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Original contribution

Frequent *β-catenin* gene mutations in atypical polypoid adenomyoma of the uterus☆,☆☆

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Summary Atypical polypoid adenomyoma (APA) is an uncommon polypoid lesion of the uterus. To clarify the mechanism of its histogenesis, we examined the functional role of *β*-catenin, with reference to expression of p21[waf1], cyclin D1, cyclin E, CD10, and α–smooth muscle actin (SMA), as well as cell proliferation, in 7 lesions. In the epithelial components, expression of nuclear *β*-catenin, p21[waf1], and cyclin D1 was increased in a stepwise fashion from normal tissue through complex atypical hyperplasia and adenomyoma to APA lesions, particularly in squamous morular areas, whereas cell proliferation, as well as cyclin E expression, was significantly decreased in the latter. Similar findings were evident in the stromal lesions, with the exception of a case of nuclear *β*-catenin. In addition, coexpression of CD10 and α-SMA markers was observed in the stromal components in 3 APA cases, in line with the results of normal secretory endometrial and adenomyoma samples, suggesting that cells progress to myofibromatous cells in response to differentiation-promoting events. Finally, *β-catenin* gene (*CTNNB1*) mutations were detected in all APA cases, the single nucleotide substitutions being in the epithelial but not the stromal components. These findings suggest that activation of *β*-catenin signaling, probably secondary to the gene abnormalities, plays an important role in the formation of the complex epithelial architecture in APAs, leading to inhibition of cell proliferation through overexpression of p21[waf1]. In contrast, changes in the stromal cell phenotype may occur through a shift from CD10 to α-SMA immunopositivity, independent of *CTNNB1* status.

1. Introduction

Atypical polypoid adenomyoma (APA), an uncommon focal and polypoid lesion of the uterus, is characterized by irregular structures of cytologically atypical endometrial epithelial components with squamous morula formation and prominent cellular smooth muscle stromal components [1,2]. Most patients with APAs are of reproductive age, nulliparous,

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Table Clinicopathlogical findings in 7 APAs, 2 AMs, 10 CAHs, and 11 normal endometrium samples

Case	Age (y)	Treatment	Morule	*CTNNB1*		Nu-β-catenin LIs			p21 ^{wafl} LIs			Cyclin D1 LIs			Cycin E LIs			Ki-67 LIs			$CD10^+$
				Nucleotides	Amino acid	Epithelium		Stroma	Epithelium		Stroma	Epithelium		Stroma	Epithelium		Stroma	Epithelium		Stroma	Stroma*
						Gla	Mo		Gla	Mo		Gla	Mo		Gla	Mo		Gla	Mo		
APA-1	34	Curettage	+	TCT37TTT	Ser→Phe	8	39.4	5.4	1.1	41.5	36	42.7	35.9	36.2	1.7	2.8	0	0.8	1.1	1.5	+
APA-2	40	Curettage	+	TCT37TGT	Ser→Cys	10.4	48.8	5.8	1.5	28.8	17.5	30	66.9	35.3	0.8	0.3	0	17.5	1.2	2.4	–
APA-3	43	Hysterectomy	+	TCT33TGT	Ser→Cys	5	47.9	4.9	0.7	2.5	32	36.6	76.1	9.1	1	0	0.3	20	1.8	1.5	+
APA-4	44	Curettage	+	TCT37GCT	Ser→Ala	55.3	61.3	13.2	1.9	1.3	7.6	19.9	36.7	30.3	6.1	*	0	9.5	0.8	1.6	+
APA-5	38	Curettage	+	TCT33TTT	Ser→Phe	12.2	57.5	3.8	19	40.3	51.4	81.8	62.5	38.1	*	*	*	29.7	1.1	3.1	–
APA-6	37	Curettage	+	GAC32CAC	Asp→His	13	19	5.8	18.8	*	25	50	36.4	18.1	2.5	*	0.9	30	2.8	1.5	–
APA-7	46	Hysterectomy	+	GAC32TAC	Asp→Tyr	10.5	16.1	1.4	9.5	55.6	0.6	17.2	54.4	1.7	9.6	40.2	0	10.7	5	2.6	–
AM-1	42	Polypectomy	–	Wild		0	*	1.1	2.8	*	8.1	15.2	*	8.6	22.1	*	0.3	3.2	*	0	+
AM-2	34	Polypectomy	–	Wild		8.3	*	0	0.8	*	4.1	10.7	*	17.2	6.5	*	0	1.8	*	0	+
CAH	44.6 ±	Curettage	–	Wild		8.5 ±	*	4.9 ±	7.4 ±	*	1.6 ±	14.6 ±	*	5.2 ±	27.8 ±	*	0.5 ±	31.7 ±	*	10.8 ±	+
(n = 10)	7.0					5.9		3.5	7.7		1.8	10.8		5.9	27.9		0.6	23.9		12.6	
Normal (P)	41 ±	Biopsy	–	NE		5.8 ±	*	3.3 ±	6.1 ±	*	1.6 ±	20.1 ±	*	10.4 ±	11.8 ±	*	3.7 ±	36.8 ±	*	34.2 ±	+
(n = 11)	9.1					1.9		2.2	8.3		1.0	8.5		8.8	12.1		3.2	13.6		19.1	

Abbreviations: CAH, complex atypical hyperplasia; NE, not evaluable; Nu, nuclear; *, more than 50% CD10-positive cells in stromal lesion; normal (P), normal proliferative endothelium.

and premenopausal, with an age range of 21 to 53 years (median, 39.7 years) [2,3]. The lesions frequently develop in the lower uterine segments [2,4]. In some cases, curettage samples obtained from the lesions may be responsible for misidentification as an invasive carcinoma because of the presence of dense proliferation of smooth muscle cells [2].

Previous studies have demonstrated conflicting results regarding the biological behavior of APAs. For example, a review of 136 APA cases indicated that 30% had residual or recurrent tumors after local excision by curettage and that the risk of coexistent endometrial hyperplasia or carcinoma was approximately 9%, indicating a potentially high risk of malignant disease [5]. In contrast, others have found that the lesions appeared to be histologically and biologically benign, as suggested by DNA ploidy studies and Ki-67 immunohistochemical staining [4,6]. Interestingly, several risk factors for APAs, including obesity, hormone replacement therapy, and prolonged estrogenic stimulation, are common to patients with endometrial hyperplasia and carcinoma [2,7], indicating the possibility of coexistence of these lesions [8-10].

β-Catenin is a multifunctional protein involved in E-cadherin–mediated cell-cell adhesion, acting as a downstream effector in the Wnt signaling pathway [11-13]. We previously demonstrated that mutations in exon 3 of the gene were frequent in endometrial carcinomas with squamous morular differentiation, suggesting that the nuclear accumulation is an initial signal for an induction of the process, leading to inhibition of cell proliferation through overexpression of $p21^{wafl}$ [14-16]. Given that the *trans*-differentiation toward the squamous morular phenotype is common in APAs [2], we hypothesized a role for β-catenin signaling in its histogenesis. To test this idea, we investigated alterations in β-catenin status with reference to expression of several cell cycle– and stromal-related molecules and cell proliferation in APAs, as well as normal, complex atypical hyperplasia (CAH) and adenomyoma (AM) lesions.

2. Materials and methods

2.1. Cases

We reviewed uterine tumor samples obtained by curettage or hysterectomy from the patient records of Kitasato University Hospital and Kanagawa Cancer Center Hospital between 1990 and 2012. According to the criteria described by Longacre et al [2], tumors were designated as APAs if they featured localized polypoid proliferation of irregular glands with various degrees of squamous morular differentiation and cellular smooth muscle or hybrid smooth muscle/fibrous stroma. In curettage samples, we used CD10 immunoreactivity patterns to distinguish APAs from