

Nuclear expression of claudin-18 in well-differentiated early gastric adenocarcinoma

Claudin-18, a tissue-specific marker of epithelial cells of the stomach and lung, is consistently expressed on the plasma membrane of the normal and neoplastic gastric epithelial cells. We analyzed 129 biopsy specimens of well-differentiated early gastric adenocarcinoma and pseudomalignant regenerative mucosa. Of note is that nuclear expression of claudin-18 was a novel diagnostic marker for gastric cancer. Negative correlation of membranous claudin-18 expression was also significant in the gastric cancer. The gastric-type cancers dominantly expressed membranous claudin-18, while nuclear claudin-18 was commonly encountered in intestinal- and mixed-type cancers. In addition, the expression of MUC1 (CA15-3), HER2, p53, CEA and nuclear claudin-18 revealed significant correlation with gastric cancers.

Ref.: Takahashi Y, et al. Nuclear staining of claudin-18 is a new immunohistochemical marker for diagnosing intramucosal well-differentiated gastric adenocarcinoma. *Pathol Int* 2020; 70(9): 644-652. doi: 10.1111/pin.12978

Materials and Methods

		Cancer	Noncancer	P value
Sex	Men	77	15	0.3145
	Women	27	9	
Age		74.0 ± 8.5	65.1 ± 15.5	< 0.0001

Cancer: n=104 (well-differentiated intramucosal tubular adenocarcinoma)

Non-cancer: n=24 (tubular adenoma n=14, regenerative mucosa n=10)

Immunostained markers: MUC2, MUC5AC, MUC6, MUC1, HER2, p53, CEA, E-cadherin, β -catenin and claudin-18

Positive: >5% for mucin core proteins, >30% for other markers

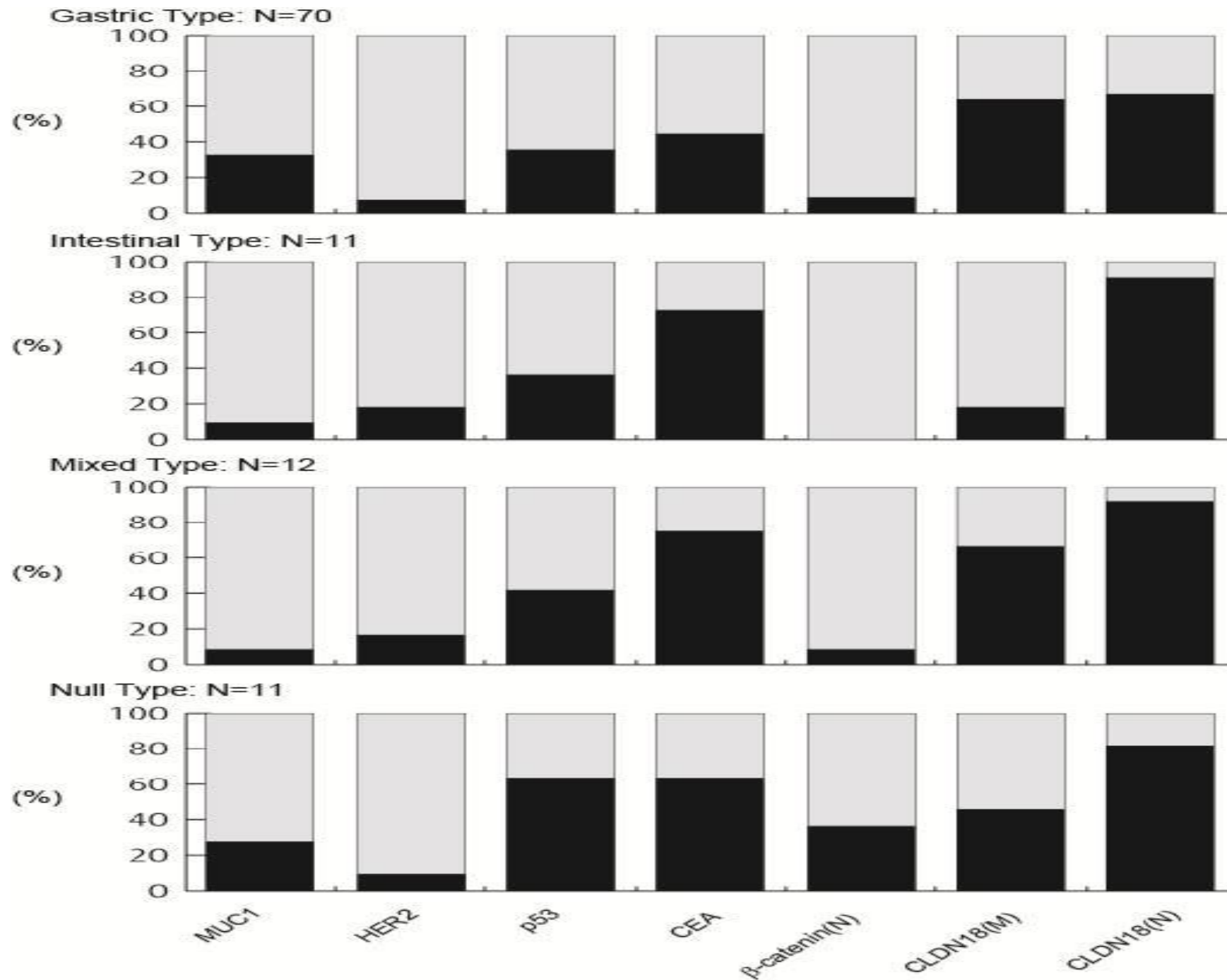
Comparison of diagnostic marker expression between cancer and non-cancer groups

Marker	Results	Cancer	Non-cancer	Uni-variate P-value	Multi-variate P-value
MUC1	Positive	28	0		
	Negative	76	24		
	Mean scores	0.84	0.04	0.0010**	0.0086**
HER2	Positive	10	1		
	Negative	94	23		
	Mean scores	1.23	0.54	0.0173*	0.0625
p53	Positive	41	0		
	Negative	63	24		
	Mean scores	1.99	0.67	0.0002**	0.0031**
CEA	Positive	55	5		
	Negative	49	19		
	Mean scores	2.48	1.58	0.0019**	0.1300
b-catenin(M)	Positive	84	22		
	Negative	20	2		
	Mean scores	3.44	3.63	0.3342	
b-catenin(N)	Positive	11	1		
	Negative	93	23		
	Mean scores	0.86	0.24	0.0703	
Claudin-18(M)	Positive	60	20		
	Negative	44	4		
	Mean scores	2.70	3.42	0.0125*	0.0158*
Claudin-18(N)	Positive	77	8		
	Negative	27	16		
	Mean scores	1.75	0.67	<0.0001**	0.0190*

Cancer: n=104
Non-cancer: n=24
(M): membranous
(N): nuclear

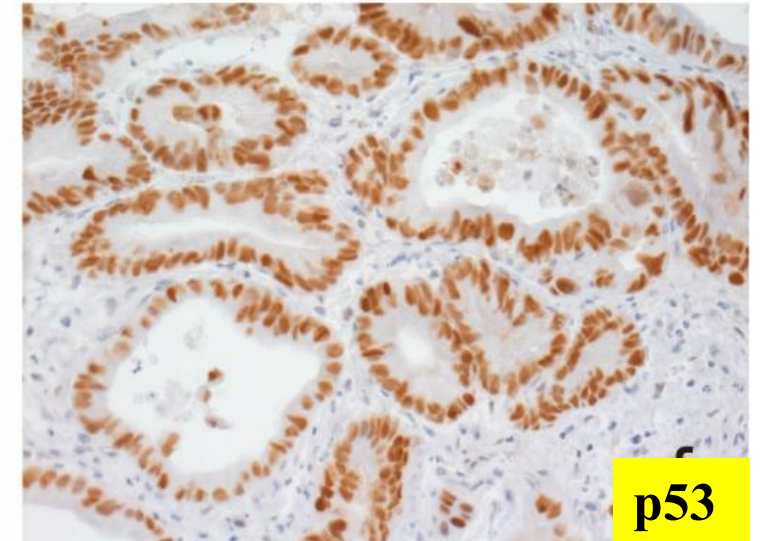
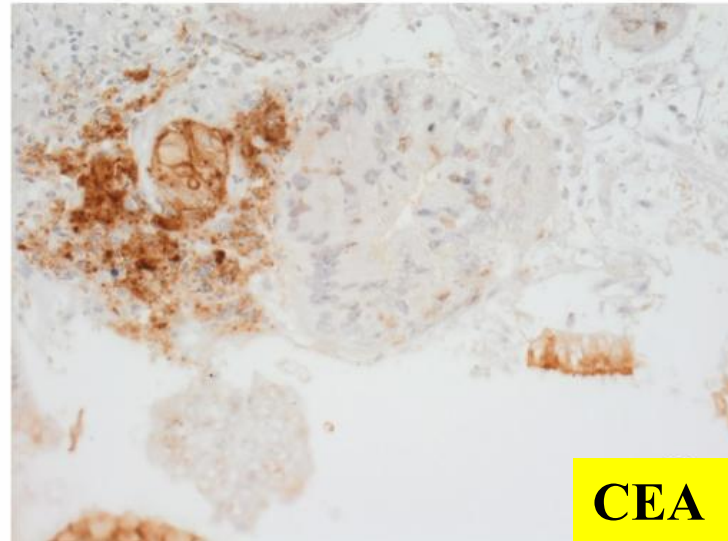
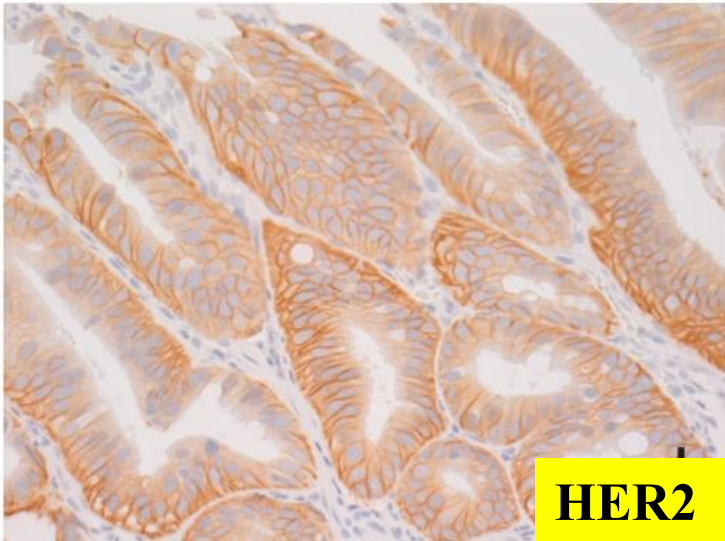
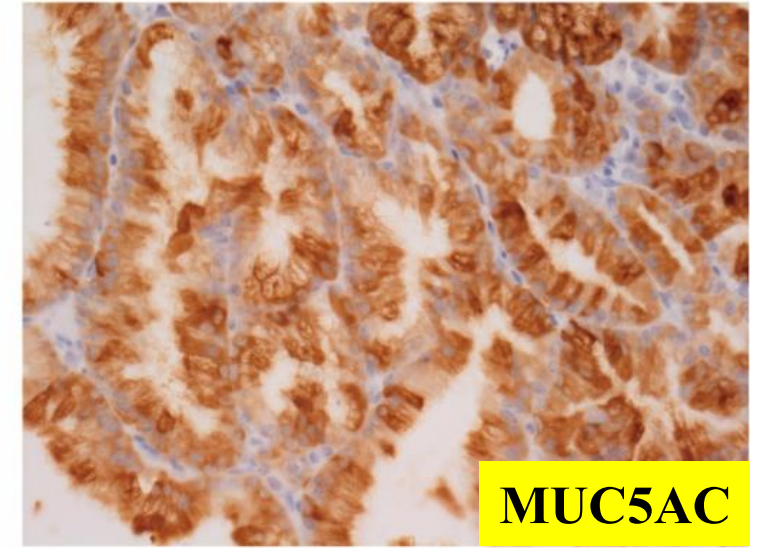
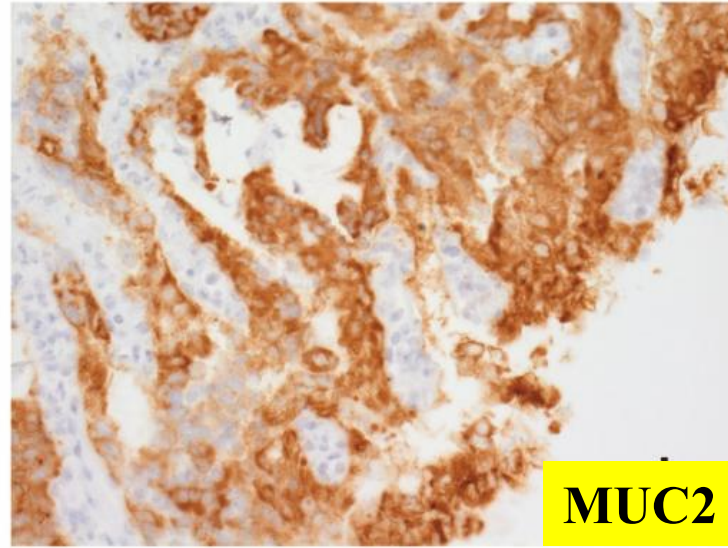
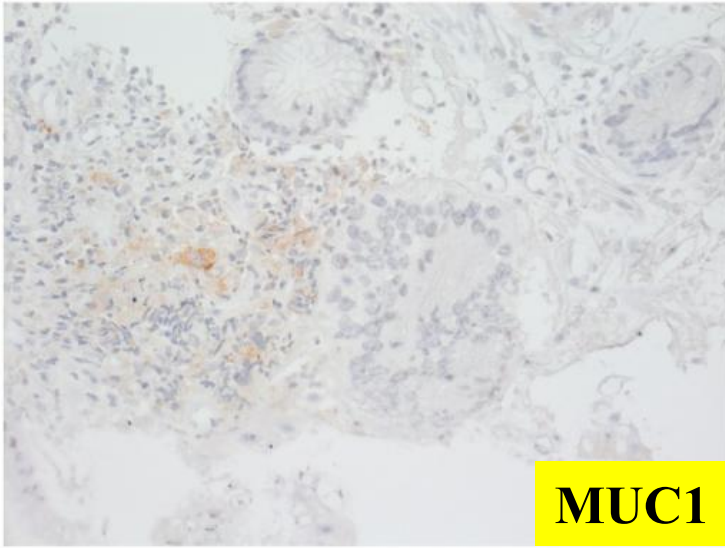
(M): membranous
(N): nuclear

Pattern A							
No. of markers*	0	1	2	3	4	5	mean
Cancer (n=104)	2	21	28	30	16	7	2.56
Non-cancer (n=24)	9	11	4	0	0	0	0.79
p<0.0001							
*As markers, the positivity of HER2, CEA, MUC1, p53, β-catenin(N) and claudin-18(N) and the negativity of claudin-18(M) were evaluated.							
Pattern B							
No. of markers**	0	1	2	3	4		mean
Cancer (n=104)	6	31	44	21	2		1.82
Non-cancer (n=24)	13	10	1	0	0		0.50
p<0.0001							
**As markers, the positivity of MUC1, p53, claudin-18(N) and negativity of claudin-18(M) were evaluated.							
# One lesion originally diagnosed as regenerative mucosa, but revised as adenocarcinoma after immunostaining was excluded from statistical analysis.							

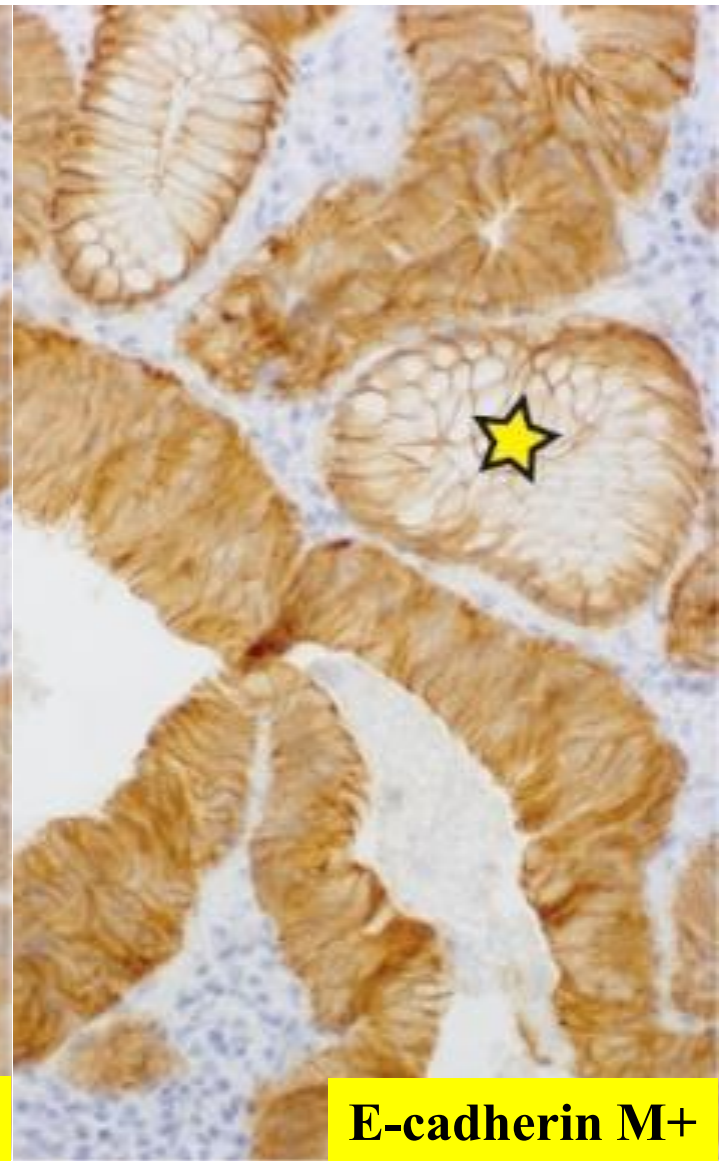
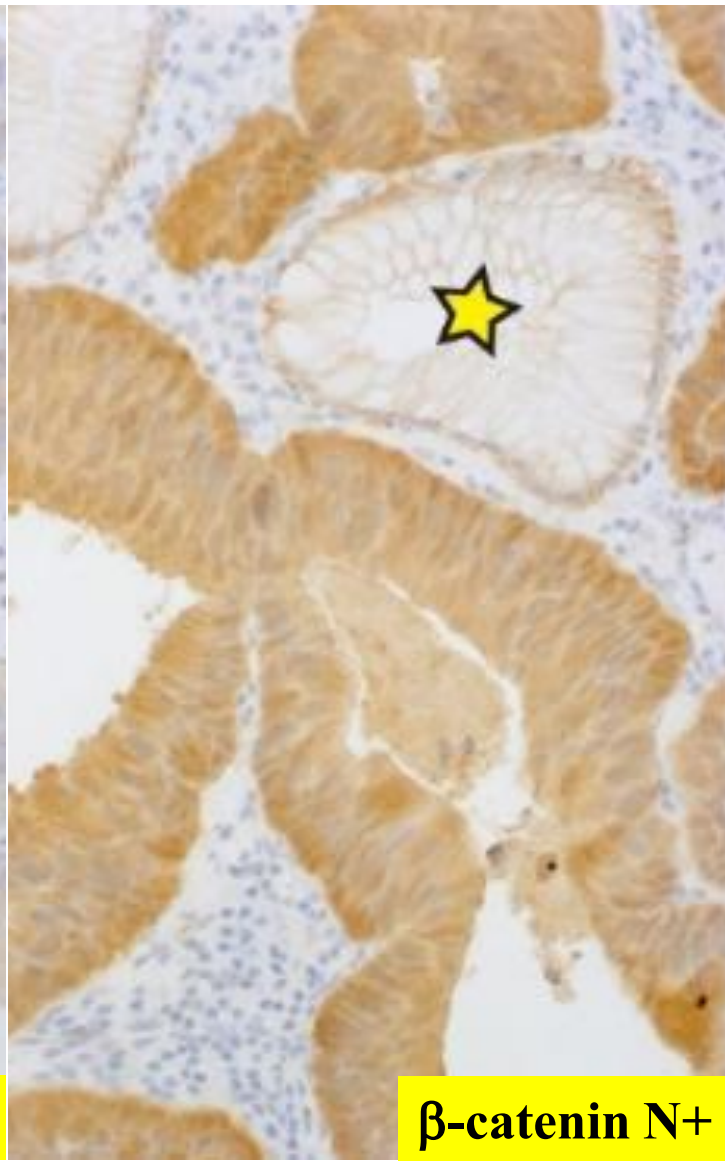
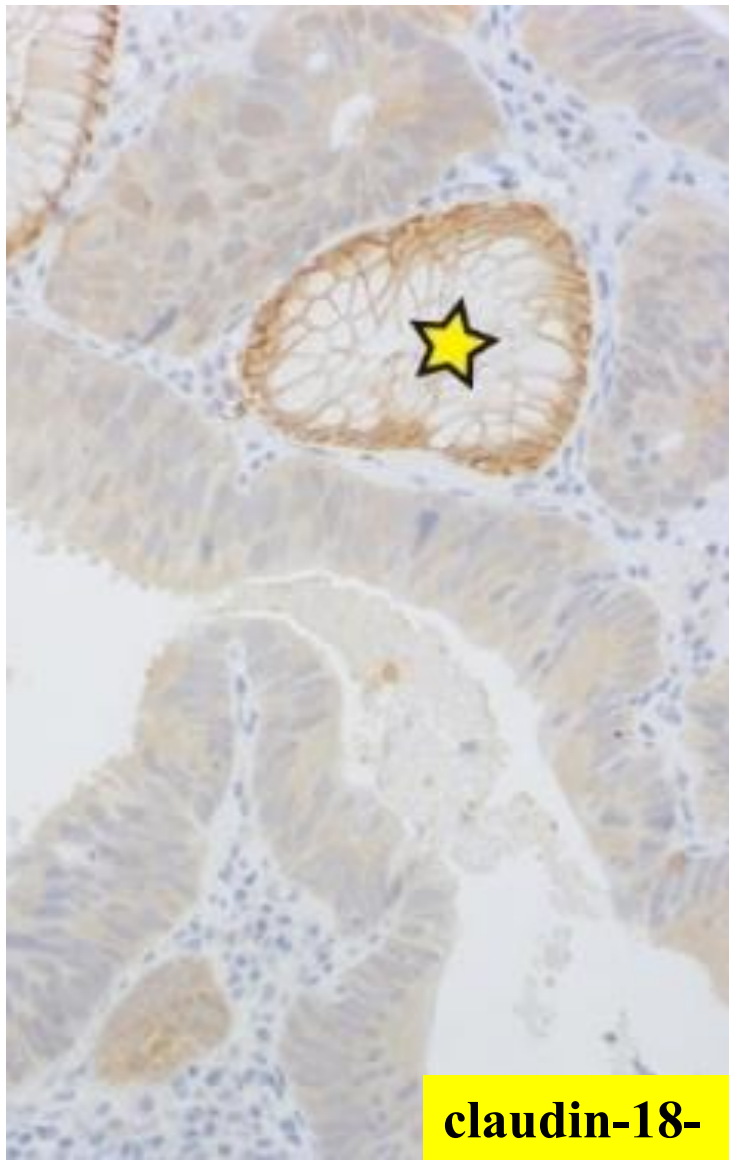


Schematic presentation of each immunohistochemical marker in gastric-, intestinal-, mixed- and null-types of intramucosal gastric cancer

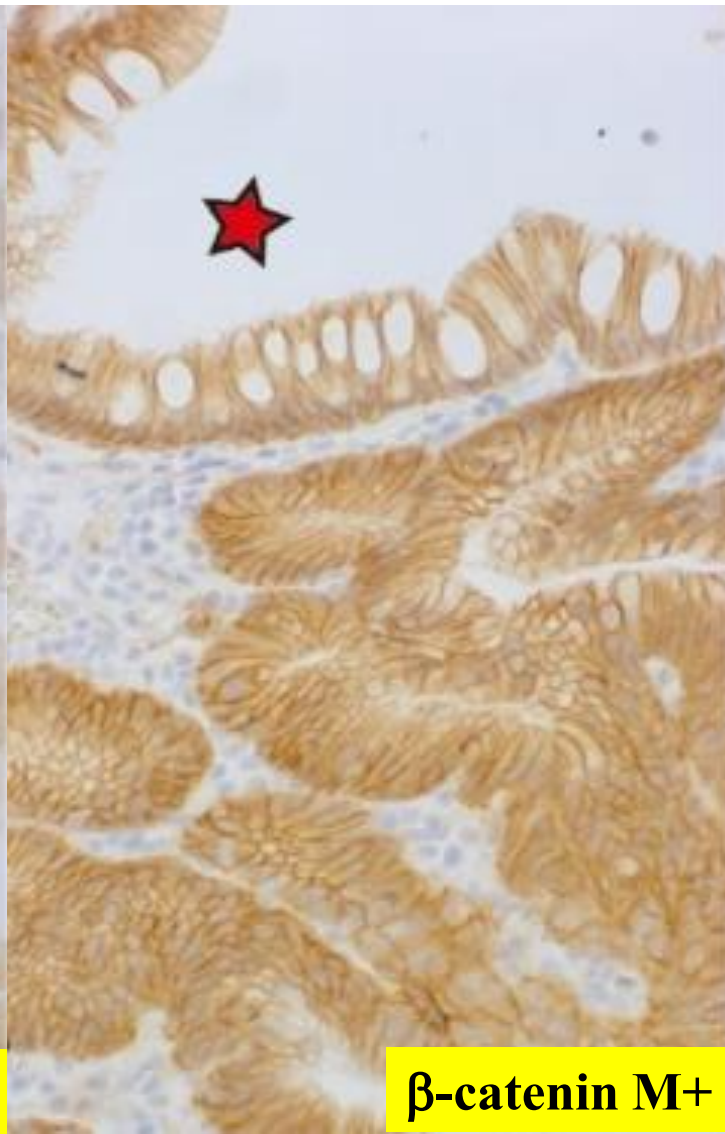
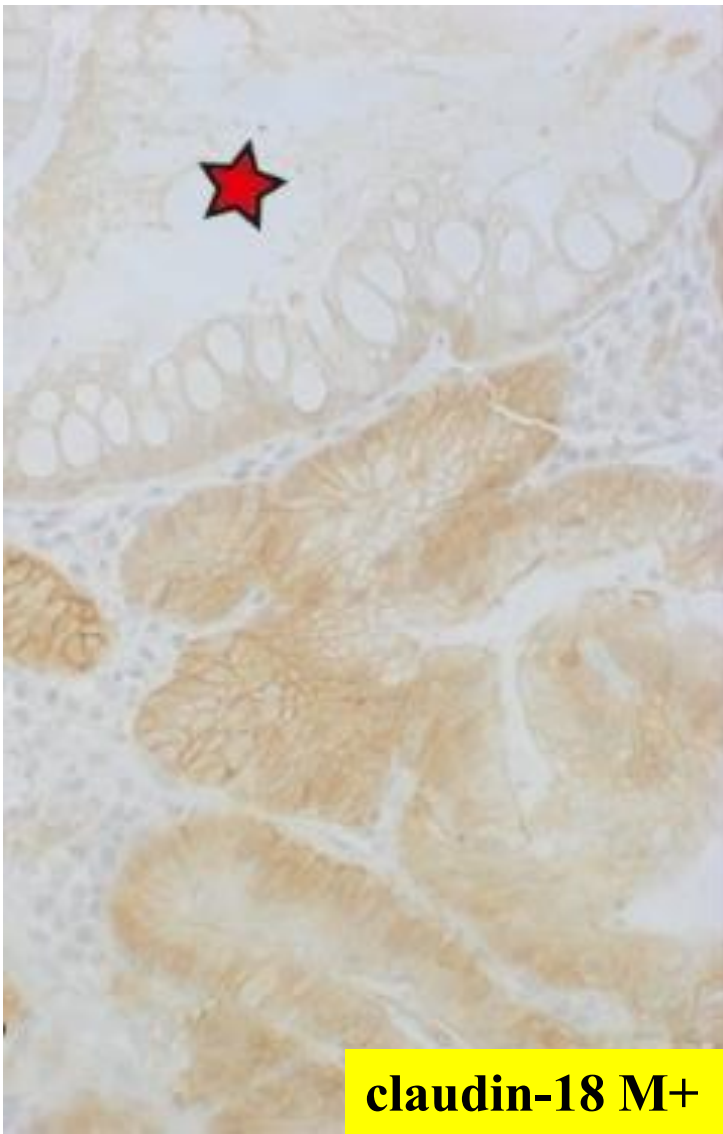
*CLDN18=claudin-18



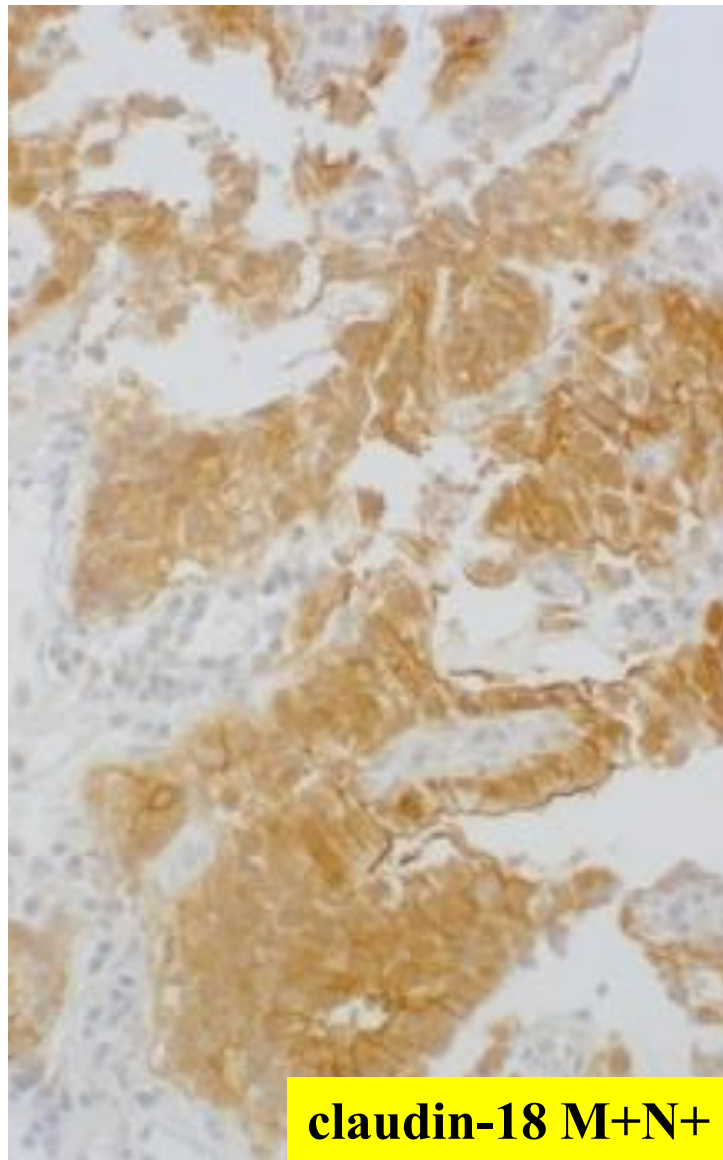
Representative expression of immunohistochemical markers evaluated in well-differentiated tubular adenocarcinoma. Expression of MUC1 (CA15-3), HER2, CEA and p53 is unique in the cancer group lesions. MUC2 is a marker of intestinal goblet cells, while MUC5AC is a marker of gastric foveolar cells.



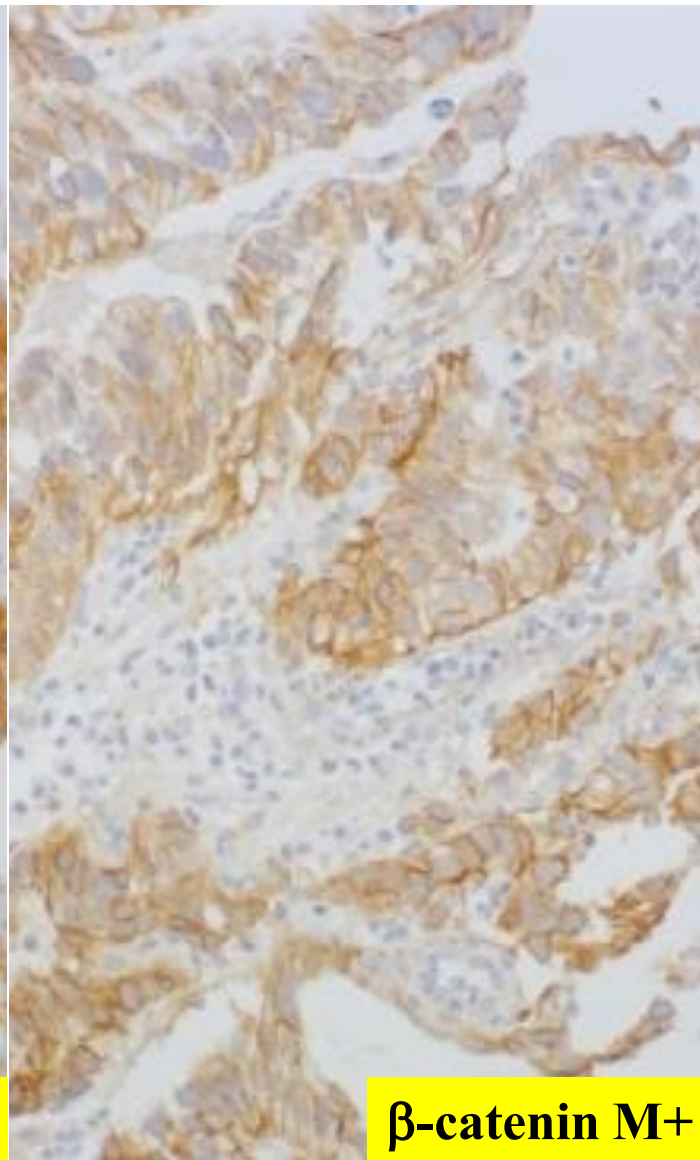
Various expression patterns of claudin-18, β -catenin and E-cadherin in early gastric cancer (1). Case 1 reveals loss of claudin-18 expression and nuclear expression of β -catenin. E-cadherin is consistently expressed on the plasma membrane. Asterisks indicate normal gastric epithelia. **Case 1**



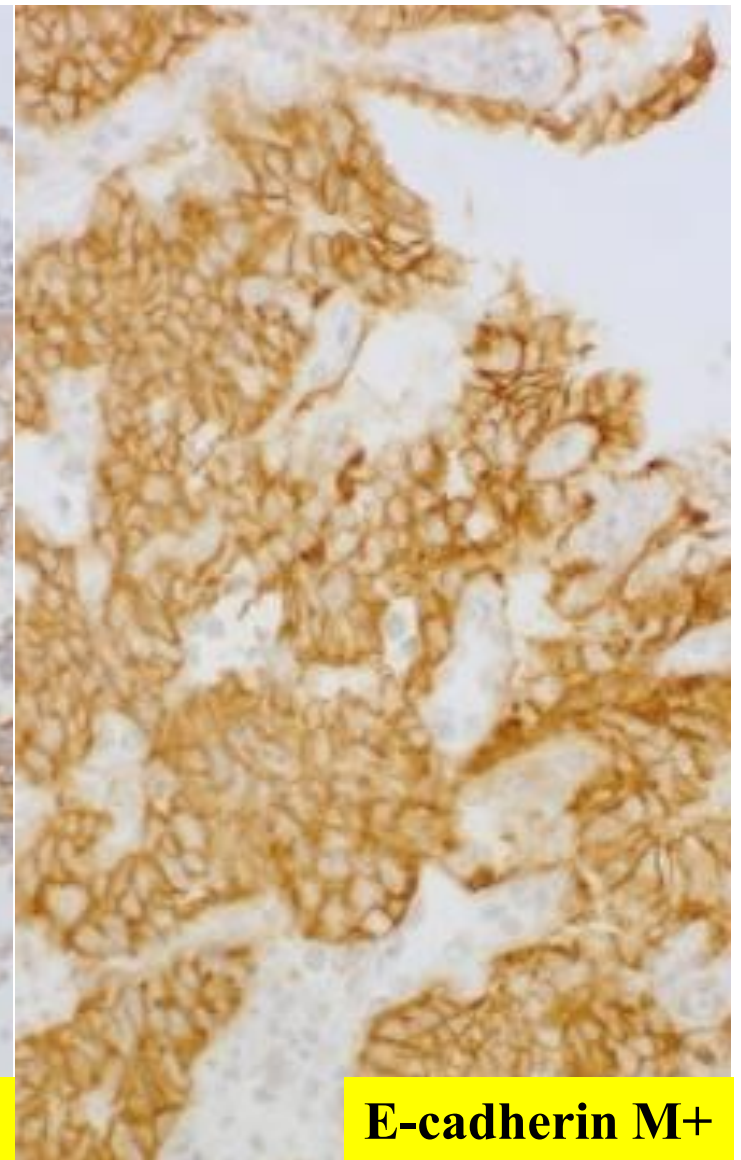
Various expression patterns of claudin-18, β -catenin and E-cadherin in early gastric cancer (1). Case 2 reveals membranous expression of claudin-18 and β -catenin. E-cadherin is consistently expressed on the plasma membrane. Asterisks indicate intestinal metaplasia with loss of claudin-18. **Case 2**



claudin-18 M+N+

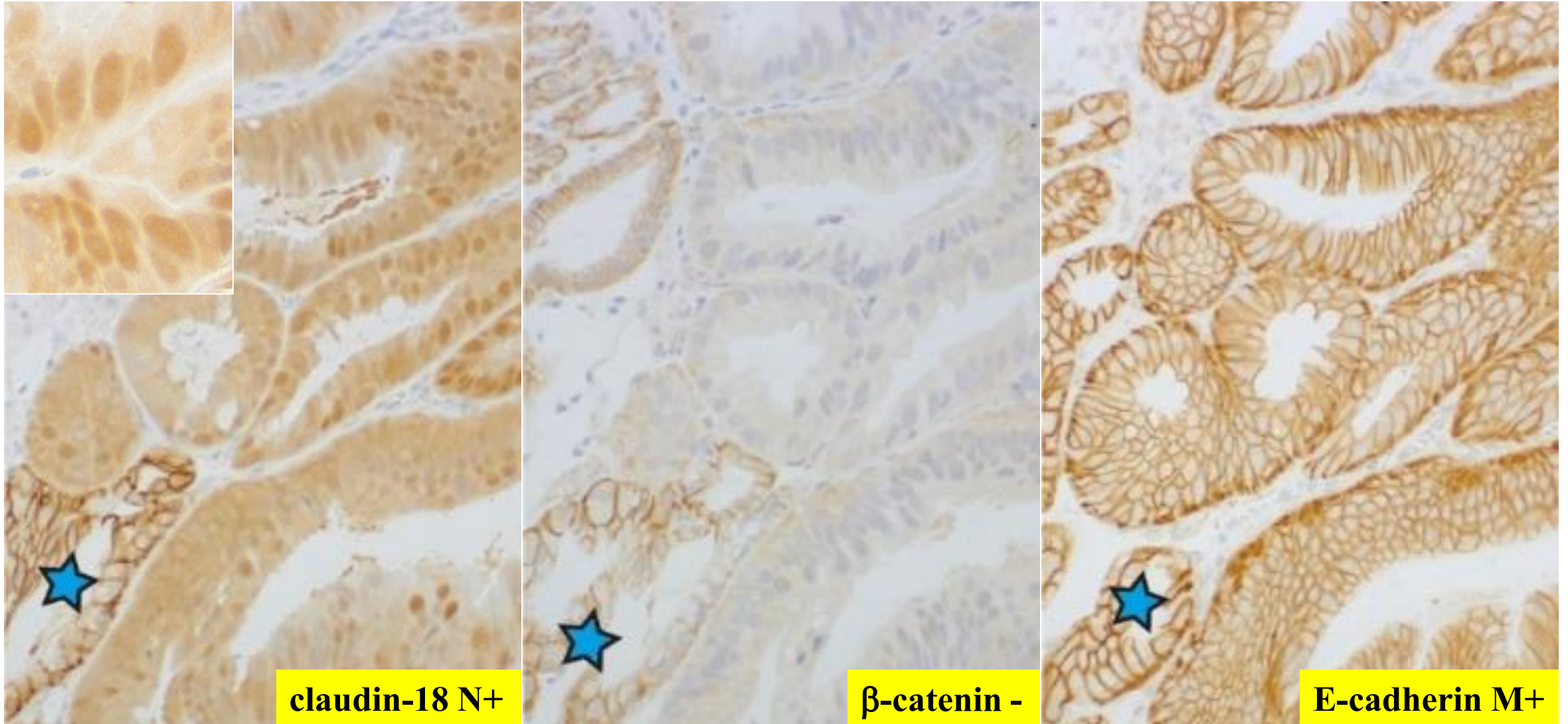


β-catenin M+

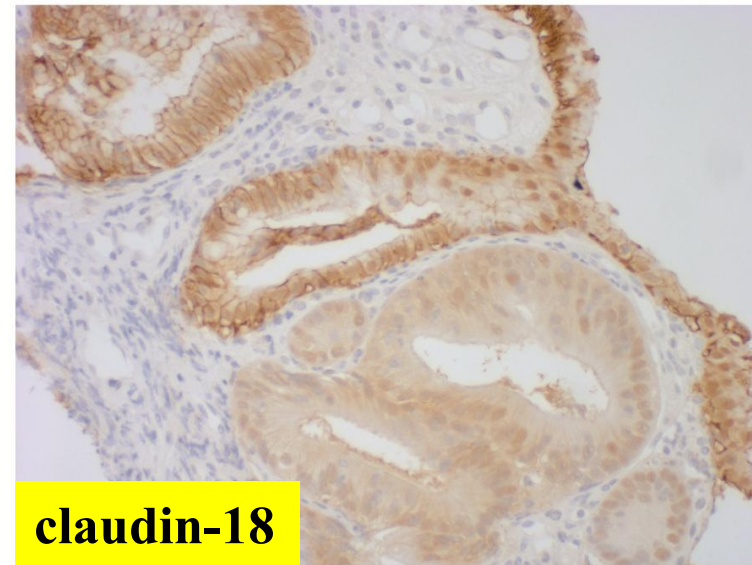
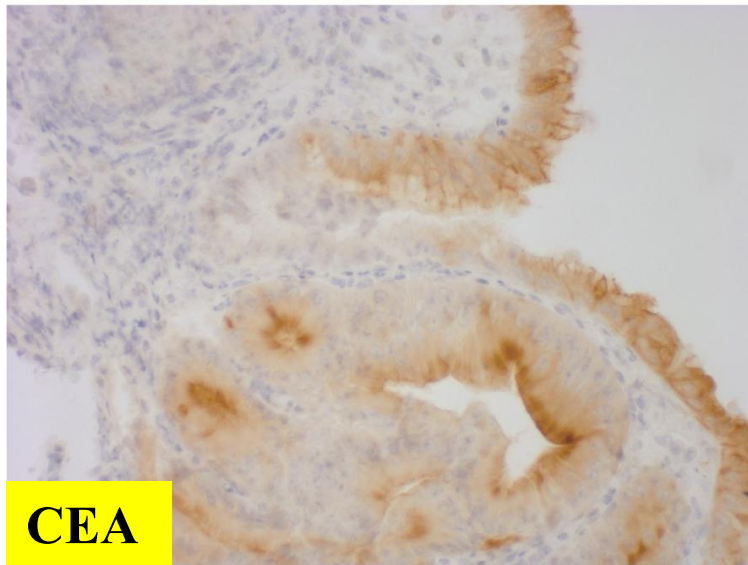
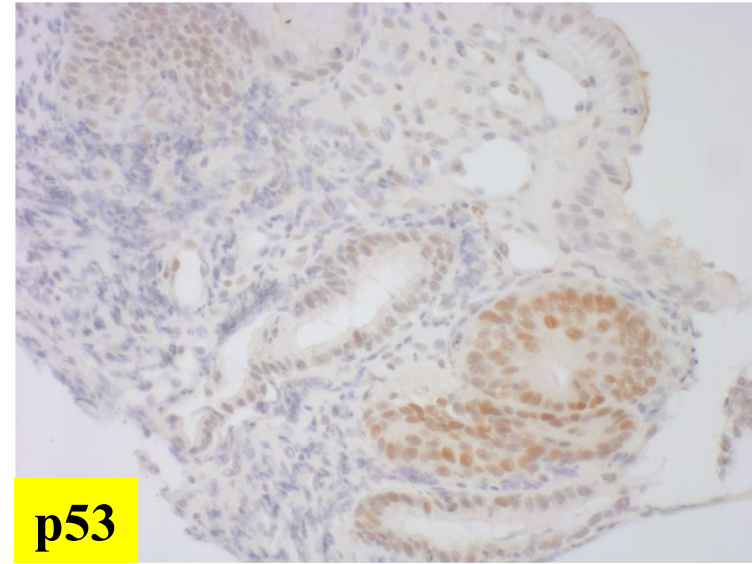
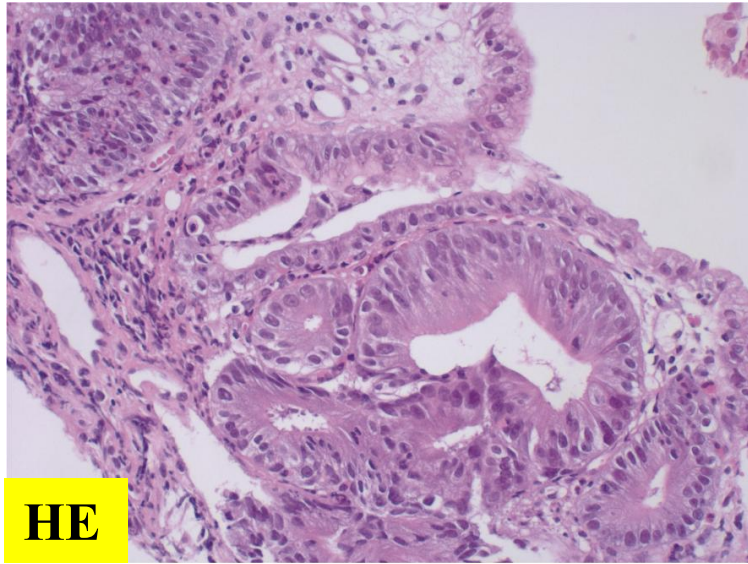


E-cadherin M+

Various expression patterns of claudin-18, β -catenin and E-cadherin in early gastric cancer (1). Case 3 reveals both membranous and nuclear expression of claudin-18 expression and membranous expression of β -catenin. E-cadherin is consistently expressed on the plasma membrane. **Case 3**



Various expression patterns of claudin-18, β -catenin and E-cadherin in early gastric cancer (1). Case 4 reveals nuclear expression of claudin-18 and loss of β -catenin expression (see also inset). E-cadherin is consistently expressed on the plasma membrane. Asterisks indicate normal pyloric gland. **Case 4**



Intramucosal gastric adenocarcinoma originally diagnosed as regenerative mucosa before immunostaining analysis. The atypical glands express p53, CEA and intranuclear claudin-18.