyps were found in postmenopausal patients. Except for one, all were >1.5 cm in diameter; the median diameter was 3.4 cm. The median diameter of the benign polyps was 1.4 cm. These findings are in line with earlier data indicating that a polyp diameter of >1.5 cm and postmenopausal status are principal risk factors for malignancy (2,3,8,9).

We found that all malignancies were restricted to the polyps; the endometrium proper was not involved and extrauterine involvement was evident in only one case that also exhibited involvement of the endometrium proper. This was consistent with the view of Hui et al.: involvement of the endometrium proper is indicative of extrauterine involvement. Also, all malignancies involved the polyp surfaces, in agreement with the data of Hui et al. (21).

The common types of malignancies originating from the surfaces of polyps are endometrioid adenocarcinoma (81.5%) and serous adenocarcinoma (20%). Clear cell carcinoma is comparatively rare (1,25). In our present study, the rates were 36%, 40%, and 16% for endometrioid, serous, and clear cell carcinomas, respectively; 8% of the cases were EICs. Our relatively high frequency of serous adenocarcinoma may be attributable to the fact that we used not only morphological criteria, but also immunohistochemical methods and p53 marker detection to diagnose such adenocarcinomas. Overexpression of mutant p53 protein is a surrogate marker of uterine serous adenocarcinoma (21).

Although transvaginal ultrasound is important for the detection of endometrial polyps associated with malignancy, histopathological examination is essential when it is sought to rule out malignancy (1,4,21,26).

Endometrial polyps, and malignancies on such polyps, can be missed even on endometrial biopsy (5,6,21,25). Guido et al. found that, of 11 false-negative endometrial biopsies performed using a Pipelle curette, the malignancies were restricted to the polyps in 5 cases (6). Onderza et al. incidentally diagnosed a malignancy in the hysterectomy specimen in only 1 of 27 patients with endometrial polyps (25). We detected malignancies accompanying polyps in hysterectomy specimens of two cases in which the endometrial samples had yielded benign diagnoses (8%).

Antunes et al. immunohistochemically evaluated the expression of Ki-67, Bcl-2, and COX2 in the stromal and glandular epithelia of malignant and benign polyps to explore the relationship between postmenopausal development of endometrial polyps and carcinogenesis. The COX2 expression level was higher in malignant polyps, but those of Ki-67 and Bcl-2 did not differ between malignant and benign polyps (10). Another study immunohistochemically compared the levels of estrogen and progesterone receptors expressed by benign and malignant polyps; the stromal expression level of the estrogen receptor was lower in malignant polyps (11).

The protein p16 is a cell cycle-dependent kinase inhibitor that negatively regulates the cell cycle. p16 is considered a potent tumor suppressor gene because it causes cell cycle arrest. Frequent structural alterations in p16 have been identified in various malignancies. Inactivation of p16 by gene deletion, mutation, or hypermethylation is evident in some endometrial carcinomas. Tsuda et al. showed that promoter hypermethylation triggered p16 protein loss in 50% of endometrioid endometrial carcinomas and 44% of endometrial hyperplasias. Thus,

alterations in p16 expression are important in endometrial tumorigenesis (27). p16 immunostaining has been used to identify normal endometrial tissue and endometrial polyps, and to distinguish endometrial polyps from hyperplastic tissue and endometrial carcinomas (12–14). Stewart et al. revealed that normal cyclical endometrium showed patchy glandular and focal stromal p16 expression while endometrial polyps displayed more extended glandular and stromal immunoreactivity for p16. Thus, p16 expression can help to distinguish polypoid and nonpolypoid mucosa (12). Moritani et al. showed that stromal p16 expression differed significantly between endometrial polyps (89%) and endometrial hyperplasia (3%). Thus, it can be a useful marker for diagnosis, especially in fragmented specimens (13). Buchynska et al. detected higher expression levels of p16 in endometrial adenocarcinomas compared with endometrial polyps (14). However, differences in immunostaining intensities between benign and malignant polyps have not previously been studied.

We detected focal and regional immunostaining for p16 in the glandular regions of 7 of the 55 benign polyps (13%) and 21 of the 25 malignant polyps (84%). Immunoreactivity was evident in glands formed by cells exhibiting tubal secretory metaplasia. Stewart et al. found that the glandular regions of 10%–80% of benign endometrial polyps stained positive for p16; the immunopositive cells usually exhibited ciliated metaplasia (12).

Carlson et al. detected metaplastic changes in 39 of 83 endometrial polyps in which endometrial intraepithelial neoplasms were evident; 14% of the changes were tubal secretory metaplasias (28). Endometrial metaplasia is a complex grouping of various forms of epithelial proliferation. Any possible relationship between metaplasia and endometrial adenocarcinoma remains unclear. (29). As is true of polyps, tubal metaplasias are common in peri- and postmenopausal women, and are associated with estrogenic stimulation (30). Estrogen receptor levels are elevated in the glandular epithelia of endometria that contain polyps as in tubal metaplasia (11).

Horree et al. showed that such tubal metaplasia regions were consistently immunopositive for p16, and also for cell cycle proteins, HIF-1 α , CAIX, and Glut-1, suggesting that endometrial tubal metaplasia is potentially a premalignant endometrial lesion (30).

Although both the etiopathogenesis of endometrial polyps and the malignancies that can develop on such polyps remain poorly understood, our findings suggest that polyps may develop upon estrogenic stimulation and that diffuse tubular metaplasia may be a stage in the development of malignancy.

The protooncogene c-Kit encodes a 145-kDa transmembrane tyrosine kinase receptor (termed CD117), the ligand of which is stem cell factor (SCF). c-Kit is weakly to moderately expressed in many normal, benign, and malignant tissues. Mutational mechanisms aside, it has been suggested that c-Kit, together with SCF, may promote tumorigenesis by stimulating tissue growth in an autocrine and/or paracrine manner (17). c-Kit is expressed in some solid tumors and may contribute to tumorigenesis and malignant transformation (18,27). Arber et al. and Scobie et al. investigated c-Kit expression in endometrial carcinomas; immunopositivity of varying intensity (50%–100%) was evident (18,31). Elmore et al. detected cytoplasmic staining of epithelial cells of the endometria in 4 of 9 adenocarcinomas and 1 endometrial polyp (17). No work has been done yet to compare benign and malignant polyps in terms of c-Kit expression level. We found that the glandular and stromal components of both benign and malignant polyps were immunostained to varying intensities. We found no difference between benign and malignant polyps in terms of c-Kit immunostaining.

Thus, both tubal metaplasia and p16 immunoreactivity may aid in the diagnosis of malignancies accompanying polyps and may appropriately alert pathologists, especially if no malignant cells are detected in small and/or fragmented biopsy samples. Clearly, clinical, pathological, immunohistochemical, and molecular studies on the etiology and carcinogenesis of endometrial polyps with larger patient numbers are needed to support our assertion.

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