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Loss of p27 expression in endometrial carcinoma patients with recurrent tumor is significantly associated with poor survival

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Summary

Purpose of investigation: This study investigates the relationship between the cyclin-dependent kinase inhibitor p27 expression status and the clinicopathological parameters in endometrial carcinomas. *Materials and Methods:* The present study employed 101 cases of endometrial tissues which included 71 cases of endometrial carcinomas and 30 cases of non-malignant endometrium. All these cases were utilized in the construction of tissue microarrays which were used later in standard IHC staining protocol to examine p27 expression. *Results:* Nineteen (26.7%) cases of endometrial carcinomas showed brown granular nuclear expression of p27 including 16 (27%) cases of endometrioid adenocarcinomas, and two (22.2%) cases of serous endometrial carcinomas. Positive p27 immunostaining was found in epithelial and stromal cells of serous carcinomas. Endometrioid adenocarcinomas showed p27 expression in epithelial cells of nine cases, stromal cells of five cases, and both stromal and epithelial cells in the remaining two cases. Thirteen (43%) control cases showed nuclear expression mainly in epithelial cells, except in three cases it was in both stromal and epithelial cells. Loss of p27 expression in endometrial carcinoma patients with recurrent tumor is significantly associated with poor survival (p-value < 0.05). There is no association between p27 expression and other clinicopathological parameters in endometrial tumors. *Conclusion:* Greater p27 staining was seen in normal and benign endometrial tissues compared to endometrial carcinomas. Loss of p27 expression gives an indication for poor survival in endometrial carcinoma patients with recurrent tumor.

Key words: Endometrial carcinoma; Immunohistochemistry; p27.

Introduction

Endometrial carcinomas are common aggressive malignant neoplasms of the female reproductive organs [1]. There are considerable differences between the main histological types of endometrial carcinomas regarding a group of factors that may influence patient treatment, such as prognosis, pattern of recurrence, and chemotherapeutic response [2-4]. Therefore, distinction between endometrial carcinoma histotypes is necessary. Thus, an immunohistochemical marker for differentiating histotypes of endometrial carcinomas and its prognosis is certain to be valuable.

P27 is a protein identified as CDK inhibitors, which is encoded by a gene called p27 Kip1 that is a family member of the Cip1/Kip1 CDK inhibitors, and located on chromosome 12p13 [5-6]. P27 interacts with a wide panel of cyclin-dependent kinases (A, B, D, and E) and show greater affinity to cyclin-cyclin-dependent kinase complexes than to the CDKs only [5, 7]. The inhibitory activity of p27 comes from binding to functional cyclin-CDK complexes, and from its ability to stop the phosphorylation process of the kinase component of the complex that is mediated by CAK [5]. Another role of p27 is to function as an extracellular mitotic and antimitotic signals mediator [5]. Overexpressed p27 leads to G1 arrest and acts as a tumor suppressor [8].

Many studies have reported that loss of p27 expression, as examined by IHC, correlates with prognostic parameters in some malignant tumors, including prostate cancer [9], lung [10], colon [11], breast [12, 13], and lymphomas [14]. Furthermore, decreased p27 expression is associated with grade of prostatic tumors [15] and colorectal carcinomas [16].

Although the function of p27 protein in the tumors of endometrium is debatable, p27 is essential to regulate endometrial proliferation, and the loss of its expression may participate in the carcinogenesis of endometrium; therefore, p27 is perhaps a main target for the regulation of endometrium growth and the pathogenesis of its malignant tumors [8, 17-18]. Although, the expression of p27 has often been noticed to be decreased or absent in endometrial

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Table 1. — *Clinicopathological characteristics of endometrial tumor patients and status of p27 immunostaining.*

		Negative		Positive		*p*-value
		n	%	n	%	
Age in years	< 40	0	0.0%	0	0.0%	0.841
	40-49	18	72.0%	7	28.0%	
	50-59	19	79.2%	5	20.8%	
	60-69	10	66.7%	5	33.3%	
	≥ 70	5	71.4%	2	28.6%	
Final diagnosis	Clear cell carcinoma	1	100.0%	0	0.0%	0.778
	Endometrioid adenocarcinoma	43	72.9%	16	27.1%	
	MMMT	1	50.0%	1	50.0%	
	Serous carcinoma	7	77.8%	2	22.2%	
Grade	I	31	77.5%	9	22.5%	0.085
	II	18	78.3%	5	21.7%	
	III	2	33.3%	4	66.7%	
	Ungraded	1	50.0%	1	50.0%	
Stage	I	31	79.5%	8	20.5%	0.648
	II	3	60.0%	2	40.0%	
	III	6	66.7%	3	33.3%	
	IV	2	66.7%	1	33.3%	
	Unstaged	10	66.7%	5	33.3%	
Differentiation	W	32	78.0%	9	22.0%	0.308
	M	15	75.0%	5	25.0%	
	P	4	50.0%	4	50.0%	
	NA	1	50.0%	1	50.0%	
Recurrence	No	42	75.0%	14	25.0%	0.525
	Yes	10	66.7%	5	33.3%	
Alive	No	10	58.8%	7	41.2%	0.207
	yes	42	77.8%	12	22.2%	

carcinomas [8, 18-20], there are few studies which reported controversy regarding the significant association between p27 immunohistochemical profile and clinicopathological parameters of endometrial carcinoma patients [18, 21].

Certainly undoubted evidence is desirable to clarify the p27 precise role in the development and progression of endometrial carcinomas, and its association with the clinicopathological parameters because recognition of such association between p27 and endometrial tumors can enhance our perception of endometrial carcinogenesis and help developing treatment and preventive plans. Therefore, the current study describes the immunohistochemical phenotype of p27 in endometrial tumors, examines the correlation between the pattern of p27 expression and the clinicopathological parameters and follow-up data of these tumors.

Materials and Methods

Seventy-one paraffin blocks of previously diagnosed endometrial carcinoma were retrieved from the archives of Pathology Department at King Abdulaziz University, Jeddah, Saudi Arabia. Thirty samples of endometrial tissue from benign conditions were also recruited as a control group. Four micron thickness sections were sliced from paraffin blocks, then stained with hematoxylin and eosin for tumors histopathological characteristics evaluations, grading, and staging. Patient's clinical data (age, type of carcinoma, size, grade and stage of carcinoma) were extracted from the patient's medical records and listed in Table 1. Control cases were chosen from individuals who were curetted for non-cancerous conditions comprising 16 proliferative endometrium, ten secretory endometrium and four endometrial polyps. The mean age of control group was 35.6 years, ranging from 22 to 50 years. All recruited tissue blocks of both benign and malignant conditions were used for tissue microarray construction in the present study. Biomedical Ethical Committee at King Abdulaziz University approved the present study.

Seventy-one primary endometrial carcinomas and 30 non-cancerous endometrial tissue samples were used for tissue microarray construction (TMA) as described by Al-Maghrabi *et al.* [22]. Blocks of TMA were cut into 4-micron thickness sections and placed on aminosilane-coated slides to be used later in immunohistochemistry.

Immunohistochemical staining of endometrial carcinoma samples, using monoclonal mouse anti-human $p27^{Kip1}$, clone SX53G8 (1:50 dilution), was performed by multimer technology: ultraViewTM DAB procedure following manufacturer's kit instructions. Immunohistochemistry procedure was conducted using BenchMark ultra automatic immunostainer. Tris-buffered saline replaced the primary antibody in a negative control slide. Human tonsil tissue section was incorporated as positive internal control. Slides were considered positive when granular brown nuclear staining was revealed in tumor cells.

P27 immunostaining was measured by two pathologists for both intensity and the frequency of positive cells. First, the fre-

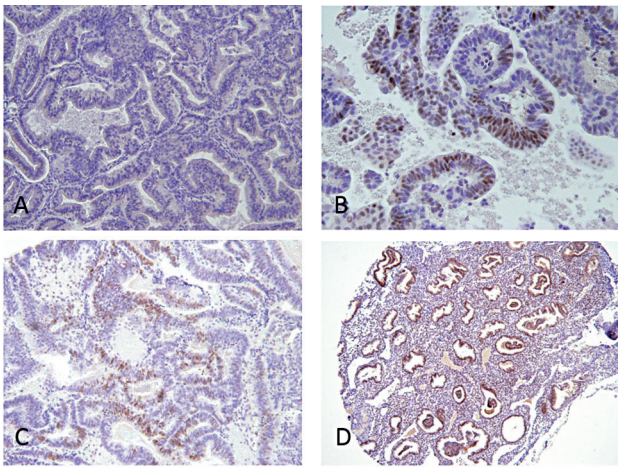

Figure 1. — Grandular nuclear p27 expression pattern in endometrial tumors. A) Negative stained endometrial adenocarcinoma (×20). B) Strong positive staining in epithelial cells of endometrioid adenocarcinoma (×40). C) Moderate positive staining in epithelial cells of endometrioid adenocarcinoma (×20). D) Strong positive stained normal endometrial tissue (×10).

quency of positive cells was measured semiquantitatively in three ×40 fields; if the three fields showed positive immunoreactivity in more than 5% of tumor cells, immunostaining was considered positive. Second, the positive cases for p27 immunostaining were scored for intensity of stain using scoring system of Al-Maghrabi *et al.* [22], i.e. weak staining +1, moderate +2, and strong +3. The score of staining intensity was accounted in the final score. If there was discrepancy in the readings between the two pathologists, the lowest value of scoring was used.

Data was statistically analysed using SPSS version 21. Fisher's exact test was applied to explore the association of p27 immunostaining with various clinicopathological variables. Log Rank (Mantel-Cox) test was applied to test for equality of survival distributions for the different categories of immunostaining. *P*-value < 0.05 was the statistical significance level.

Results

Seventy-one endometrial neoplastic cases were revised. Clinicopathological parameters of these tumors are presented in Table 1. The most common type was endometrioid adenocarcinoma and less frequently, papillary serous adenocarcinoma, malignant mixed Müllerian tumors (MMMT) and clear cell carcinoma (Table 1). The median age of these cases was 55 (range 26 - 86) years. FIGO histologic classification was used for grading endometrial tumors, taking into consideration that the presence of notable nuclear atypia increases the glandular grade by one. Only 56 endometrial tumors have been found to be staged using FIGO staging system. The whole number of mortalities in the full panel of cases was 17 (23.9%). Tumor recurrences were seen in 15 (21.1%) cases (Table 1), ten of these patients were deceased because of their tumor, and the remaining five patients were still alive at the latest follow-up.

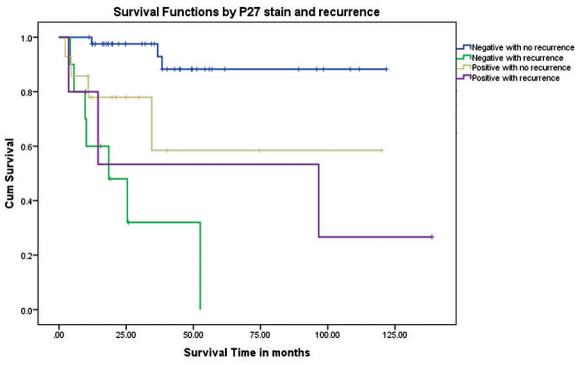

Figure 2. — Kaplan Meier survival curves by pattern of p27 immunostaining shows significantly poor survival behavior associated with stromal immunostaining in endometrial carcinoma.

Positive granular nuclear expression of p27 was detected in 19 (26.7%) cases of endometrial tumors (Figure 1) which include 16 endometrioid adenocarcinomas of which nine cases showed positive transformed epithelial cells, five cases revealed positive stromal cells, and both stromal and epithelial cells of the remaining two cases were positive. Two (22.2%) cases of papillary serous carcinomas were found strongly positive for p27 immunostaining in stromal cells and epithelial cells. while epithelial cells of one case of MMMT was found strongly positive for p27 immunostaining. There was considerable heterogeneity of p27 immunostaining between endometrial tumors in respect of the number of positively stained cells which ranged from 5% to 100% and intensity of staining which was moderate/intense in 63% of positive tumors and weak in 37%. Thirteen (43%) control cases (nine cases of secretory, three proliferative endometrium, and one polyp) showed moderate to strong granular nuclear expression mainly in epithelial cells except three cases expressed p27 in both stromal and epithelial cells. No statistical difference in p27 expression was observed between tumor cases and control group. This study did not find relationship between p27 expression and other clinicopathological parameters in endometrial tumors.

The result of log-rank (Mantel-Cox) test for equality of survival distributions for the different pattern of p27 immunostaining showed that loss of p27 expression in endometrial carcinoma patients with recurrent tumor is significantly associated with poor survival (*p*-value < 0.05) (Figure 2).

Discussion

Endometrial cancer rated sixth amongst the Saudi female population in 2010. Endometrial endometrioid adenocarcinoma is the commonest type accounting for more than 70%,

and less frequently, serous carcinoma, clear cell adenocarcinoma, and others [23]. An immunohistochemical marker that assists distinguishing among these endometrial carcinomas histotypes is undoubtedly to be supportive in determining the accurate curative plan. To the present authors' knowledge, the current paper is the first study in Middle East that explored p27 expression status in endometrial carcinomas and its association with other clinicopathological parameters in gynecologic malignancies of the tested Saudi female population.

Progressive p27 loss has been observed during the progression of neoplasia from benign to malignant cancers of the breast, lung, colon, prostate, and ovary and has been associated with adverse clinical outcomes in malignancies of epithelial, hematopoietic, and mesenchymal origin [12, 13, 16, 24-28]. The functional role of p27 protein in the carcinogenesis of endometrium and its expression status remain debatable.

In the present study, p27 immunoreactivity was less frequent in carcinomas (26.7%) compared with noncancerous endometrium (43%). The present findings are consistent with some studies which showed a consecutive reduction in the immunohistochemical expression of p27 in a range from normal to endometrial carcinoma [8, 18, 29-32]. On the other hand, it differs from other studies which reported increased p27 expression in endometrial carcinomas [21, 33-36].

The current study is the first to report that loss of p27 expression is significantly associated with poor survival in a fraction of endometrial carcinoma patients who had recurrent tumor. This finding is in line with the result of Catzavelos *et al.* [12] who reported decreased p27 expression is a predictor of poor survival in breast cancer, and contradict the findings of Al-Maghrabi *et al.* who reported that decreased p27 immunoreactivity is associated with longer survival in colorectal cancer [37]. The present authors' observation did not show significant relationship between the immunostaining of p27 and any other clinicopathological prognostic parameters of endometrial carcinoma patients such as age, histotype, grade, stage, and this conclusion is in line with many studies even some of those which reported increased p27 expression [33-36, 38-39], and contradict the findings of Watanabe *et al.* [21] who reported increased p27 immunoreactivity and correlated with higher grade, advanced stage, involvement of lymph nodes, invasion of deep myometrium, and poor prognosis.

In respect of control group, the frequency of p27 nuclear expression (43%) was lower than those of many other studies, which ranged from 53% to 100% of the samples of normal endometrium; some of these studies found positive p27 expression in both epithelial and stromal cells and mostly in the secretory phase of endometrium by using IHC [8, 18, 21, 29-31, 38].

The discrepancies among the current report and earlier studies can be clarified by immunostaining technique sensitivity, staining scoring methods, diversity of populations, and sample size differences. The present report study which attempted to evaluate the application of p27 immunostaining in the diagnosis and prognosis of endometrial carcinomas had some weak points, such as endometrial hyperplasia and hyperplasia with atypia have been not included, the relatively small sample size, and the semi-quantitative analysis of immunohistochemical staining. Nevertheless, larger comprehensive research studies are unquestionably important for assessing the diagnostic and prognostic usage of p27 immunostaining in endometrial tumors.

Conclusion

The present findings with decreased expression of p27 expression from normal to malignant endometrium are in favor of the tumour suppression role of p27. Greater p27 staining was seen in normal and benign endometrial tissues compared to endometrial carcinomas. Loss of p27 expression gives an indication for poor survival in endometrial carcinoma patients with recurrent tumor.

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