Chapter 26
Pancreas and Ampulla

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Abstract This chapter provides a practical overview of frequently used markers in the diagnosis and differential diagnosis of both common and rare pancreatic and ampullary neoplasms, with a specific focus on pancreatic ductal adenocarcinoma and its mimickers, neuroendocrine neoplasms, acinar cell carcinoma, and solid pseudopapillary neoplasm of the pancreas. This chapter contains 47 questions; each question is addressed with tables, concise notes, and representative pictures, if applicable. In addition to the literature review, the authors have included their own experience and tested numerous antibodies reported in the literature. The most effective diagnostic panels of antibodies have been recommended for many entities, such as SMAD4/DPC4, pVHL, maspin, S100P, and IMP3 being suggested as the best diagnostic panel for identifying pancreatic ductal adenocarcinoma and Bcl10 to confirm a diagnosis of acinar cell carcinoma. Some newly described markers such as ATRX/DAXX, PAX6, INSM1, TTMP, islet-1, and PDX-1 for neuroendocrine neoplasm have been discussed. In addition, a small panel of IHC markers including pVHL, CRP, and albumin (by RNA in situ hybridization) has been recommended to confirm a diagnosis of intrahepatic cholangiocarcinoma since these three markers are usually negative in a pancreatic ductal adenocarcinoma. Furthermore, immunophenotypes of normal pancreatic and ampullary tissues have been described, which tends to be neglected in the literature.

Pancreas

1. Summary of applications and limitations of useful markers (Table 26.1)
2. Summary of useful markers for common tumors (Table 26.2)
3. Markers for normal pancreatic ducts and acini (Table 26.3)
4. Markers for autoimmune pancreatitis (Table 26.4)
5. Markers for ductal adenocarcinoma of the pancreas (Table 26.5)
6. Markers for adenosquamous carcinoma of the pancreas (Table 26.6)
7. Markers for colloid carcinoma of the pancreas (Table 26.7)
8. Markers for medullary carcinoma of the pancreas (Table 26.8)
9. Markers for undifferentiated carcinoma of the pancreas (Table 26.9)
10. Markers for hepatoid carcinoma of the pancreas (Table 26.10)
11. Markers for signet ring cell carcinoma of the pancreas (Table 26.11)
12. Markers for undifferentiated carcinoma with osteoclast-like giant cells (Table 26.12)
13. Markers for acinar cell carcinoma (Table 26.13)
14. Markers for pancreatic neuroendocrine neoplasm (Table 26.14)
15. Markers for solid and pseudopapillary neoplasm of the pancreas (Table 26.15)
16. Markers for pancreatoblastoma (Table 26.16)
17. Markers for serous cystadenoma (Table 26.17)
18. Markers for mucinous cystic neoplasm (Table 26.18)
19. Markers for intraductal papillary mucinous neoplasm (Table 26.19)
20. Markers for intraductal oncocytic papillary neoplasm (Table 26.20)
21. Markers for pancreatic intraepithelial neoplasia 1 and 2 (Table 26.21)
22. Markers for pancreatic intraepithelial neoplasia 3 (Table 26.22)
23. Markers for intraductal tubulopapillary neoplasm of the pancreas (Table 26.23)
24. Markers for chronic pancreatitis (Table 26.24)

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Differential Diagnosis

25. Ductal adenocarcinoma versus chronic pancreatitis (Table 26.25)
26. Ductal adenocarcinoma versus intrahepatic cholangiocarcinoma (Table 26.26)
27. Useful IHC markers in differentiating well-differentiated neuroendocrine tumors from pancreatic islets/islet cell hyperplasia in FNA samples and small tissue biopsy (Table 26.27)
28. Useful IHC markers in differentiating pancreatic neuroendocrine tumors from well-differentiated neuroendocrine tumors of other organs (Table 26.28)
29. Pancreatic neuroendocrine neoplasm versus solid pseudopapillary neoplasm (Table 26.29)
30. Pancreatic neuroendocrine neoplasm versus acinar cell carcinoma (Table 26.30)
31. Pancreatic neuroendocrine neoplasm versus pancreatoblastoma (Table 26.31)
32. Useful IHC markers in differentiating pancreatic neuroendocrine tumor grade 3 from poorly differentiated neuroendocrine carcinoma (Table 26.32)
33. Acinar cell carcinoma versus solid pseudopapillary neoplasm (Table 26.33)
34. Acinar cell carcinoma versus ductal adenocarcinoma (Table 26.34)
35. Acinar cell carcinoma versus pancreatoblastoma (Table 26.35)
36. Solid pseudopapillary neoplasm versus pancreatoblastoma (Table 26.36)
37. Markers for hematopoietic malignancies in the pancreas (Table 26.37)
38. Markers for differentiating pancreatic spindle cell neoplasms (Table 26.38)
39. Metastases in the pancreas (Table 26.39)
40. Prognostic markers for pancreatic adenocarcinoma (Table 26.40)
41. Predictive markers for pancreatic neuroendocrine neoplasm (Table 26.41)

Ampulla

42. Markers for normal ampulla of Vater (Table 26.42)
43. Markers for intestinal-type ampullary adenocarcinoma (Table 26.43)
44. Markers for pancreatobiliary-type ampullary adenocarcinoma (Table 26.44)
45. Intestinal-type ampullary adenocarcinoma versus pancreatobiliary-type (Table 26.45)
46. Ampullary adenocarcinoma versus pancreatic adenocarcinoma (Table 26.46)
47. What are the useful IHC markers in differentiating among ampullary normal/reactive mucosa from adenoma and adenocarcinoma (Table 26.47)

Note: *GML* Geisinger Medical Laboratories

[a]PAS for glycogen is usually positive, and mucicarmine for mucin is usually negative

Both pVHL and MUC6 tend to show diffuse and strong cytoplasmic and membranous staining; in contrast, both NSE and inhibin-alpha more frequently show focal and weak staining. One should be aware that a significant number of cases may be positive for MOC-31 and CA19-9, which are also positive in a high percentage of pancreatic mucin-producing neoplasms and ductal carcinomas

An example of serous cystadenoma diffusely and strongly positive for pVHL, MUC6, and inhibin-alpha is shown in Figs. 26.42, 26.43, 26.44, and 26.45

References: [1, 2, 75, 107]

Note for all tables "+"—usually >70% of cases are positive; "−"—<5% of cases are positive; "+ or −"—usually >50% of cases are positive; "− or +"—<50% of cases are positive: ND—no data available; V—variable.

Table 26.1 Summary of applications and limitations of useful markers

Antibodies	Staining pattern	Function	Key applications and pitfalls
Albumin	C	Produced by normal hepatocytes. A main protein of human blood plasma to regulate the oncotic pressure of blood. Transport substances such as fatty acid, hormones, bilirubin, metals, and ions	By RNA ISH. Positive in intrahepatic cholangiocarcinoma, hepatocellular carcinoma, some hepatoid carcinomas and a small percentage of ACCs. negative in DAC
AKR1B10	C	Aldo-keto reductase family 1B10	Positive in DAC and negative in chronic pancreatitis
Annexin A8	C	A member of the annexin family of calcium-regulated membrane binding proteins	Positive in DAC; usually negative or weakly positive in normal ducts
ATRX/DAXX	N	ATRX (alpha thalassemia/mental retardation syndrome X-linked) is transcriptional regulator, regulating nuclear matrix and chromatin association and involving in the gene regulation at interphase and chromosomal segregation in mitosis. DAXX (death domain-associated protein) is a transcriptional factor interacting with many other proteins such as Fas and protein C	Approximately 50% of pancreatic NETs lose one of these two markers; intact expression in NETs from other organs and poorly differentiated pancreatic neuroendocrine carcinomas

Table 26.1 (continued)

Antibodies	Staining pattern	Function	Key applications and pitfalls
Bcl10	C	B-cell lymphoma/leukemia 10 is a protein that, in humans, is encoded by the Bcl10 gene and contains a caspase recruitment domain (CARD), and has been shown to induce apoptosis and to activate NF-kappa B	Positive in ACC and negative in DAC and P-NETs
Ber-EP4 (EpCAM)	M + C	Epithelial adhesion molecule; expressed in various adenocarcinomas and normal glandular epithelium; usually negative in mesothelioma	Positive in DAC, also positive or weakly positive in normal ducts
Beta-catenin	N or M	A subunit of the cadherin protein complex. Has been implicated as an integral component in the Wnt signaling pathway. Normally expressed in membrane of epithelial cells and is important for the function of E-cadherin Mutation results in nuclear accumulation	N and M staining in >90% of SPN; N staining also reported in significant numbers of PB and some ACC; M staining in normal ducts, DAC, and P-NET
CA19-9	C	Also called carbohydrate antigen 19-9 or sialylated Lewis (a) antigen; overexpressed in adenocarcinoma of colon and pancreas	Positive in DAC; also positive or weakly positive in normal ducts
Calponin	C	A smooth muscle marker	Serous microcystic adenoma; a smooth muscle marker
CDX-2	N	A caudal-related homeobox transcription factor expressed in intestinal epithelium	Positive in IPMN, CC, some MCN, and about 10% of DAC
CEA	C	Carcinoembryonic antigen. Expressed in various adenocarcinomas and normal glandular epithelium	Positive in DAC; usually negative in normal ducts
CEL	C	Carboxyl ester lipase	Positive in ACC, similar to Bcl10
Chromogranin	C	Present in the cores of amine and peptide hormone and neurotransmitter dense-core secretory vesicles	Positive in P-NET; rarely positive in SPN and ACC
CK17	M + C	Epithelial marker	Positive in DAC and usually negative in normal/reactive ducts
CK19	M + C	Epithelial marker	Positive in DAC; increasing malignant potential when positive in P-NET
CK20	M + C	Epithelial marker	Positive in most CC and MCN and some DAC
CK7	M + C	Epithelial marker	Positive in DAC; usually negative in ACC and SPN
Claudin 18	C	Component of tight junctions	Positive in DAC; usually negative or weakly positive in normal ducts
Claudin 4	C	Component of tight junctions	Positive in DAC; usually weakly positive in normal ducts
Claudin 5	M	Component of tight junctions	Positive in SPN; negative in ACC, P-NET and PB
Claudin 7	M	Component of tight junctions	Positive in ACC, P-NET and PB; negative or focal cytoplasmic positivity in SPN
CRP	C	C-reactive protein. An acute-phase protein of hepatic origin. Its blood plasma level rise in response to inflammation and some cancers	Positive in intrahepatic cholangiocarcinoma and negative in DAC
DPC4/SMAD4	N	Tumor suppressor gene	Loss of expression in most invasive mucinous carcinomas, about 60% of DACs and up to 20% of ACCs; positive in normal ducts
E-cadherin	M	An adhesion molecule expressed in epithelial lineage	Loss of expression in SPN and undifferentiated carcinoma, some ACC and PB; M staining in others
Glypican-3	C	An established immunomarker for hepatocellular carcinoma and yolk sac tumor	Can be positive in ACC but not in DAC
IMP3 (KOC)	C	Also known as K homology domain-containing protein overexpressed in cancer (KOC). Encodes a protein with four K-homologous domains; regulation of tumor cell proliferation	Positive in DAC and P-NET; usually negative in normal/reactive ducts
INSM1	N	Insulinoma-associated protein 1; a transcription factor	A highly sensitive and specific marker for neuroendocrine tumor
Islet-1	N	The human insulin gene enhancer-binding protein islet-1 is a transcription factor involving in the differentiation of pancreatic endocrine cells	Positive in 90% of P-NETs, 89% of duodenal NETs, 100% rectal NETS, and 38% of colonic NETs

(continued)

Table 26.1 (continued)

Antibodies	Staining pattern	Function	Key applications and pitfalls
Maspin	C + N	Related to the serpin family of protease inhibitors; plays a role in tumor invasion and metastasis	Positive in DAC; usually negative in normal/reactive ducts and acini
Mesothelin	M + C	A 40 kD protein expressed in normal mesothelium and overexpressed in some cancers, such as mesothelioma, ovarian carcinoma, and DAC	Positive in DAC; usually negative in normal ducts and ACC
MOC-31	M	Epithelial specific antigen/Ep-CAM; expressed in various adenocarcinomas and normal glandular epithelium; usually negative in mesothelioma	Positive in DAC; also positive or weakly positive in normal ducts and acini
MUC1	C + M	Mucin 1; a membrane-associated glycoprotein expressed in various tumor types	Positive in DAC; negative or infrequently positive in CC and IPMN
MUC2	C + M	Mucin 2. A membrane-associated glycoprotein expressed in various tumor types	Positive in CC and frequently positive in IPMN but negative in DAC
MUC4	C + M	Mucin 4. A membrane-associated glycoprotein expressed in various tumor types	Positive in DAC and usually negative in normal/reactive ducts
MUC5AC	C + M	Mucin 5AC. A membrane-associated glycoprotein expressed in various tumor types	Positive in DAC, IPMN, and some MCN; usually negative in normal pancreatic ducts
MUC6	C	Mucin 6. A membrane-associated glycoprotein expressed in various tumor types	Positive in CC, SCA, some IPMN, and normal ducts; usually negative in DAC
OTP	N	Orthopedia homeobox; a transcription factor	Positive in over 80% of pulmonary carcinoids and pulmonary neuroendocrine cell hyperplasia; and negative in other non-pulmonary neuroendocrine tumors
p53	N	Tumor suppressor gene	Overexpression more frequently seen in DAC and neuroendocrine carcinoma but can be seen in reactive conditions
PAX6	N	Paired box 6 (PAX6) is a transcriptional factor presenting during embryonic development and plays a critical role in ocular development	Positive in approximately 60% of P-NETs and a small percentage of NETs from upper GI tract
PAX8	N	A member of the paired box (PAX) family of transcription factors, involved in development of thyroid follicular cells and expression of thyroid specific genes, and together with PAX2 involved in regulation of the organogenesis of the kidney and the Müllerian system	Polyclonal anti-PAX8 antibody positive in P-NET (non-specific cross reaction with PAX6); also positive in thyroid follicular cell tumors, renal cell carcinomas, ovarian carcinomas, endometrial adenocarcinomas, and thymic tumors
PDX1	N	Pancreatic duodenal homeobox 1 (PDX1) is a Hox-type transcription factor that regulates both exocrine and endocrine pancreatic differentiation and maintains the beta-cell function	Positive in P-NET, duodenal NET, and the vast majority of insulin and gastrin secreting NETs
PR		Progesterone receptor	Positive in approximately 60% of P-NET and 80% of SPN
PSCA	C	Prostate stem cell antigen. Glycosylphosphatidylinositol-anchored cell membrane glycoprotein; overexpressed in prostatic carcinoma, bladder and pancreatic carcinomas	Positive in DAC; may be positive in normal ducts and acini
pVHL	M + C	von Hippel–Lindau tumor suppressor gene	Positive in both normal ducts and part of acini; negative in DAC, ACC, mucinous tumors, and SPN
Rb	N	Retinoblastoma protein (Rb) is a tumor suppressor protein. One of the important functions of Rb is to prevent excessive cell growth by inhibiting cell cycle progression	Loss of expression in pancreatic neuroendocrine carcinoma and retained expression in well differentiated NETs
S100A6	N + C	Belongs to the family of S100 calcium-binding proteins	In most DAC and a small portion of reactive ducts
S100P	N + C	Belongs to the family of S100 calcium-binding proteins	In most DAC; usually negative or cytoplasmic staining in normal/reactive ducts and other entities (P-NET, ACC, and SPN)
SOX11	N	SRY-box 11 (SOX11) is a DNA-binding transcriptional factor involving in embryonic neurogenesis	Positive in SPN; also positive in mantle cell lymphoma
TAG 72 (B72.3)	M + C	Tumor-associated glycoprotein 72; expressed in various adenocarcinomas and normal glandular epithelium	Positive in DAC; also positive or weakly positive in normal ducts
Trypsin	C	An enzyme of pancreatic origin; catalyzes the hydrolysis of proteins to smaller polypeptide units	Positive in ACC and negative in SPN; background staining is a common problem

Table 26.1 (continued)

Antibodies	Staining pattern	Function	Key applications and pitfalls
TTMP	C	TPA-induced transmembrane protein that may serve a role in inhibiting pancreatic cancer cell proliferation in vitro through induction G0/G1 arrest	Loss of expression in pancreatic NETs
TFE3	N	Transcriptional factor E3 binds to MUE3-type E-box sequences in the promoter of TFE3 gene; efficient DNA-binding requires dimerization with itself or with another MiT/TFE family such as TFEB or MiTF	Positive in SPN; xp11 translocational renal cell carcinoma and alveolar soft part sarcoma, and a subset of epithelioid hemangioendothelioma

Note: *N* nuclear staining; *M* membranous staining; *C* cytoplasmic staining; *RNA ISH* ribonucleic acid in situ hybridization; *ACC* acinar cell carcinoma; *DAC* ductal adenocarcinoma; *NET* neuroendocrine tumor; *P-NET* pancreatic neuroendocrine tumor; *SPN* solid pseudopapillary neoplasm; *PB* pancreatoblastoma; *IPMN* intraductal papillary mucinous neoplasm; *CC* colloid carcinoma; *MCN* mucinous cystic neoplasm; *SCA* serous cystadenoma

References: [1–98]

Table 26.2 Summary of useful markers for common tumors

Antibodies	DAC	ACC	P-NET	SPN	PB
CK7	+	– or +	+ or –	–	+ or –
CK19	+	– or +	– or +	–	+ or –
Mesothelin	+	–	–	–	+ or –
S100P	+	–	–	–	+ or –
Maspin	+	–	–	–	+ or –
SMAD4/DPC4	Loss (50%)	Loss (20%)	No loss	No loss	No loss
Beta-catenin	M+	M or N+	M+	N and C	N and C+ or M+
E-cadherin	+	+	+	–	– or +
SOX11	–	–	–	+	–
Chromogranin	–	–	+	–	– or +
CD10	–	–	+	+	– or +
Bcl10	–	+	–	–	+ or –
IMP3	+	–	+ or –	–	– or +
Trypsin	–	+	–	–	+
Claudin 5	ND	–	–	M+	–
Claudin 7	ND	M+	M+	- or focally C+	M+

Note: *M* membranous staining; *N* nuclear staining; *C* cytoplasmic staining; *DAC* ductal adenocarcinoma; *ACC* acinar cell carcinoma; *P-NET* pancreatic neuroendocrine tumor; *SPN* solid pseudopapillary neoplasm; *PB* pancreatoblastoma; *SMAD4/DPC4* mothers against decapentaplegic homolog 4/deleted in pancreatic carcinoma, locus 4; *CD10* cluster of differentiation 10

The immunostaining results on PB are largely dependent upon the components in the tumor, such as acinar, squamous, ductal, or even endocrine component

References: [1–58, 64, 84, 87, 99]

Table 26.3 Markers for normal pancreatic ducts and acini

Antibodies	Pancreatic ducts	Pancreatic acini
ATRX/DAXX	+	+
Bcl10	–	+
CAM 5.2	+	+
CK7	+	+
CK20	–	–
CK19	Focally +	–
CK17	Usually –	–
S100P	– or C+	–
S100A6	– or weakly C+ or N+	–
pVHL	+	Focally +
mCEA	– or weakly + on luminal side	–
CA19-9	– or focally +	Weakly +
Trypsin	–	+
MOC-31	+	+
Ber-EP4	+	+
TAG 72 (B72.3)	–	–
IMP3 (KOC)	– or very focally +	–
Maspin	Usually –	–
Annexin A8	Weakly +	Weakly +
Claudin 4	Weakly +	Weakly +
Claudin 18	Focally +	+
PSCA	+	+
Mesothelin	Weakly +	–
MUC1	Weakly + on luminal side	–
MUC2	–	–
MUC4	–	–
MUC5AC	–	–
MUC6	+	–
DPC4/SMAD4	+	+
p53	– or very weakly +	–
CDX-2	– or +	– or +

Note: *C* cytoplasmic staining; *N* nuclear staining; *CAM 5.2* a low molecular weight cytokeratin; *mCEA* monoclonal carcinoembryonic antigen

The table is from Geisinger Medical Laboratories (GML) data based on 40 cases on tissue microarray (TMA) sections and routine sections; the stains were performed on both the Dako and Ventana Systems

Normal and reactive pancreatic ducts are usually negative for CK20, CK17, maspin, IMP3, S100P (nuclear staining), mCEA, trypsin, MUC2, MUC4, and MUC5AC

Approximately 10% of pancreatic ducts and acini are focally positive for CDX-2

Table 26.4 Markers for autoimmune pancreatitis

Antibodies	AIP-Type I	AIP-Type II
VHL	+	+
IgG	+	+
IgG4	+, >50 positive plasma cells/HPF	–
IL-8	Negative/low	+

Note: *AIP* autoimmune pancreatitis; *HPF* high-power field

In an autoimmune pancreatitis (AIP), type I, the infiltrating plasma cells are predominately immunoglobulin G4 (IgG4)-positive plasma cells. An immunostain for IgG4 may be helpful in diagnosing a difficult case. In general, in type I AIP, >50 IgG4-posiitve plasma cells per high-power field are usually observed. Reactive pancreatic ducts in an AIP are negative for S100P, maspin, and IMP3, and positive for VHL. It should be cautioned, however, that the presence of abundant IgG4-positive plasma cells does not preclude the diagnosis of pancreatic adenocarcinoma because in a small subset of pancreatic adenocarcinoma cases the cancer-adjacent tissue may show features of autoimmune pancreatitis. Additionally, expression of interleukin-8 (IL-8) was detected in the ductal epithelium, lymphocytes, and neutrophils in the majority of AIP type II cases but was almost entirely negative in type I AIP cases. Examples of type I AIP with many IgG4-positive plasma cells are shown in Fig. 26.1 and 26.2

Reference: [100]

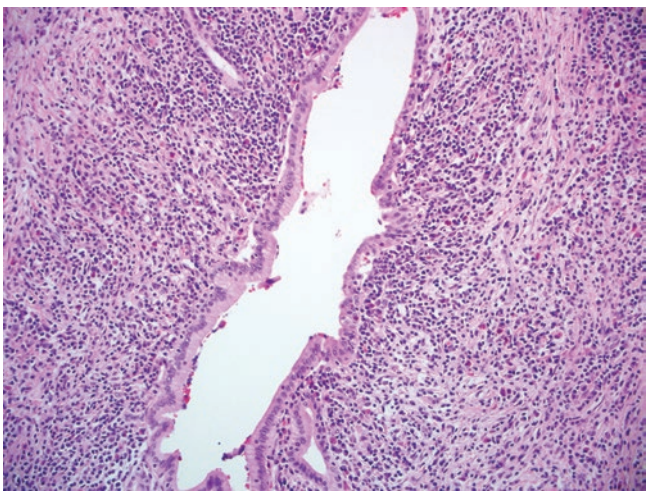


Fig. 26.1 Autoimmune pancreatitis on H&E stained slide

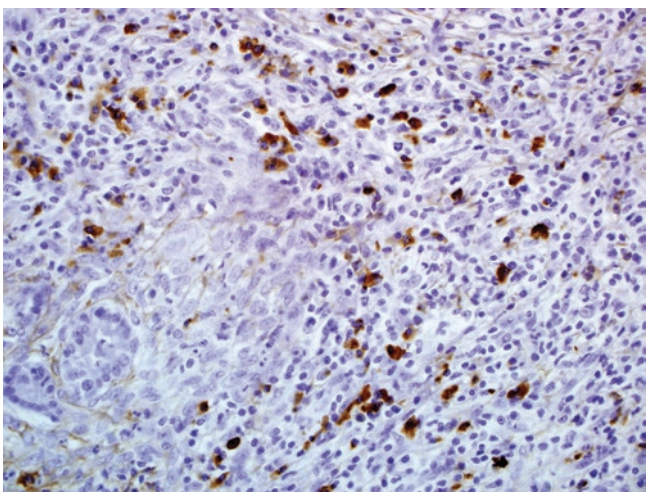


Fig. 26.2 Showing many IgG4-positive plasma cells

Table 26.5 Markers for ductal adenocarcinoma of the pancreas

Antibodies	Literature	GML data (N=70)
pVHL	–	100% negative
Maspin	+	100%
IMP3 (KOC)	+	90%
S100P	+	96%
SMAD4/DPC4	40–60% loss	51%
S100A6	+	96%
CAM 5.2	+	75%
CK7	+	96%
CK20	– or focally +	15%
CK17	+	60%
CK19	+	75%
Mesothelin	+	57%
mCEA	+	85%
MOC-31	+	97%
CA19-9	+	84%
Annexin A8[a]	+	ND
MUC1	+	95%
MUC2	–	4%
MUC4	+	50%
MUC5AC	+	67%
MUC6	– or +	17%
Claudin 4	+	94%
Claudin 18	+	80%
PSCA	+ or –	56%
p53	+ or –	60%
CDX-2	– or +	5%
Fascin[a]	+	85%
CDH17	+ or –	18% (17/95)
Annexin A10	+	ND
AKR1B10	+	ND
Plectin-1	+	ND

[a]Note: *GML* Geisinger Medical Laboratories; *CDH17* cadherin 17

Strong background staining is frequently seen in both Annexin A8 and fascin

GML data are based on TMA sections containing 50 cases and 20 cases of routine sections

Many markers have been reported in the literature. However, our experience shows that pVHL, maspin, S100P, and IMP3 are the best panel of markers in the distinction of DAC from normal/reactive pancreatic ducts. Representative cases for these four markers are shown in Figs. 26.3, 26.4, 26.5, 26.6, and 26.7. It should be noted that maspin is positive in both normal gastric mucosa and duodenal mucosa. Background staining for S100P sometimes is present. In this instance, S100A6 can be a good substitute, although weak nuclear and cytoplasmic staining for S100A6 can be seen in normal/reactive pancreatic ducts

Other markers including MUC1, MUC5AC, CA19-9, mesothelin, and p53 are shown in Figs. 26.8, 26.9, 26.10, 26.11, and 26.12

Normal pancreatic ducts and acini are usually positive for MOC-31, PSCA, claudin 4, and claudin 18, which limits the application of these markers in the distinction between DAC and reactive ducts. Strong background staining is frequently seen with annexin A8 and fascin; in addition, many stromal cells and endothelial cells are positive for fascin

Table 26.5 (continued)

Among the group of cytokeratins being tested (CK7, CK20, CK17, CK19, CAM 5.2), CK17 appears to be the only promising marker in differentiating adenocarcinoma from normal/reactive ducts since it usually lacks expression or is only very focally positive in normal ducts

Loss of DPC4/SMAD4 expression has been reported in approximately 60% of pancreatic DACs, which can be useful in differentiating pancreatic origin from other epithelial neoplasms, including an ovarian mucinous neoplasm. However, it is not entirely pancreas-specific because loss of expression has been reported in other tumors such as metastatic colonic adenocarcinomas. Examples of DAC positive and negative for DPC4/SMAD4 are shown in Figs. 26.13 and 26.14

References: [1–34, 37–39, 41–44, 58–62]

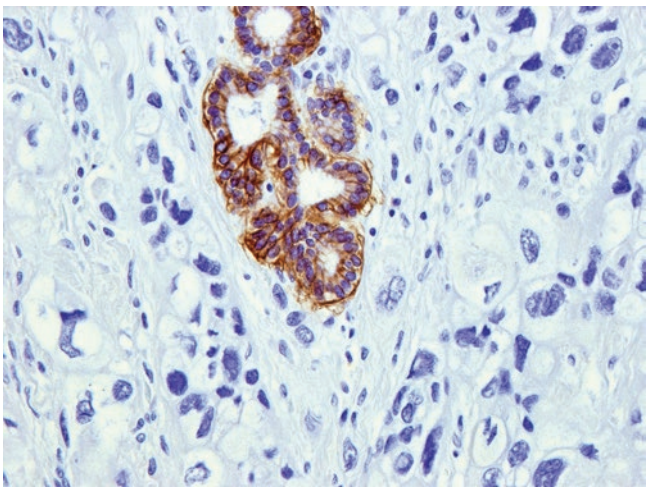


Fig. 26.3 Invasive ductal adenocarcinoma showing loss of expression of pVHL, and normal ducts show membranous and cytoplasmic staining

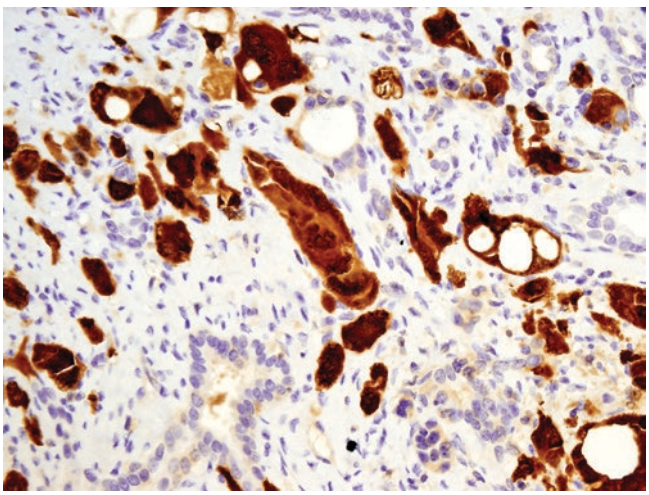


Fig. 26.4 High-grade adenocarcinoma showing nuclear and cytoplasmic staining for maspin

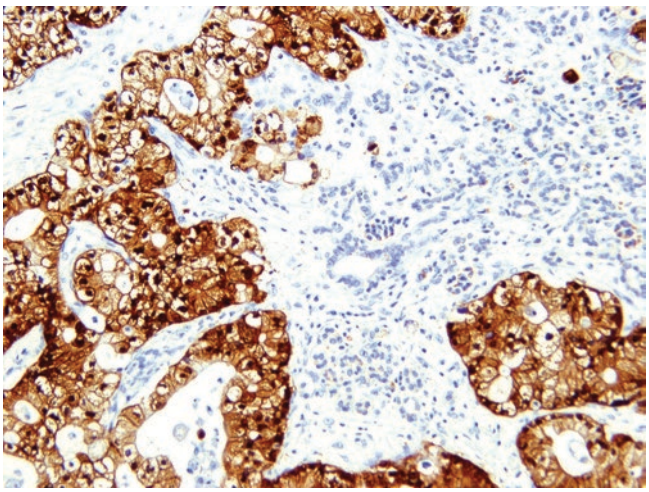


Fig. 26.5 Nuclear and cytoplasmic positivity of S100P in ductal adenocarcinoma, whereas the normal ducts are negative. Note that only nuclear staining or nuclear and cytoplasmic staining is regarded as positive

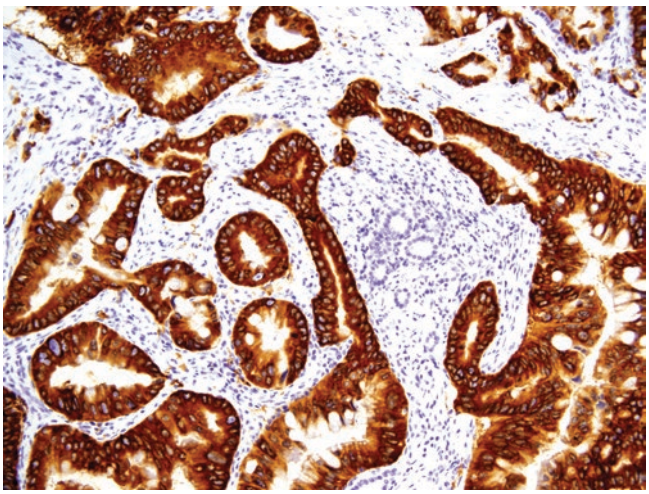


Fig. 26.6 Strong cytoplasmic staining for IMP3 seen in ductal adenocarcinoma

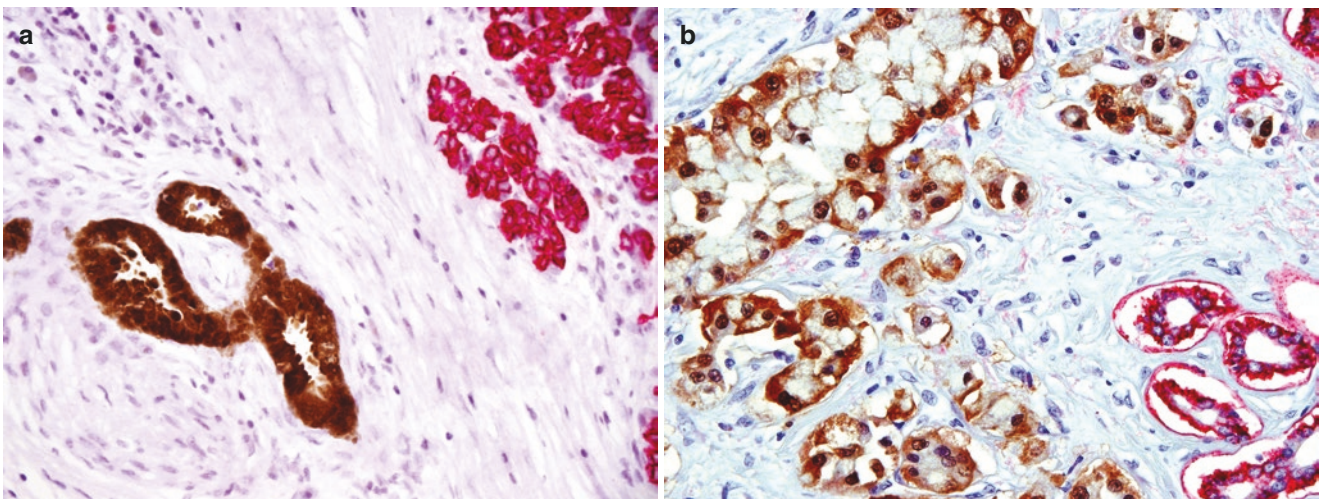


Fig. 26.7 Double-staining technique (**a**) showing carcinoma positive for maspin (brown) and normal ducts positive for pVHL (purple). Double-staining technique (**b**) showing carcinoma positive for S100P (brown) and normal ducts positive for pVHL (purple)

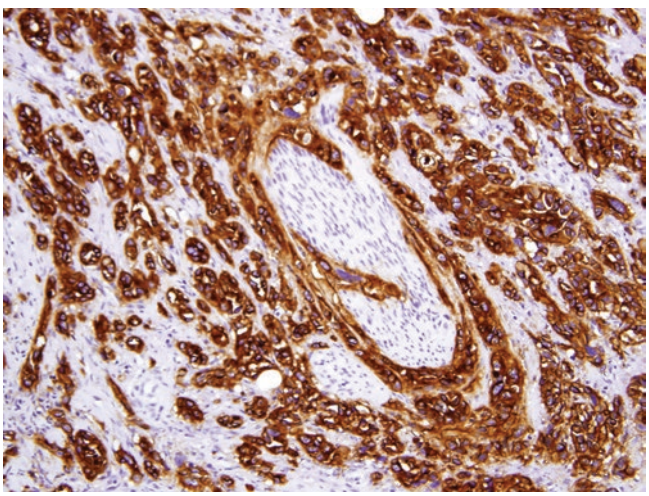


Fig. 26.8 Ductal adenocarcinoma showing strongly positive cytoplasmic staining for MUC1

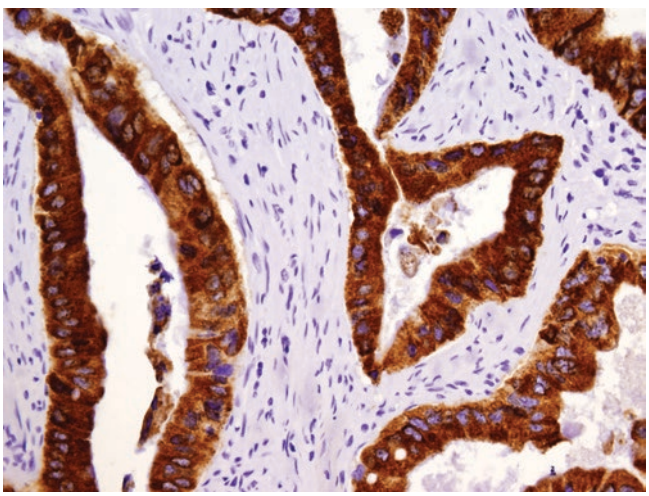


Fig. 26.9 MUC5AC

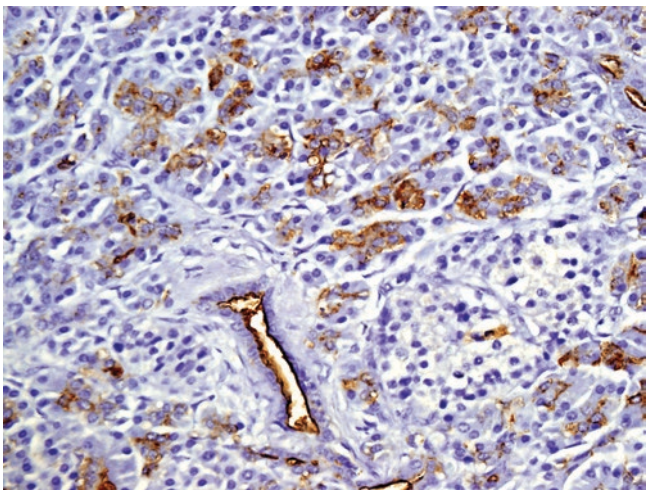


Fig. 26.10 CA19–9 is not a very useful marker since it is also expressed in normal ducts and acini as shown in this figure

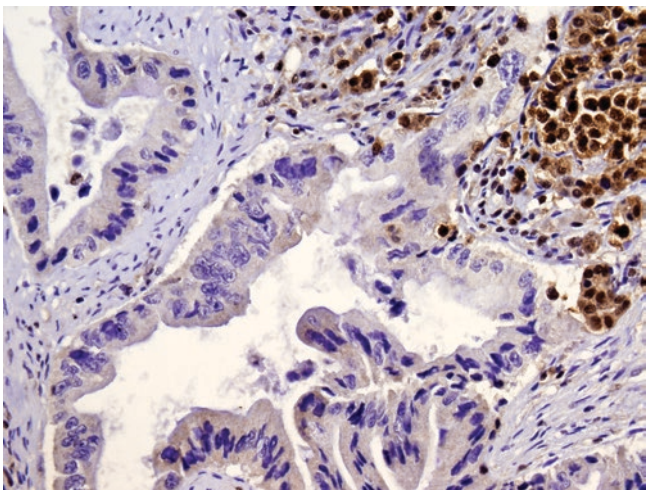


Fig. 26.13 Ductal adenocarcinoma showing loss of expression of DPC4/SMAD4 (Fig. 26.13)

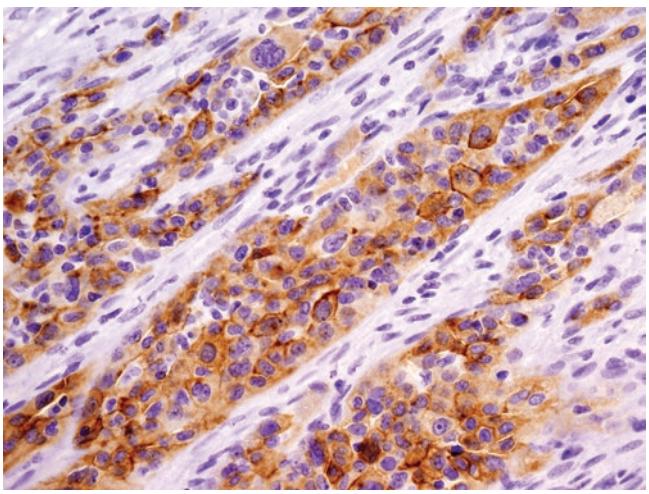


Fig. 26.11 Ductal adenocarcinoma showing membranous staining for mesothelin

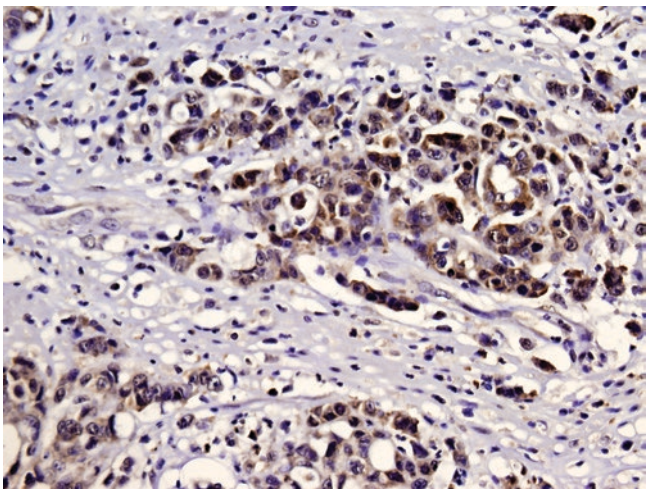


Fig. 26.14 Positive staining for DPC4/SMAD4 (Fig. 26.14). Note that inflammatory and stromal cells show nuclear positivity as an internal positive control

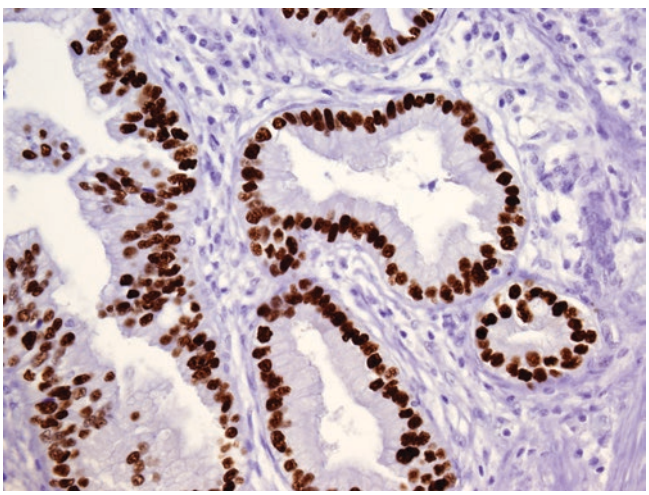


Fig. 26.12 Strong nuclear staining for p53 in ductal adenocarcinoma

Table 26.6 Markers for adenosquamous carcinoma of the pancreas

Antibodies	Literature
CK7	+
CK19	+
CEA	+
CA19-9	+
CK5/6	+
CK903	+
p63	+

Adenosquamous carcinoma can be seen in both the gallbladder and the ampulla

References: [1–3]

Table 26.7 Markers for colloid carcinoma of the pancreas

Antibodies	Literature
MUC1	– or +
MUC2	+
CDX-2	+
CK7	+
CK20	+ or –
CA19-9	+
CEA	+
pVHL	–
S100P	+
IMP3	+
Maspin	+

MUC2 and CDX-2 are usually positive in colloid carcinoma, which is useful in differentiating it from DAC. A case of colloid carcinoma with MUC2 and CDX-2 positivity is shown in Fig. 26.15

In contrast, DAC tends to be positive for MUC1 and negative for MUC2 and CDX-2. Other markers, including S100P, pVHL, IMP3, and maspin, have limited value in the distinction of these two entities

Colloid carcinoma (noncystic mucinous adenocarcinoma) can also be seen in the gallbladder and the ampulla

References: [1–3, 101]

Table 26.8 Markers for medullary carcinoma of the pancreas

Antibodies	Literature
CK7	+
CK20	–
CEA	+ or –
CA19-9	+ or –
MLH1	+ or –
MSH2	+ or –
MSH6	+ or –
PMS2	+ or –
E-cadherin	+

Note: *MLH* MutL homolog; *MSH* MutS protein homolog; *PMS2* postmeiotic segregation increased 2

Approximately 30% of reported cases demonstrate microsatellite instability (MSI) with loss of expression of either MLH1/PMS2 or MSH2/MSH6. Most reported cases show loss of expression of MLH1/PMS2. Kirsten rat sarcoma viral oncogene homolog (K-ras) mutation is an infrequent finding in medullary carcinoma compared to DAC. A representative case with loss of expression of MSH2 is shown in Figs. 26.16 and 26.17

References: [1, 2, 102–104]

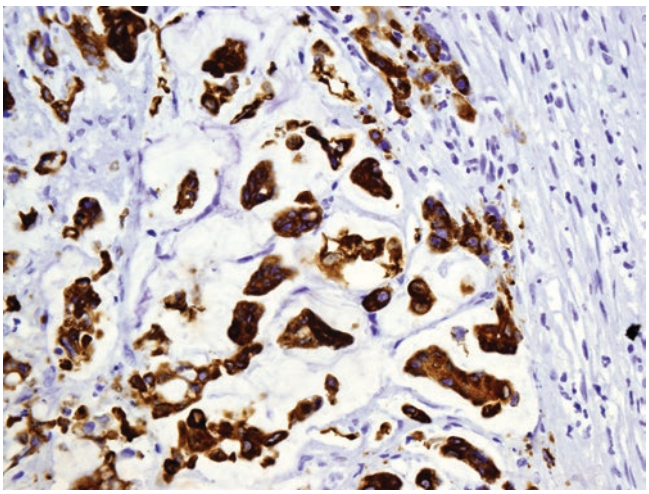


Fig. 26.15 MUC2 is frequently positive in colloid carcinoma and negative in ductal adenocarcinoma

Table 26.9 Markers for undifferentiated carcinoma of the pancreas

Antibody	Literature
CK7	+ or –
CK19	+ or –
CEA	+ or –
MUC1	+ or –
CA19-9	+ or –
Vimentin	+ or –
CK20	–
E-cadherin	–
MSI markers	+

Loss of expression of E-cadherin in this tumor is a characteristic finding. Immunostaining for the other markers can vary depending on the degree of differentiation of the tumor. The tumor is positive for mismatch repair (MMR) markers (MLH1, MSH2, MSH6, and PMS2), which can be useful in the distinction from medullary carcinoma of the pancreas since both tumors show poorly differentiated histomorphology

References: [1, 105]

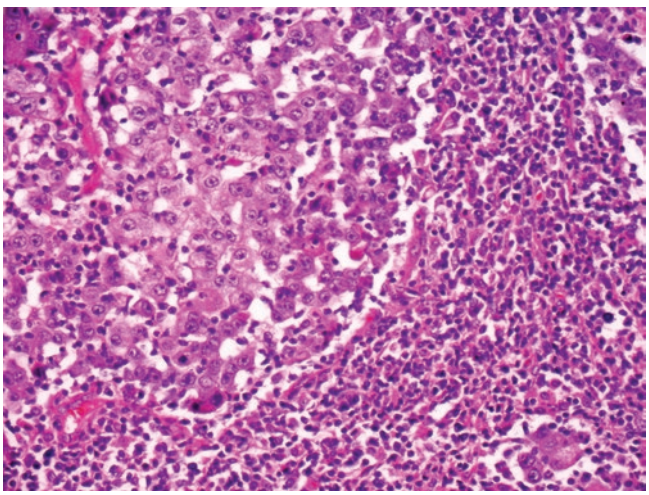


Fig. 26.16 Medullary carcinoma on H&E-stained slide (Fig. 26.16) with loss of expression of mismatch repair (MMR) protein MSH6 (Fig. 26.17). Note that the lymphoid cells serve as an internal positive control

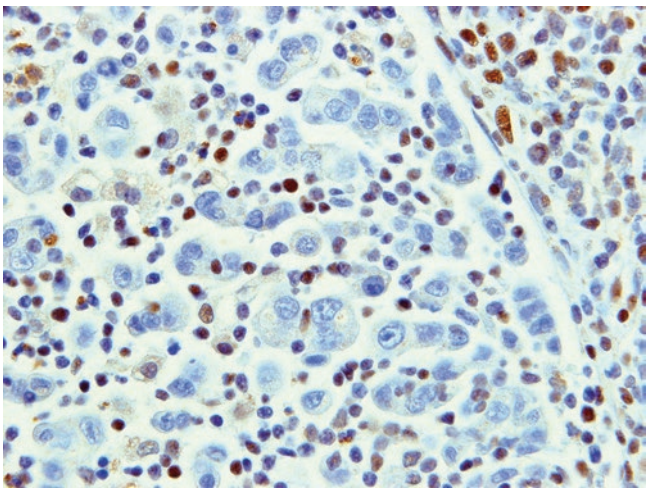


Fig. 26.17 Medullary carcinoma on H&E-stained slide (Fig. 26.16) with loss of expression of mismatch repair (MMR) protein MSH6 (Fig. 26.17). Note that the lymphoid cells serve as an internal positive control

Table 26.10 Markers for hepatoid carcinoma of the pancreas

Antibodies	Literature
Arginase 1	+
Hep Par 1	+
Glypican 3	+ or –
SALL4	+ or –
Polyclonal CEA	Canalicular +
CD10	Canalicular +
AFP	+ or –
CK7	+ or –
Bile stain[a]	+ or –

Note: [a]*Bile stain* a histochemical stain; *Hep Par 1* hepatocyte paraffin 1; *SALL4* sal-like protein 4; *AFP* alpha-fetoprotein

An example of hepatoid carcinoma of the pancreas is shown in Figs. 26.18 (hematoxylin and eosin [H&E] stain) and Fig. 26.19 (arginase 1 immunostaining). Hepatoid carcinoma can also be seen in the gallbladder and the ampulla

References: [1, 106]

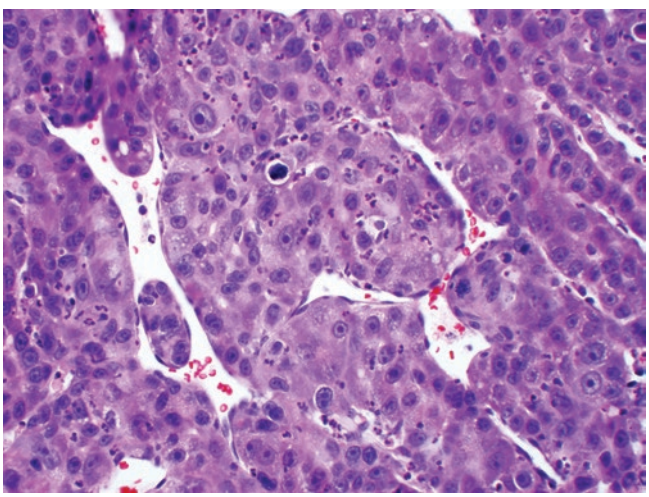


Fig. 26.18 Hepatoid carcinoma of the pancreas on H&E-stained slide (Fig. 26.18), which shows positive for arginase-1 (Fig. 26.19)

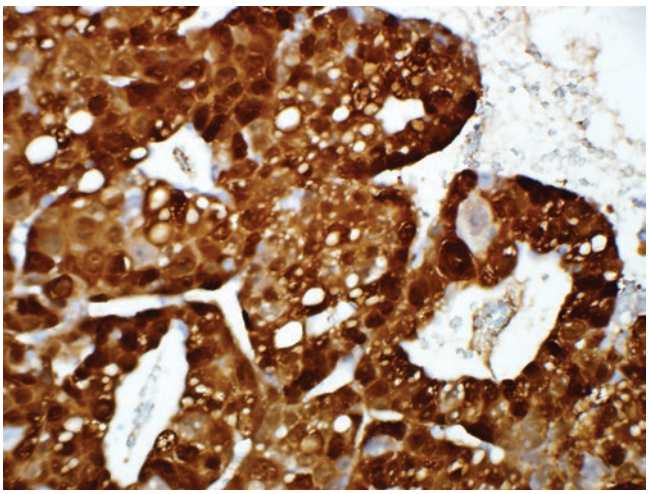


Fig. 26.19 Hepatoid carcinoma of the pancreas on H&E-stained slide (Fig. 26.18), which shows positive for arginase-1 (Fig. 26.19)

Table 26.11 Markers for signet ring cell carcinoma of the pancreas

Antibodies	Literature
CK7	+
CK20	+ or –
CEA	+
MOC-31	+
CDX-2	+ or –
CA19-9	+ or –

Signet ring cell carcinoma can also be seen in the gallbladder and the ampulla

Reference: [1]

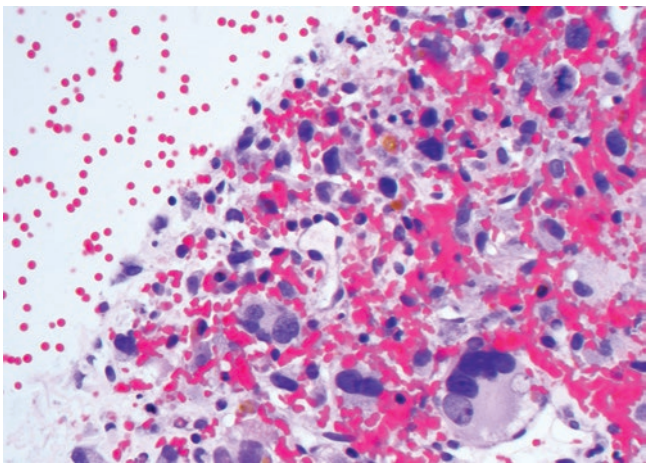
Table 26.12 Markers for undifferentiated carcinoma with osteoclast-like giant cells

Antibodies	Malignant mononuclear cells	Benign giant cells
AE1/AE3	+ or –	–
CK7	+ or –	–
CK20	–	–
Vimentin	+	+
CD68	–	+
IMP3 (KOC)	+	–

Note: *AE1/AE3* cytokeratin AE1/AE3, an epithelial marker

An example of undifferentiated carcinoma with osteoclast-like giant cells is shown in Figs. 26.20, 26.21, 26.22, and 26.23: H&E stained section (Fig. 26.20), multinucleated giant cells positive for CD68 (Fig. 26.21), both histiocytes and tumor cells positive for vimentin (Fig. 26.22), and tumor cells positive for IMP3 (Fig. 26.23)

References: [1–3]



Figs. 26.20 Undifferentiated carcinoma with osteoclast-like giant cells is shown in Fig. 26.20 on H&E-stained section. Multinucleated giant cells are positive for CD68 (Fig. 26.21), both histiocytes and tumor cells are positive for vimentin (Fig. 26.22), and tumor cells are positive for IMP3 (Fig. 26.23)

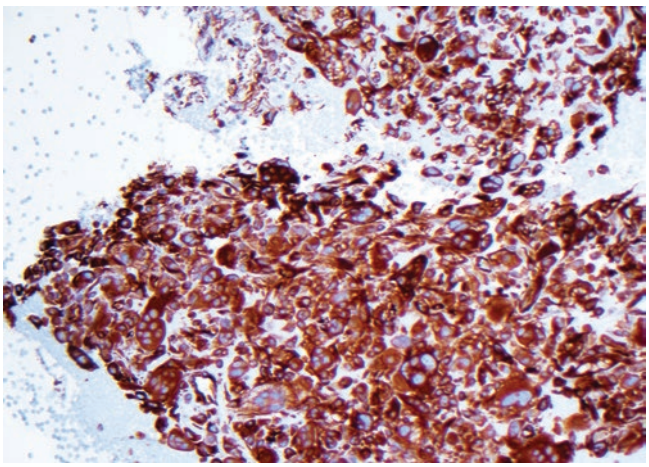


Fig. 26.22 Undifferentiated carcinoma with osteoclast-like giant cells is shown in Fig. 26.20 on H&E-stained section. Multinucleated giant cells are positive for CD68 (Fig. 26.21), both histiocytes and tumor cells are positive for vimentin (Fig. 26.22), and tumor cells are positive for IMP3 (Fig. 26.23)

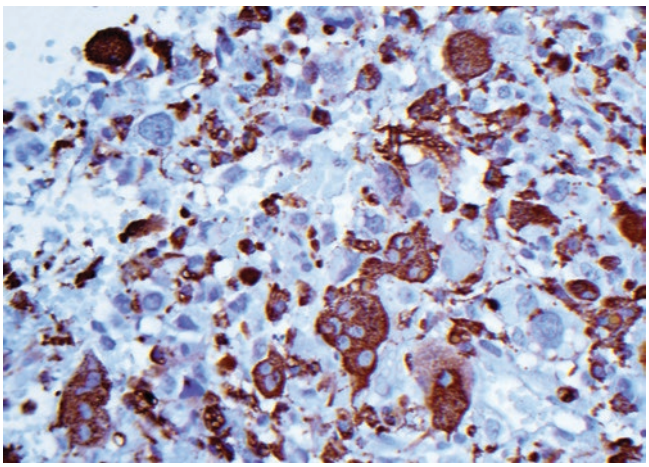


Fig. 26.21 Undifferentiated carcinoma with osteoclast-like giant cells is shown in Fig. 26.20 on H&E-stained section. Multinucleated giant cells are positive for CD68 (Fig. 26.21), both histiocytes and tumor cells are positive for vimentin (Fig. 26.22), and tumor cells are positive for IMP3 (Fig. 26.23)

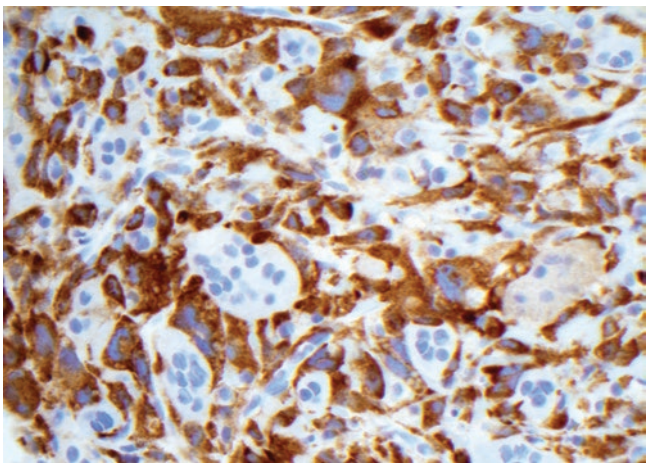


Fig. 26.23 Undifferentiated carcinoma with osteoclast-like giant cells is shown in Fig. 26.20 on H&E-stained section. Multinucleated giant cells are positive for CD68 (Fig. 26.21), both histiocytes and tumor cells are positive for vimentin (Fig. 26.22), and tumor cells are positive for IMP3 (Fig. 26.23)

Table 26.13 Markers for acinar cell carcinoma

Antibodies	Literature
Bcl10	+
CEL	+
CK7	- or focally +
Trypsin	+
Glypican-3	+ or –
Chromogranin	- or scattered positive cells
SMAD4/DPC4	Loss expression in 20% cases
AE1/AE3	+
CK19	– or focally +
CK20	–
CEA	+ or –
MOC-31	+ or –
PDX-1	+ (90% cases)
Beta-catenin	M and N+ (about 20%)
p53	+ in 30% cases
S100P	–
pVHL	–
Vimentin	+ or –

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

Approximately 20% of ACCs may show both nuclear and membranous positivity for beta-catenin. Loss of expression of SMAD4/DPC4 has been reported in approximately 20% of cases. A histochemical stain of periodic acid–Schiff-diastase (PAS-D) is usually positive in ACC. Trypsin is usually positive but may give a strong background staining

Chromogranin and synaptophysin are usually negative or show only scattered positivity in endocrine cells/acinar tumor cells. When >25% of tumor cells are positive for neuroendocrine markers, the tumor should be regarded as mixed acinar and neuroendocrine carcinoma. Similarly, if >25% of ductal adenocarcinoma component is present, the tumor should be regarded as mixed acinar–ductal carcinoma

In our experience and in the literature, Bcl10 has been demonstrated to be the most sensitive and specific marker to confirm the diagnosis of ACC. Recent molecular studies revealed that up to 20% of ACCs may show loss of expression of SMAD4/DPC4. An example of ACC with solid and trabecular growth pattern is shown in Fig. 26.24. The tumor cells are diffusely positive for Bcl10 (Fig. 26.25), loss of SMAD4 expression (Fig. 26.26), and a high Ki-67 proliferative index (Fig. 26.27). The tumor cells are negative for beta-catenin, vimentin, chromogranin, synaptophysin, maspin, and S100P and only very focally positive for CK7

References: [1, 5, 7, 25–28, 33, 46, 47, 55, 63–65, 84–86]

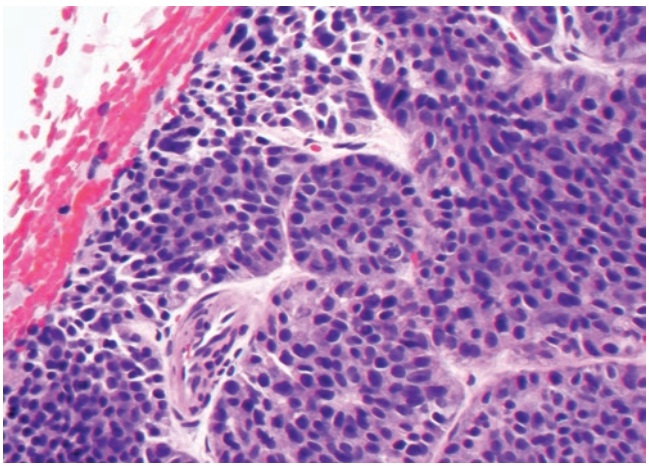


Fig. 26.24 Acinar cell carcinoma with solid and trabecular growth pattern is shown in Fig. 26.24; and the tumor cells are diffusely positive for Bcl10 (Fig. 26.25), loss of SMAD4 expression (Fig. 26.26), and a high Ki-67 proliferative index (Fig. 26.27)

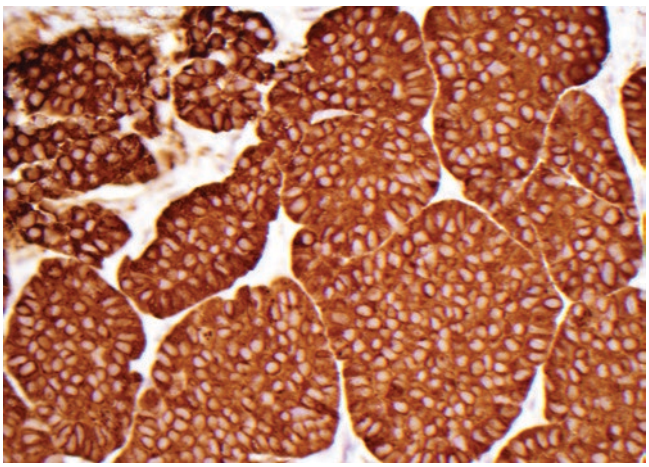


Fig. 26.25 Acinar cell carcinoma with solid and trabecular growth pattern is shown in Fig. 26.24; and the tumor cells are diffusely positive for Bcl10 (Fig. 26.25), loss of SMAD4 expression (Fig. 26.26), and a high Ki-67 proliferative index (Fig. 26.27)

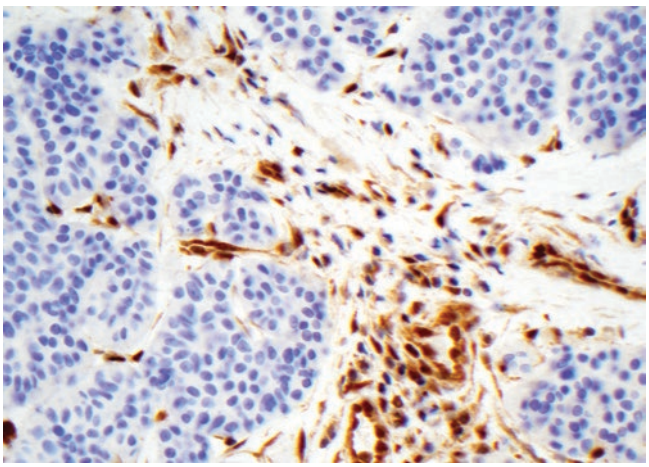


Fig. 26.26 Acinar cell carcinoma with solid and trabecular growth pattern is shown in Fig. 26.24; and the tumor cells are diffusely positive for Bcl10 (Fig. 26.25), loss of SMAD4 expression (Fig. 26.26), and a high Ki-67 proliferative index (Fig. 26.27)

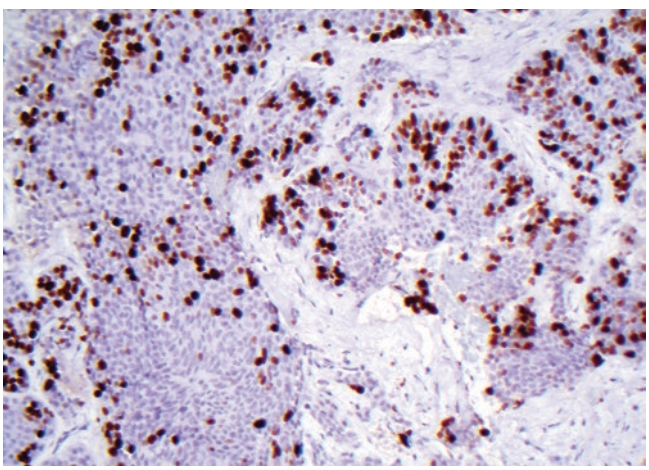


Fig. 26.27 Acinar cell carcinoma with solid and trabecular growth pattern is shown in Fig. 26.24; and the tumor cells are diffusely positive for Bcl10 (Fig. 26.25), loss of SMAD4 expression (Fig. 26.26), and a high Ki-67 proliferative index (Fig. 26.27)

Table 26.14 Markers for pancreatic neuroendocrine neoplasm

Antibodies	Literature	GML data
Synaptophysin	+	100% (16/16)
Chromogranin	+	100% (16/16)
INSM1	+	100% (35/35)
Beta-catenin	M+	100% (16/16)
CD56	+	44% (7/16)
PR	– or +	56% (9/16)
ER	–	0 (0/16)
PAX6	+ or –	60% (21/35)
ATRX/DAXX	Loss in 50% cases	45% (14/35)
TTMP	– (Loss)	ND
PAX8	+ or –	47% (15/32)
PDX1	+ or –	ND
Islet-1	+ or –	ND
CAM 5.2	+	100% (16/16)
CK7	+ or –	0 (0/16)
CK20	–	6% (1/16)
Vimentin	–	38% (6/16)
CDX-2	V	6% (1/16)
Insulin	V	13% (2/16)
CK19	+ or –	25% (4/16)

Note: *GML* Geisinger Medical Laboratories; *M* membranous staining; *ER* estrogen receptor

The 2017 WHO classification of P-NETs was based on counting mitoses or Ki-67 proliferative index. P-NETs are divided into (1) P-NET, grade 1 (0–1 mitosis/10 high power field [HPF] or <2% Ki-67 index); (2) P-NET, grade 2 (2–20 mitoses/10 HPF or 3–20% Ki-67 index); (3) P-NET, grade 3 (>20 mitoses/10HPF or >20% Ki-67 index; and (4) pancreatic neuroendocrine carcinoma (large cell neuroendocrine carcinoma or small cell carcinoma; >20 mitoses/10 HPF or >20% Ki-67 index)

Our study of a small number of cases ($N = 16$) showed that one case was positive for beta-catenin with both nuclear and cytoplasmic staining. CK7 and CK20 were negative in all cases except one case with focal (5%) CK20 immunoreactivity. Nine of 16 cases were diffusely and strongly positive for PR. Our data demonstrated that loss of ATRX or DAXX was seen in 45% of P-NETs, and PAX6 positivity was present in 60% of P-NETs. INSM1 is a recently described neuroendocrine marker with nuclear staining that has been shown to be positive in 100% of P-NETs

A representative case with vacuolated cytoplasm (lipid-rich pancreatic neuroendocrine neoplasm) is shown in Figs. 26.28 and 26.29, with positive staining for chromogranin, synaptophysin, and CD56. CD56 is the most sensitive but relatively nonspecific marker for neuroendocrine differentiation; however, in our study only 44% of cases were positive for CD56. An example of pancreatic neuroendocrine neoplasm with positive staining for PR, PAX8 (polyclonal antibody), and islet-1 is shown in Figs. 26.30, 26.31, 26.32, and 26.33. An example of P-NET with positive staining for PAX6, loss of expression of ATRX, and intact expression of DAXX is shown in Figs. 26.34, 26.35, 26.36, and 26.37 CK19 positivity in P-NET may be associated with a more aggressive clinical behavior

References: [1, 4, 5, 66–73, 96, 98]

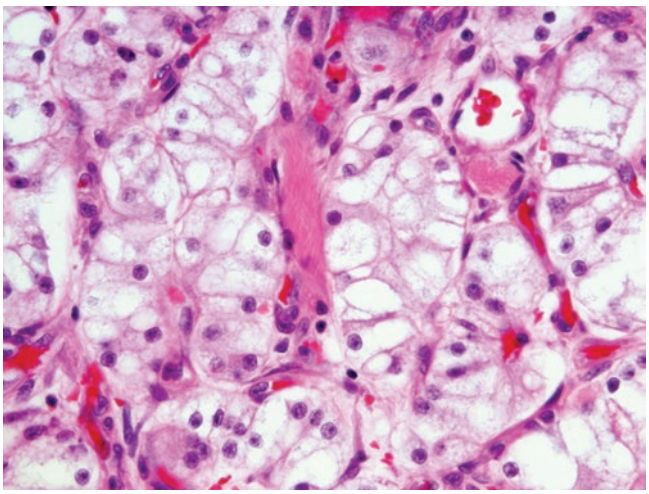


Fig. 26.28 Lipid-rich variant of pancreatic neuroendocrine tumor (Fig. 26.28) positive for chromogranin (Fig. 26.29)

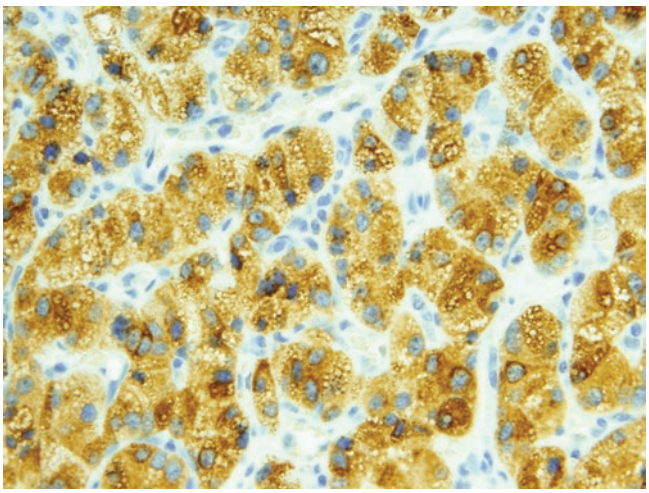


Fig. 26.29 Lipid-rich variant of pancreatic neuroendocrine tumor (Fig. 26.28) positive for chromogranin (Fig. 26.29)

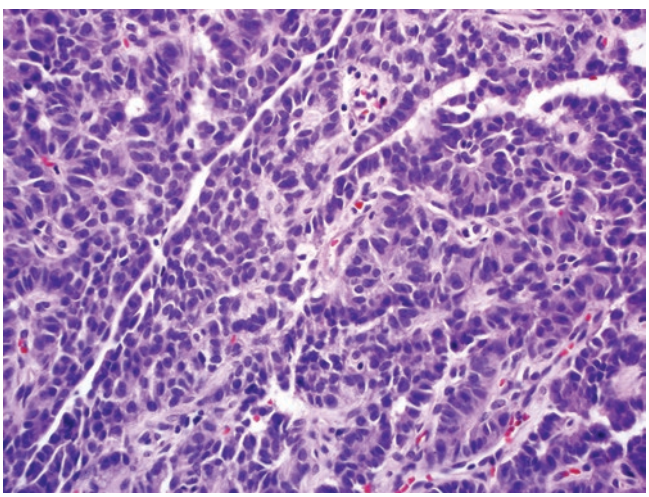


Fig. 26.30 Pancreatic neuroendocrine tumor (Fig. 26.30) with positive staining for PR (Fig. 26.31), PAX8 (Fig. 26.32), and islet-1 (Fig. 26.33)

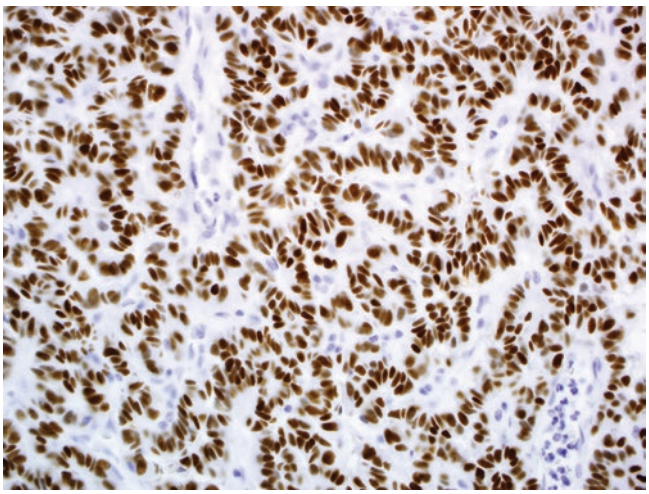


Fig. 26.31 Pancreatic neuroendocrine tumor (Fig. 26.30) with positive staining for PR (Fig. 26.31), PAX8 (Fig. 26.32), and islet-1 (Fig. 26.33)

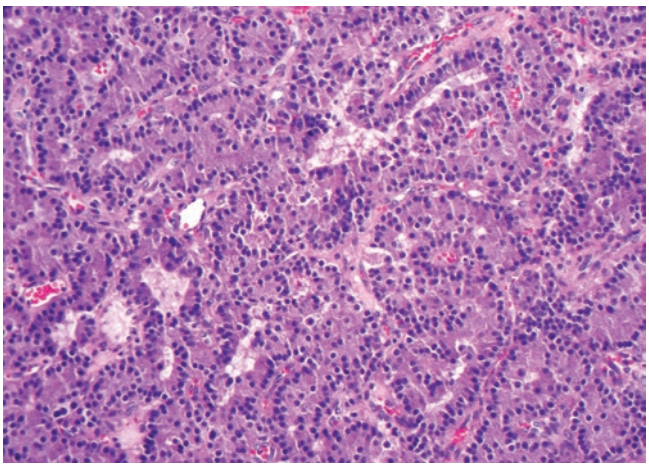


Fig. 26.34 P-NET (Fig. 26.34) with positive for PAX6 (Fig. 26.35), loss of expression of ATRX (Fig. 26.36), and intact expression of DAXX (Fig. 26.37)

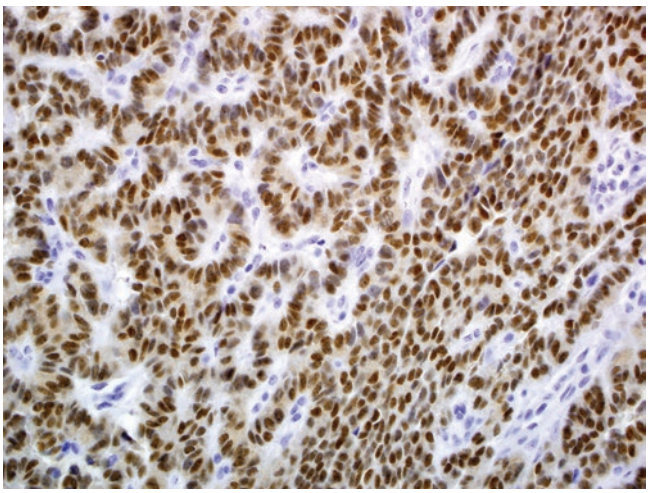


Fig. 26.32 Pancreatic neuroendocrine tumor (Fig. 26.30) with positive staining for PR (Fig. 26.31), PAX8 (Fig. 26.32), and islet-1 (Fig. 26.33)

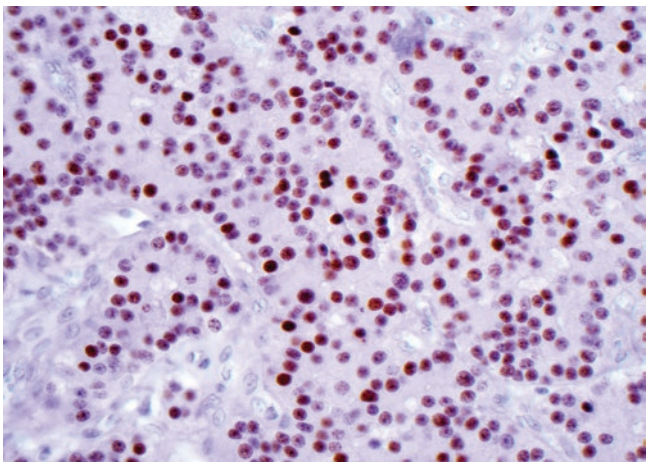


Fig. 26.35 P-NET (Fig. 26.34) with positive for PAX6 (Fig. 26.35), loss of expression of ATRX (Fig. 26.36), and intact expression of DAXX (Fig. 26.37)

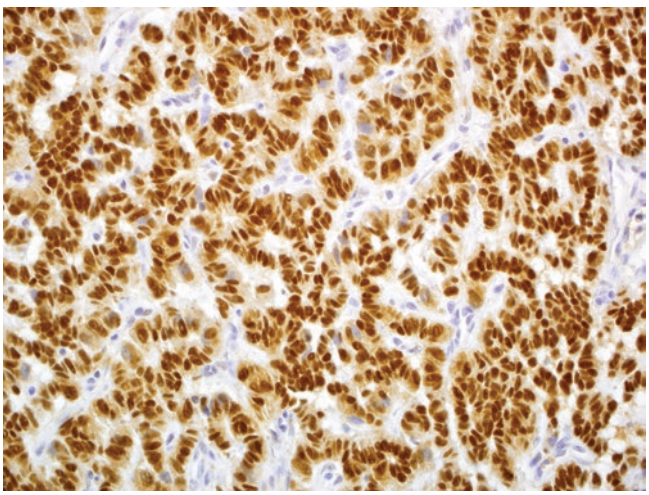


Fig. 26.33 Pancreatic neuroendocrine tumor (Fig. 26.30) with positive staining for PR (Fig. 26.31), PAX8 (Fig. 26.32), and islet-1 (Fig. 26.33)

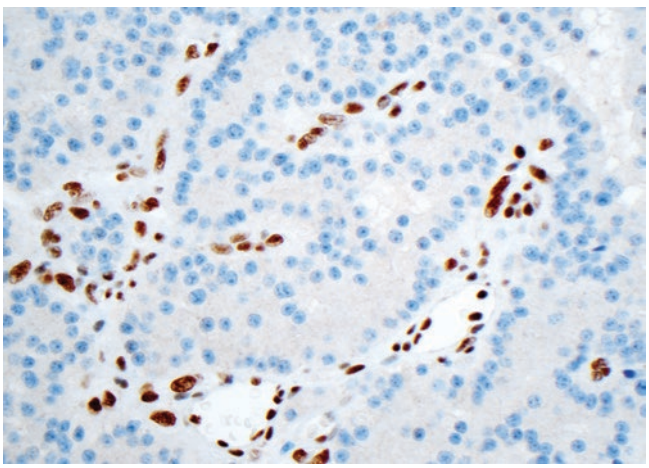


Fig. 26.36 P-NET (Fig. 26.34) with positive for PAX6 (Fig. 26.35), loss of expression of ATRX (Fig. 26.36), and intact expression of DAXX (Fig. 26.37)

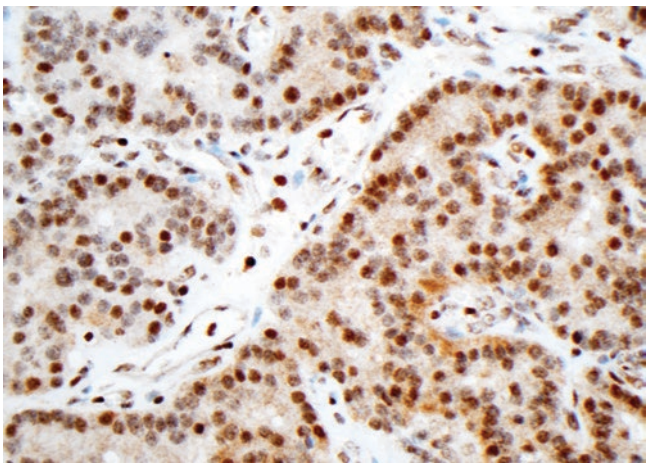


Fig. 26.37 P-NET (Fig. 26.34) with positive for PAX6 (Fig. 26.35), loss of expression of ATRX (Fig. 26.36), and intact expression of DAXX (Fig. 26.37)

Table 26.15 Markers for solid pseudopapillary neoplasm of the pancreas

Antibodies	Literature
Beta-catenin	N and M+
E-cadherin	–/loss
Chromogranin	–
CD10	+
SOX11	+
TFE3	+
AE1/AE3	Focally + or -
CK7	–
Vimentin	+
Trypsin	–
Alpha-1 antitrypsin	+
CD56	+
NSE	+ or –
Synaptophysin	– or +
Claudin 5	M +
Claudin 7	– or focally C +
PR	+ or –
ER	–
CD99	+ (cytoplasmic dot)

Note: *N* nuclear staining, *M* membranous staining; *C* cytoplasmic staining; *NSE* neuron-specific enolase

Beta-catenin, E-cadherin, CD10, and chromogranin are the effective panel of antibodies to confirm the diagnosis of solid pseudopapillary neoplasm of the pancreas. Over 90% of SPNs show both nuclear and membranous staining for beta-catenin. A recent study demonstrated that the majority of SPNs were positive for both TFE3 and SOX11. A representative case is shown in Figs. 26.38, 26.39, 26.40, and 26.41

References: [1, 5, 37, 45–52, 74, 87]

Table 26.16 Markers for pancreatoblastoma

Antibodies	Acinar	Endocrine	Ductal
CK7	+	–	+
CK19	+	–	+
CAM 5.2	+	+	+
Trypsin	+	–	–
Bcl10	+	–	–
NSE	–	+	–
Synaptophysin	–	+	–
Chromogranin	–	+	–
CEA	–	–	+
TAG 72 (B72.3)	–	–	+

Note: Most pancreatoblastomas consist of both acinar and squamoid components; some may also contain endocrine and ductal components. The immunostaining results are largely dependent upon the components in the tumor. Nuclear staining of beta-catenin has been reported in a significant percentage of cases, which is similar to the findings in SPN and ACC. The "squamoid component" usually lacks the typical squamous phenotype, that is, positive for CK5/6, p40, CK14, and CK17. Instead, it is usually positive for epithelial membrane antigen (EMA), CK8, CK18, and CK19 but negative for CK7

AFP may be positive in some cases, which is in keeping with the primitive nature of this neoplasm

References: [1, 5, 7, 53, 54, 56, 57]

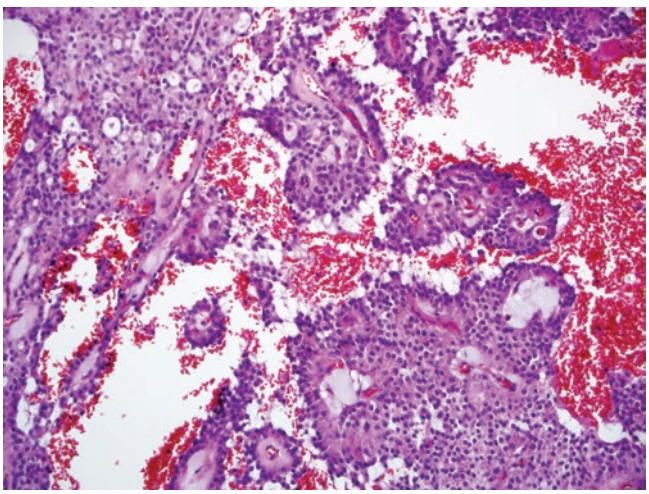


Fig. 26.38 Solid pseudopapillary neoplasm (Fig. 26.38) showing nuclear and cytoplasmic staining for beta-catenin (Fig. 26.39), loss of E-cadherin (Fig. 26.40), and positive staining for CD10 (Fig. 26.41). Note that normal pancreatic ducts show membranous staining for beta-cadherin and E-cadherin

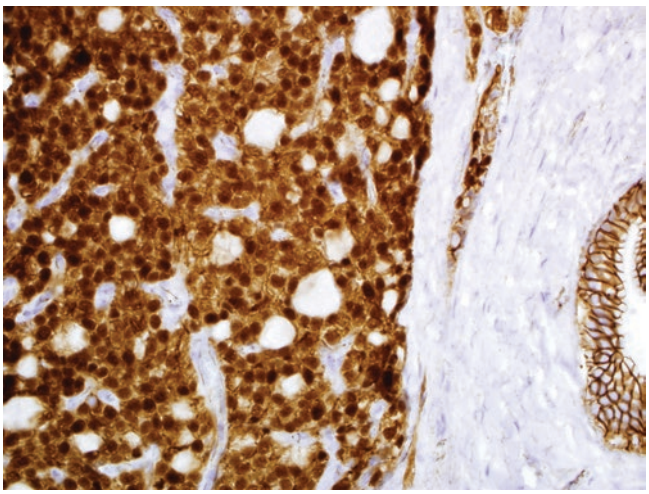


Fig. 26.39 Solid pseudopapillary neoplasm (Fig. 26.38) showing nuclear and cytoplasmic staining for beta-catenin (Fig. 26.39), loss of E-cadherin (Fig. 26.40), and positive staining for CD10 (Fig. 26.41). Note that normal pancreatic ducts show membranous staining for beta-cadherin and E-cadherin

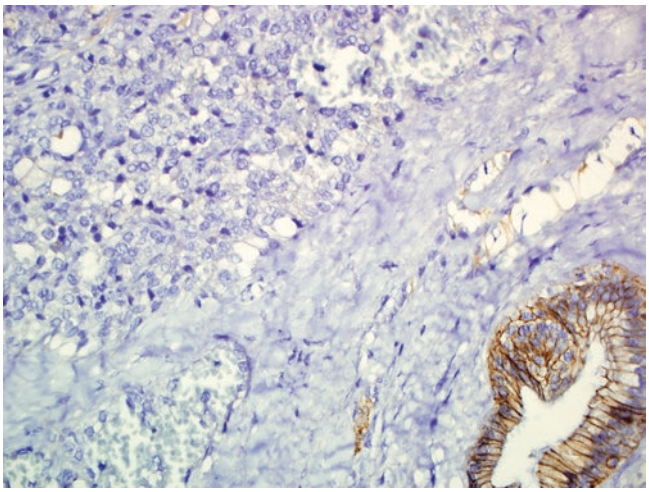


Fig. 26.40 Solid pseudopapillary neoplasm (Fig. 26.38) showing nuclear and cytoplasmic staining for beta-catenin (Fig. 26.39), loss of E-cadherin (Fig. 26.40), and positive staining for CD10 (Fig. 26.41). Note that normal pancreatic ducts show membranous staining for beta-cadherin and E-cadherin

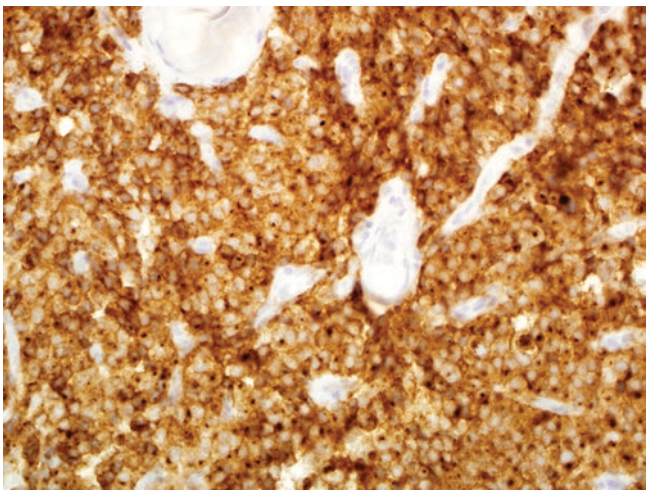


Fig. 26.41 Solid pseudopapillary neoplasm (Fig. 26.38) showing nuclear and cytoplasmic staining for beta-catenin (Fig. 26.39), loss of E-cadherin (Fig. 26.40), and positive staining for CD10 (Fig. 26.41). Note that normal pancreatic ducts show membranous staining for beta-cadherin and E-cadherin

Table 26.17 Markers for serous cystadenoma

Antibodies	Literature	GML data (N=13)
pVHL	+	100% (13/13)
MUC6	+ or –	92% (12/13)
Inhibin-alpha	+	92% (12/13)
CK7	+	100% (13/13)
CK20	–	0 (0/13)
S100P	–	0 (0/13)
Synaptophysin	+ or –	0 (0/13)
CD56	+ or –	ND
Chromogranin	–	0 (0/13)
TAG 72 (B72.3)	–	0 (0/13)
CEA	–	0 (0/13)
CA19-9	– or +	31% (4/13)
MOC-31	–	70% (9/13)
PAS[a]	+	100% (13/13)
Mucicarmine[a]	–	0 (0/13)

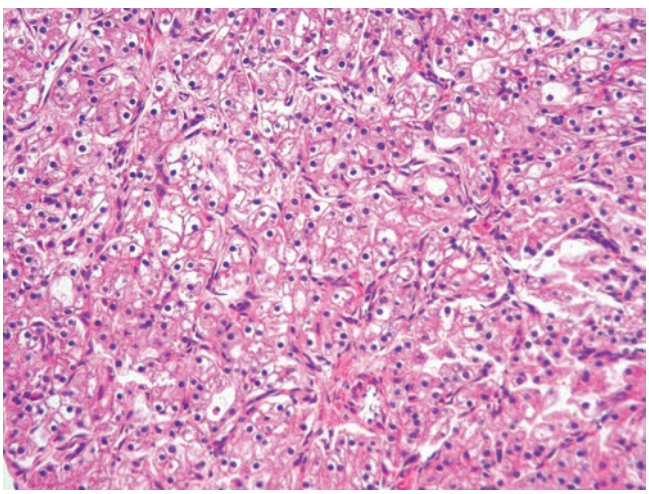


Fig. 26.42 Solid variant of serous microcystic adenoma (Fig. 26.42) positive for pVHL (Fig. 26.43), MUC6 (Fig. 26.44), and inhibin-alpha (Fig. 26.45)

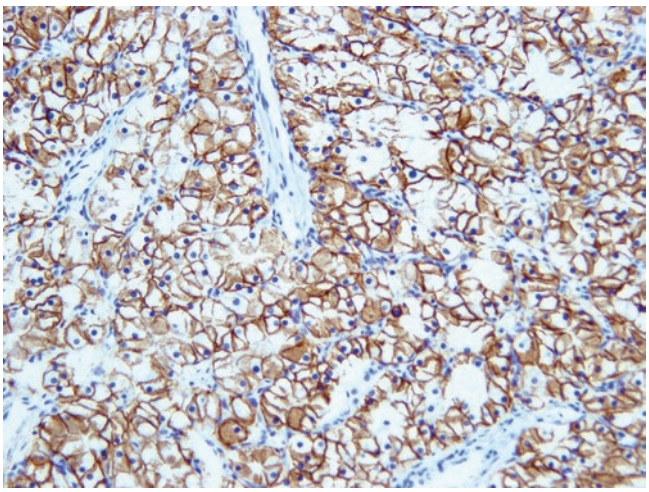


Fig. 26.43 Solid variant of serous microcystic adenoma (Fig. 26.42) positive for pVHL (Fig. 26.43), MUC6 (Fig. 26.44), and inhibin-alpha (Fig. 26.45)

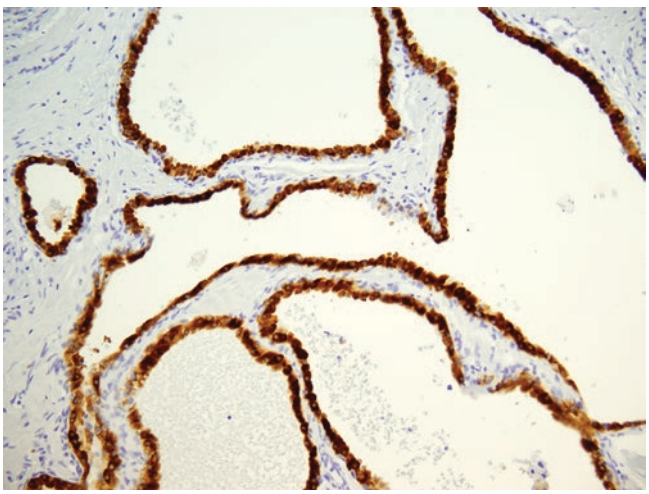


Fig. 26.44 Solid variant of serous microcystic adenoma (Fig. 26.42) positive for pVHL (Fig. 26.43), MUC6 (Fig. 26.44), and inhibin-alpha (Fig. 26.45)

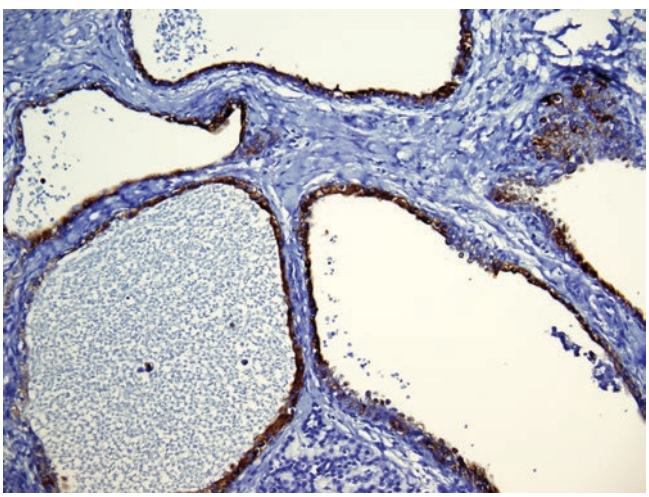


Fig. 26.45 Solid variant of serous microcystic adenoma (Fig. 26.42) positive for pVHL (Fig. 26.43), MUC6 (Fig. 26.44), and inhibin-alpha (Fig. 26.45)

Table 26.18 Markers for mucinous cystic neoplasm

Antibodies	Literature	GML data (N=12)
CK7	+	100% (12/12)
S100P	+	67% (8/12)
pVHL	–	33% (4/12)
CD10	+	33% (4/12)
ER	+	25% (3/12)
Inhibin-alpha	+ or –	67% (8/12)
PR	+ or –	50% (6/12)
CK20	– or +	33% (4/12)
CAM 5.2	+	100% (12/12)
CEA	+	100% (12/12)
CA19-9	+	92% (11/12)
CDX-2	–	25% (3/12)
MUC1	–	17% (2/12)
MUC2	– or +	0 (0/12)
MUC5AC	+	67% (8/12)
MUC6	–	50% (6/12)
DPC4/SMAD4	+	100% (12/12)

The ovarian-type stroma in MCN is usually positive for ER, PR, CD10, and inhibin-alpha. Expression of different types of mucin is not very useful in differentiating MCN from IPMN. MUC2 is frequently expressed in goblet cells of MCN

Our data showed that all four S100P-negative cases were positive for pVHL; CDX-2 was only focally positive; CD10 was also expressed in the lining mucinous epithelium in two cases. The staining for ER, PR, and inhibin-alpha tended to be focal (<10% of the tumor stained) and weak. The positivity rate for ER was lower than reported in the literature, which may be due to inadequate fixation in formalin since the majority of specimens were grossed in a fresh state

References: [1, 2, 76, 108]

Table 26.19 Markers for intraductal papillary mucinous neoplasm

Antibodies	Literature	GML data (N=18)
CK7	+	100% (18/18)
S100P	+	18/18 (100%)
pVHL	–	0 (0/18)
Maspin	+	ND
CK19	+	75% (12/16)
CK20	– or +	62.5% (10/16)
CDX-2	+ or –	37.5% (6/16)
CEA	+	100% (18/18)
CA19-9	+	62.5% (10/16)
MUC1	V	50% (9/18)
MUC2	V	44% (8/18)
MUC5AC	+	100% (18/18)
MUC6	ND	78% (14/18)
DPC4/SMAD4	+	100% (18/18)

Note: *GML* Geisinger Medical Laboratories

Intestinal-type IPMN is usually positive for MUC2, CDX-2, and CK20

Gastric foveolar-type IPMN is usually negative for both MUC1 and MUC2. Pancreatobiliary-type IPMN is usually positive for MUC1 and negative for MUC2 and CDX-2

Expression of S100P and loss of expression of pVHL are present in all types of IPMN. Expression of DPC4/SMAD4 is present in all tested cases. MUC6 tends to be expressed in the basal layer of epithelial cells; the papillary structures projecting into the cystic space are frequently negative for MUC6

References: [1, 2, 19, 40, 77, 108]

Table 26.20 Markers for intraductal oncocytic papillary neoplasm

Antibodies	Literature
TAG 72 (B72.3)	+
Mesothelin	+
Hep Par 1	+
MUC1	+
CEA	+ or –
CA19-9	+ or –
CDX-2	–
Claudin 4	–
pVHL	–
S100P	+

References: [1, 33]

Table 26.21 Markers for pancreatic intraepithelial neoplasia 1 and 2

Antibodies	Literature
S100P	+
pVHL	–
p53	– or +
Maspin	+ or –
IMP3	+ or –
Annexin A8	– or +
Mesothelin	– or +
Claudin 18	– or +

References: [1, 6, 10–13, 17, 19–22, 26–30, 33–35, 42, 43]

Table 26.22 Markers for pancreatic intraepithelial neoplasia 3

Antibodies	Literature
pVHL	–
S100P	+
Maspin	+
IMP3	+
MUC1	+
E-cadherin	Loss
MUC2	–
MUC4	+
MUC5AC	+
MUC6	+
DPC4/SMAD4	+
p53	+ or –
Claudin 18	+
Annexin A8	+
Mesothelin	+

References: [1, 6, 10–13, 17, 19–22, 26–30, 33–35, 42, 43]

Table 26.23 Markers for intraductal tubulopapillary neoplasm of the pancreas

Antibodies	Literature
CK7	+
CK20	– or +
CK19	+
CEA	+
CA19-9	+
MUC5AC	–
MUC6	+
MUC1	– or +
MUC2	–
p16	–/+
p53	–/+
SMAD4	No loss
Ki-67	Low
Mucicarmine	+

References: [1, 109]

Table 26.24 Markers for chronic pancreatitis

Antibodies	Literature	GML data
S100P	- or cytoplasmic only	- or cytoplasmic only
pVHL	+	+
Maspin	–	–
IMP3	–	–
SMAD4/DPC4	No loss	No loss
Mesothelin	–	Weakly+
PSCA	–	+
Annexin A8	–	Weakly+
Claudin 18	–	Weakly+
mCEA	+ or –	Weakly+ on luminal side
MOC-31	+	+
CA19-9	+	+

Note: *GML* Geisinger Medical Laboratories

Our experience showed that 100% of benign and reactive pancreatic ductal cells are positive for pVHL; in contrast, ductal carcinomas are negative for pVHL in nearly 100% of cases. Non-neoplastic ducts are usually negative for S100P, IMP3, and maspin. In autoimmune pancreatitis, the infiltrating plasma cells are predominately IgG4-positive. An immunostain for IgG4 may be helpful in diagnosing a difficult case [79–81]. It should be cautioned, however, that the presence of abundant IgG4-positive plasma cells does not preclude the diagnosis of pancreatic DAC because in a small subset of pancreatic DAC cases, the cancer-adjacent tissue may show features of autoimmune pancreatitis

References: [1, 9–13, 17, 19–22, 26–29, 32, 34, 35, 78–80]

Table 26.25 Ductal adenocarcinoma versus chronic pancreatitis

Antibodies	Ductal adenocarcinoma	Pancreatitis
Maspin	+	–
pVHL	–	+
S100P	+	- or cytoplasmic + only
IMP3	+	–
MUC5AC	+ or –	–
CK17	+ or –	Usually
DPC4/SMAD4	Loss in 50%	+
p53	+ or –	– or very weakly +
mCEA	+	Usually – or focally +
Mesothelin	+	–
MUC1	+	+ or –
Annexin A8	+	–
Claudin 18	+	– or weakly +

It has been demonstrated that 100% of benign and reactive pancreatic ductal cells are positive for pVHL; in contrast, ductal carcinoma is negative for pVHL in nearly 100% of cases. Our experience showed that maspin, IMP3, and S100P are the three best positive markers for identifying adenocarcinoma. Very weak positivity in non-neoplastic ducts can be seen in maspin and S100P stains. Markers like TAG 72 (B72.3), MOC-31, and Ber-EP4 are usually positive in adenocarcinoma, but they are frequently positive or weakly positive in normal or reactive ducts as well

References: [1, 9–13, 17, 19–22, 26–29, 32–35, 38, 39, 42, 44]

Table 26.26 Ductal adenocarcinoma versus intrahepatic cholangiocarcinoma

Antibodies	Ductal adenocarcinoma	Intrahepatic cholangiocarcinoma
pVHL	–	+
Albumin	–	+
CRP	–	+
CK17	60%	15%
MUC5AC	60%	15%

A small panel of IHC markers including pVHL, albumin (by RNA ISH), and CRP is useful in differentiating a pancreatic ductal adenocarcinoma from an intrahepatic cholangiocarcinoma (ICC). In particular, expression of pVHL, albumin by RNA ISH, and CRP was reported in approximately 75%, 80% and 80% of ICCs, respectively. In contrast, these three markers were usually negative in pancreatic ductal adenocarcinomas. Other markers mentioned in the table above, including CK17 and MUC5AC, may be potentially useful for this purpose. An example of ICC positive for pVHL, CRP, and albumin by RNA ISH is shown in Figs. 26.46, 26.47, 26.48, and 26.49

References: [88–92]

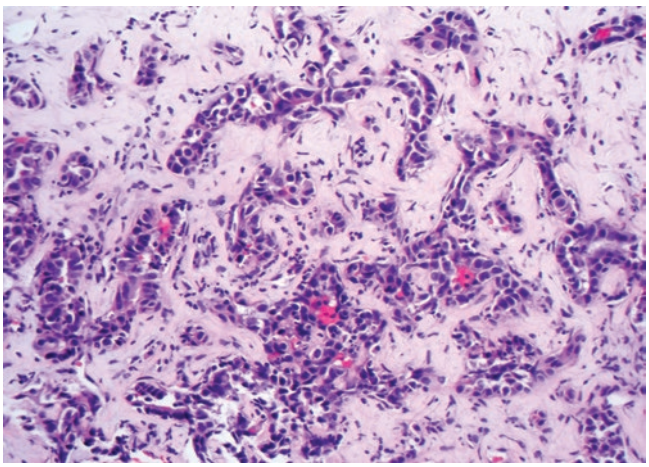


Fig. 26.46 Intrahepatic cholangiocarcinoma (Fig. 26.46) with positive staining for pVHL (Fig. 26.47), C-reactive protein (Fig. 26.48), and albumin (focal positivity) by RNA ISH (Fig. 26.49)

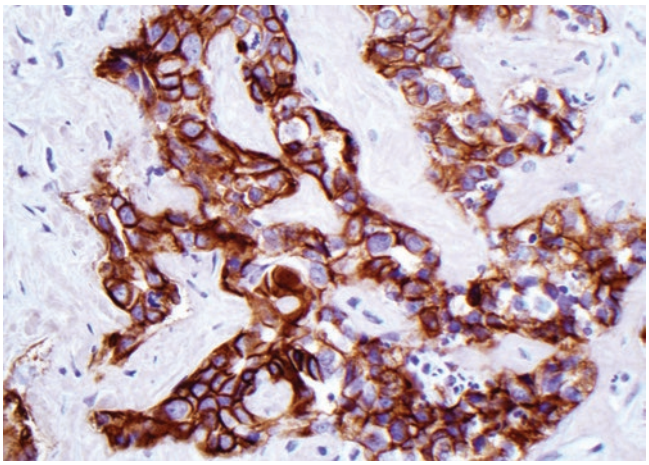


Fig. 26.47 Intrahepatic cholangiocarcinoma (Fig. 26.46) with positive staining for pVHL (Fig. 26.47), C-reactive protein (Fig. 26.48), and albumin (focal positivity) by RNA ISH (Fig. 26.49)

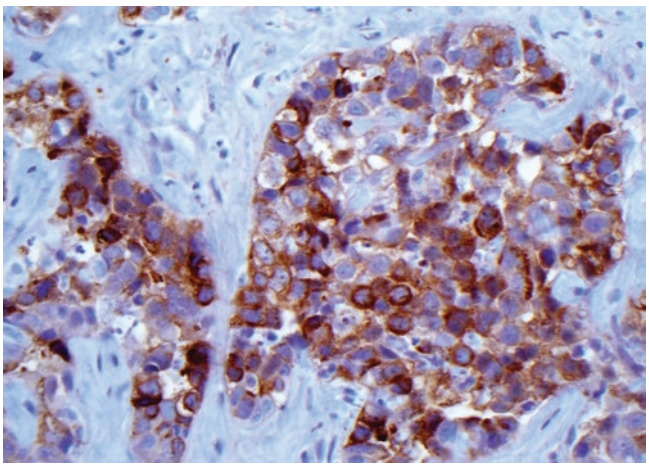


Fig. 26.48 Intrahepatic cholangiocarcinoma (Fig. 26.46) with positive staining for pVHL (Fig. 26.47), C-reactive protein (Fig. 26.48), and albumin (focal positivity) by RNA ISH (Fig. 26.49)

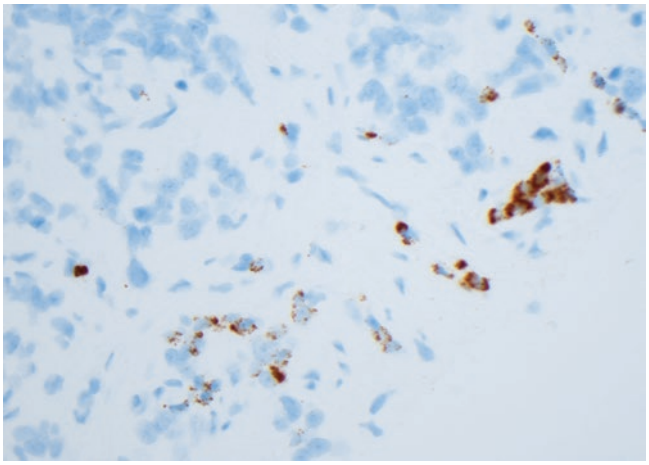


Fig. 26.49 Intrahepatic cholangiocarcinoma (Fig. 26.46) with positive staining for pVHL (Fig. 26.47), C-reactive protein (Fig. 26.48), and albumin (focal positivity) by RNA ISH (Fig. 26.49)

Table 26.27 Useful IHC markers in differentiating well-differentiated neuroendocrine tumors from pancreatic islets/islet cell hyperplasia

Antibodies	Pancreatic neuroendocrine tumor	P-islets/islet cell hyperplasia
TTMP	– (Loss of expression)	Intact expression
ATRX/DAXX	Loss in 50% cases	Intact expression
Insulin/glucagon/somatostatin	Usually only positive for one marker	Usually positive for more than one marker
Ki-67	Usually >1%	Usually <1%

Reference: [98]

Table 26.29 Pancreatic neuroendocrine tumor versus solid pseudopapillary neoplasm

Antibodies	P-NET	SPN
Beta-catenin	M+	N+, C+
E-cadherin	+	–
Chromogranin	+	–
Cytokeratin	+	–
TFE3	–	+
SOX11	–	+
ATRX/DAXX	Loss in 50%	No loss
Vimentin	–	+
CD10	–	+

Note: *M* membranous staining; *N* nuclear staining; *C* cytoplasmic staining; *P-NET* pancreatic neuroendocrine tumor; *SPN* solid pseudopapillary neoplasm

Over 90% of SPNs show nuclear and cytoplasmic positivity for beta-catenin and loss of expression of E-cadherin. Expression of chromogranin in SPN has not been reported. Expression of SOX11 and TFE3 has been reported in over 90% of SPNs

References: [1, 2, 45–52, 87]

Table 26.30 Pancreatic neuroendocrine neoplasm versus acinar cell carcinoma

Antibodies	P-NET	ACC
Chromogranin	+	Usually–
Bcl10	–	+
Trypsin	–	+
PAX6	60% +	–
ATRX/DAXX	Loss in 50%	No loss
SMAD4/DPC4	No loss	Loss in 25%
Glypican 3	–	50% +
Beta-catenin	M+	M or N+M
E-cadherin	+	+ or –

Note: *P-NET* pancreatic neuroendocrine tumor; *ACC* acinar cell carcinoma; *M* membranous staining; *N* nuclear staining

References: [1, 55]

Table 26.28 Useful IHC markers in differentiating pancreatic neuroendocrine tumors from well-differentiated neuroendocrine tumors of other organs

Antibodies	P-NET	L-NET	U-NET	I-NET	A-NET	R-NET
CK7	7%	33%	13%	0	0	41%
CK20	5%	0	0	0	22%	6%
TTF1	0	17%	0	0	0	0
CDX2	2%	0	25%	92%	78%	6%
PAX6/PAX8	55%	0	25%	0	0	0
ATRX/DAXX[a]	50% loss	No loss	No loss	No loss	No loss	No loss
PR	70%	0	0	0	0	0
OTP	8%	80%	0	0	0	0

Note: P-NET (pancreatic NET, *N* = 33), L-NET (lung-NET, *N* = 40), U-NET (gastric and duodenal NET, *N* = 8), I-NET (ileal NET, *N* = 30), A-NET (appendiceal NET, *N* = 18), R-NET (rectal NET, *N* = 22); TTF1—thyroid transcription factor 1

[a]Approximately 50% of P-NETs showed loss of expression of ATRX or DAXX

A recent study demonstrated that orthopedia homeobox (OTP), a transcription factor, was a highly sensitive and specific marker for diagnosing pulmonary carcinoids with the diagnostic sensitivity of 80% and specificity of (close to) 100%. Our study of a small number of pulmonary carcinoids showed approximately 60% of cases with diffuse and strong nuclear staining for OTP. The current data suggest that OTP is a much more sensitive marker than TTF1 in confirming the diagnosis of a metastatic pulmonary carcinoid. In general, the diagnostic sensitivity for TTF1 in a metastatic pulmonary carcinoid is <50%. Caution should be taken since rare pancreatic well-differentiated NETs can be positive for OTP in our study

References: [97, 110]

Table 26.31 Pancreatic neuroendocrine tumor versus pancreatoblastoma

Antibodies	P-NET	PB
Beta-catenin	M+	Usually N+M
E-cadherin	+	Usually –
Chromogranin	+	Usually –
CK7	+	– or +
PAX6	60%+	–
Bcl10	–	+
ATRX/DAXX	Loss in 50%	No loss

Note: *P-NET* pancreatic neuroendocrine tumor; *PB* pancreatoblastoma; *N* nuclear staining; *M* membranous staining

This panel of immunomarkers is very useful for a PB mainly composed of acinar and squamoid components. In a PB case with additional ductal and neuroendocrine components, the staining results can be more complicated. In general, nuclear positivity for beta-catenin and loss of E-cadherin expression are highly suggestive of PB after the exclusion of ACC and SPN

References: [1, 53, 54, 56, 57]

Table 26.32 Useful IHC markers in differentiating pancreatic well-differentiated neuroendocrine tumor grade 3 from poorly differentiated neuroendocrine carcinoma

Antibodies	P-NET, G3	P-NEC
Ki-67	<55%	>55%
ATRX/DAXX	Loss in 45% cases	No loss
P53	–	Positive in 70%
Rb	No loss	Loss in 50–90%
SMAD4/DPC4	No loss	Loss in rare cases

Note: P-NET, G3 pancreatic well-differentiated neuroendocrine tumor grade 3; *P-NEC* pancreatic poorly differentiated neuroendocrine carcinoma

In the 2017 WHO classification of neuroendocrine neoplasm, well-differentiated NET can be further classified into G1, G2, and G3. The distinction between well-differentiated NET, G3 from a poorly differentiated neuroendocrine carcinoma (including large cell and small cell subtype NEC) can be challenging. Tumor necrosis, brisk mitoses, loss of trabecular growth pattern, and higher N/C ratio of tumor cells are features of poorly differentiated NEC and can sometimes been present in NET, G3. Importantly, most NET, G3 cases have a prior history of low-grade NET and tend to be heterogeneous in grade instead of a pure grade 3 throughout the tumor. There is no absolute cutoff number for Ki-67 proliferative index; however, a pure poorly differentiated NEC usually has a Ki-67 index of >55%. In contrast, a well-differentiated NET, G3 tends to have a Ki-67 index of <55%. Approximately 50% of NET G3s show loss of expression of DAXX or ATRX that has not been reported in a poorly differentiated NEC. A significant percentage of NECs are positive for p53 (67%) and negative for Rb, with >91% for small cell subtype NEC and 50–60% for large cell subtype NEC [82]. Loss of SMAD4/DPC4 has been reported in rare NEC cases

References: [81–83]

Table 26.33 Acinar cell carcinoma versus solid pseudopapillary neoplasm

Antibodies	ACC	SPN
CD10	–	+
Beta-catenin	M or M+N	M+N
Bcl10	+	–
Trypsin	+	–
E-cadherin	+	–
AE1/AE3	+	– or focal +
PR	–	+ or –
CK	+	–
SOX11	–	+
TFE3	–	+

Note: *ACC* acinar cell carcinoma; *SPN* solid pseudopapillary neoplasm; *M* membranous staining; *N* nuclear staining; *C* cytoplasmic staining

Interpretation of trypsin immunostaining can be difficult due to the presence of background staining

Up to 25% of ACCs may show both nuclear and cytoplasmic staining for beta-catenin

References: [1, 45–50, 52, 54]

Table 26.34 Acinar cell carcinoma versus ductal adenocarcinoma

Antibodies	ACC	DAC
CK7	– or very focally +	+
Mesothelin	–	+ or –
S100P	–	+
Bcl10	+	–
Trypsin	+	–
Glypican-3	+/–	–
IMP3	–	+
Vimentin	+ or –	–
CK19	– or focally +	+ or –
DPC4/SMAD4	Loss in 20%	Loss in 50%

Note: *ACC* acinar cell carcinoma; *DAC* ductal adenocarcinoma

References: [1, 25–29, 31, 32, 54, 63–65]

Table 26.35 Acinar cell carcinoma versus pancreatoblastoma

Antibody	ACC	PB
Beta-catenin	M+ or M and N+	M and N+, or M+
E-cadherin	M+	– or M+
CK7	– or focally +	Focally+
Trypsin	+	+

Note: *ACC* acinar cell carcinoma; *PB* pancreatoblastoma; *M* membranous staining; *N* nuclear staining

Identification of squamoid component/squamoid differentiation is the key to making a distinction between these entities. However, the "squamoid component" usually lacks the typical squamous phenotype, that is, positive for CK5/6, p40, and other high molecular weight cytokeratins. Approximately 25% of ACCs may show nuclear beta-catenin staining and loss of expression of E-cadherin; in contrast, over 90% of PBs show nuclear and cytoplasmic beta-catenin positivity and loss of expression of membranous E-cadherin

References: [1, 53–57]

Table 26.36 Solid pseudopapillary neoplasm versus pancreatoblastoma

Antibody	SPN	PB
Claudin5	M+	–
Claudin 7	-or focally C+	M+
PR	+ or –	–
CD10	+	Usually –
Bcl10	–	+
Trypsin	–	+
Cytokeratin	– or focally +	+
Beta-catenin	N and M+	N and M+ or M+
E-cadherin	–	– or +

Note: *SPN* solid pseudopapillary neoplasm; *PB* pancreatoblastoma; *M* membranous staining; *C* cytoplasmic staining; *N* nuclear staining

Interpretation of trypsin immunostaining can be difficult due to the presence of background staining

Expression of beta-catenin and E-cadherin has a limited value in the distinction between SPN and PB

References: [1, 45–57]

Table 26.37 Markers for hematopoietic malignancies in the pancreas

Markers	B-cell lymphoma	Myeloid sarcoma	Plasmacytoma/ MM	Hodgkin's lymphoma
CD3	–	+ or –	–	–
CD20	+	–	–	–
CD15	–	–	–	+
CD30	– or +	–	–	+
CD38	–	–	+	–
CD138	–	–	+	–
CD117	–	+	–	–
CD34	–	+	–	–
CD43	+ or –	+	–	–
EMA	–	–	+ or –	–

Note: *MM* multiple myeloma

CD43 is a sensitive but not specific marker for myeloid sarcoma (granulocytic sarcoma); CD138 is a sensitive and specific marker for MM/plasmacytoma; MM is frequently positive for both CD138 and EMA, which may mislead one to call it an epithelial neoplasm

References: [1, 111]

Table 26.38 Markers for differentiating pancreatic spindle cell neoplasms

Antibodies	PSC	GP	SM	PEcoma	NGT	SFT	SMN	KS	RMS
CK	+	–	–	–	–	–	–	–	–
S100	–	+/–	+	–	+	–	–	–	–
SMA	–	–	–	+	–	+/–	+	–	+/–
Desmin	–	–	–	–	–	–	+	–	+
HMB-45	–	–	+	+	–	–	–	–	–
Chromogranin	–	+	–	–	–	–	–	–	–
STAT6	–	–	–	–	–	+	–	–	–
CD34	–	–	–	–	–	+	–	+/–	–
SOX10	–	–	+	–	+	–	–	–	–
Myogenin	–	–	–	–	–	–	–	–	+
HHV-8	–	–	–	–	–	–	–	+	–

Note: *PSC* pancreatic sarcomatoid carcinoma; *GP* gangliocytic paraganglioma; *SM* spindle cell melanoma; *PEComa* perivascular epithelioid cell neoplasm; *NGT* neurogenic tumor such as neurofibroma and schwannoma; *SFT* solitary fibrous tumor; *SMN* smooth muscle neoplasm; *KS* Kaposi sarcoma; *RMS* rhabdomyosarcoma; *HMB-45* human melanoma black 45; *HHV-8* human herpes virus 8

An example of pancreatic PEComa is shown in Figs. 26.50, 26.51, 26.52, and 26.53. Figure 26.50 demonstrates a mixed population of spindle and epithelioid cells with bland nuclear features, abundant granular cytoplasm, in conspicuous nucleoli, and no mitosis or tumor necrosis. The neoplastic cells are diffusely positive for SMA (Fig. 26.51), focally positive for HMB-45 (Fig. 26.52), with a low Ki-67 index (Fig. 26.53), and negative for S100, SOX10, CD68, and cytokeratin (not shown)

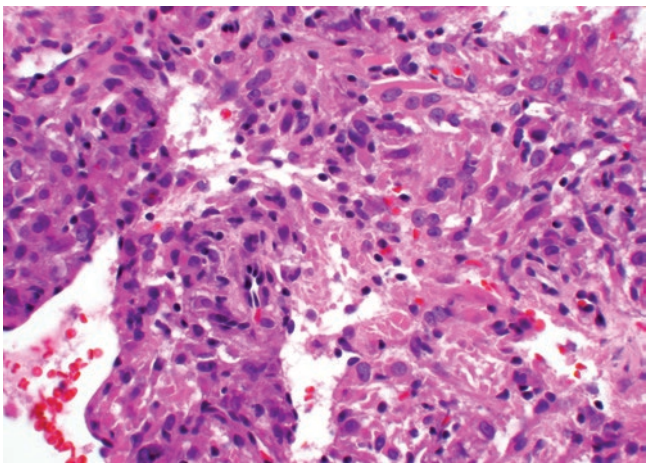


Fig. 26.50 Pancreatic PEComa with a mixed population of spindle and epithelioid cells (Fig. 26.50). The neoplastic cells are diffusely positive for SMA (Fig. 26.51), focally positive for HMB-45 (Fig. 26.52), with a low Ki-67 index (Fig. 26.53)

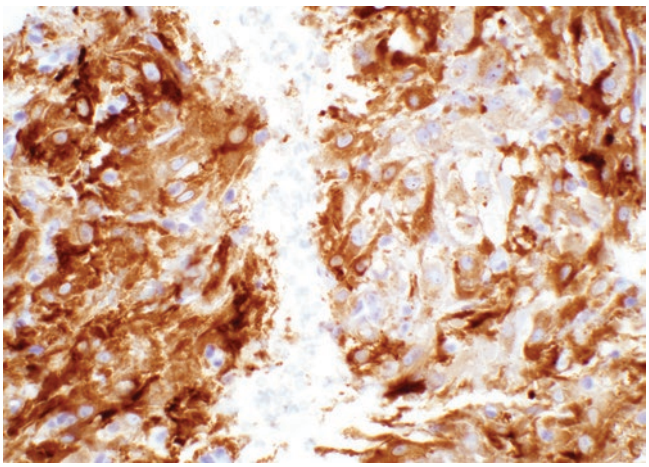


Fig. 26.52 Pancreatic PEComa with a mixed population of spindle and epithelioid cells (Fig. 26.50). The neoplastic cells are diffusely positive for SMA (Fig. 26.51), focally positive for HMB-45 (Fig. 26.52), with a low Ki-67 index (Fig. 26.53)

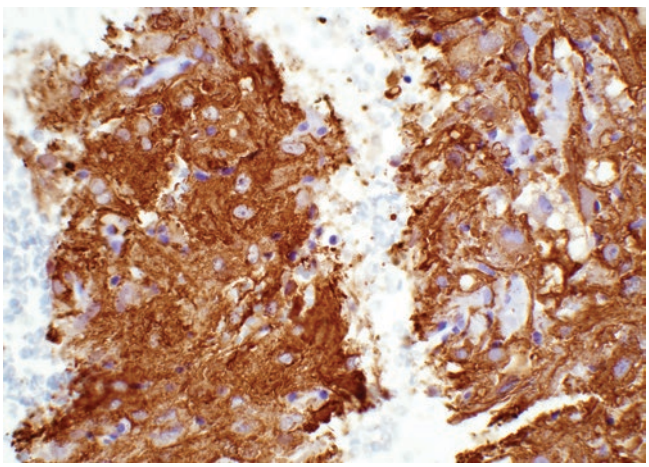


Fig. 26.51 Pancreatic PEComa with a mixed population of spindle and epithelioid cells (Fig. 26.50). The neoplastic cells are diffusely positive for SMA (Fig. 26.51), focally positive for HMB-45 (Fig. 26.52), with a low Ki-67 index (Fig. 26.53)

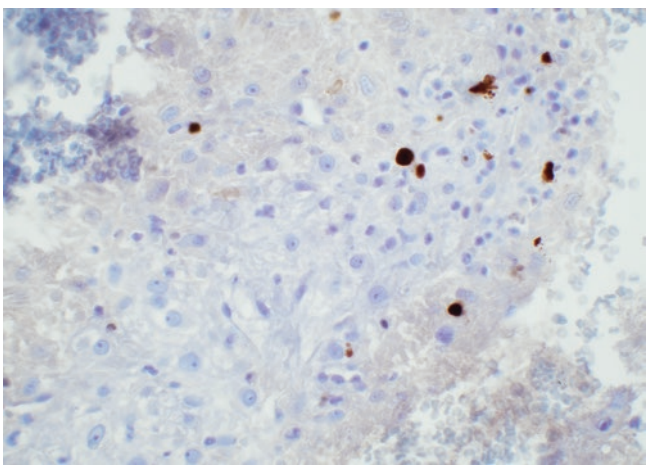


Fig. 26.53 Pancreatic PEComa with a mixed population of spindle and epithelioid cells (Fig. 26.50). The neoplastic cells are diffusely positive for SMA (Fig. 26.51), focally positive for HMB-45 (Fig. 26.52), with a low Ki-67 index (Fig. 26.53)

Table 26.39 Metastases in the pancreas

Markers	PDC	Kidney	Lung-A	Mela-noma	Stomach	Lung-S	Colon	Breast
CK7	+	–	+	–	+	+ or –	–	+
CK20	–	–	–	–	+ or –	–	+	–
S100	–	–	+ or –	+	–	–	–	– or +
TTF1	–	–	+	–	–	+	–	–
CDX-2	–	–	–	–	+ or –	–	+	–
PAX8	–	+	–	–	–	–	–	–
KIM-1	–	+	–	–	–	–	–	–
CD10	–	+	–	–	–	–	–	–
ER	–	–	-	–	–	–	–	+
GATA3	– or +	–	–	–	–	–	–	+
INSM1	–	–	–	–	–	+	–	–
SMAD4	– or +	+	+	+	+	+	+	+

Note: *PDC* pancreatic ductal carcinoma; *Lung-A* lung adenocarcinoma; *Lung-S* lung small cell carcinoma, *KIM-1* kidney injury molecule 1; *GATA3* GATA-binding protein 3; *INSM1* insulinoma associated protein-1

Mucinous adenocarcinomas of the lung are frequently positive for CDX-2 and negative for TTF1; in addition, a small percentage of lung adenocarcinomas can be positive for ER

S100 is a highly sensitive (98%) but not specific marker for screening melanoma. Caution should be taken if the sample is fixed in alcohol, since the S100 antigen is not preserved well after alcohol fixation. If melanoma is suspected, then other markers including MART-1 and HMB-45 should be done. If a spindle cell melanoma or desmoplastic melanoma is suspected, SOX10 is another sensitive and specific marker to use

GATA3 is a recently described marker that has been reported to be positive in approximately 80% of urothelial carcinomas and over 90% of breast carcinomas, including 50–60% of ER-negative breast carcinomas. The expression of GATA3 has also been reported in approximately 80% of paragangliomas and a significant percentage of salivary gland tumors, including 100% of salivary duct carcinomas and mammary analogue secretory carcinomas. Our unpublished data also show that approximately 10% of pancreatic DACs can be positive for GATA3. A small percentage of squamous cell carcinomas may express GATA3. Aberrant GATA3 expression has been reported in carcinomas of other organs as well

Some metastatic small cell carcinomas of the lung can be negative for both synaptophysin and chromogranin, but they are very infrequently negative for INSM1 and CD56. The Ki-67 proliferative index tends to be very high (>50%); it would be extremely unusual to have a small cell carcinoma with a low Ki-67 index. The majority (>90%) of metastatic colorectal adenocarcinomas are positive for both CK20 and CDX-2; however, it should be noted that medullary carcinoma of the colon with MSI-high frequently shows loss of expression of both CDX-2 and CK20. In this case, the tumor cells would demonstrate loss of expression of either MLH1/PMS2 or MSH2/MSH6 and usually be positive for at least one of these three IHC markers: special AT-rich sequence-binding protein 2 (SATB2), CDH17, and calretinin. Caution should be taken since some of medullary carcinoma of the colon may show diffuse positivity for CK7 and negativity for CK20 and CDX2, which may mimic primary pancreatic ductal carcinoma and other CK7 positive metastatic carcinomas

References: [1–3, 5–8, 58, 70, 112–116]

Table 26.40 Prognostic markers for pancreatic adenocarcinoma

Markers	Literature	Association
DNMT1	Overexpression	Advanced stage
Hyaluronan	High level	Low tumor grade and nodal metastasis
HDAC1	Overexpression	Advanced stage
uPAR	Gene amplification	Poor prognosis
Dkk-3	Low expression	Poor prognosis
MicroRNAs	Overexpression of 155, 203, 210, and 222	Poor prognosis
ALCAM/CD166	Overexpression	Poor prognosis
DPC4/SMAD4	Loss of expression	Poor prognosis
S100A6	Nuclear positivity	Poor prognosis

Note: *DNMT1* DNA methyltransferase 1; *HDAC1* histone deacetylase-1; *uPAR* urokinase type plasminogen activator receptor; *ALCAM* activated leukocyte cell adhesion molecule; *Dkk-3* Dickkopf-related protein 3

References: [1, 117–121]

Table 26.41 Predictive markers for pancreatic neuroendocrine neoplasm

Markers	Literature	Association
ACTH	+	Poor prognosis
ATRX	Loss of expression	Poor prognosis
APOBEC3B	Loss of expression in 47% of NET G3 and 97% of NECs	Lymph node metastasis
CK19 (RCK 108 antibody)	+	Poor prognosis
Ki-67	>5%	Metastatic disease
67-kD laminin receptors	+	Metastatic disease
CD44 isoforms (v6 and v9)	+	Good prognosis
Topoisomerase II alpha	Overexpression	Malignant
CD99	Loss of expression	Poor prognosis
Survivin	Nuclear +	Poor prognosis

Note: *ACTH* adrenocorticotropic hormone; *APOBE3CB* apolipoprotein B MRNA editing enzyme catalytic subunit 3B; *NET G3* well-differentiated neuroendocrine tumors grade 3; *NEC* neuroendocrine carcinoma

References: [1, 122–131]

Table 26.42 Markers for normal ampulla of Vater

Antibodies	GML Data ($N = 20$)
CK7	80% (16/20)
CK20	100% (20/20)
CK17	0 (0/20)
CK19	100% (20/20)
MUC1	0 (0/20)
MUC2	100% (20/20)
pVHL	60% (12/20)
S100P	50% (10/20)
Maspin	95% (19/20)
IMP3	40% (8/20), focal
Villin	90% (18/20)
CDX-2	100% (20/20)
Hep Par1	85% (17/20)
CEA	100% (20/20)
Ber-EP4	100% (20/20)
MOC-31	100% (20/20)

The data are from Geisinger Medical Laboratories (GML) and based on 20 cases of ampullary biopsy specimens

pVHL, maspin, IMP3, and S100P are a panel of very useful markers in the distinction of normal pancreatic ducts from pancreatic DAC. The frequent expression of these four markers in normal ampulla makes them less useful in the diagnosis of ampullary adenocarcinoma

Table 26.43 Markers for intestinal-type ampullary adenocarcinoma

Antibodies	Literature
CK7	– or +
CK20	+
CDX-2	+
Hep Par 1	+
Villin	+
MUC2	+
CK17	–
MUC1	–
MUC5AC	–

References: [2, 8, 33, 132, 133]

Table 26.44 Markers for pancreatobiliary-type ampullary adenocarcinoma

Antibodies	Literature
S100P	+
pVHL	–
CK17	+
CK7	+ or –
CK20	–
CDX-2	–
Hep Par 1	–
MUC2	–
Villin	+ or –
MUC1	+
MUC5AC	+

References: [8, 33, 132, 133]

Table 26.45 Ampullary adenocarcinoma, intestinal type versus pancreatobiliary type

Antibodies	Pancreatobiliary type	Intestinal type
MUC1	+	–
MUC2	–	+
CK20	–	+
CDX-2	–	+
Hep Par 1	–	+
CK17	+	–
CK7	+ or –	– or +
S100P	+	ND
MUC5AC	+	–
Villin	V	+

References: [2, 8, 33, 112, 133]

Table 26.46 Ampullary adenocarcinoma versus pancreatic ductal adenocarcinoma

Antibodies	ADCI	ADCP	DAC
CK7	– or +	+ or –	+
CK20	+	–	– or +
CDX-2	+	–	–
Mesothelin	ND	ND	+
IMP3	ND	ND	+
Hep Par 1	+	–	–
MUC1	–	+	+
MUC2	+	–	–

Note: *ADCI* ampullary adenocarcinoma intestinal type; *ADCP* ampullary adenocarcinoma pancreatobiliary type; *DAC* pancreatic ductal adenocarcinoma

References: [1, 2, 8, 33, 133]

Table 26.47 Useful IHC markers in differentiating among ampullary normal/reactive mucosa, adenoma, and adenocarcinoma

Antibodies	Adenocarcinoma	Adenoma	Normal/reactive
VHL	–	–	60%
S100P	+	+/–	50%, weak
IMP3	+	+/–	40%, weak
p53	75%	–	–
HMGA2	80%	–	8%
CK17/MUC1	+/–	+/–	–

Note: *HMGA2* high mobility group AT-hook 2

Reference: [134]

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