Ki-67 distribution, α-methylacyl-CoA racemase (AMACR) expression and mucin phenotypes are associated with non-polypoid growth in ulcerative colitis-associated neoplasia

Okano S, Fukata M, Murakami T, Nojiri S, et.at Histopathology. 2024 Oct;85(4):671-685. IF3.9

【背景】 潰瘍性大腸炎関連腫瘍（**ulcerative colitis-associated neoplasia**：UCAN）は、多巣性に腫瘍形成することが特徴である。散発制腫瘍として内視鏡的に治療された後に異時性に複数の病変が発生することが報告されている。

【目的】潰瘍性大腸炎（UC）患者における粘膜内病変の免疫組織化学的（IHC）特徴および臨床病理学的特性の違いを評価すること。

【対象と方法】 UC 患者の全結腸切除症例のうち、癌または異形成を伴う粘膜内病変 35 例、および非 UC 患者から内視鏡的に切除された散発性腺腫（SA；sporadic adenoma）71 例を対象とした。UC 病変は、conventional UCAN 群 （p53 変異パターンと正常な β カテニン発現を示す群)と、非 conventional UCAN 群に分類した。それぞれ、Ki-67 陽性細胞の分布、α-メチルアシル-CoA ラセマーゼ（AMACR）の発現、および粘液形質を免疫組織化学的染色で比較し、臨床病理学的特徴を調査した。

【結果】conventional UCAN 群および非 conventional UCAN 群は、左側結腸および直腸に多く発生した。SA 病変と比較して、UCAN 病変の発症年齢は腺腫に比較して若く、腫瘍陰窩における Ki-67 の基底側発現パターンが多くみられた。conventional UCAN 群は非ポリープ状が多くみられ、SA 病変よりも AMACR の正常発現頻度が高い傾向にあった。UC 病変はそれぞれの免疫染色の結果は不均一であり、複数の病変を持つ患者（n=8）のうち、2 人に免疫染色の結果が一致した非 conventional UCAN 病変が認められた。

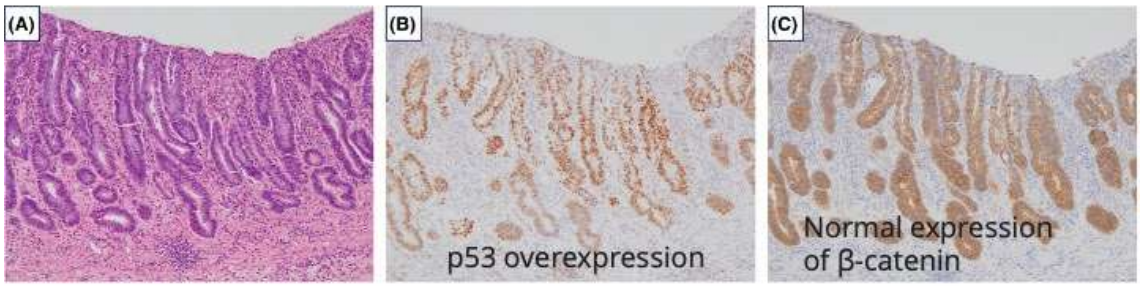
【結論】Ki-67 の基底分布、AMACR の正常発現、および非腸型粘液形質は、UCAN を示唆する特徴的な所見であった。加えて、非ポリープ状の形態も UCAN の特徴であった。

Take Home Messages

1. Ki-67 の基底分布と AMACR の正常発現は、UCAN を特徴付ける所見である。
2. conventional UCAN は非ポリープ状の形態を示すことが多い。

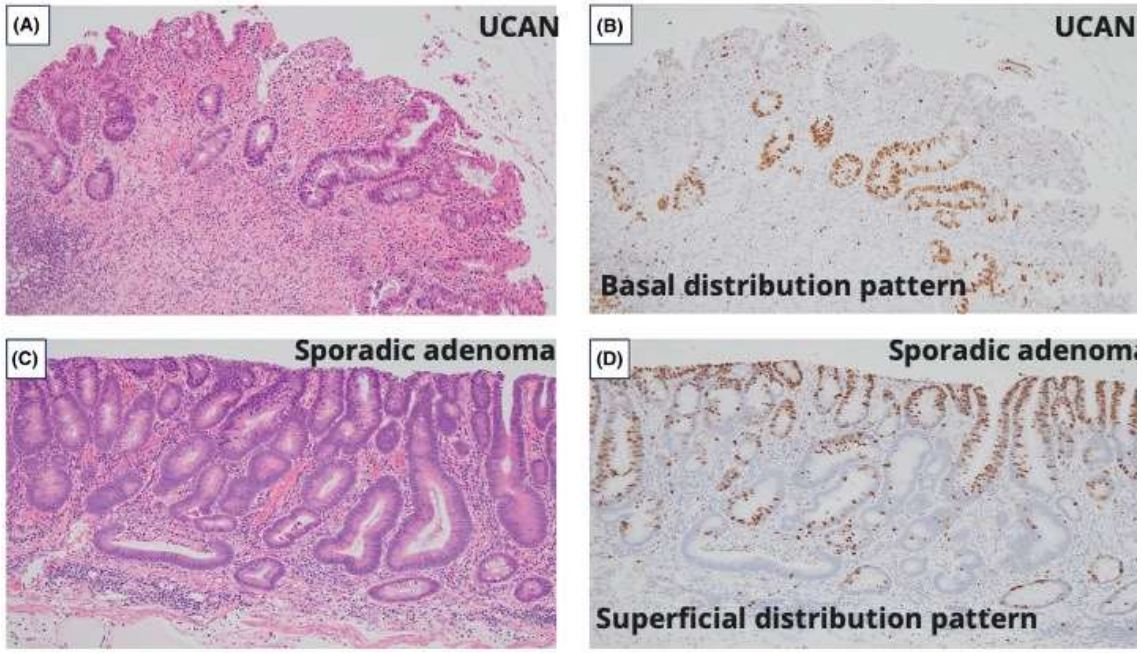
Fig 1

Conventional ulcerative colitis-associated neoplasia (UCAN).



Non-conventional ulcerative colitis-associated neoplasia (UCAN).

Fig 2. Typical immunohistochemical findings for Ki-67 in UCAN



Supply: Definitive patterns of Ki-67 positive cell distribution

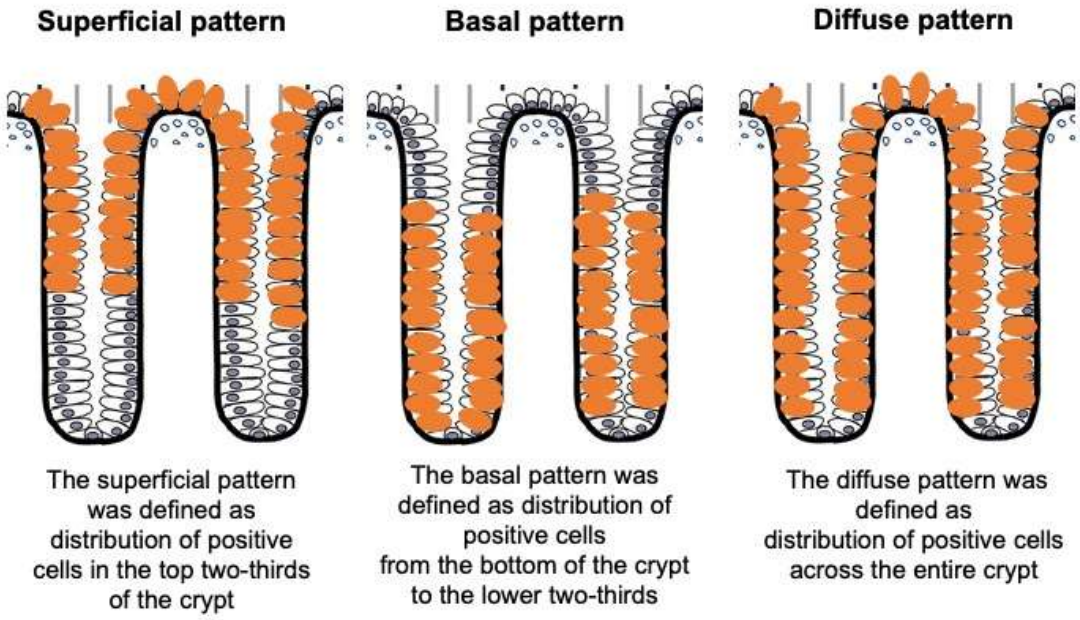
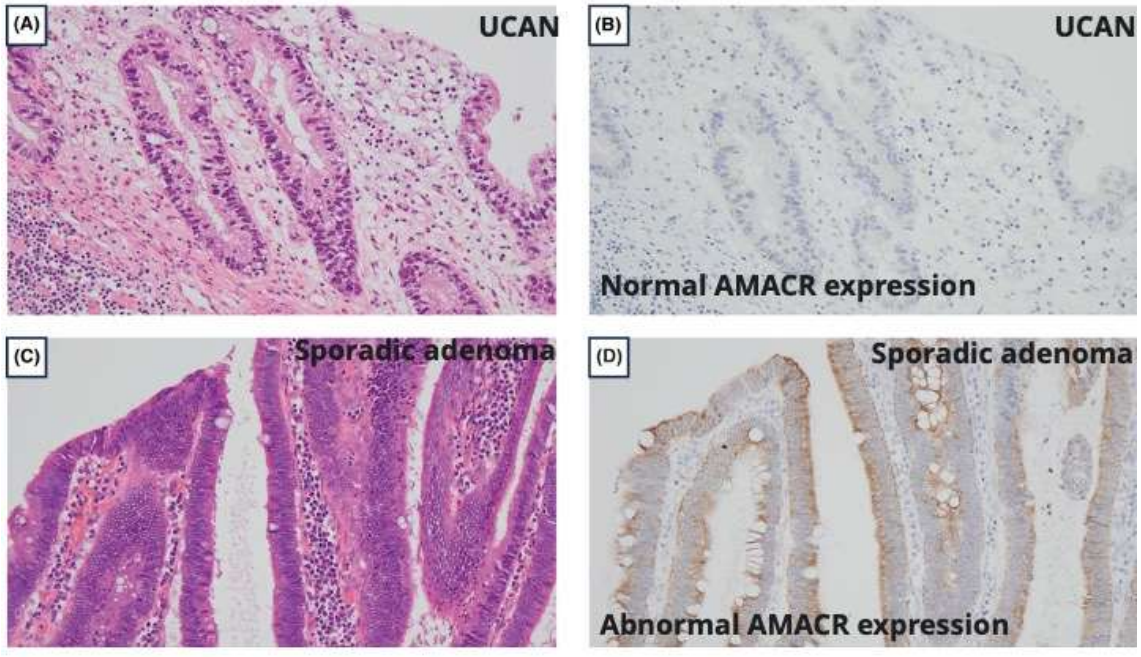
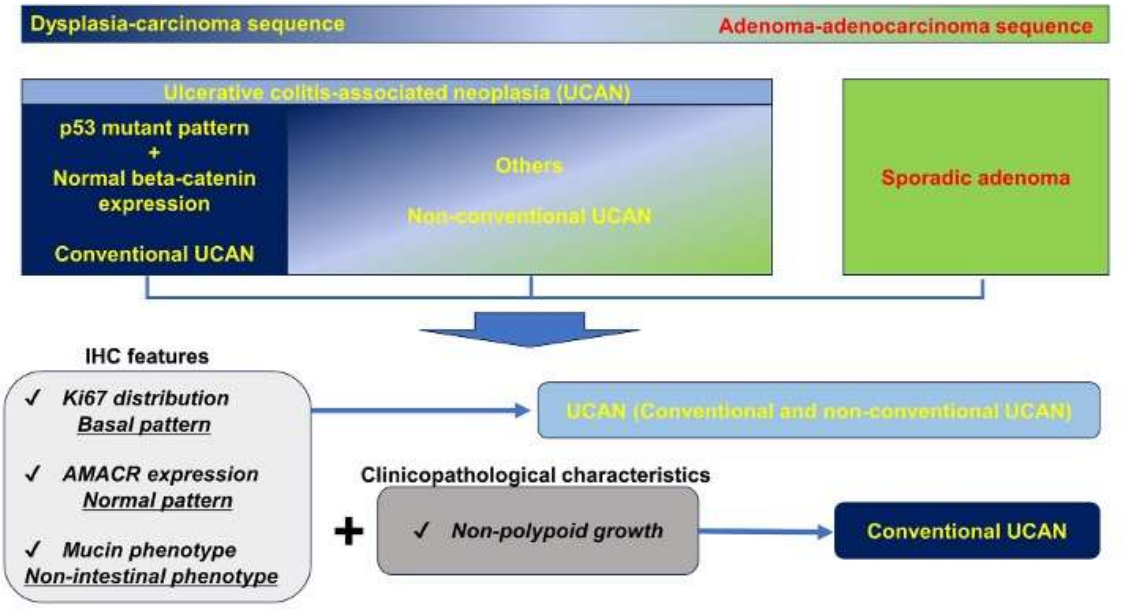


Fig 3. Immunohistochemical staining of AMACR in UCAN



Graph Abstract



UCANの免疫組織化学的特徴：Ki-67基底側分布パターン、AMACRの正常発現、および非腸型の粘液形質。また、非ポリープ状増殖は従来型UCANを示唆する。

Table1:Clinicopathological characteristics of conventional UCAN group and non-conventional UCAN group and SA group

Table 1. Clinicopathological characteristics of conventional UCAN group and non-conventional UCAN group and SA group

	Conventional UCAN group (17 lesions from 16 patients*)	Non-conventional UCAN group (18 lesions from 13 patients*)	SA group (71 lesions)	Conventional UCAN group versus non-conventional UCAN group *P*-value	Conventional UCAN group versus SA group *P*-value	Non-conventional UCAN group versus SA group *P*-value
Age (years), median (IQR)	52.0 (30.0–60.0)	55.5 (36.0–67.0)	72.0 (57.0–78.0)	0.27**	<0.001*	<0.001*
Gender, male *n* (%)	12 (71)	16 (89)	47 (66)	0.23**	1.0**	0.082**
UC disease duration (months), median (IQR)	176.0 (119.0–242.5)	190.5 (119.3–330.3)	NA	0.75*	NA	NA
UC disease extent, *n* (%)						
Proctitis	0 (0)	0 (0)	NA	1.0**	NA	NA
Left-sided	2 (12)	2 (11)	NA	1.0**	NA	NA
Extensive	15 (88)	16 (89)	NA	1.0**	NA	NA
Degree of inflammation, *n* (%)						
MES0	6 (35)	2 (11)	NA	0.12**	NA	NA
MES1	4 (24)	9 (50)	NA	0.16**	NA	NA
MES2	6 (35)	5 (28)	NA	0.63***	NA	NA
MES3	1 (6)	2 (11)	NA	1.0**	NA	NA
PSC, *n* (%)	1 (6)	0 (0)	0 (0)	0.49**	0.19**	1.0**
Location, *n* (%)						
Cecum	1 (6)	0 (0)	9 (13)	0.49**	0.68**	0.19**
Ascending colon	1 (6)	0 (0)	16 (23)	0.49**	0.12**	0.035**
Transverse colon	0 (0)	2 (11)	15 (21)	0.49**	0.037**	0.51**
Descending colon	1 (6)	0 (0)	5 (7)	0.49**	1.0**	0.58**
Sigmoid colon	4 (24)	6 (33)	10 (14)	0.71**	0.46**	0.083**
Rectum	10 (59)	10 (56)	16 (23)	1.0**	0.0064***	0.014***
Left colon and rectum	15 (88)	16 (89)	31 (44)	1.0**	<0.001**	<0.001**
Size (mm), median (IQR)	25.0 (12.5–53.5)	17.5 (11.5–31.5)	26.0 (20.5–36.5)	0.43*	0.58*	0.018*
Morphology, *n* (%)						
Polypoid	6 (35)	10 (56)	35 (49)			

Continued

Table 1. (Continued)

	Conventional UCAN group (17 lesions from 16 patients*)	Non-conventional UCAN group (18 lesions from 13 patients*)	SA group (71 lesions)	Conventional UCAN group versus non-conventional UCAN group *P*-value	Conventional UCAN group versus SA group *P*-value	Non-conventional UCAN group versus SA group *P*-value
Non-polypoid	11 (65)	8 (44)	36 (51)	0.33***	0.42***	0.83***
Grade, *n* (%)						
High-grade dysplasia	13 (77)	11 (61)				
Low-grade dysplasia	4 (24)	7 (39)		0.33***		
Tubular adenoma, *n* (%)						
High-grade†			29 (41)			
Low-grade			33 (47)			
Tubulovillous adenoma, *n* (%)						
High-grade†			3 (4)			
Low-grade			6 (8)			
Villous adenoma, *n* (%)						
High-grade†			1 (1)			
Low-grade			1 (1)			

IQR, interquartile range; MES, Mayo endoscopic subscore; NA, not available; PSC, primary sclerosing cholangitis; SA, sporadic adenoma; UC, ulcerative colitis; UCAN, ulcerative colitis-associated neoplasia.
*Mann–Whitney *U* test.
**Fisher's exact test.
***χ^2 test.
†Two cases had conventional UCAN and atypical UCAN, and one case had one conventional UCAN and two atypical UCAN.
‡High-grade adenoma includes lesions called intramucosal adenocarcinoma in Japan, which do not invade the lamina propria.

1. cUCANとNon-cUCANに臨床病理学的差異は見られない。
2. cUCANとNon-cUCANはSA:散発性腺腫と比べて、年齢、性別、発生部位に差異がある

3. ボンフェローニ補正は不明

Table2

Table 2. Result of immunohistochemistry for each groups

Immunohistochemical features	(i) Conventional UCAN group (n = 17)	(ii) Non-conventional UCAN group (n = 18)	(iii) SA group (n = 71)	(i) Versus (iii) P-value	(ii) Versus (iii) P-value	(i) Versus (ii) P-value
Ki-67 distribution: basal pattern	8 (47%)	6 (33%)	2 (3%)	< 0.001**	< 0.001**	0.41*
AMACR: normal expression	7 (41%)	3 (17%)	1 (1%)	< 0.001**	0.025**	0.14**
MUC2: positive	16 (94%)	17 (94%)	70 (99%)	0.35**	0.36**	1.0**
MUC5AC: positive	8 (47%)	10 (56%)	26 (37%)	0.58*	0.18*	0.61*
MUC6: positive	0 (0%)	2 (11%)	1 (1%)	1.0**	0.1**	0.49**
CD10: positive	2 (12%)	4 (22%)	5 (7%)	0.62**	0.078**	0.65**
Mucin phenotypes						
Intestinal phenotype	8 (47%)	6 (33%)	45 (63%)	0.22*	0.04*	0.41*
Non-intestinal phenotype	9 (53%)	12 (67%)	26 (37%)	0.27*	0.031*	0.67*
Gastric phenotype	0 (0%)	0 (0%)	0 (0%)	1.0**	1.0**	1.0**
Gastric intestinal mixed phenotype	8 (47%)	11 (61%)	26 (37%)	0.43*	0.11*	0.4*
Unclassified phenotype	1 (6%)	1 (6%)	0 (0%)	0.19**	0.2**	1.0**

SA, sporadic adenoma; UCAN, ulcerative colitis-associated neoplasia; AMACR, α-methylacyl-CoA racemase; MUC, mucin.
*χ^2 test.
**Fisher's exact test.

Table3

Table 3. Clinicopathological differences in lesions presenting Ki-67 basal pattern

	Conventional UCAN group Ki-67 basal pattern (n = 8)	Non-conventional UCAN group Ki-67 basal pattern (n = 6)	P-value
Age (years), median (IQR)	43.5 (26.8-60.5)	44.5 (24.8-66.8)	0.94*
Gender, male n (%)	5 (63)	5 (83)	0.58**
UC disease duration (months), median (IQR)	155.0 (92.0-234.5)	103.5 (79.5-192.3)	0.48*
UC disease extent, n (%)			
Proctitis	0 (0)	0 (0)	1.0**
Left-sided	0 (0)	1 (17)	0.43**
Extensive	8 (100)	5 (83)	0.43**
Degree of inflammation, n (%)			
MES0	3 (38)	0 (0)	0.21**
MES1	2 (25)	2 (33)	1.0**
MES2	2 (25)	3 (50)	0.58**
MES3	1 (13)	1 (17)	1.0**
PSC, n (%)	1 (13)	0 (0)	1.0**
Location, n (%)			
Caecum	1 (13)	0 (0)	1.0**
Ascending colon	0 (0)	0 (0)	1.0**
Transverse colon	0 (0)	1 (17)	1.0**
Descending colon	1 (13)	0 (0)	1.0**
Sigmoid colon	3 (38)	1 (17)	0.58**
Rectum	3 (38)	4 (67)	0.27**
Size (mm), median (IQR)	22.5 (11.3-52.0)	38.5 (10.0-92.5)	0.65*
Morphology, n (%)			
Polypoid	1 (13)	3 (50)	
Non-polypoid	7 (88)	3 (50)	0.24**
Grade, n (%)			
High-grade dysplasia	6 (75)	4 (67)	
Low-grade dysplasia	2 (25)	2 (33)	1.0**

MES, Mayo endoscopic subscore; PSC, primary sclerosing cholangitis; UC, ulcerative colitis; UCAN, ulcerative colitis-associated neoplasia; IQR, interquartile range.
*Mann–Whitney U-test.
**Fisher's exact test.

cUCANとnon-cUCANのKi-67basal patternに臨床病理学的差異は見られない。

Table4

Table 4. Clinicopathological differences in lesions presenting normal expression of AMACR

Characteristics	Conventional UCAN group normal expression of AMACR (n = 6)	Non-conventional UCAN group normal expression of AMACR (n = 4)	P-value
Age (years), median (IQR)	31.0 (28.3-41.8)	44.5 (28.5-63.5)	0.45*
Gender, male n (%)	5 (83)	4 (100)	1.0**
UC disease duration (months), median (IQR)	170.0 (104.0-223.8)	116.0 (69.0-300.3)	0.59*
UC disease extent, n (%)			
Proctitis	0 (0)	0 (0)	1.0**
Left-sided	1 (17)	0 (0)	1.0**
Extensive	5 (83)	4 (100)	1.0**
Degree of inflammation, n (%)			
MES0	3 (50)	0 (0)	0.20**
MES1	0 (0)	2 (50)	0.13**
MES2	3 (50)	2 (50)	1.0**
MES3	0 (0)	0 (0)	1.0**
PSC, n (%)	1 (17)	0 (0)	1.0**
Location, n (%)			
Caecum	1 (17)	0 (0)	1.0**
Ascending colon	0 (0)	0 (0)	1.0**
Transverse colon	0 (0)	0 (0)	1.0**
Descending colon	1 (17)	0 (0)	1.0**
Sigmoid colon	1 (17)	0 (0)	1.0**
Rectum	3 (50)	4 (100)	0.20**
Size (mm), median (IQR)	44.0 (13.8-78.5)	30.5 (21.3-48.0)	0.75*
Morphology, n (%)			
Polypoid	1 (17)	3 (75)	
Non-polypoid	5 (83)	1 (25)	0.19**
Grade, n (%)			
High-grade dysplasia	4 (67)	3 (75)	
Low-grade dysplasia	2 (33)	1 (25)	1.0**

IQR, interquartile range; MES, Mayo endoscopic subscore; PSC, primary sclerosing cholangitis; UC, ulcerative colitis; UCAN, ulcerative colitis-associated neoplasia; AMACR, α-methylacyl-CoA racemase.
*Mann–Whitney U-test.
**Fisher's exact test.

cUCANとnon-cUCANのAMACR発現に臨床病理学的差異は見られない。

Table5

Table 5. Clinicopathological differences in lesions presenting non-intestinal phenotype

	Conventional UCAN group non-intestinal phenotype (n = 9)	Non-conventional UCAN group non-intestinal phenotype (n = 12)	P-value
Age (years), median (IQR)	56.0 (39.0-59.0)	60.5 (44.8-67.0)	0.20*
Gender, male n (%)	5 (56)	12 (100)	0.021**
UC disease duration (months), median (IQR)	218.0 (170.0-284.0)	190.5 (136.0-355.0)	0.86*
UC disease extent, n (%)			
Proctitis	0 (0)	0 (0)	1.0**
Left-sided	1 (11)	0 (0)	0.43**
Extensive	8 (89)	12 (100)	0.43**
Degree of inflammation, n (%)			
MES0	4 (44)	1 (8)	0.11**
MES1	3 (33)	9 (75)	0.087**
MES2	2 (22)	1 (8)	0.55**
MES3	0 (0)	1 (8)	1.0**
PSC, n (%)	0 (0)	0 (0)	1.0**
Location, n (%)			
Cecum	0 (0)	0 (0)	1.0**
Ascending colon	1 (11)	0 (0)	0.43**
Transverse colon	0 (0)	0 (0)	1.0**
Descending colon	0 (0)	0 (0)	1.0**
Sigmoid colon	3 (33)	4 (33)	1.0**
Rectum	5 (56)	8 (67)	0.67**
Size (mm), median (IQR)	40.0 (17.5-57.5)	22.5 (12.8-48.0)	0.39*
Morphology, n (%)			
Polypoid	5 (56)	6 (50)	
Non-polypoid	4 (44)	6 (50)	0.80**
Grade, n (%)			
High-grade dysplasia	7 (78)	8 (67)	
Low-grade dysplasia	2 (22)	4 (33)	0.66**

IQR, interquartile range; MES, Mayo endoscopic subscore; PSC, primary sclerosing cholangitis; UC, ulcerative colitis; UCAN, ulcerative colitis-associated neoplasia.
*Mann–Whitney U-test.
**Fisher's exact test.

Table6

Table 6. Immunohistochemical and morphological features of multiple lesions in ulcerative colitis-associated neoplasia

Case	Location	Visibility	Morphology	p53	β-catenin	Ki-67	AMACR	Mucin phenotype
Case 1	Rectum	Yes	Polypoid	Mutant	Normal	Diffuse	Normal	Intestinal
	Rectum	Yes	Non-polypoid	Wild	Normal	Basal	Abnormal	Intestinal
Case 2	Ascending colon	No	Non-polypoid	Mutant	Normal	Superficial	Normal	Non-intestinal
	Sigmoid colon	Yes	Non-polypoid	Mutant	Normal	Basal	Normal	Non-intestinal
Case 3	Rectum	No	Non-polypoid	Mutant	Normal	Basal	Normal	Non-intestinal
	Sigmoid colon	No	Non-polypoid	Wild	Normal	Basal	Abnormal	Intestinal
Case 4	Rectum	Yes	Polypoid	Wild	Normal	Superficial	Normal	Non-intestinal
	Sigmoid colon	No	Non-polypoid	Wild	Normal	Superficial	Normal	Non-intestinal
	Sigmoid colon	No	Non-polypoid	Wild	Normal	Superficial	Normal	Non-intestinal
Case 5	Rectum	Yes	Polypoid	Wild	Normal	Basal	Abnormal	Non-intestinal
	Sigmoid colon	Yes	Polypoid	Mutant	Normal	Superficial	Abnormal	Intestinal
Case 6	Rectum	Yes	Polypoid	Wild	Normal	Superficial	Normal	Non-intestinal
	Rectum	Yes	Polypoid	Wild	Normal	Superficial	Normal	Non-intestinal
Case 7	Sigmoid colon	No	Polypoid	Wild	Normal	Superficial	Normal	Non-intestinal
	Transverse colon	No	Polypoid	Wild	Normal	Basal	Abnormal	Non-intestinal
Case 8	Rectum	No	Non-polypoid	Wild	Normal	Diffuse	Normal	Non-intestinal
	Sigmoid colon	No	Non-polypoid	Wild	Normal	Superficial	Abnormal	Non-intestinal

AMACR, α-methylacyl-CoA racemase.