Acta Histochemica 118 (2016) 430–434

Contents lists available at ScienceDirect

Acta Histochemica

journal homepage: www.elsevier.de/acthis

Clusterin immunoexpression is associated with early stage endometrial carcinomas

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ARTICLE INFO

Article history:
Received 31 January 2016
Received in revised form 2 March 2016
Accepted 6 April 2016

Keyword:
Clusterin
Endometrial carcinoma
Immunohistochemistry

ABSTRACT

Clusterin has anti-apoptotic, regeneration and migration stimulating effects on tumor cells. This study investigates the relation between clusterin expression and the clinicopathological parameters in endometrial carcinomas. Seventy one cases of previously diagnosed endometrial carcinoma (including 59 endometrioid adenocarcinoma, 9 serous adenocarcinoma, 1 clear cell adenocarcinoma, and 2 malignant mixed Mullerian tumor) and 30 tissue samples of non-cancerous endometrium (including 16 proliferative endometrium, 10 secretory endometrium and 4 endometrial polyps) were employed for clusterin detection using tissue microarrays and immunostaining. A total number of 23 (32.4%) cases were positive for clusterin immunostaining. Brown granular cytoplasmic expression of clusterin was detected in 33.9% of endometrioid adenocarcinomas, 22.2% papillary serous endometrial carcinomas. Three (10%) control cases showed granular cytoplasmic expression. Positive clusterin immunostaining was found more frequent in well differentiated and stage I endometrial carcinomas, showing significant statistical association (p-value = 0.036 and p-value = 0.002 respectively). Significant difference in clusterin expression was observed between tumor cases and control group (P-Value = 0.019), i.e., endometrial carcinoma cases are more than four times likely to show positive clusterin immunostaining (odds ratio 4.313 with 95% confidence interval 1.184–15.701). This study did not find relation between clusterin expression and disease recurrence, survival or any of the other clinicopathological parameters in endometrial tumors. The results of our study confirms the diagnostic values of clusterin in supporting the diagnosis of endometrioid carcinoma. When clusterin is expressed in endometrial tumors, it is associated with lower stage. The correlation of clusterin with tumor stage suggests involvement of this molecule in endometrial tumor progression.

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1. Introduction

Endometrial carcinomas are the commonest aggressive malignant neoplasm of the female reproductive organs in developed countries (Jemal et al., 2008). There are substantial disparities between the main histotypes of endometrial carcinomas about a series of factors that may affect the treatment of patient, including prognosis, recurrence pattern, and chemotherapeutic response (Fadare et al., 2013; Soslow et al., 2007; Hamilton et al., 2006). Such factors necessitate accurate distinction between histotypes of endometrial carcinomas. Nevertheless, considerable interobserver inconsistency continues between pathologists in endometrial carcinoma histotyping (Fadare et al., 2012; Gilks et al., 2013). Thus, an immunohistochemical diagnostic and predictive marker for distinguishing histological types of endometrial carcinomas is undoubtedly to be worthwhile.

Clusterin is a glycoprotein encoded by *CLU* gene located on chromosome 8p21-p12 (Fink et al., 1993). This molecule has been found in many tissues and is believed to have several biological roles engaged in various normal and pathological states, for example, tissue differentiation, cell proliferation, cell–cell interaction, cell death, aging, neurodegeneration, tumorigenesis, chemotherapy resistance, and cell survival (Rosenberg and Silkensen, 1995;

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http://dx.doi.org/10.1016/j.acthis.2016.04.003
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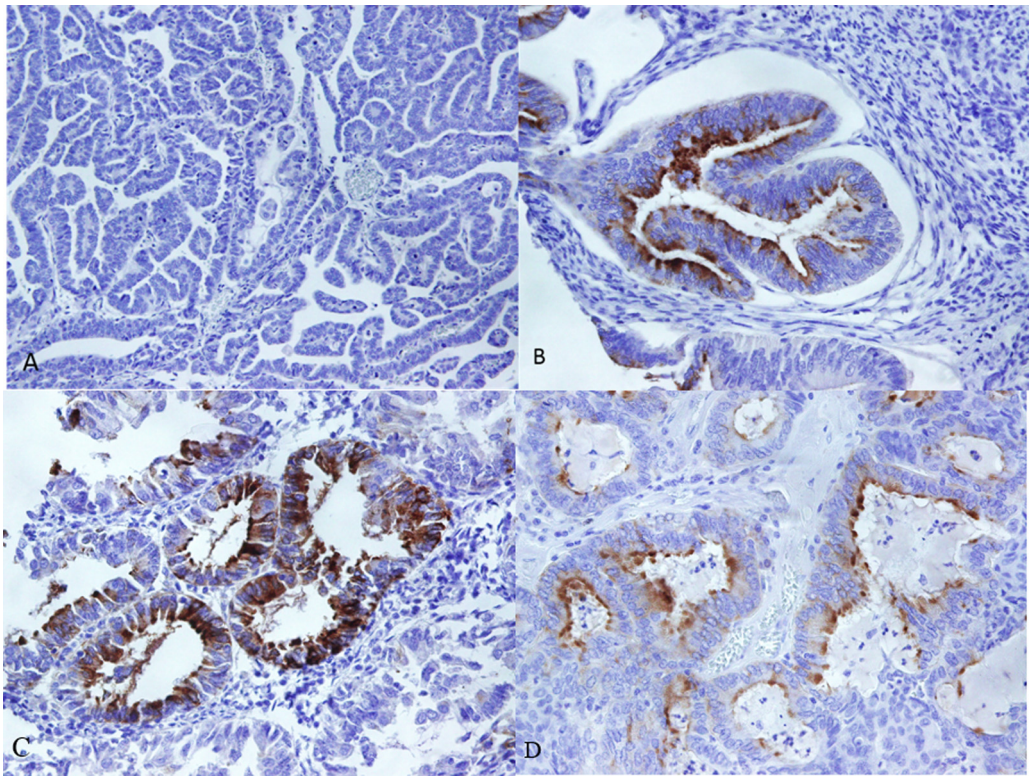

Fig. 1. Granular cytoplasmic clusterin expression pattern in endometrial tumors. (A) Negative stained endometrioid adenocarcinoma (20×); (B) strong positive stained endometrioid adenocarcinoma (40×); (C) strong positive staining in selective tumor glands and cells endometrioid adenocarcinoma (40×); (D) moderate positive stained endometrioid adenocarcinoma (40×).

Trougakos and Gonos, 2002; Shannan et al., 2006; Muhammad and Saad, 2015). Overexpression of clusterin has been detected in various malignant tumors, including kidney (Kurahashi et al., 2005), breast (Flanagan et al., 2010), prostate (Muhammad and Saad, 2015), lung (Panico et al., 2013), ovary (Xie et al., 2005), liver (Zheng et al., 2015) and colon (Pucci et al., 2004), proposing that anti-apoptotic role looks the main clusterin function in transformed cells. However, downregulated expression of clusterin has also been described in malignancies such as neuroblastoma (Santilli et al., 2003), esophageal (Zhang et al., 2003), prostatic (Scaltriti et al., 2004), and pancreatic carcinomas (Xie et al., 2002). These conflicting studies imply that the expression of clusterin is possibly controlled by different mechanisms in varied histotypes of carcinomas. The current study defines the immunohistochemical phenotype of clusterin in endometrial tumors, examines the relation between the expression of clusterin and the clinicopathological parameters and follow up data.

2. Material 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. These cases covered the period from January 2001 to December 2012. 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, 10

Table 1
Clinicopathological characteristics of endometrial tumor patients.

		Clusterin Stain				P-Value
		Negative		Positive		
		Count	%	Count	%	
Age in Years	<40	5	100.0	0	0.0	0.106[a]
	40–49	15	75.0	5	25.0	
	50–59	13	54.2	11	45.8	
	60–69	12	80.0	3	20.0	
	>=70	3	42.9	4	57.1	
Tumor histotype	Endometrioid adenocarcinoma	39	66.1	20	33.9	0.463[a]
	Serous carcinoma	7	77.8	2	22.2	
	MMMT	2	100.0	0	0.0	
	Clear cell carcinoma	0	0.0	1	100.0	
Grade	I	24	60.0	16	40.0	0.205[a]
	II	16	69.6	7	30.4	
	III	6	100.0	0	0.0	
	Ungraded	2	100.0	0	0.0	
Stage	I	19	48.7	20	51.3	0.002[a]
	II	5	100.0	0	0.0	
	III	8	88.9	1	11.1	
	IV	2	66.7	1	33.3	
	Unstaged	14	93.3	1	6.7	
Differentiation	W	25	61.0	16	39.0	0.036[b]
	M	14	70.0	6	30.0	
	P	7	87.5	1	12.5	
	NA	2	100.0	0	0.0	
Recurrence	NO	35	62.5	21	37.5	0.120[c]
	yes	13	86.7	2	13.3	
Alive	NO	14	82.4	3	17.6	0.234[c]
	yes	34	63.0	20	37.0	

[a] Fisher's exact test exact sig. (2-sided).
[b] Kendall's tau-b test (1-sided).
[c] Chi-square test (2-sided).

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