Markers and Immunoprofile of Tumors of the Gastrointestinal Tract

7

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CDX-2		
Expression pattern: nuclear		
Main diagnostic use	Expression in other tumors	Expression in normal cells
Colorectal adenocarcinoma	Gastric adenocarcinoma, carcinoids of gastrointestinal tract, islet pancreas tumors, sinonasal carcinoma, adenocarcinomas of urinary bladder, ovarian mucinous adenocarcinoma, adenocarcinoma of uterine cervix	Intestinal epithelium and intestinal metaplasia, pancreatic epithelial cell
Positive control: appendix		

Diagnostic Approach Caudal-related homeobox 2 (CDX-2) is an intestine specific transcription factor protein regulating the differentiation and proliferation of intestinal epithelial cells. The expression of CDX-2 begins normally in the post-gastric mucosa in the late stages of embryogenesis of the gastrointestinal tract and is characteristic for different types of adult intestinal mucosa including absorptive, goblet, and Paneth cells in addition to neuroendocrine cells.

The expression of CDX-2 protein is found in esophageal and gastrointestinal adenocarcinomas in addition to gastrointestinal neuroendocrine tumors in different intensities, whereas the highest frequency and intensity is characteristic for the colorectal adenocarcinomas (Fig. 7.1) [1]. CDX-2 is also an early marker for esophageal Barrett's metaplasia as the expression of CDX-2 initiates the transformation of squamous epithelium into columnar epithelium with goblet cells.

The expression of CDX-2 is usually associated with the expression of cytokeratin 20. CDX-1 is a further transcription factor and a marker for gastrointestinal tumors analogous to CDX-2.

Diagnostic Pitfalls The expression of CDX-2 is reported in many non-gastrointestinal adenocarcinomas. High expression level of CDX-2 is found in bladder adenocarcinoma derived from intestinal urachus, pancreatic adenocarcinoma, biliary adenocarcinoma, and mucinous ovarian carcinoma. CDX-2 expression is also reported in

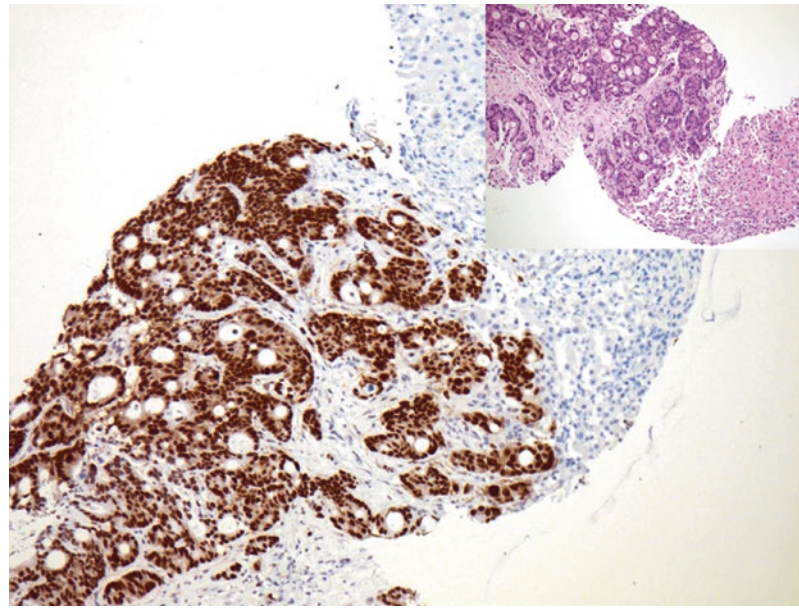

Fig. 7.1 Strong nuclear CDX-2 expression in metastatic colonic adenocarcinoma

rare cases of prostatic cancer. Pulmonary adenocarcinoma with mucinous differentiation can also be positive for CDX-2; this type of pulmonary adenocarcinoma is also positive for cytokeratin 20 and lacks the expression of TTF-1 [2, 3]. Some neuroendocrine tumors outside the GIT are also reported to be positive for CDX-2 [4]. The loss of CDX-2 expression has been noted in anaplastic high-grade gastrointestinal adenocarcinomas and in medullary adenocarcinomas.

SATB-2		
Expression pattern: nuclear		
Main diagnostic use	Expression in other tumors	Expression in normal cells
Colorectal adenocarcinoma and medullary carcinoma, osteosarcoma	Hepatocellular carcinoma, laryngeal squamous cell carcinoma, neuroendocrine tumors of the colon and rectum	Colorectal epithelium, neuronal cells of the central nervous system, hepatocytes, kidney, epithelial cells of the epididymis and seminiferous ducts
Positive control: appendix		

Diagnostic Approach **S**pecial AT-rich sequence-**b**inding protein **2** (SATB-2) is a nuclear matrix-associated transcription factor and DNA-binding protein involved in the differentiation of osteoblasts. In the gastrointestinal tract, SATB-2 is selectively expressed in colorectal epithelium, while gastric and small intestinal mucosa and pancreatic epithelium lack the expression of SATB-2. SATB-2 is a specific marker for colorectal adenocarcinomas including medullary carcinoma (Fig. 7.2). In routine histopathology, SATB-2 is usually used in combination with cytokeratin 20. SATB-2 is also selectively expressed in neuroendocrine tumors of the left colon and rectum whereas other neuroendocrine tumors reported to be negative or weak positive for this marker [5]. Low expression level of SATB-2 is reported in a subset of pulmonary adenocarcinomas in addition to ovarian carcinomas. Adenocarcinomas of the upper gastrointestinal tract and pancreas typically lack the expression of SATB-2. SATB-2 is also an important diagnostic marker for osteosarcoma [6, 7].

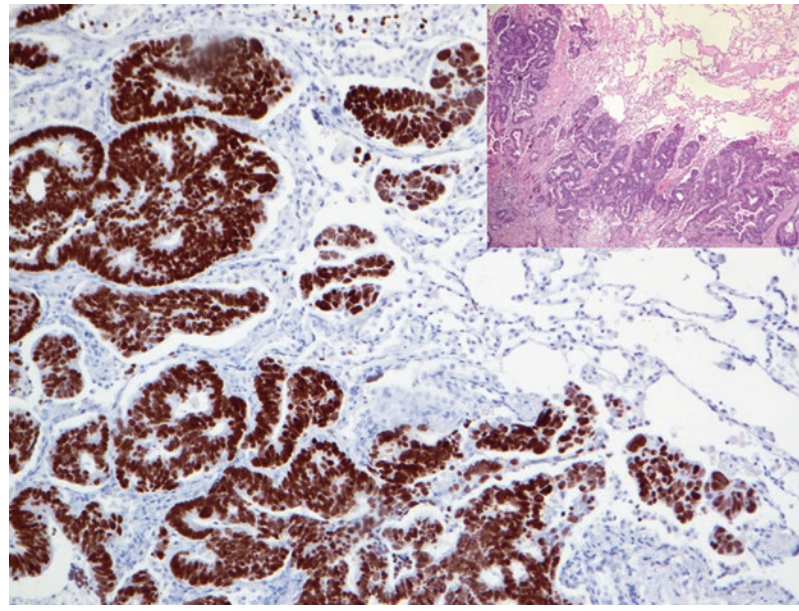

Fig. 7.2 Nuclear SATB-2 expression in metastatic rectal adenocarcinoma (lung metastases)

Cadherin-17 (CDH17)		
Expression pattern: membranous and cytoplasmic		
Main diagnostic use	Expression in other tumors	Expression in normal cells
Esophageal and gastrointestinal adenocarcinoma	Pancreatic ductal carcinoma, gastrointestinal and pancreatic neuroendocrine tumors, cholangiocellular carcinoma, osteosarcoma	Gastrointestinal epithelium, pancreas, gall bladder mucosa, adrenal cortex, pituitary gland
Positive control: appendix		

Diagnostic Approach **C**alcium-dependent **adhe**sion molecule **17** (CDH17) also known as liver-intestine cadherin (LI-cadherin) is a member of the cadherin family regulated by CDX-2. CDH17 is normally expressed in gastrointestinal and pancreatic epithelium and related adenocarcinomas (Fig. 7.3) [8, 9].

CDH17 is generally negative in pulmonary adenocarcinoma, breast carcinoma, papillary thyroid carcinoma, transitional cell carcinoma, renal cell carcinoma, hepatocellular carcinoma, and mesothelioma.

Villin: Villin is an actin-binding protein and a component of brush border of different epithelial types including cells of intestinal mucosa, mucosa of fallopian tubes, and seminiferous ducts and cells lining proximal renal tubules. Villin is a marker for gastrointestinal adenocarcinomas. Ovarian, endometrioid, and renal cell carcinomas may also be positive for villin. Villin expression is also reported in well-differentiated neuroendocrine tumors of different origin.

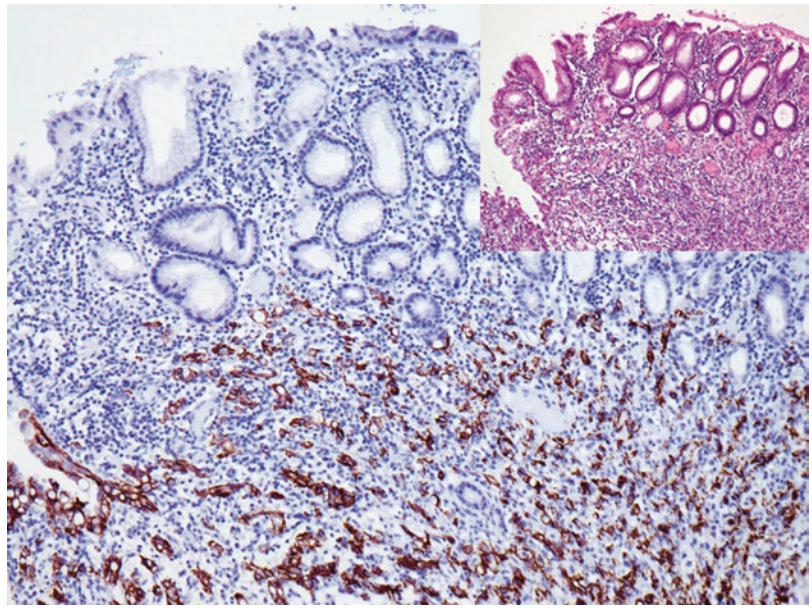

Fig. 7.3 CDH17 expression in cells of gastric adenocarcinoma

Immunoprofile of gastrointestinal tumors				
Tumor type	+ in >90% (+)	+ in 50–90% (±)	+ in 10–50% (∓)	+ in <10% (−)
A. Esophageal and gastric tumors				
Squamous cell carcinoma of the esophagus	*CK5*/6, CK8, CK14, CK18, CK19, *p63*, *p40*	β-Catenin, cyclin D1		CK7, CK20
Adenocarcinoma of the esophagus	CK7, CK8, CK18, CK19	E-Cadherin, CDX-2, cyclin D1, villin	CK20	CK5/6, p40
Adenocarcinoma of the stomach	CK8, CK18, CK19, villin, EMA, CDH-17	CK7, CEA, CDX-2, glicentin	CK20	CK5/6, CK14, CK17, CA125, *SATB-2*
B. Intestinal tumors				
Adenocarcinoma of the duodenum and small bowel	CK8, CK18, CK19, *CDX-2*[a], villin	*CK7*, CK20, *PDX-1*, AMACR	Hep Par-1	*SATB-2*
Adenocarcinoma of the ampullary region	CK8, CK18, CK19, CK7, *PDX-1*		CK20,CDX-2	
Colorectal adenocarcinoma	CK8, CK18, CK19, *CK20, CDX-2, SATB-2*, CEA, villin, MUC-2	β-Catenin[b], CD10	CK7	CA125, CK5/6, CK14, AMACR, GATA-3, thrombomodulin
Colorectal mucinous adenocarcinoma	*CK20, CDX-2, SATB-2*, villin, β-catenin[b]		CK7, PDX-1	
Basaloid (cloacogenic) carcinoma	CK1, *CK5/6*, CK8, CK15, CK17, CK18, CK19	CK10	CK7	CK20
Anorectal squamous cell carcinoma	CK5/6, CK10, CK17, CK18, CK19			CK7, CK20
Anal Paget's disease	CK7, CK8, CK18, EMA, MUC-2	CEA	CK20, GCDFP-15	MUC-1
C. Gastrointestinal neuroendocrine tumors				
Broad-spectrum markers for gastrointestinal neuroendocrine tumors/ carcinoma: NET[c] G1 NET[d] G2 NEC[e] G3 (small and large cell type)	*Synaptophysin, chromogranin,* NSE, S100, *CD56* Epithelial markers: CK8/18, CK19, CK-MNF *Proliferation index (Ki-67) in NET G1: <2% NET G2: 3–20% NEC G3: >20%*	CDX-2, villin		CK20
Gastric ECL[f] cell NET	Broad-spectrum neuroendocrine markers		Histamine, gastrin	
Gastric EC cell NET	Broad-spectrum neuroendocrine markers		Serotonin	

Immunoprofile of gastrointestinal tumors				
Gastrinoma NET	Broad-spectrum neuroendocrine markers, gastrin			
NET of small bowel and colon	Broad-spectrum neuroendocrine markers, serotonin, CEA	CD56, CDX-2, villin, somatostatin	Pancreatic polypeptide, CK7, CK20	E-Cadherin, β-catenin
Mixed adenoneuroendocrine carcinoma (MANEC)	Broad-spectrum neuroendocrine markers, E-cadherin, β-catenin	CEA	Somatostatin, pancreatic polypeptide, serotonin	
L-cell NET	Broad-spectrum neuroendocrine markers	Pancreatic polypeptide, glucagon-like peptides		
Tubular carcinoid	Broad-spectrum neuroendocrine markers	Glucagon, serotonin		S100
NEC G3; small and large cell type	Broad-spectrum neuroendocrine markers, pan-CK, CK8/18, CK19	Vimentin, CDX-2	TTF-1, CK7	CK20

[a]Usually negative in medullary-type adenocarcinoma
[b]Nuclear stain
[c]Well-differentiated neuroendocrine tumor (carcinoid)
[d]Well-differentiated neuroendocrine carcinoma (atypical carcinoid)
[e]Poorly differentiated neuroendocrine carcinoma
[f]Enterochromaffin like cells

7.2 Gastrointestinal Mesenchymal Tumors

7.2.1 Diagnostic Antibody Panel for Gastrointestinal Stromal Tumors (GIST)

CD34, CD117 (c-Kit), PDGFR-α, DOG-1

7.2.2 Diagnostic Antibody Panel for Miscellaneous Mesenchymal Gastrointestinal Tumors

sm-Actin, h-Caldesmon, Calponin, Smoothelin, SOX-10, CDE34, β-Catenin

CD117 (c-kit; mast cell growth factor receptor; steel factor receptor)		
Expression pattern: membranous/cytoplasmic		
Main diagnostic use	Expression in other tumors	Expression in normal cells
GIST, seminoma, mast cell disease, melanoma, CML, AML, adenoid cystic carcinoma, thymoma and thymic carcinoma	Clear cell sarcoma, small cell lung carcinoma, pulmonary large cell carcinoma, Ewing sarcoma/PNET, follicular and papillary thyroid carcinoma, renal oncocytoma, renal chromophobe carcinoma, hepatocellular carcinoma, Merkel cell carcinoma, synovial sarcoma, osteosarcoma, chondrosarcoma, angiosarcoma, neuroblastoma, glioma	Interstitial cells of Cajal, hematopoietic progenitor cells, mast cells, melanocytes, germ cells, glial and Purkinje cells, basal cells of the epidermis, secretory cells of the breast, thymic epithelial cells, endothelial cells, renal tubular cells, ovarian stroma, and corpus luteum
Positive control: brain tissue		

Diagnostic Approach CD117 (c-kit) is a member of tyrosine kinase growth factor receptor type III family. This family includes c-Kit, platelet-derived growth factor receptor (PDGFR-α), macrophage colony-stimulating factor, and FMA-like tyrosine kinase 3 and is composed of extracellular domain, transmembrane domain, and intracellular kinase domain. Normally, the activation of CD117 takes place after the binding to the stem cell factor. CD117 is involved in the differentiation of hematopoietic cells, mast cells, germ cells, melanocytes, and intestinal cells of Cajal.

In routine immunohistochemistry, CD117 has a very wide expression spectrum and is usually used as a guide marker for the diagnosis of many tumors. The expression of CD117 is found in more than 90% of gastrointestinal stroma tumors (GISTs), whereas single or multiple activating mutations of the c-Kit gene are found in about 80% of GISTs, mainly in exon 11 and less frequently in exons 9, 13, and 17. The co-expression of CD34 and DOG-1 is a characteristic profile for the diagnosis of GIST (Fig. 7.4). CD117 is also a very helpful marker for the diagnosis of other tumors such as seminoma, mast cell tumors, chronic and acute myelogenous leukemia, thymoma, adenoid cystic carcinoma, a subset of T-ALL, and multiple myeloma [10].

Diagnostic Pitfalls 5–8% of the GISTs are associated mutations within the PDGFR-α gene (mainly in exon 18) and are usually negative for CD117. These tumors show frequently epithelioid morphology and are commonly positive for PDGFR-α and/or DOG-1 [11, 12].

Platelet-Derived Growth Factor Receptor α: PDGFR-α is a tyrosine kinase receptor, a member of the type III tyrosine kinase receptor family involved in embryonic development of different tissue types and immune response. PDGFR-α is an important marker for CD117-negative GISTs as activating mutations within the PDGFR-α gene–mainly in exons 12, 14, and 18–are found in CD117-negative GISTs. CD117-positive GISTs usually lack the expression of PDGFR-α. In the interpretation of the PDGFR-α immunostain, it is important to consider that a subset of desmoid tumors is positive for this marker. Normally, PDGFR-α stains ganglion and Schwann cells, thyroid follicular cells, and spermatogonia [13, 14].

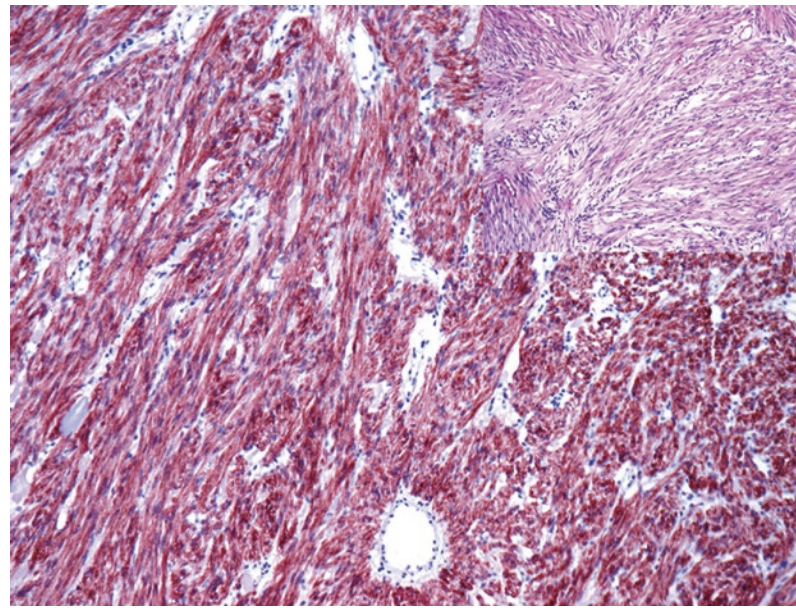

Fig. 7.4 GIST showing strong CD117 expression

DOG-1		
Expression pattern: membranous/cytoplasmic		
Main diagnostic use	Expression in other tumors	Expression in normal cells
GIST	Acinic cell carcinoma of salivary glands, uterine leiomyoma, synovial sarcoma, chromophobe renal cell carcinoma, renal oncocytoma, esophageal squamous cell carcinoma, hepatocellular carcinoma, biliopancreatic and acinar adenocarcinoma	Cajal cells, gastric surface epithelium, salivary gland and pancreatic acini, gallbladder epithelium, myoepithelial cells
Positive control: GIST		

Diagnostic Approach DOG-1 (anoctamin-1) is a transmembrane chloride channel protein highly expressed in the cells of Cajal of the gastrointestinal tract. DOG-1 is a highly specific marker to gastrointestinal stroma tumors (GISTs) and reacts with more than 90% of this tumor identity (Fig. 7.5). The expression spectrum of DOG-1 is different than that of CD117, but there is a high concordance between the expressions of both markers in GISTs [15–17]. Unlike CD117, DOG-1 is constantly negative in seminoma, myeloid, and mast cell tumors. DOG-1 is also an interesting marker that discriminates acinic cell carcinomas of salivary glands from other adenocarcinomas with the similar morphology as long as biliopancreatic adenocarcinomas are not in the differential diagnosis.

Diagnostic Pitfalls Low DOG-1 expression is found in up to 50% of intramural gastrointestinal leiomyoma. These are usually strongly positive for actin and h-caldesmon.

CD34: CD34 is a cell surface adhesion glycoprotein listed with the endothelial markers. CD34 labels the majority of GISTs but lacks the specificity consequently must be used in a panel with DOG-1 and CD117. In gastrointestinal mesenchymal tumors, CD34 labels also the stromal cells of inflammatory fibroid polyp of the gastrointestinal tract (Fig. 7.6).

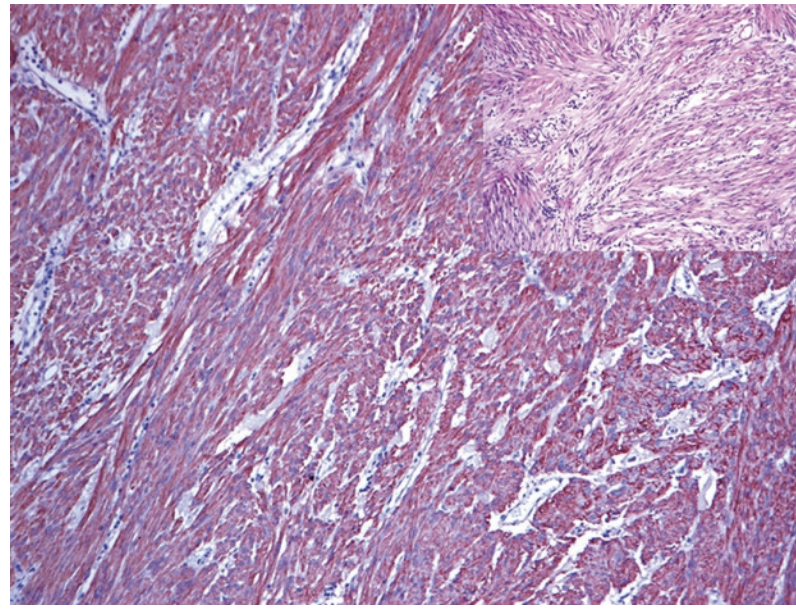

Fig. 7.5 Strong DOG-1 expression in GIST

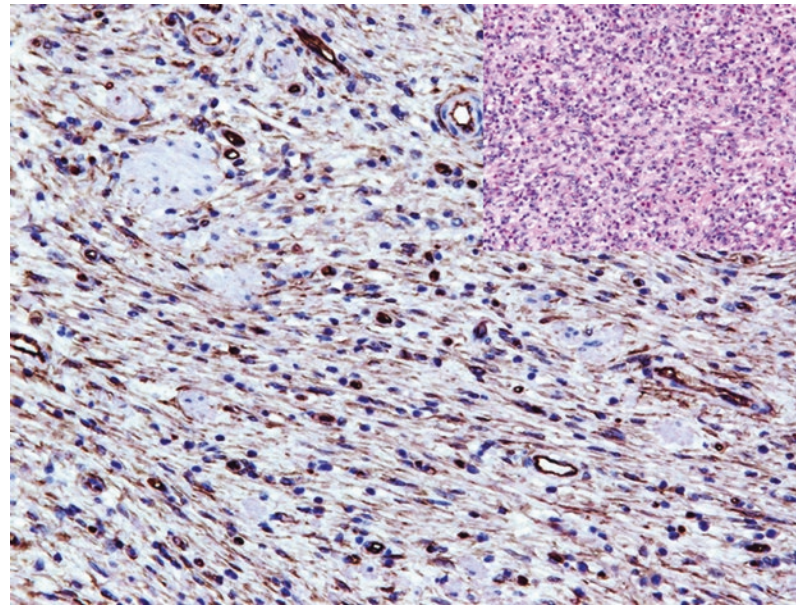

Fig. 7.6 CD34 labels stroma cells of inflammatory fibroid polyp of the gastrointestinal tract

Immunophenotype of mesenchymal gastrointestinal tumors

Tumor type	+ in >90% (+)	+ in 50–90% (±)	+ in 10–50% (∓)	+ in <10% (−)
Gastrointestinal stromal tumor (GIST)	*CD117* (c-Kit)[a], *DOG-1,* vimentin	*CD34*, CD99, nestin, bcl-2, D2–40, tau, h-caldesmon	sm-Actin, S100, CK8, CK18, PDGFR-α[b]	Synaptophysin, chromogranin, desmin, PGP9.5, calponin, β-catenin
Gastrointestinal autonomic nerve tumor (plexosarcoma) (GANT as subtype of GIST)	*CD117*, vimentin	CD34, NSE, synaptophysin, β-catenin, PGP9.5	Chromogranin, S100, neurofilaments, h-caldesmon	Desmin, actin, calponin
Inflammatory fibroid polyp of the gastrointestinal tract	*Stromal cells* CD34, fascin, cyclin D1	Calponin, CD35	Sm-Actin	CD117, S100, desmin, h-caldesmon, bcl-2
Granular cell tumor	S100, *Sox-10*, CD56, NSE, laminin, nestin	CD68, inhibin, PGP 9.5, calretinin		GFAP, neurofilaments, EMA, pan-CK
Plexiform fibromyxoma	Actin, CD10		Desmin	CD117, DOG-1
Calcifying fibrous tumor	Vimentin			Actin, desmin, h-caldesmon, CD34, CD117, pan-CK
Mesenteric fibromatosis	Vimentin, β-catenin[c]	sm-Actin	Desmin, CD117	calponin, pan-CK, S100

[a]GISTs with epithelioid morphology are frequently CD117 negative
[b]PDGFR-α positive in CD117-negative GISTs
[c]Nuclear and cytoplasmic stain (Fig. 7.7)

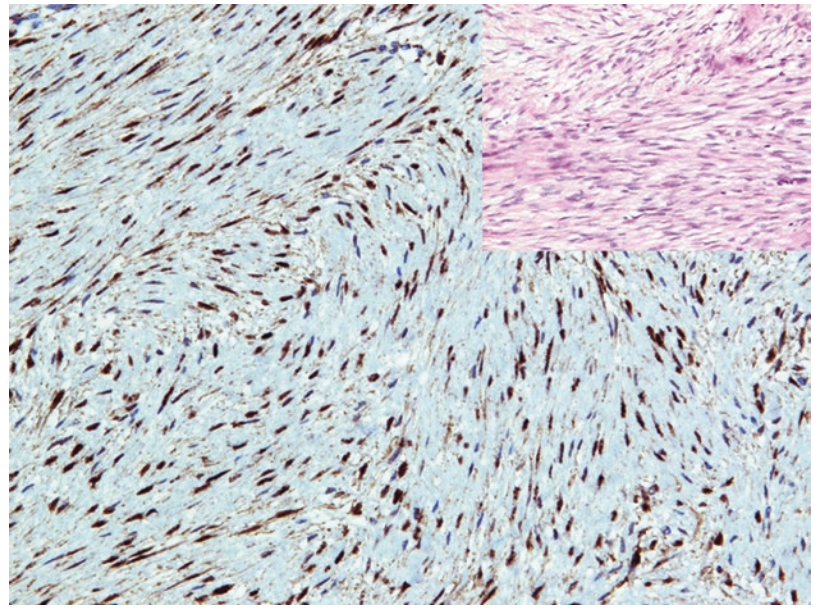

Fig. 7.7 Mesenteric fibromatosis with strong nuclear β-catenin expression

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