ORIGINAL ARTICLE

Stromal p16 Expression Helps Distinguish Atypical Polypoid Adenomyoma From Myoinvasive Endometrioid Carcinoma of the Uterus

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Mazur MT.

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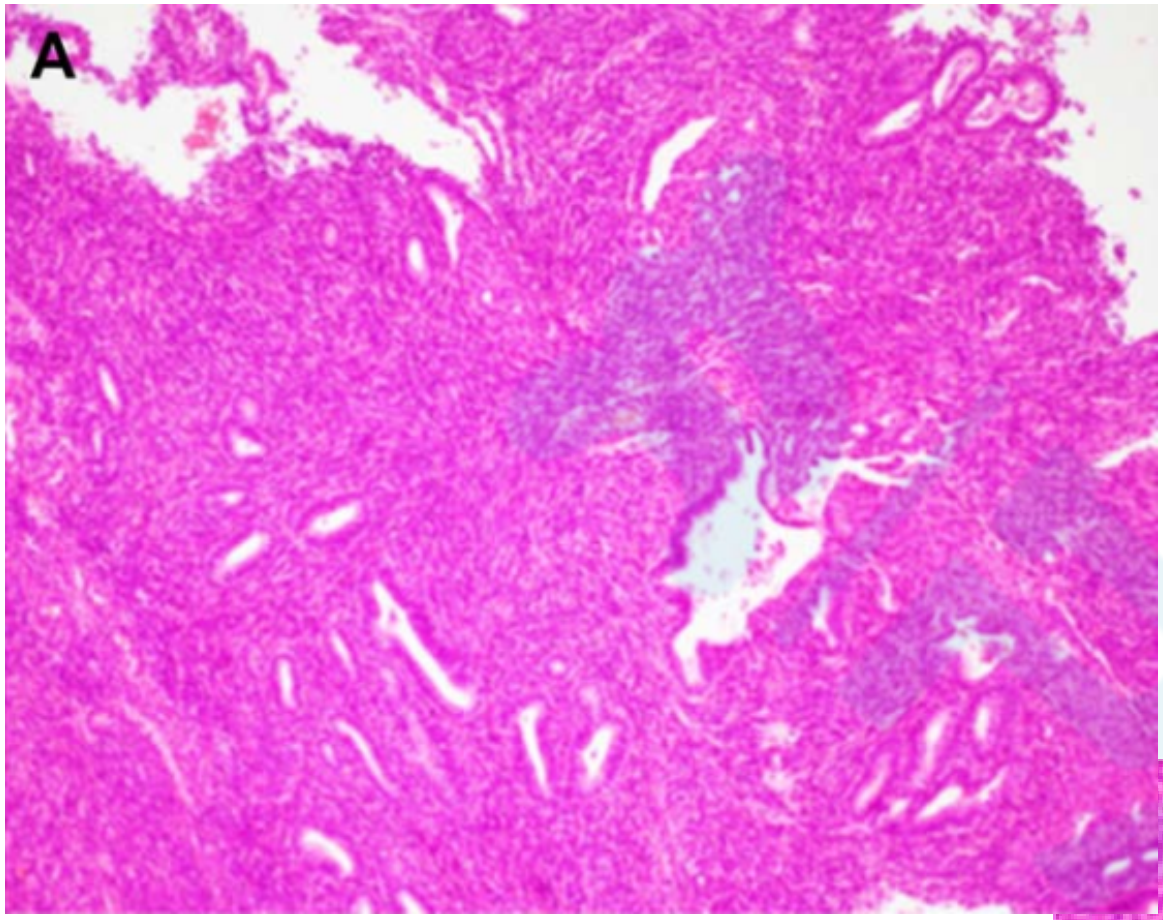
Atypical Polypoid Adenomyoma

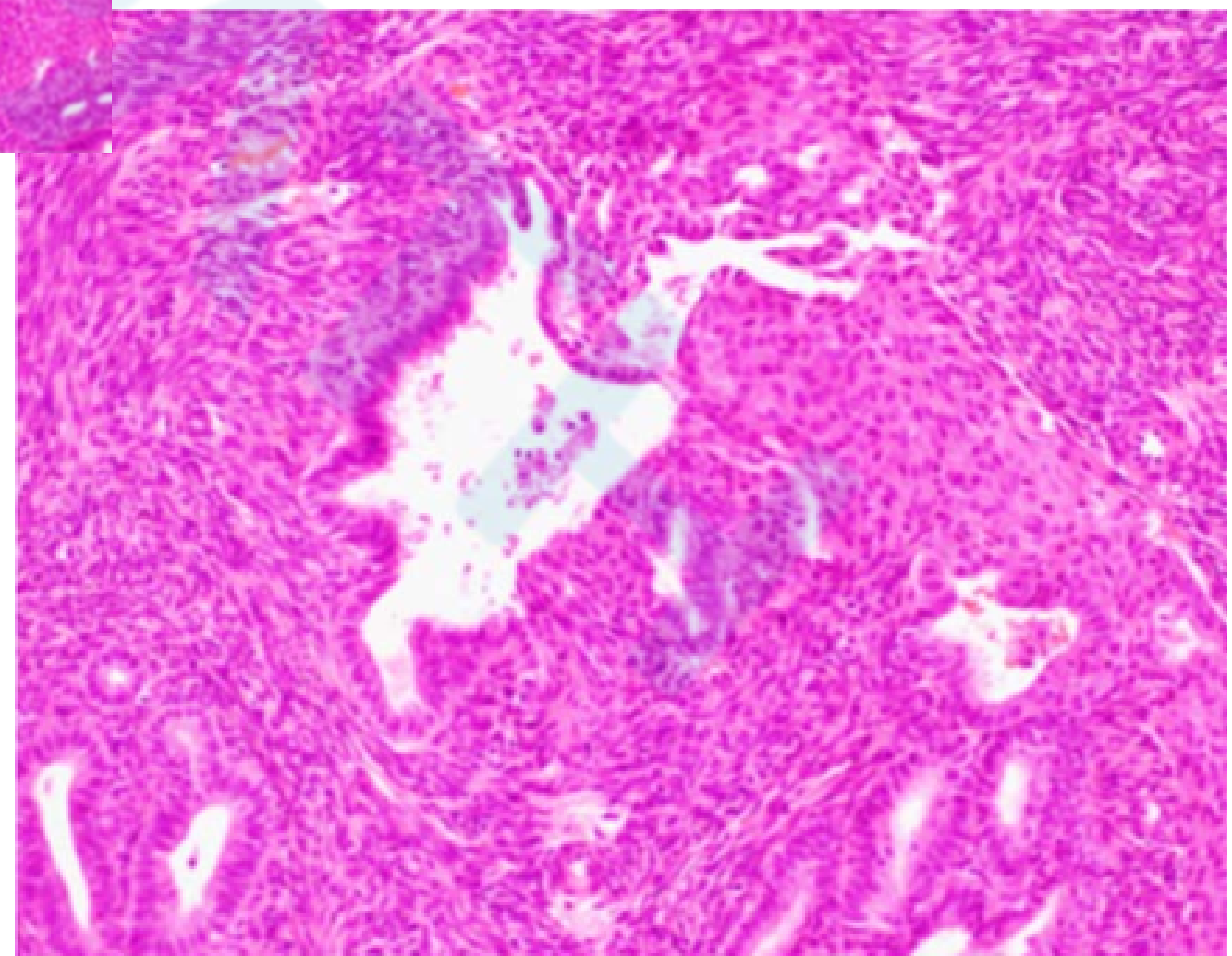
- A rare mixed epithelial and mesenchymal tumor which is characterized histopathologically by the presence of disorganized hyperplastic glands showing cytological atypia embedded in intersecting fascicles of fibromuscular stromal cells.

- ICD-O: 8932/0



Histopathological features of the endometrial curettage. A: Irregularly distributed endometrial glands surrounding short fascicles of spindle cells (H&E, 1003).

B: The glandular cells have mild to moderately enlarged nuclei, and squamous morules are present within the glands. Nuclear atypia is not noted in the spindle cells.



BACKGROUND

- Atypical polypoid adenomyoma (APA) is a polypoid lesion that is comprised of atypical endometrial glands and fibromuscular stroma, which pathologists often confuse with myoinvasive endometrioid carcinoma.

- This distinction is clinically important because fertility preservation is feasible for patients with APA, which usually affect reproductiveage women.

BACKGROUND

- In previous studies, some APA cases had molecular alterations that also underlie endometrial carcinoma such as mutations in KRAS and CTNNB1, deletion of PTEN, and MLH-1 promoter hypermethylation.

- However, these alterations do not distinguish APA from endometrioid carcinoma because these mutations can be found in both lesions.

BACKGROUND

- Previous studies have investigated the expression of muscular and endometrial stromal markers in APA.

- Some studies suggested that stromal expression of CD10 and h-caldesmon were useful to differentiate APA from myoinvasive carcinoma.

- However, few studies have examined other immunohistochemical and molecular features of the stromal components of APA.

BACKGROUND

- In contrast, some fibroepithelial lesions have characteristic alterations in their stromal components such as p16 expression and gene rearrangements involving high-mobility group AT-hook 1 (HMGA1) or HMGA2 in endometrial polyps.

- Mouse double minute 2 homolog (MDM2)/CDK4/HMGA2 amplification in uterine adenosarcomas.

- Gene mutations of mediator complex subunit 12 (MED12) and/or promoter of telomerase reverse transcriptase (TERT) in breast fibroadenomas and phyllodes tumors.

BACKGROUND

- In this study, we examined the stromal component properties of APA to find differential markers between APA and myoinvasive endometrioid carcinoma.

MATERIALS AND METHODS

●Case Selection (Jichi Medical University, Tochigi, Japan. between 2000 and 2017. Myoinvasive endometrioid carcinoma of the uterine corpus were randomly retrieved from the pathology archive (15+15+54))

●Immunohistochemical Analysis

(α-smooth muscle actin (SMA), desmin, h-caldesmon, CD10, β-catenin, HMGA1, HMGA2, estrogen receptor (ER), p53, p16, and MDM2)

●Mutational Analysis of MED12 and the TERT Promoter

●Statistical Analysis

RESULTS

- The cases were designated as APA when they were composed of irregular glands with various degrees of squamous or morular differentiation and cellular smooth muscular or hybrid smooth muscle/fibrous stroma.

- For comparison with APA, myoinvasive endometrioid carcinoma of the uterine corpus were randomly retrieved from the pathology archive, including 15 cases with a desmoplastic reaction (DR) and 15 cases without.

Clinicopathologic Features

TABLE 1. Clinicopathologic Features of Study Cases of APA

Case No.	Age	Initial Symptoms	Treatments	Outcome (mo)
1	35	Asymptomatic	Curettage MPA	NED (60)
2	51	Asymptomatic	Curettage	NED (93)
3	42	NA	Hysterectomy	NED (211)
4	43	Abnormal uterine bleeding	Hysterectomy	NED (42)
5	44	Abnormal uterine bleeding	Hysterectomy	NED (132)
6	34	Asymptomatic	Polypectomy	NED (85)
7	26	Asymptomatic	Polypectomy MPA	NED (25)
8	32	NA	Hysterectomy	NED (156)
9/10	32	Abnormal uterine bleeding	Curettage (case 9) Polypectomy (case 10) MPA	Endometrioid carcinoma (39)
11/12	35	Abnormal uterine bleeding	Polypectomy (cases 11 and 12)	NED (29)

MPA indicates medroxyprogesterone acetate; NA, not available; NED, no evidence of disease.

RESULTS

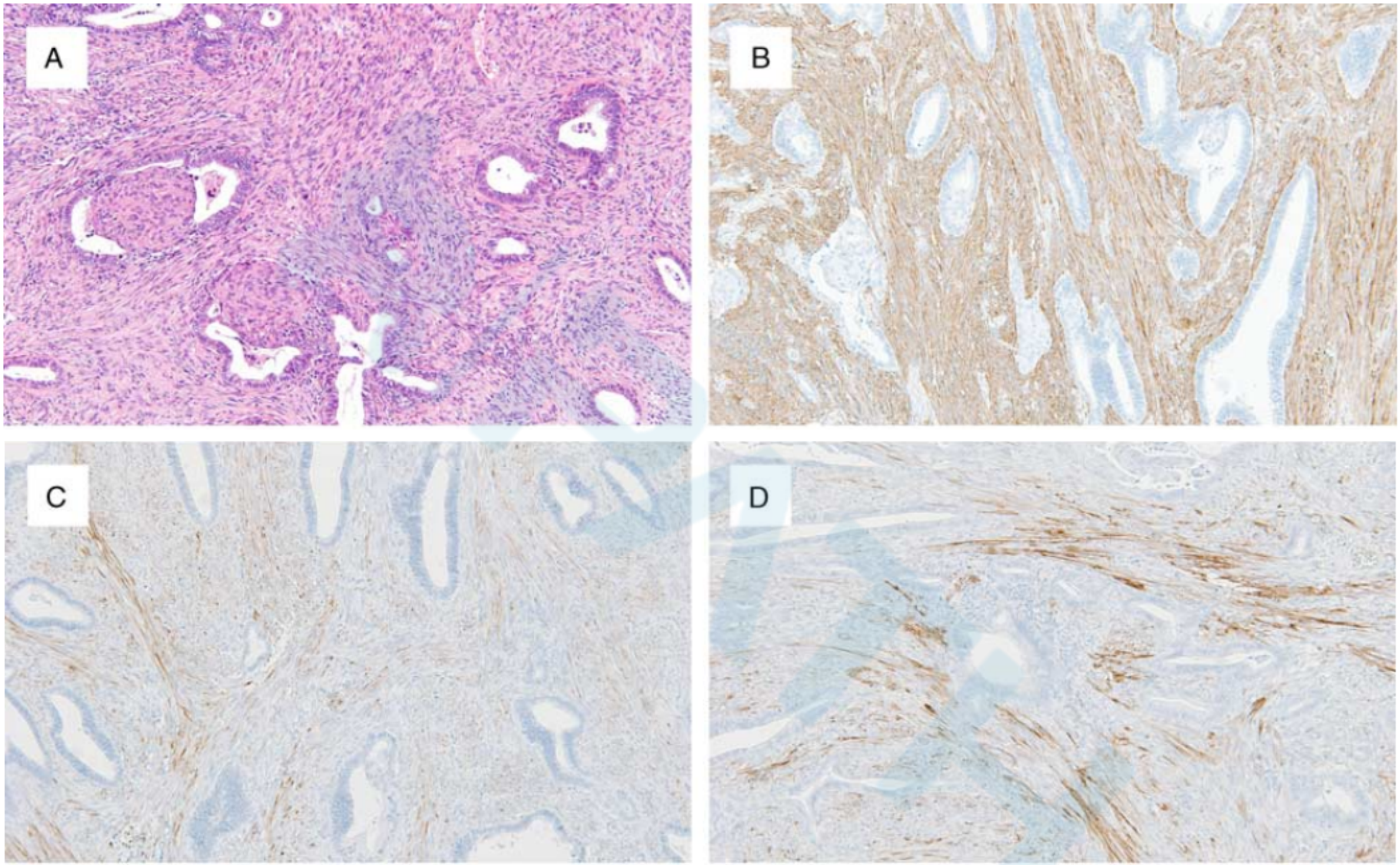
Immunohistochemical Findings

TABLE 2. Immunohistochemical Findings of the Stromal Component of APA

Case No.	SMA	Desmin	h-caldesmon	CD10	ER	β-catenin	p16	p53	HMGA1	HMGA2	MDM2
1	3+	0	0	3+	3+	0	3+	1+	0	0	0
2	3+	0	0	1+	3+	0	1+	0	0	0	0
3	3+	2+	2+	0	2+	0	3+	0	0	0	0
4	3+	1+	1+	2+	3+	0	3+	0	0	0	0
5	3+	0	1+	0	1+	0	1+	0	0	0	0
6	3+	0	0	1+	3+	0	3+	1+	0	0	1+
7	3+	0	0	3+	3+	0	3+	0	0	0	0
8	3+	0	0	1+	1+	0	3+	0	0	0	0
9	3+	1+	1+	0	3+	0	3+	1+	0	1+	0
10	3+	1+	2+	0	2+	0	3+	0	0	0	0
11	3+	1+	2+	3+	3+	0	3+	1+	0	3+	3+
12	3+	1+	1+	1+	3+	0	3+	1+	0	2+	2+

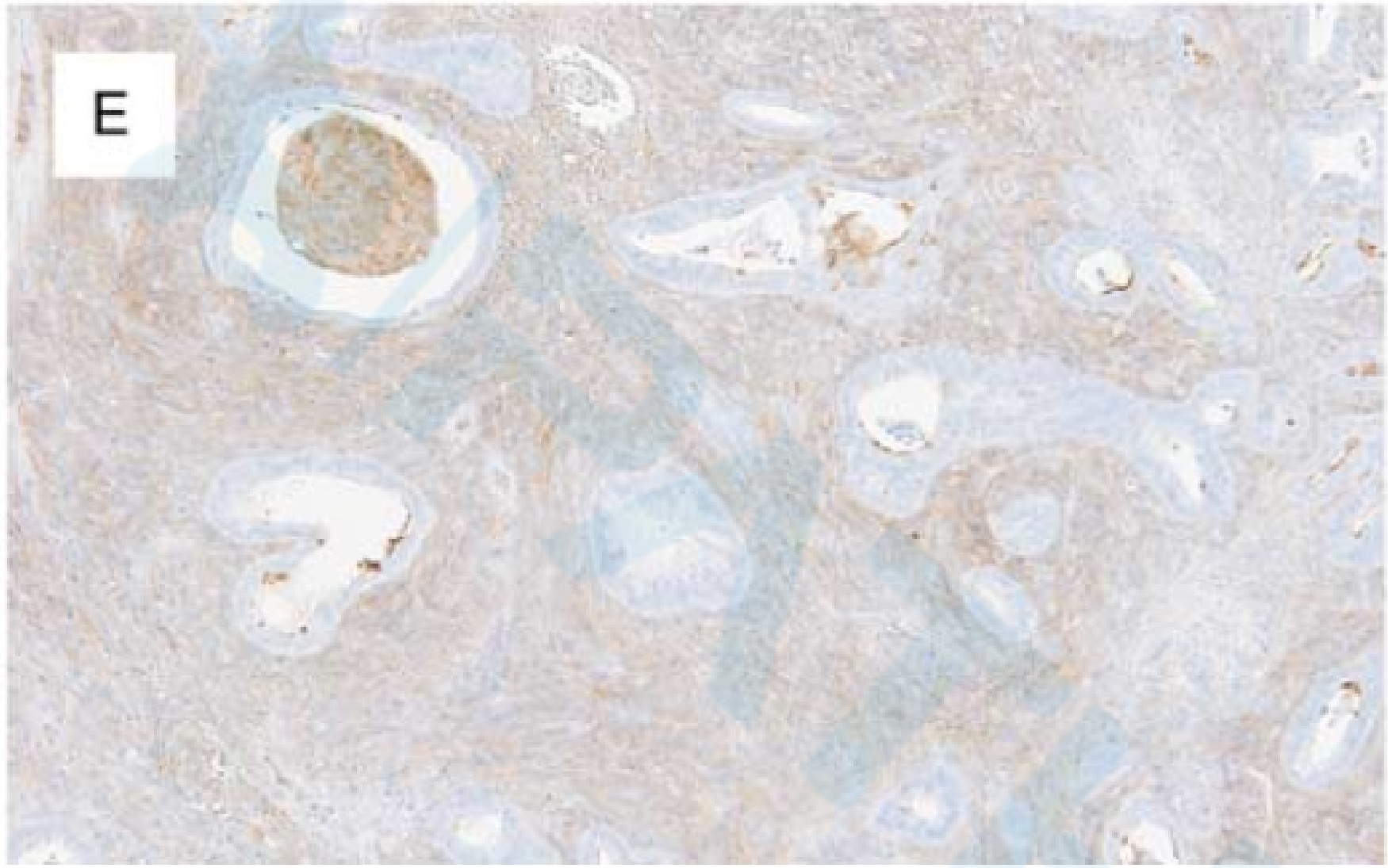
12例APA的基质均表现为弥漫性的SMA表达
8例间质表达Desmin和 h-caldesmon
9例可以观察到间质成分CD10的表达
12例里β-catenin的核都不阳。
12例HMGA1都是阴性的
3例HMGA2是阳性的
3例 MDM2是阳性的
12例P53是阴性或者局灶弱阳性的表达
12例P16都是阳性的

RESULTS



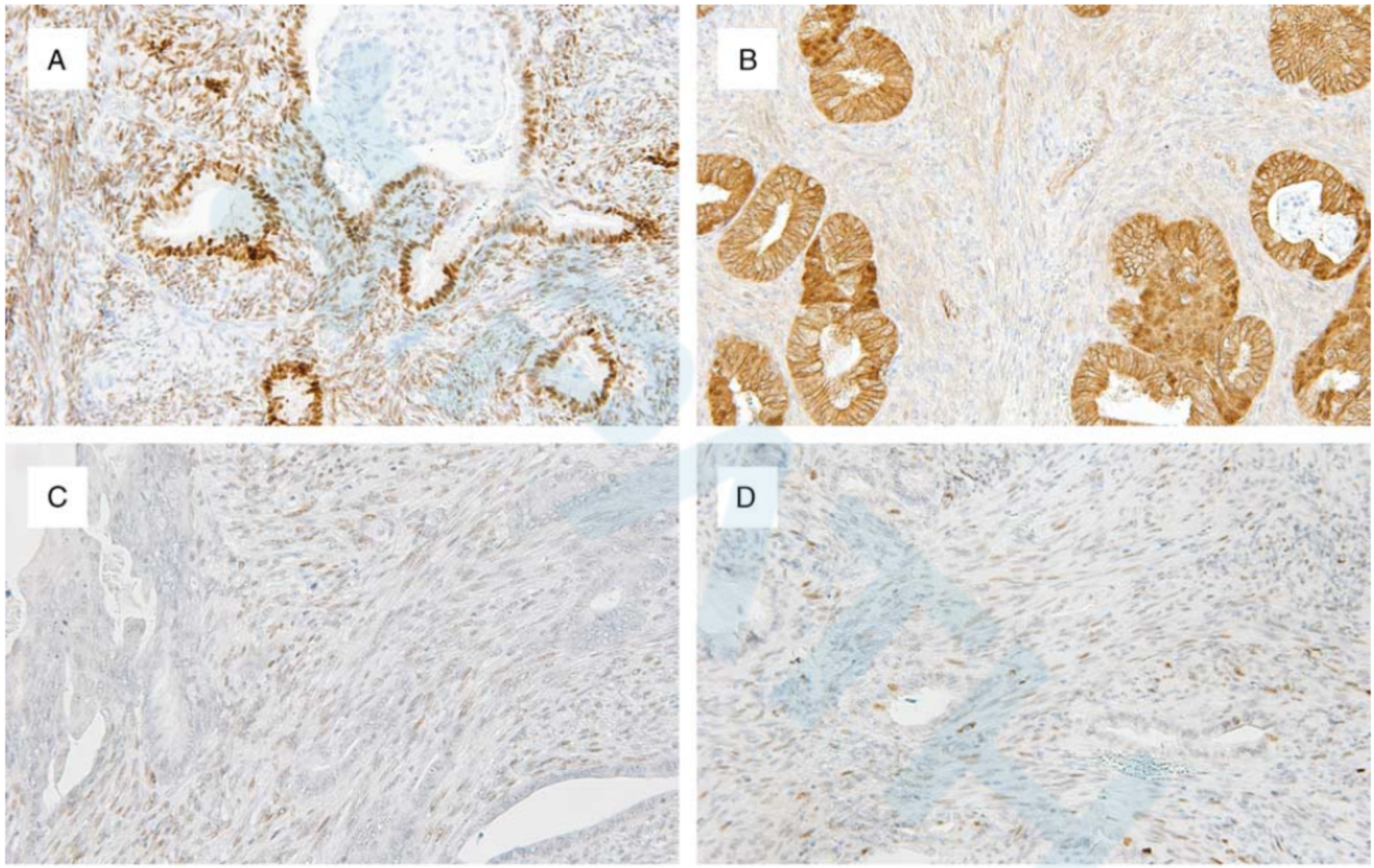
A, Histomorphology of APA. Atypical glands with squamous morules were embedded in the fibromuscular stroma. B, All cases showed strong and diffuse expression of SMA.C, In desmin-positive cases, bundles of spindle cells were stained in stromal components. D, h-caldesmon was focally positive in the spindle cells of stromal components.

RESULTS



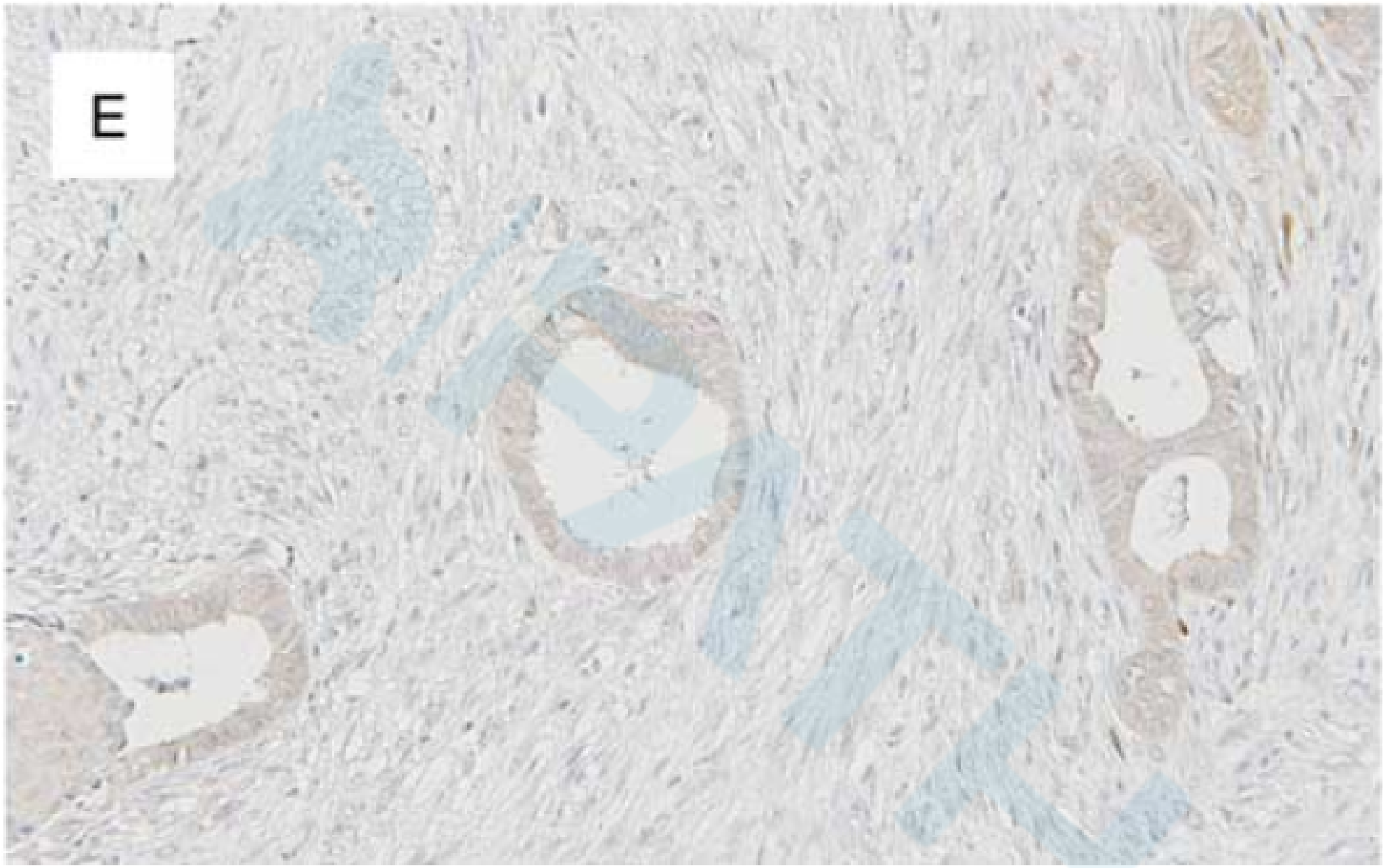
E, Stromal components showed CD10 expression. Squamous morules were also positive for CD10.

RESULTS



A, Stromal cells showed the positive expression of the ER, whereas squamous morules were negative for the ER. B, β -catenin was negative in the nuclei of stromal cells, but positive in squamous morules.Some cases showed the stromal expression of HMGA2 (C) and MDM2 (D).

RESULTS



Stromal components showed the weak expression of p53.

RESULTS

No Mutation of MED12 Exon 2 and TERT Promoter in APA

- We analyzed MED12 exon 2 and the TERT promoter in all 12 APA cases, but no mutations were detected.

RESULTS

Comparison of Stromal Expression of Muscle Markers, p16, and CD10, With Myoinvasive Endometrioid Carcinoma

- p16 was universally expressed in the stromal components of APA. We selected p16 as a potential diagnostic immunohistochemical marker to compare with myoinvasive endometrioid carcinoma.

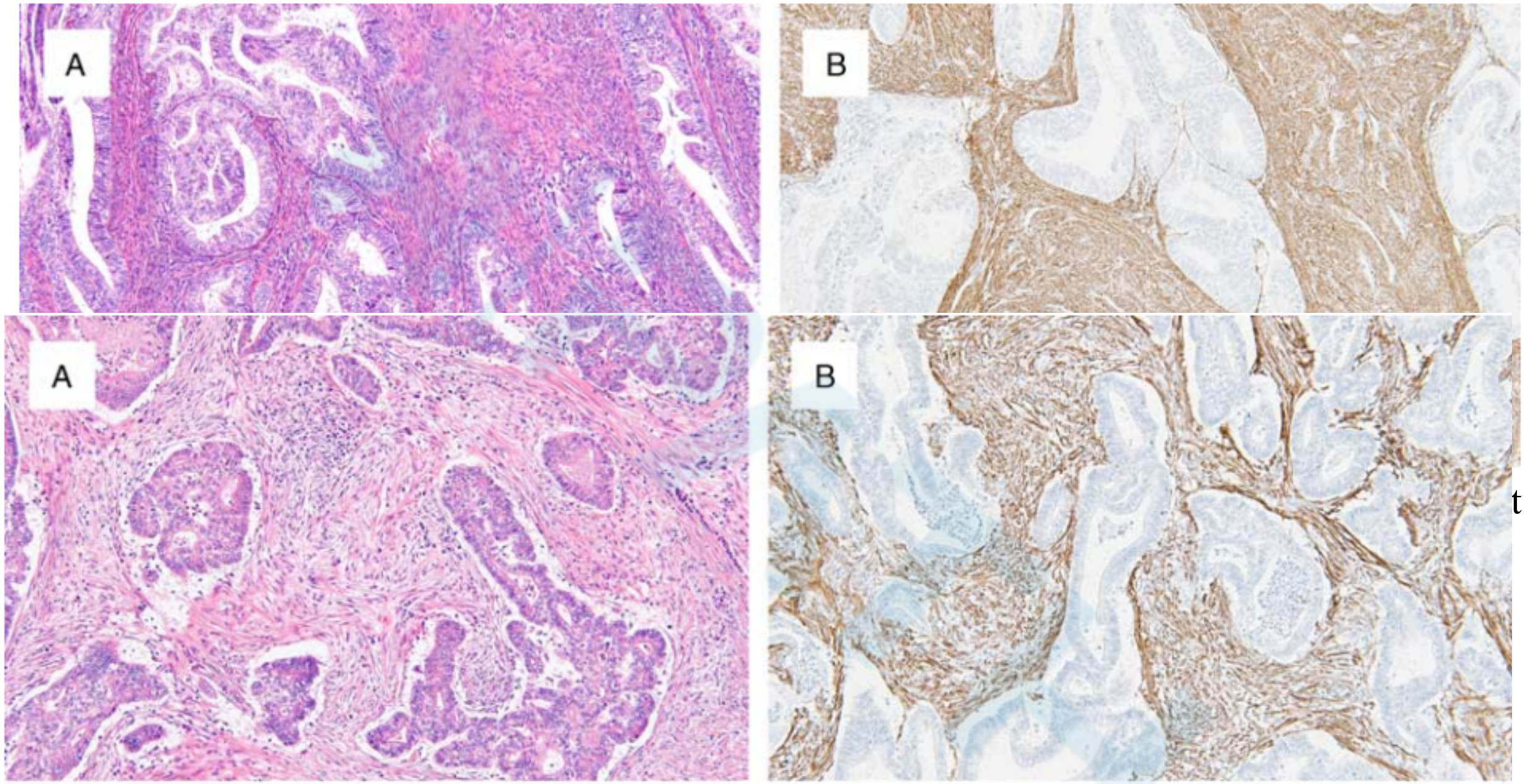
- We also examined muscle and endometrial stromal markers including CD10 and h-caldesmon, which were previously described as useful differential markers.

RESULTS

TABLE 3. Immunohistochemical Status of Stromal Components of Myoinvasive Endometrioid Carcinoma With or Without a DR

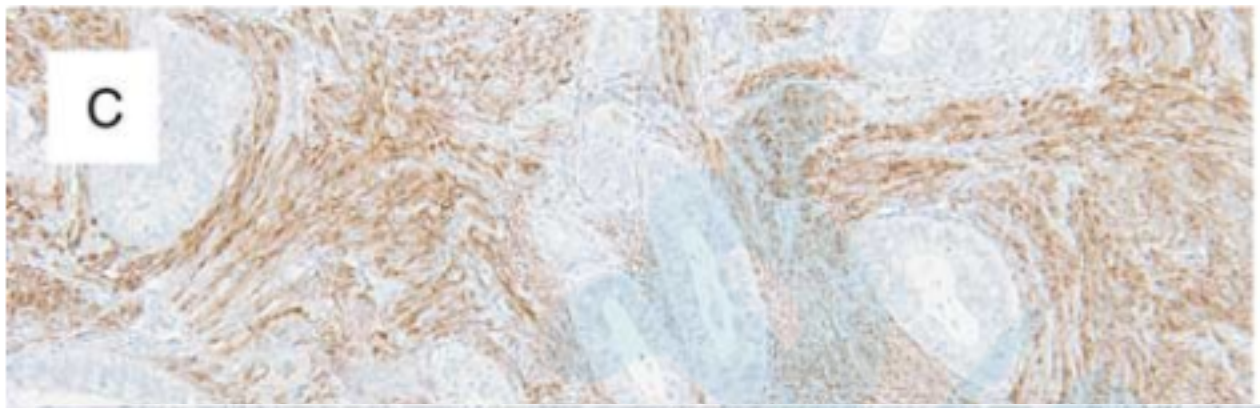
Expression Extent	0	1+	2+	3+
SMA				
All cases (n = 30)	0	0	0	30
DR (+) (n = 15)	0	0	0	15
DR (−) (n = 15)	0	0	0	15
Desmin				
All cases (n = 30)	8	7	1	14
DR (+) (n = 15)	8	7	0	0
DR (−) (n = 15)	0	0	1	14
h-caldesmon				
All cases (n = 30)	8	7	1	14
DR (+) (n = 15)	8	7	0	0
DR (−) (n = 15)	0	0	1	14
CD10				
All cases (n = 30)	8	9	12	1
DR (+) (n = 15)	7	3	4	1
DR (−) (n = 15)	1	6	8	0
p16				
All cases (n = 84)	83	1	0	0
DR (+) (n = 42)	41	1	0	0
DR (−) (n = 42)	42	0	0	0

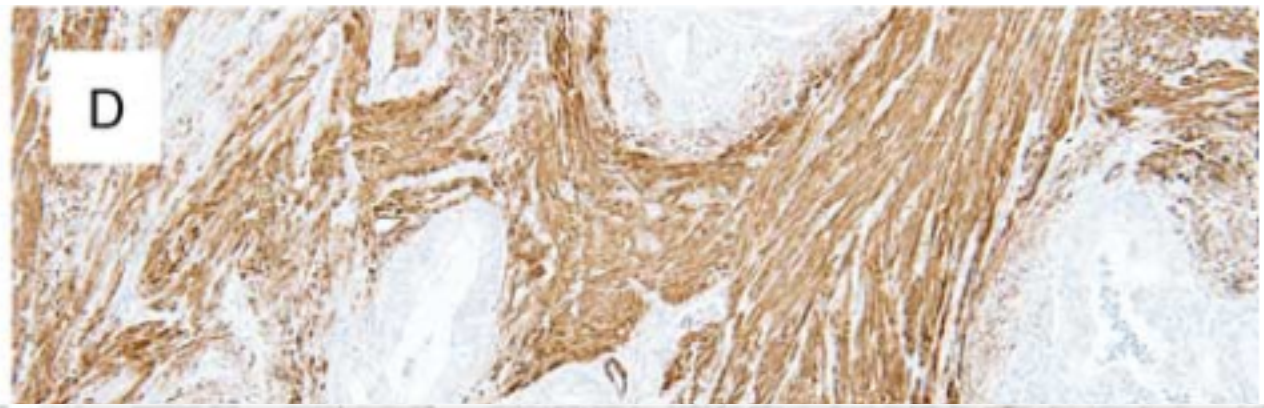
RESULTS

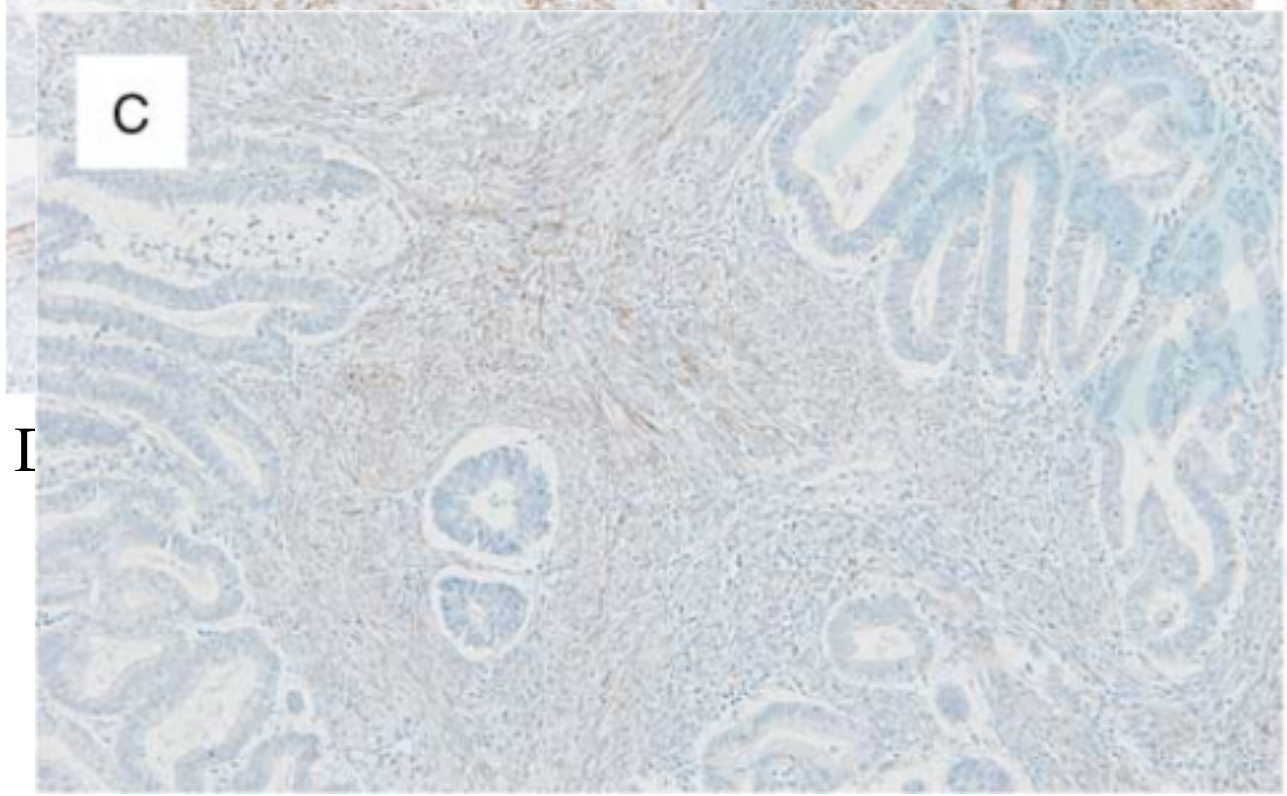


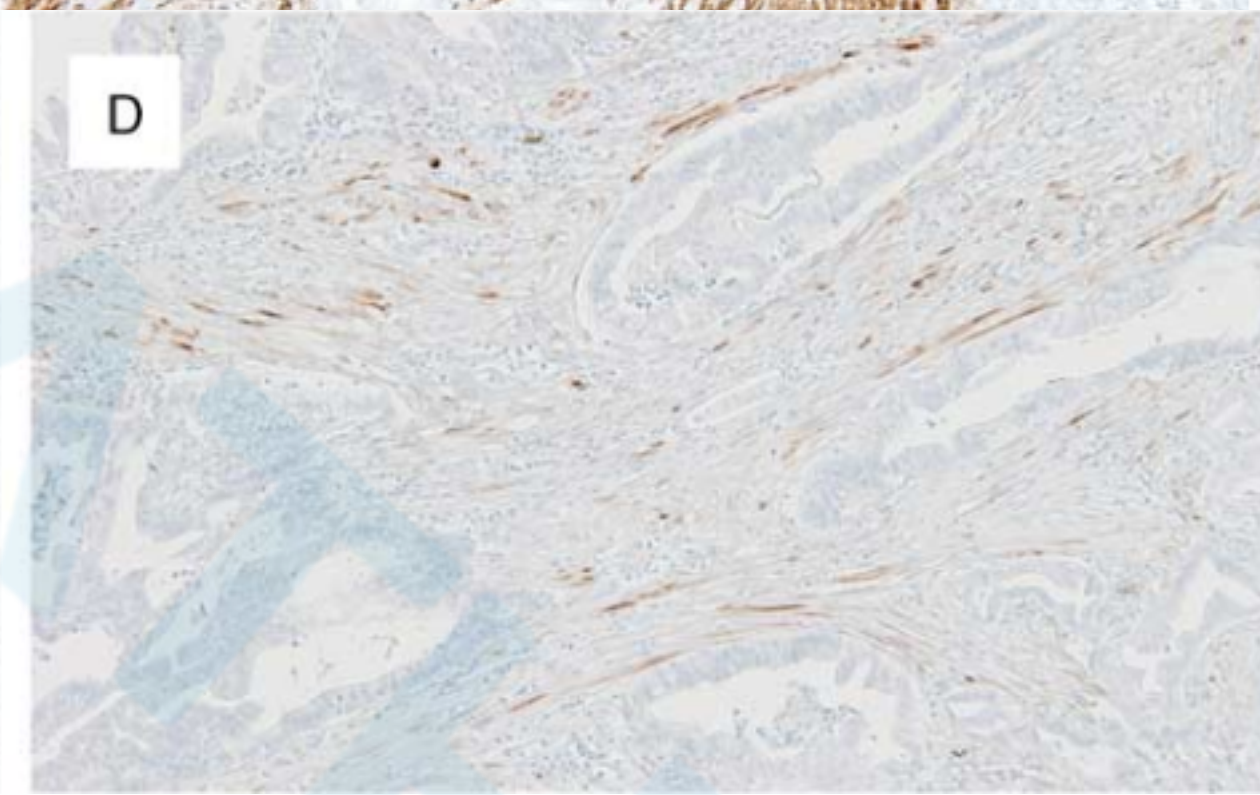
SMA showed strong and diffuse expression in the stroma.

RESULTS









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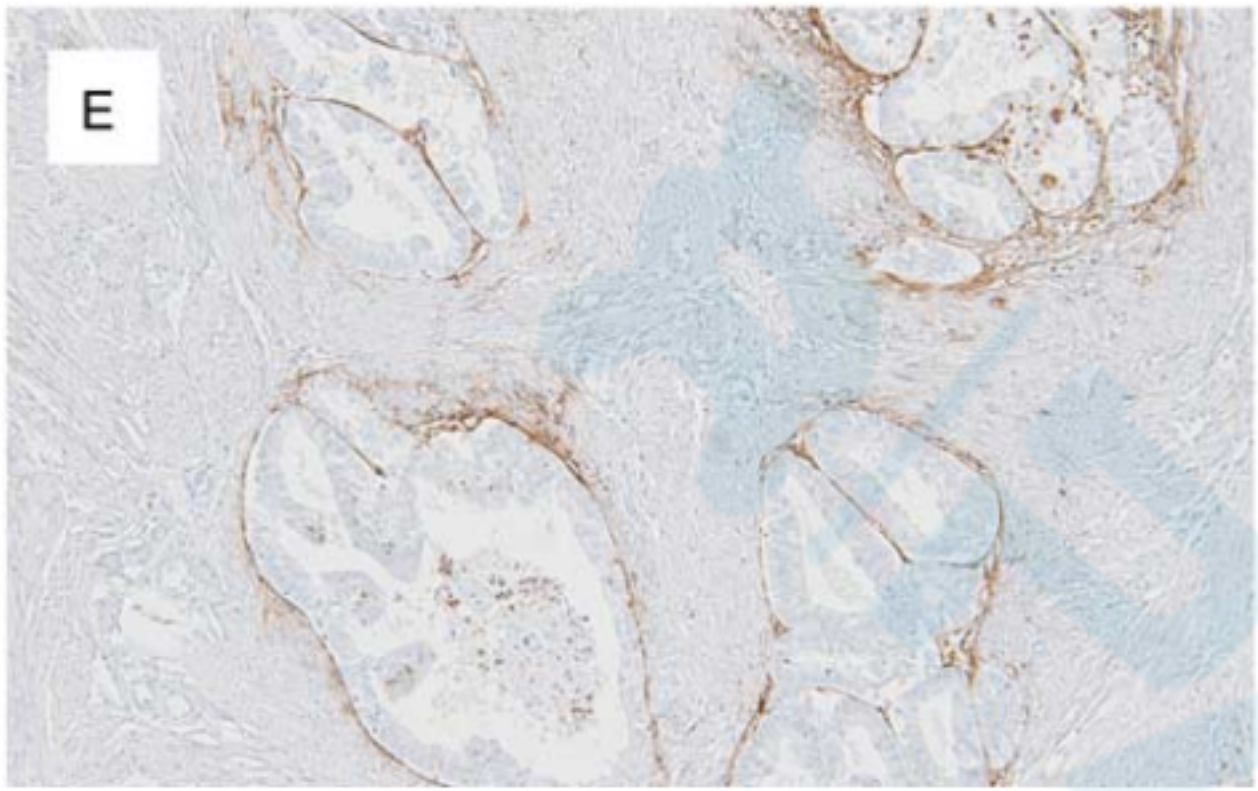
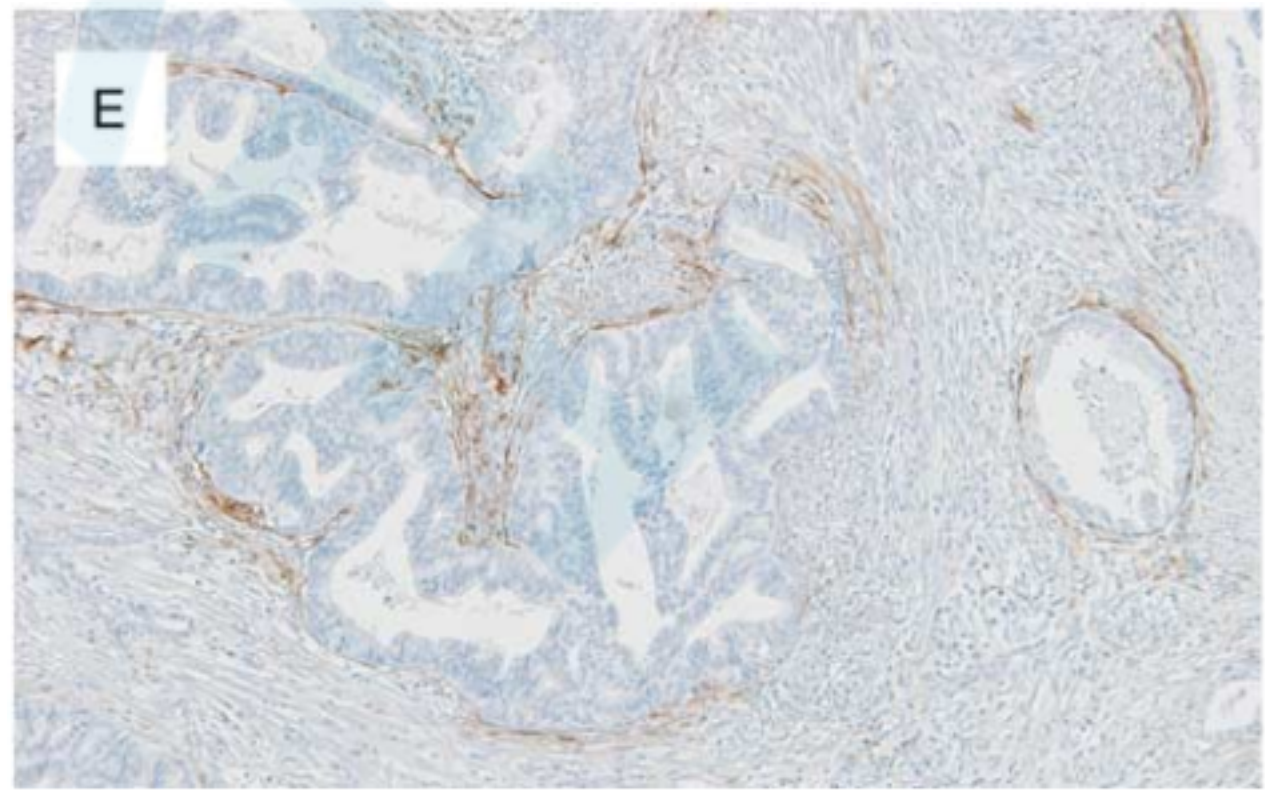
Desmin and h-caldesmon also showed diffuse expression in myoinvasive carcinoma without a DR (Figs. 3C, D). In myoinvasive carcinoma with a DR, desmin and h-caldesmon showed patchy expression patterns in 7 of 15 cases (Figs. 4C, D).

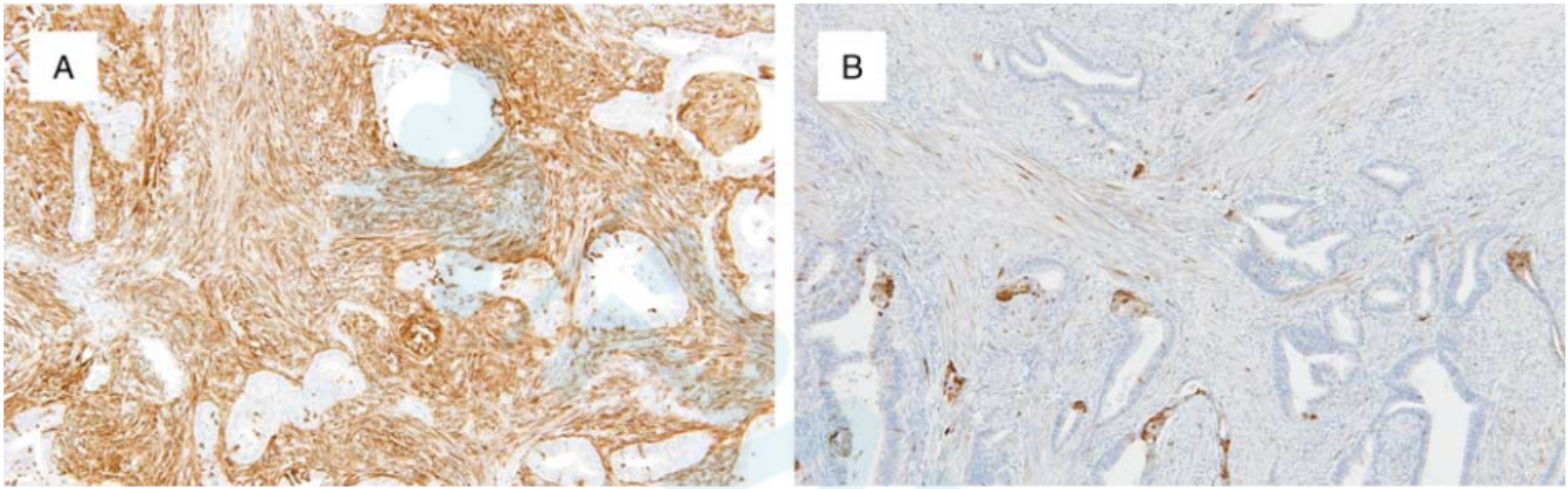
RESULTS



CD10 was positive in 14 of 15 cases without a DR and 8 of 15 cases with or without a DR.

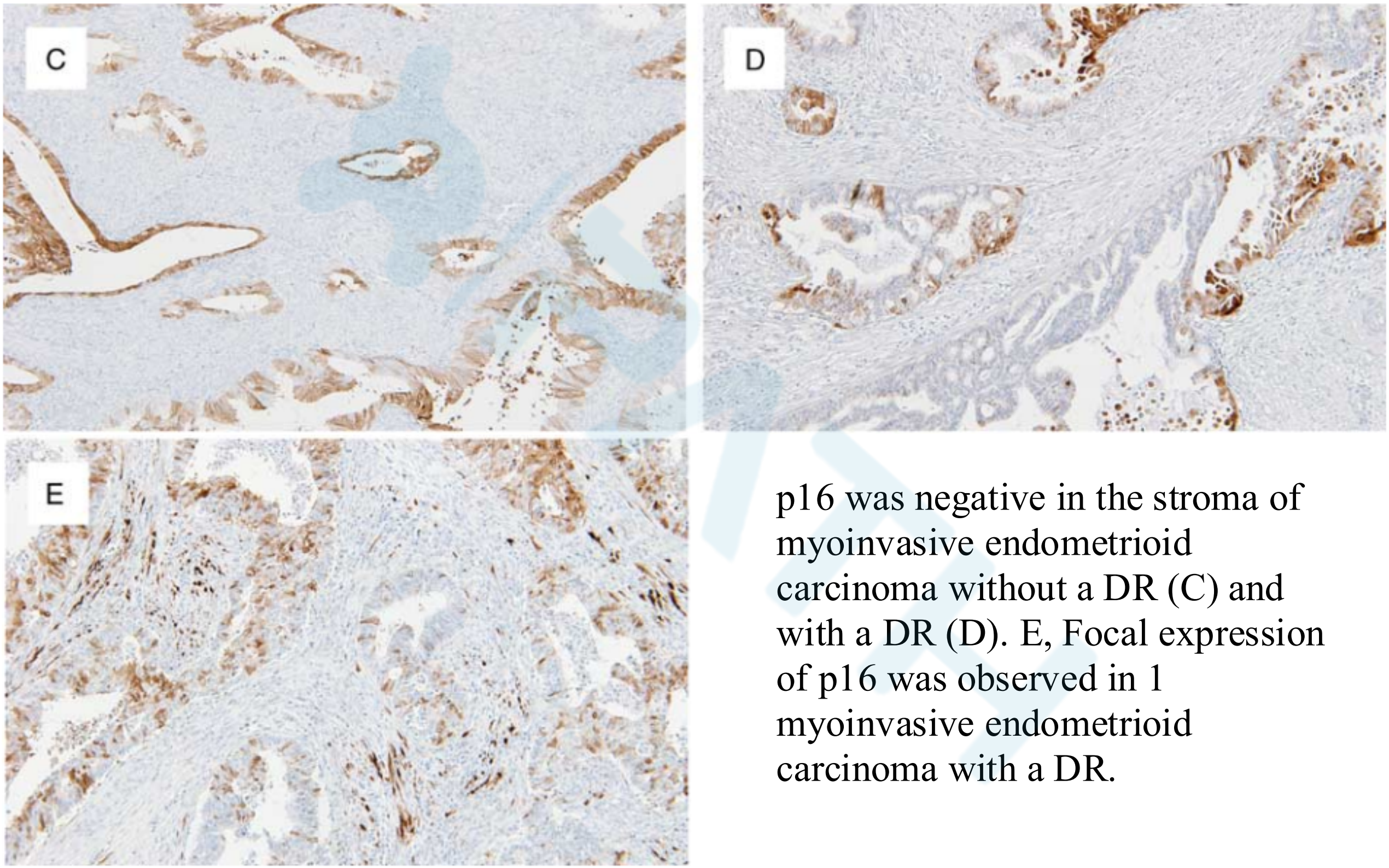
CD10 mainly stained in the immediate periglandular area and showed a “fringe-like staining pattern”.





Stromal p16 expression in APA and myoinvasive endometrioid carcinoma. Most cases of APA showed diffuse p16 expression in the stroma (A), whereas focal expression was observed in 1 cases (B)

RESULTS



p16 was negative in the stroma of myoinvasive endometrioid carcinoma without a DR (C) and with a DR (D). E, Focal expression of p16 was observed in 1 myoinvasive endometrioid carcinoma with a DR.

RESULTS

TABLE 4. Immunohistochemical Comparison of Stromal Components Between APA and Myoinvasive Endometrioid Carcinoma

		Myoinvasive Endometrioid Carcinoma					
	APA (n = 12)	All Cases (n = 30)		DR (+) (n = 15)		DR (−) (n = 15)	
	No. Positive Cases (%)	No. Positive Cases (%)	*P*	No. Positive Cases (%)	*P*	No. Positive Cases (%)	*P*
SMA	12 (100)	30 (100)	1	15 (100)	1	15 (100)	1
Desmin	6 (50)	22 (73)	0.16	7 (46)	1	15 (100)	**0.0031**
h-caldesmon	7 (58)	22 (73)	0.46	7 (46)	0.70	15 (100)	0.009
CD10	8 (66)	22 (73)	0.71	8 (53)	0.69	14 (93)	0.13
p16	12 (100)	1* (1)	**< 0.001**	1* (2)	**< 0.001**	0* (0)	**< 0.001**

*Stromal p16 expression was examined in 84 cases of myoinvasive endometrioid carcinoma, including 42 with and 42 without a DR.
Each *P*-value was obtained by comparison of the proportion of the positive cases between APA and myoinvasive endometrioid carcinoma.
The Bonferroni-corrected *P*-value for significance was 0.0033 (0.05/15).
Significant *P* values are shown in bold.

DISCUSSION

clinicopathologic analysis

- The mean age: 37 y
- APA mainly affected premenopausal women
- Common symptom :abnormal uterine bleeding
- The location of APA was not confined to the lower uterine segment, it has also been detected in the uterine cervix and fundus.

DISCUSSION

immunohistochemical and molecular analyses

- All cases of APA were immunohistochemically positive for p16 in the stromal components, and its expression was diffuse in most cases.
- In clinical settings, APA itself may comprise endometrial carcinoma. It may show stromal p16 expression in the area of carcinoma, representing a potential pitfall when the stromal p16 expression is used as a marker of APA.

DISCUSSION

- desmin :A significant difference was observed in the expression of desmin between APA and myoinvasive carcinoma without a DR (P = 0.0031, Table 4).

- h-caldesmon : the expression of h-caldesmon was not detected in APA or myoinvasive endometrioid carcinoma with a DR.

DISCUSSION

- CD10： Some cases of myoinvasive carcinoma, particularly those with a DR, showed the negative stromal expression of CD10 and lacked the "fringe-like staining pattern."
- We observed the stromal expression of HMGA2 in 3 cases, 2 of which also expressed MDM2. As HMGA2 expression often reflects genetic alterations, such as rearrangements in endometrial polyps and the amplification of uterine adenosarcoma, these alterations may be involved in APA and warrant further study.

LIMITATION

- The number of APA cases included was small.
- Furthermore, the molecular analysis was limited to Further genetic and molecular analyses of stromal components may provide a more complete histogenesis of APA.

THANK YOU