Chapter 29
Lower Gastrointestinal Tract and Microsatellite Instability (MSI)

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Abstract By conventional definition, the lower gastrointestinal (GI) tract includes the appendix, entire colon, and anus. Diseases involving these organs are traditionally classified into nonneoplastic and neoplastic categories. Clinical application of immunohistochemistry (IHC) is most useful in the diagnosis of neoplastic lesions, with a few exceptions such as to identify of viral pathogens in infectious colitis and to facilitate diagnosis of Hirschsprung's disease. For diagnosis of neoplasm, IHC is particularly useful in several aspects: (1) to help confirm glandular dysplasia associated with inflammatory bowel disease (IBD) and to differentiate it from sporadic adenoma in challenging cases; (2) to confirm diagnosis and grade of neuroendocrine tumors; (3) to confirm diagnosis of a poorly differentiated or undifferentiated colonic adenocarcinoma variant, such as medullary carcinoma; (4) to help differentiate commonly encountered benign and malignant primary mesenchymal tumors; (5) to differentiate primary carcinomas from various morphological mimickers from other organ systems, such as carcinomas of the gynecological and genitourinary systems; and, (6) to initiate Lynch syndrome screening in patients with diagnosed colorectal cancer.

In this chapter, we provide an overview of the most useful markers in the diagnosis of lower GI tract diseases, albeit many of them are shared with the upper GI chapter. The content is organized into 19 diagnostic issues frequently encountered in daily practice. The use of both individual markers and other relevant markers to form effective panels to address specific diagnostic challenges are illustrated in a tabular format. Concise notes with representative microscopic pictures are included whenever deemed necessary.

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F. Lin et al. (eds.), *Handbook of Practical Immunohistochemistry*, https://doi.org/10.1007/978-3-030-83328-2_29

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Note for All Tables: "+"—usually greater than 70% of cases are positive; "−"—less than 5% of cases are positive; "+ or −"—usually more than 50% of cases are positive; "− or +"—less than 50% of cases are positive: ND—no data available; V—variable.

Anus

Table 29.1 Staining patterns of commonly used markers in normal colonic mucosa

Markers	GML data ($N = 20$)
AE1/3	100% (20/20)
CK7	0 (0/20)
CK20	100% (20/20)
CAM5.2	100% (20/20)
CDH17	100% (20/20)
SATB2	100% (20/20)
CK17	0 (0/20)
CK19	100% (20/20)
EMA	10% (2/20)
Vimentin	0 (0/20)
B72.3	0 (0/20)
MOC-31	100% (20/20)
BerEP4	100% (20/20)
CEA	100% (20/20)
CA19-9	15% (3/20)
CD15	100% (20/20)
Villin	100% (20/20, weak)
CD56	0 (0/20)
Chromogranin	100% (20/20, scattered cells)
CD10	0 (0/20)
B-catenin	100% (20/20)
MUC1	25% (5/20)
MUC2	100% (20/20)
MUC4	100% (20/20)
MUC5AC	0 (0/20)
MUC6	0 (0/20)
CDX2	100% (20/20)
p53	0 (0/20)
Hep Par 1	0 (0/20)

Note: CK20 staining is much stronger in the surface epithelium than in the deeper colonic glands. Rare CK7-positive cells are usually present in the crypt base and may be representative of stem cells. MUC4 positivity is very weak, and immunoreactivity for MUC1 is only focal (<25% of the tissues stained). CK19 reactivity is weak and only on the surface colonic epithelium. MUC2 is positive only in goblet cells. MOC-31, BerEP4, and CEA are positive in all cases, but B72.3 is negative. Chromogranin reveals scattered positively stained enteroendocrine cells. Beta-catenin shows membranous staining in all cases

Table 29.2 Staining patterns of commonly used markers in usual colorectal adenocarcinoma

Markers	GML data ($N = 38$)
AE1/3	97% (37/38)
CK7	3% (1/38)
CK20	97% (37/38)
CDH17	97% (37/38)
SATB2	97% (37/38)
CK17	0 (0/38)
CK19	16% (6/38), weak
CAM5.2	100% (38/38)
MUC1	16% (6/38)
MUC2	55% (21/38)
MUC4	74% (29/38)
MUC5AC	26% (10/38)
MUC6	8% (3/38)
ER	0 (0/38)
PR	0 (0/38)
GCDFP-15	0 (0/38)
S100P	55% (21/38)
IMP3 (KOC)	50% (19/38)
Maspin	89% (34/38)
Pvhl	16% (6/38)
CA19-9	55% (21/38)
CDX2	95% (36/38)
TTF-1	0 (0/38)
CEA	100% (38/38)
MOC31	31% (8/38)
BerEP4	100% (38/38)
CD10	16% (6/38)
Vimentin	0 (0/38)
Beta-catenin	63% (24/38)
Villin	82% (31/38)
Napsin A	29% (11/38)
Hep Par1	11% (4/38)
P504S	90% (33/38)

Note: Based on GML TMA data, SATB2 appears to be the most specific marker for colorectal carcinoma and may be used to distinguish it from adenocarcinoma of the upper GI tract, including small intestinal adenocarcinoma. Figure 29.1 shows an example of SATB2-positive colonic adenocarcinoma metastasizing to the small intestinal mucosa. Focal positivity (<25% of the tumor cells stained) for pVHL, napsin A, and Hep Par1 is noted in 6, 11, and 4 cases, respectively. CD10 positivity is seen on the luminal surface. The positivity for MUC5AC and CK7 is usually focal (<10% of the tumor cells) and in tumors from the cecum and right colon

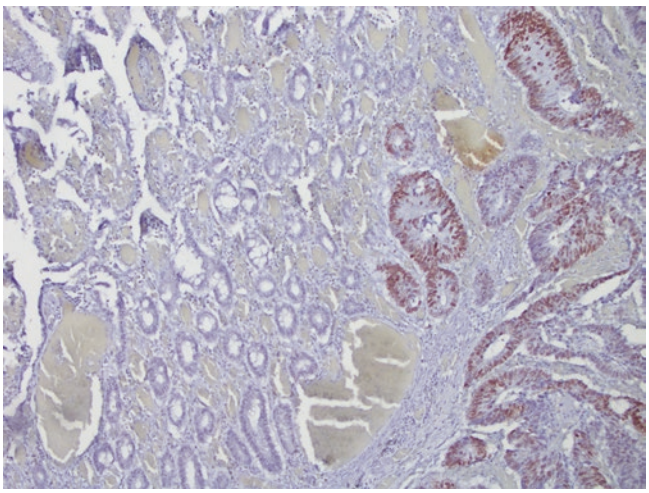

Fig. 29.1 An example of metastatic colonic adenocarcinoma involving small intestinal mucosa. SATB2 nuclear immunoreactivity highlights metastatic tumor cells in the right while the normal small intestinal glands lack immunoreactivity

Table 29.3 Markers helpful in differentiating common benign glandular proliferative lesions involving the appendix

Markers	Endometriosis	Endosalpingiosis	Mesothelial cyst
CK20	− or +	−	−
CDH17	−	−	−
SATB2	−	−	−
PAX8	+	+	−
CD10	Stroma +	−	−
ER	+	+	−
WT1	−	− or +	+
Calretinin	−	−	+

Note: These lesions are quite common and usually obvious to diagnose. However, in challenging cases, they may be difficult to distinguish from low-grade mucinous adenocarcinoma, implants of borderline or malignant ovarian tumors, and metastatic adenocarcinoma of the colon and other organs

References: [1, 2]

Table 29.4 Useful markers differentiate goblet cell adenocarcinoma, classic neuroendocrine tumor, and conventional adenocarcinoma

Markers	Goblet cell adenocarcinoma	Classic neuroendocrine tumor	Conventional adenocarcinoma
SATB2	+	− or +	+
CEA	+	− or +	+
Synaptophysin	+	+	−
Chromogranin	+	+	−
CK7	+ or −	− or +	− or +
CK20	− or +	− or +	− or +
CDX2	+	+ or −	+
Ki-67	0–80%	Usually <20%	>80%
P53	− or +	− or +	+
MUC1	− or +	NA	− or +
MUC2	+	NA	−

Note: According to WHO 2019, low-grade or high-grade appendiceal goblet cell adenocarcinoma replaces the old terms "carcinoid goblet cell carcinoid" and "mixed adenocarcinoma ex-goblet cell carcinoid." The goblet cell adenocarcinoma can also be graded by a three-tiered system (Grades 1, 2, and 3) based on the proportion of tumors that consists of low-grade (tubular and clustered growth) and high grade (loss of tubular or clustered growth) patterns. This category of tumors should be differentiated from classic neuroendocrine tumor or conventional adenocarcinoma with tubular and/or signet ring cell features by morphological features, and immunostaining patterns of listed markers. An example of low-grade goblet cell adenocarcinoma is shown in Fig. 29.2a–d

References: [3, 4]

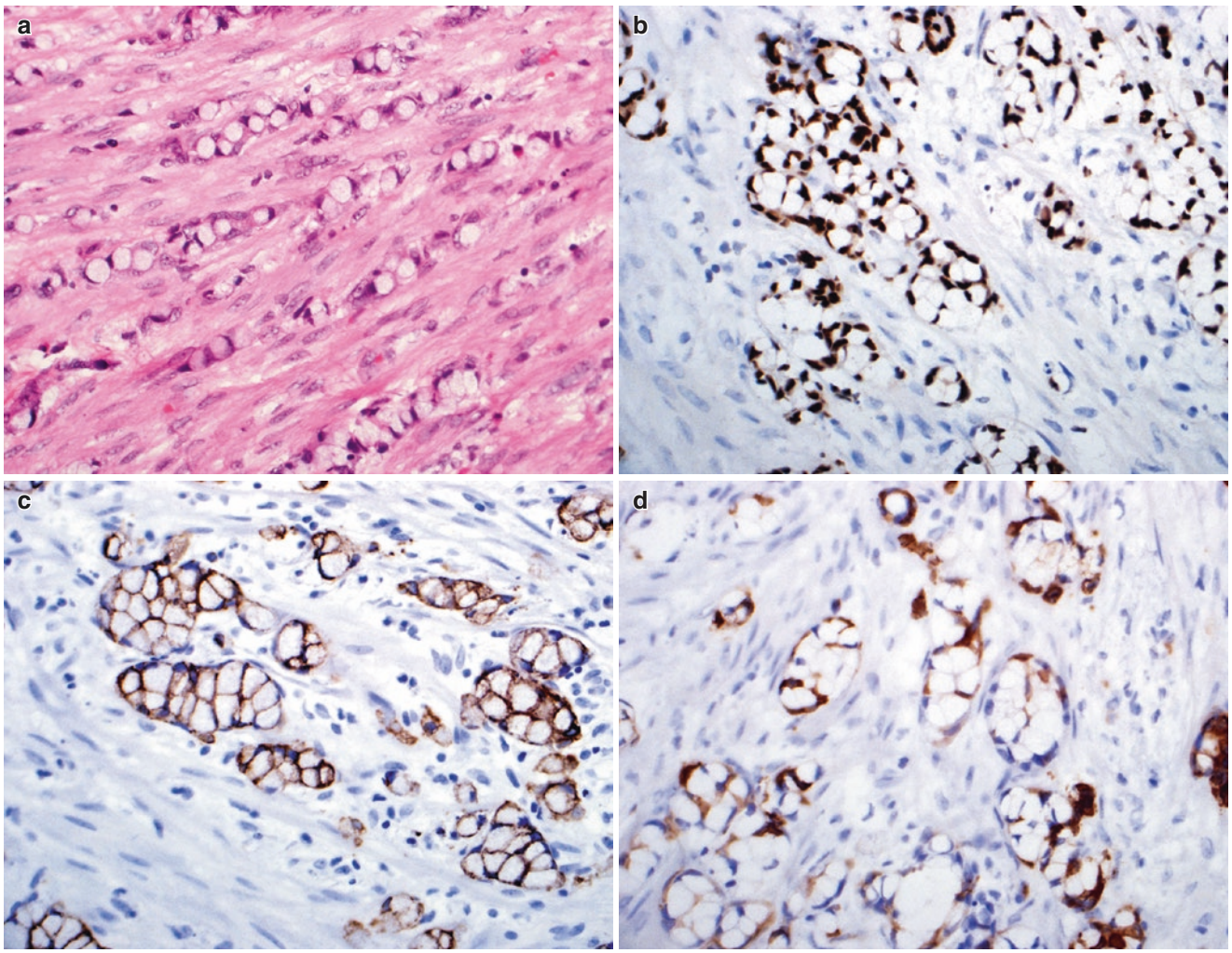

Fig. 29.2 Goblet cell carcinoid tumor of the appendix. H&E tissue section shows the tumor cells with goblet cell morphology infiltrating the appendiceal wall (**a**). The tumor cells demonstrate positive nuclear immunoreactivity for CDX2 (**b**), CK20 (**c**) and CK7 (**d**). The tumor cells are also positive for synaptophysin and chromogranin (not shown)

Table 29.5 Markers to distinguish mucinous tumors of appendiceal versus ovarian origin

Markers	Appendiceal	Ovarian
CK7	− or +	+
CK20	+	+ or −
CDX2	+	− or +
CDH17	+	−
SATB2	+	−
PAX8	−	+ (in about 20%)
WT1	−	− or +
MUC2	+	−
Beta-catenin	N+ and M+	M+

Note: *N* nuclear staining, *M* membranous staining

CK7 is usually diffusely positive in ovarian mucinous tumors, while CK20 and CDX2 are usually "focal or patchy" positive. In contrast, both CDX2 and CK20 are diffusely positive in most appendiceal tumors with variable CK7 positivity. CDH17 and SATB2 are two recently described markers showing promising discriminatory power. Similar to CDX2, they are diffusely positive in most appendiceal tumors while negative or only focally positive in ovarian mucinous tumors. PAX8 is also a helpful marker for this differential diagnosis. Approximately 20–30% of primary ovarian mucinous tumors are positive for PAX8, while it is almost always negative in appendiceal tumors. On the contrary, nuclear beta-catenin staining is almost always negative in ovarian tumors and is positive in approximately 10–20% of appendiceal tumors

References: [5–18]

Table 29.6 Commonly used markers for diagnosis of Hirschsprung's disease and potential pitfalls

Antibody	Interpretation and pitfalls
Neuron specific enolase (NSE)	Highlights ganglion cells to exclude Hirschsprung's disease; specific but not very sensitive.
Calretinin	Usually negative in hypertrophied nerve fibers in Hirschsprung's disease; nonspecific staining is common, particularly in mast cells; in patients with short-segment aganglionosis, it may show weak positivity in nerve fibers.
Acetylcholine esterase (AChE)	Increased number of haphazardly arranged positive nerve fibers in muscularis mucosae and lamina propria; requires freshly frozen tissue for the assay.

Note: Although the diagnosis of Hirschsprung's disease still depends on a thorough examination of hematoxylin and eosin (H&E) sections to ensure the absence of ganglion cells in an adequate specimen, recent papers indicate that calretinin staining can be particularly helpful in challenging cases if correctly interpreted. An example of immunostaining for calretinin is demonstrated in Fig. 29.3a, b

References: [19–22]

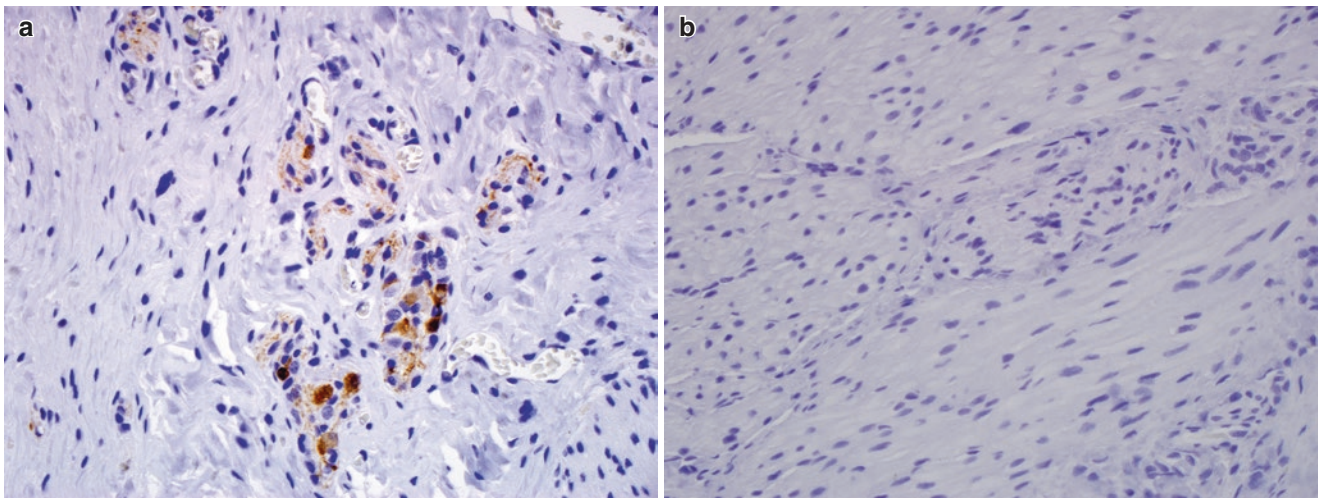

Fig. 29.3 Loss of calretinin immunoreactivity in hypertrophied nerve bundles in Hirschsprung's disease. Nerves and ganglia show positive immunoreactivity for calretinin in normal control (**a**). In addition to the absence of ganglion cells, the thick nerve bundles in Hirschsprung's disease exhibit loss of calretinin immunoreactivity (**b**)

Table 29.7 Different staining patterns between usual colonic adenocarcinoma and some of its unique variants

Markers	Usual colonic adenocarcinoma	Mucinous/signet ring cell carcinoma	Medullary carcinoma		Micropapillary carcinoma
			Literature	GML ($N = 18$)	
CDH17	+	+ or −	+ or −	16 (89%)	+
SATB2	+	+ or −	+ or −	16 (89%)	+
CDX2	+	− or +	− or +	12 (67%)	+
CK7	−	− or +	− or +	1 (6%)	−
CK20	+	+ or −	− or +	5 (29%)	+
MSI	Absent	Present in about 50% of cases	Present in >80% of cases	15 (83%)	Usually absent
Calretinin	−	− or +	+ or −	12 (67%)	−
MUC1	− or +	"−" in signet ring cell carcinoma	− or +	N/D	Positive in basal-lateral aspects of the tumor cells at the tumor–stromal interface

Note: MSI (microsatellite instability), particularly, with CIMP (CPG island methylator phenotype) high phenotype may lead to aberrant expression of CDX2, CK7, and CK20 in a subset of colonic adenocarcinomas. Loss or markedly reduced expression of CK20 and CDX2 is a frequent finding in medullary carcinoma of the colon. To complicate this matter further, some cases with the absence of expression CK20 and CDX2 may also show CK7 positivity. Our own data indicate that CDH17 and SATB2 are two markers not affected by MSI status. In the study, 98% of colonic medullary carcinomas retain the positivity of one of the two markers, and 100% of the tumors show positivity when the two markers are used in combination. Figure 29.4a shows an example of colonic medullary carcinoma. It is immunoreactive to both CDH17 (Fig. 29.4b) and SATB2 (Fig. 29.4c). In addition, it is strongly diffusely positive for calretinin immunostaining (Fig. 29.4d)

References: [17, 23–30]

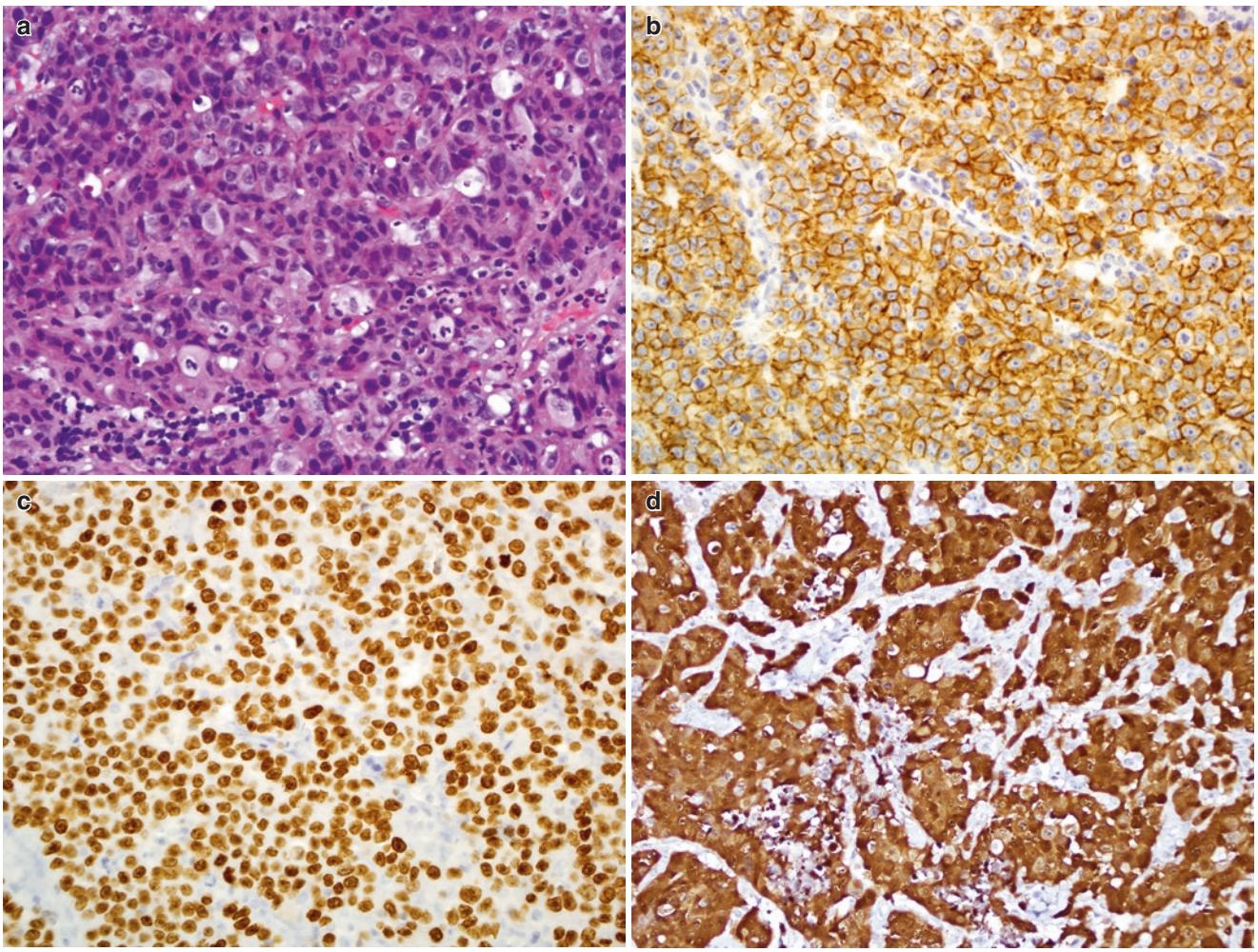

Fig. 29.4 Colonic medullary carcinoma. Hematoxylin and eosin (H&E) tissue section shows a sheet of tumors with primitive appearance (**a**); tumor cells show membranous immunoreactivity to CDH17 (**b**) and nuclear immunoreactivity to SATB2 (**c**). In addition, they are also strongly and diffusely positive for calretinin (**d**)

Table 29.8 Markers to differentiate colorectal adenocarcinoma from metastatic adenocarcinomas of the breast, pancreas, and lung

Markers	CRC	MBAC	MPADC	MLAC
CK7	−	+	+	+
CK20	+	−	+ or −	−
CDX2	+	−	− or +	− or +
GATA3	−	+	−[a]	−
GCDFP-15	−	+ or −	−	−
Mammaglobin	−	+	−	−
Beta-catenin	N+	M+	M+	M+
MUC2	+ or −	−	−	− or +
TTF-1	−	−	−	+
Napsin A	−	−	−	+
HNF4-a	+	NA	NA	_

Note: *CRC* colorectal adenocarcinoma, *MBAC* metastatic breast adenocarcinoma, *MPADC* metastatic pancreatic ductal carcinoma, *MLAC* metastatic lung adenocarcinoma, *N* nuclear staining, *M* membranous staining

[a]Our unpublished data showed that a small percentage (<10%) of pancreatic adenocarcinomas can be focally positive for GATA3

References: [14–17, 23, 31–36]

Table 29.9 Markers to differentiate colorectal adenocarcinoma from common gynecological carcinomas

Markers	Colorectal adenocarcinoma	Endocervical adenocarcinoma	Endometrioid adenocarcinoma	Serous carcinoma
CK7	–	+	+	+
CK20	+	–	–	–
CDX2	+	– or +	–	–
PAX8	–	+	+	+
PAX2	–	–	– or +	– or +
ER	–	+ or –	+	+ or –
P53	+ or –	– or +	– or +	Strongly diffusely "+" or completely "–"
WT1	–	–	–	+
P16	– or +	Diffuse, +	Patchy, – or +	Diffuse, +
Beta-catenin	N+	M+	M+	M+

Note: *N* nuclear staining, *M* membranous staining
Diffuse—nearly 100% of tumor cells stained; patchy—only a variable number of tumor cells stained
References: [3–18, 23, 35]

Table 29.10 Markers to differentiate colorectal adenocarcinoma from primary adenocarcinomas of the bladder, urachus, and prostate

Markers	Colorectal carcinoma	Prostatic adenocarcinoma	Bladder adenocarcinoma	Urachal adenocarcinoma
CK7	–	+	+ or –	+ or –
CK20	+	–	+ or –	+
CDH17	+	–	ND	ND
SATB2	+	–	–	ND
CDX2	+	–	+ or –	+
mCEA	+	–	+ or –	–
NKX3.1	–	+	–	ND
PSA	–	+	–	–
PSAP	–	+	–	–
Beta-catenin	N+	M+	M+	M+

Note: *N* nuclear staining, *M* membranous staining
References: [14–17, 37–43]

Table 29.11 Markers to differentiate colorectal adenocarcinoma from peritoneal mesothelioma

Markers	Adenocarcinoma	Mesothelioma
Calretinin	–	+
D2–40	–	+
CK5/6	–	+
WT1	–	+
CEA	+	–
MOC-31	+	–
CDH17	+	–
SATB2	+	–
CDX2	+	–
AE1/3	+	+

References: [14–17, 44–46]

Table 29.12 Markers to distinguish well-differentiated neuroendocrine tumors (WD-NETs) of the colorectal origin versus other organ systems

Markers	Colorectal	Pancreatic	Lung	Gastric	Small intestine
SATB2	+	–	–	–	–
CDH17	+	– or +	– or +	– or +	+
CDX2	+ or –	–	–	– or +	+ or –
PDX1	– or +	+ or –	– or +	+ or –	+ or –
TTF-1	–	–	+	–	–
PAX8[a]	–	+ or –	–	–	–

[a]PAX8—polyclonal antibody
References: [14, 15, 47–50]

Table 29.13 Markers to differentiate common colonic mucosal mesenchymal polyps

Marker	Schwann cell hamartoma	Intestinal mucosal perineurioma[a]	IFP	Ganglioneuroma
CD34	–	–	+	–
S100	+	–	–	+
NSE	+ or –	–	–	+
EMA	–	+	–	–
GLUT 1	–	+	–	–
Claudin 1	–	+	–	–

[a]Intestinal mucosal perineurioma is also known as colorectal fibroblastic polyp; IFP—inflammatory fibroid polyp. An example of Schwann cell hamartoma is shown in Fig. 29.5a (20×) with positive S100 immunoreactivity in Fig. 29.5b (20×). An example of intestinal mucosal perineurioma is shown in Fig. 29.5c (20×) with positive GLUT1 immunoreactivity in Fig. 29.5d

References: [51–54]

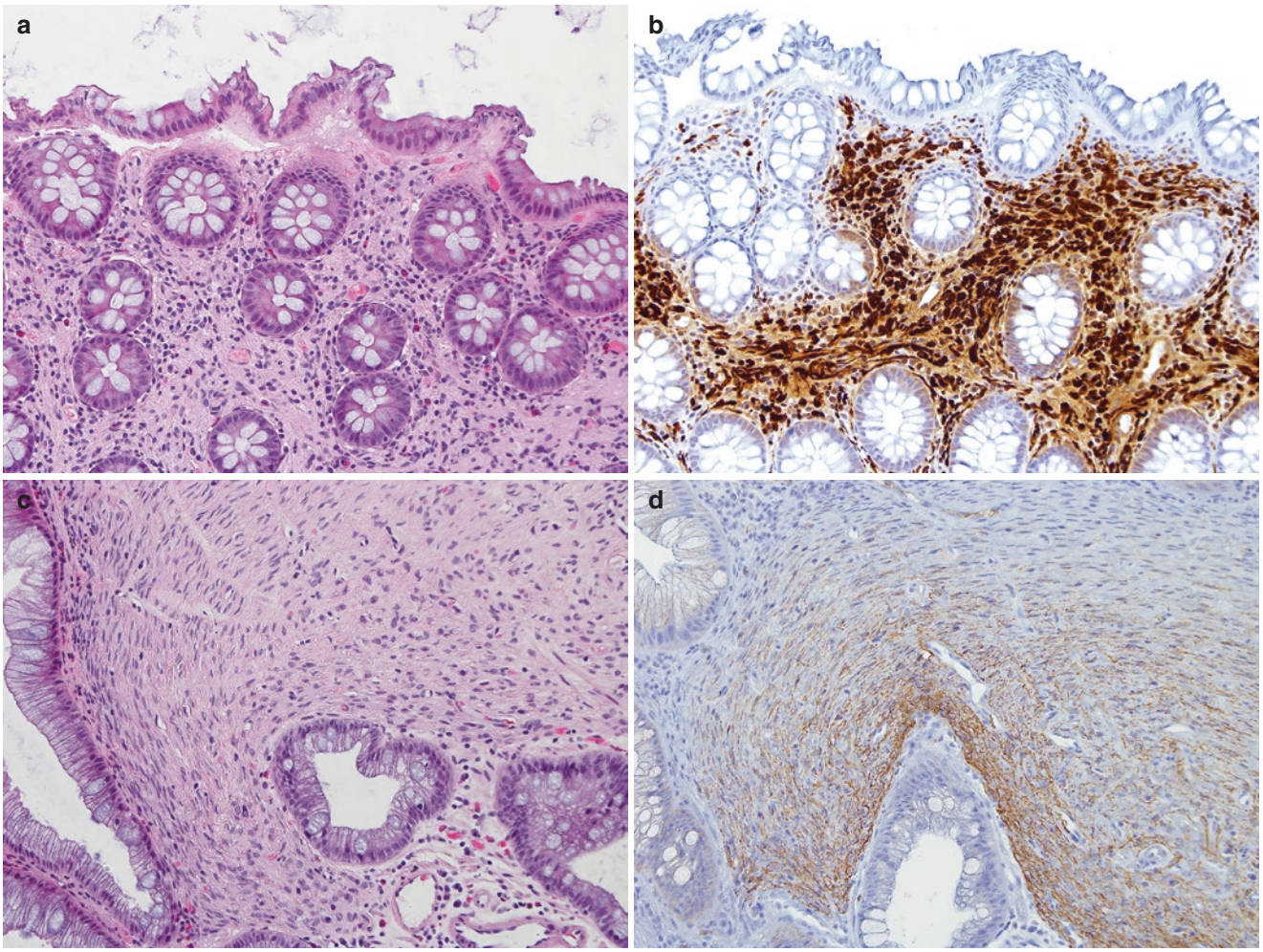

Fig. 29.5 Schwann cell hamartoma and intestinal mucosal perineureoma. Hematoxylin and eosin (H&E)-stained sections of both lesions show spindle cell proliferation without ganglion cells. Schwann cell hamartoma, H&E stain (**a**) and demonstrating diffuse and strong immunoreactivity to S100 (**b**); intestinal mucosal perineurioma, H&E stain (**c**), and demonstrating positive immunoreactivity to GLUT 1 (**d**)

Table 29.14 Markers to differentiate common mesenchymal tumors of the colon and rectum

Marker	GIST	Leiomyosarcoma	Schwannoma	Kaposi sarcoma	SFT	Granular cell tumor
Desmin	− or +	+	−	−	−	−
SMA	− or +	+	−	+ or −	−	−
CD117	+	−	−	− or +	−	−
CD34	+ or −	−	−	+	+	−
S100	−	−	+	−	−	+
NSE	−	−	+ or −	−	−	−
HHV8	−	−	−	+	−	−
CD99	−	−	−	−	+	−
Bcl2	−	−	−	+/−	+ or −	−

Note: *GIST* gastrointestinal stromal tumor, *SFT* solitary fibrous tumor. An example of a granular cell tumor of the ascending colon is shown in Fig. 29.6a. S100 immunostaining pattern of the tumor is shown in Fig. 29.6b

References: [55–60]

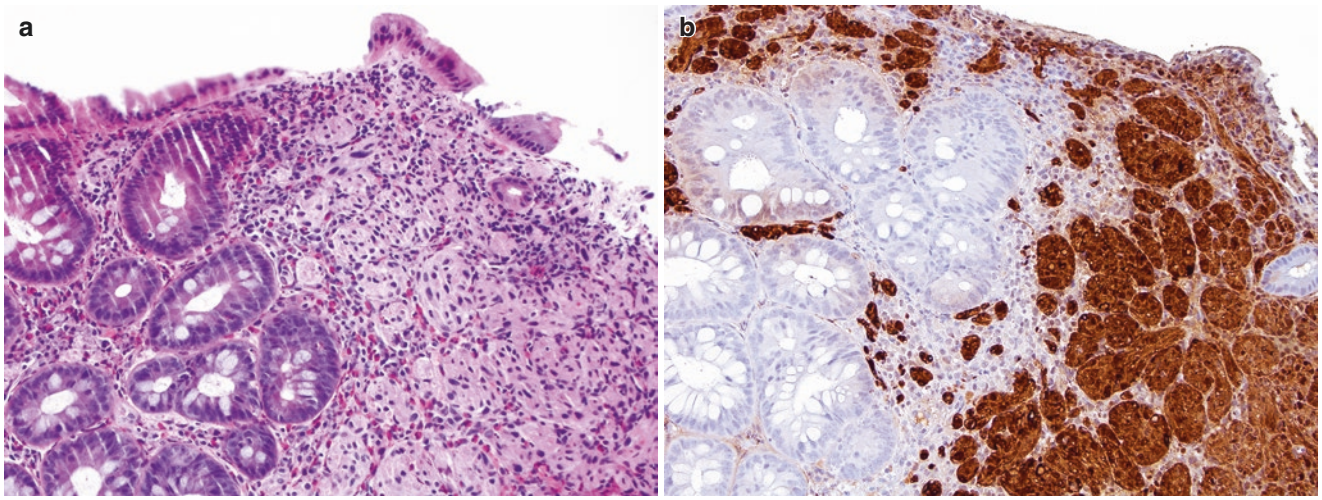

Fig. 29.6 Granular cell tumor of the ascending colon. The tumor cells exhibit characteristic eosinophilic granular cytoplasm (**a**). They are strongly and diffusely positive for S100 (**b**)

Table 29.15 Markers useful to confirm dysplasia in inflammatory bowel disease (IBD) and to differentiate IBD-associated dysplasia from sporadic adenoma

Markers	Reactive atypia	Colitis dysplasia	Sporadic adenoma
p53	− or +, usually weak	+, clonal pattern	+ or −
P504S	− or +	+	− or +
Beta-catenin	M+	M+	N+
CK7	− or +	+ or −	−
SATB2	No loss	Loss in 41% (15/37)	No loss

Note: p53 staining pattern in dysplasia/dysplasia-associated lesion or mass (DALM) (now tended to use the term "IBD/colitis associated dysplasia") is usually intensive, uniformly, and diffusely involving basal crypts. This is presumably due to mutations in p53 genes. The pattern is quite different from that seen in reactive atypia, usually weak and scattered. Using p53 together with P504S can further increase sensitivity and specificity. The combination of p53 and beta-catenin is sometimes helpful to distinguish DALM from sporadic adenomas. A recent paper suggests that CK7 positivity in inflammatory bowel disease (IBD) is also helpful to confirm low-grade dysplasia. A pattern of CK7 and p53 double positivity is frequently seen in IBD-associated dysplasia

References: [61–70]

Table 29.16 Common mismatch repair (MMR) protein nuclear expression patterns and risk assessment of Lynch syndrome

MLH1	PMS2	MSH2	MSH6	Risk
Intact	Intact	Intact	Intact	Low
Loss	Loss	Intact	Intact	Upon further tests
Intact	Intact	Loss	Loss	High
Intact	Loss	Intact	Intact	High
Intact	Intact	Intact	Loss	High

Note: In addition to the listed common patterns, rarer patterns are also possible particularly after all the artificial possibilities and technical issues are excluded. A suggested algorithm to assess the risk of Lynch syndrome by using immunohistochemical markers of MMR proteins is seen in Fig. 29.7

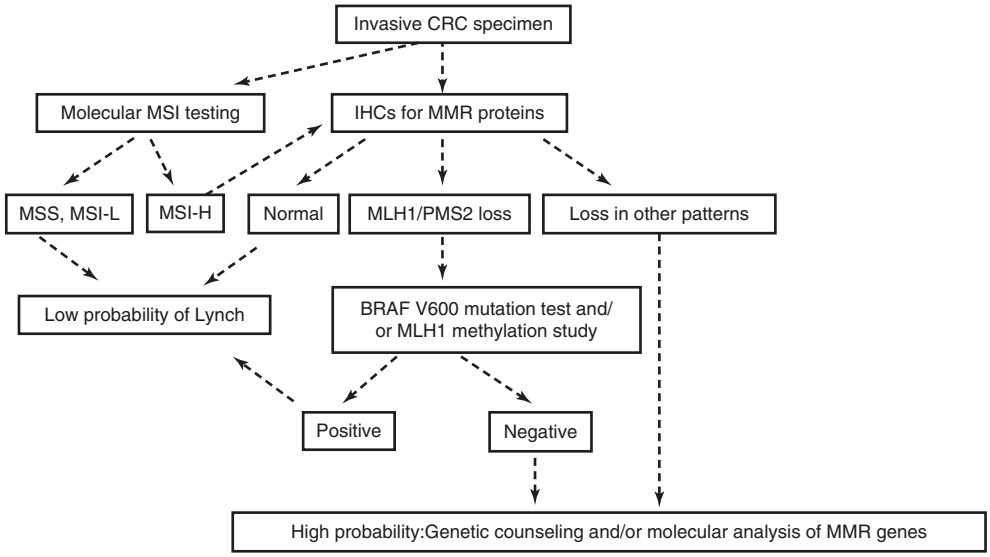

Fig. 29.7 Algorithm to assess the risk of Lynch syndrome in colorectal carcinoma

Table 29.17 Markers to differentiate adenocarcinoma of anal duct origin from small intestinal, colorectal adenocarcinoma, endocervical and prostatic adenocarcinoma

Markers	Anal duct carcinoma	Small intestinal carcinoma	Colorectal carcinoma	Endocervical carcinoma	Prostatic carcinoma
CK7	+	+	–	+	+
CK20	–	– or +	+	– or +	–
CDH17	–	+	+	–	–
SATB2	–	– or +	+	–	–
CDX2	–	+	+	– or +	–
PAX8	–	–	–	+	– or +
ER/PR	–	–	–	+	–
HPV	–	–	–	+	–
PSA	–	–	–	–	+

Note: An example of CK7 immunoreactivity in anal duct carcinoma is shown in Fig. 29.8
References: [71–75]

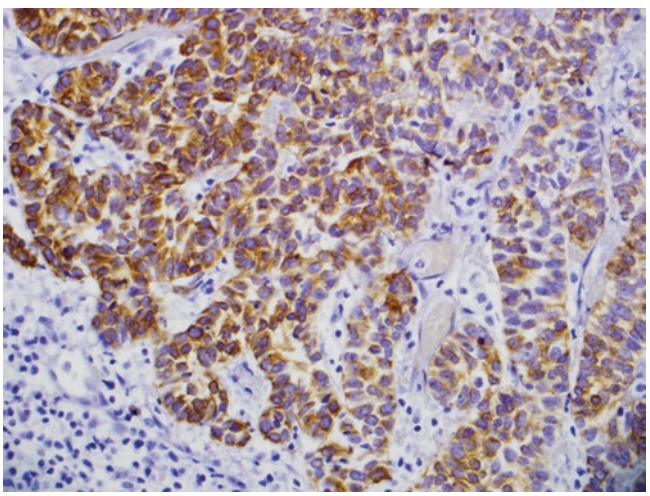

Fig. 29.8 Anal gland adenocarcinoma. The tumor cells exhibit positive CK7 immunoreactivity

Table 29.18 Markers to distinguish anal Paget's disease versus melanoma in situ

Markers	Anal Paget's disease associated with colorectal carcinoma	Primary anal Paget's disease (not associated with underlying carcinoma)	Melanoma in situ
CK7	+	+	–
CK20	+	–	–
GCDFP-15	–	+	–
Mucin	+	+	–
Melan-A	–	–	+
SOX10	–	–	+
S100	–	–	+

Note: An example of CK20 reactivity in anal Paget's disease with underlying mucinous adenocarcinoma is shown in Fig. 29.9
References: [76–81]

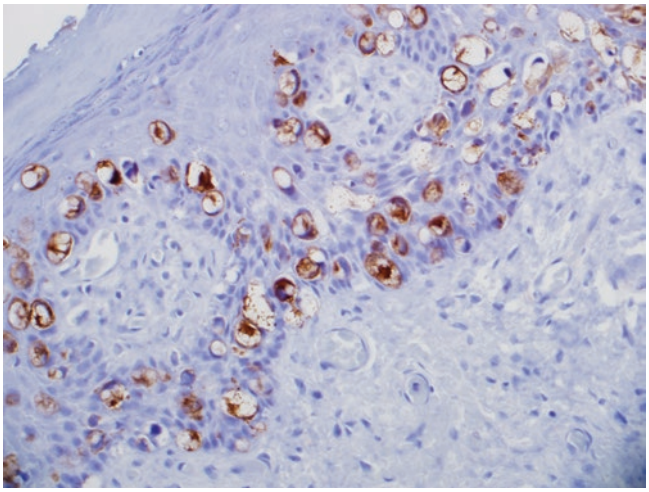

Fig. 29.9 Anal Paget's disease with underlying mucinous adenocarcinoma. The tumor cells involve the overlying epidermis with pagetoid spreading and exhibit positive CK 20 immunoreactivity

Table 29.19 Markers for anal squamous cell carcinoma versus basal cell carcinoma versus melanoma versus urothelial carcinoma versus small cell carcinoma

Markers or antibodies	Squamous cell carcinoma	Basal cell carcinoma	Melanoma	Urothelial carcinoma	Small cell carcinoma
AE1/3	+	+	–	+	+ (dot-like pattern)
p63	+	+	–	+ or –	–
P40	+	+	–	+	–
CK903	+	+	–	+	–
CK5/6	+	+	–	+ or –	–
CK17	+ or –	+	–	+	–
BerEP4	–	+	–	+	–
P16	+ or –	–	–	–	–
SOX2	+	–	–	–	–
SOX10	–	–	+	–	–
S100	–	–	+	–	–
Melan-A	–	–	+	–	–
HMB-45	–	–	+	–	–
GATA3	– or +	–	–	+	–
Synaptophysin	–	–	–	–	+
Chromogranin	–	–	–	–	+
CD56	–	–	–	–	+

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