7 Proximal Small Intestine: Neoplastic Patterns and Mimics

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Contents

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Normal Tissue at the Wrong Site (Heterotopias)

Gastric Heterotopia

Gastric heterotopia is most commonly encountered in the duodenal bulb (Fig. 7.1). No aetiology has been established, although an embryological remnant is most likely [1]. The use of proton pump inhibitor medication induces hyperplasia of otherwise incidental rests, probably accounting for the increased prevalence of this finding which is now seen in up to 5% of all duodenal bulb biopsies.

Histologically there are well organised, demarcated gastric body-type glands within the intestinal mucosa (Fig. 7.2) [1–3]. The extent varies from a few glands to extensive replacement of native mucosa. Occasionally Helicobacter can be found. Secondary changes may include:

1. Stromal inflammation
2. Helicobacter infection
3. Ulceration (usually with Helicobacter infection)
4. Cystic dilatation resembling cystic fundic gland polyp (particularly in patients taking proton pump inhibitor medication)
5. Foveolar hyperplasia sometimes producing a gastric hyperplastic-type polyp

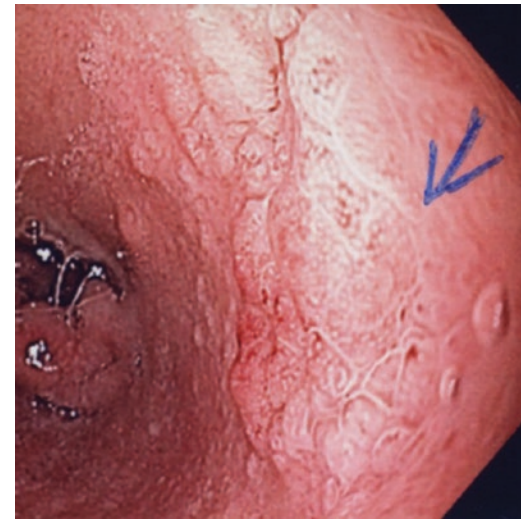

Fig. 7.1 Gastric heterotopia duodenum—endoscopic view

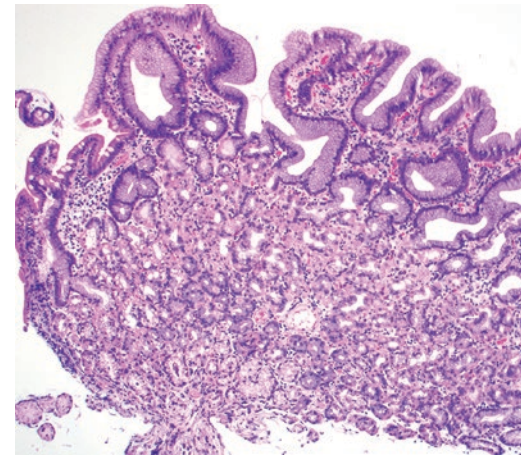

Fig. 7.2 Gastric heterotopia in D1- note the overlying foveolar hyperplasia

There is no risk for dysplasia or malignancy. Diagnostic considerations include (1) gastric

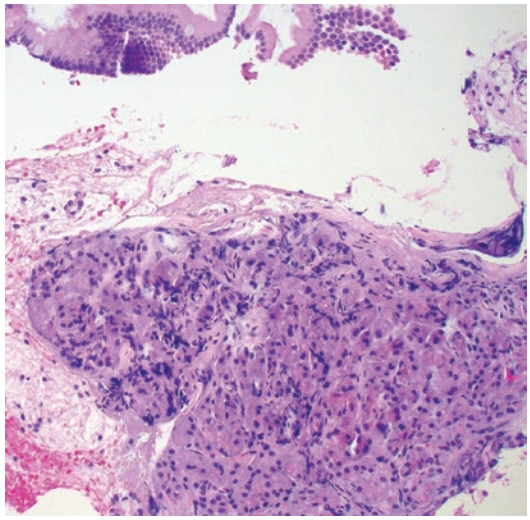

Fig. 7.3 Pancreatic heterotopia with acini

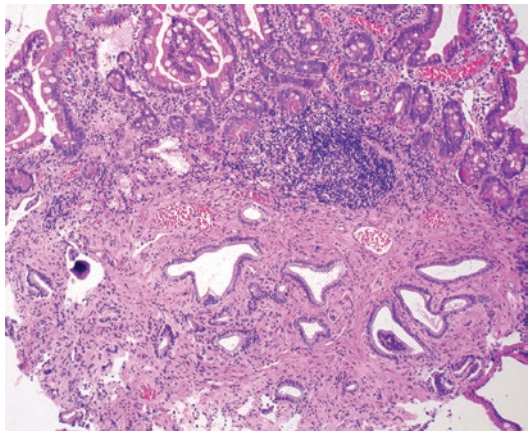

Fig. 7.4 Adenomyoma pattern of pancreatic heterotopia - duct elements within a smooth muscle proliferation

metaplasia, which comprises the antral-type epithelium involving the superficial mucosa of the duodenal bulb region in the setting of duodenitis, and (2) pyloric gland adenoma, which consists of pyloric-type rather than body-type glands.

Pancreatic Heterotopia (Syn. Ectopic Pancreas, Pancreatic Rest)

Pancreatic heterotopia comprises various admixtures of non-neoplastic pancreatic ducts, pancreatic acini and islets of Langerhans. Based on these components, a three-tier classification has been developed [4, 5]:

Class I—all three elements present

Class II—acini and ducts but no islets (Fig. 7.3)

Class III—ducts with rare (or no) acini

A fourth class comprising only endocrine elements also occurs but is exceedingly rare.

The duct structures in Class III lesions may be associated with smooth muscle proliferation and the term "adenomyoma" is alternatively used for this situation (Fig. 7.4).

Pancreatic heterotopia usually resides in the submucosa/base of mucosa and endoscopic biopsies may not include diagnostic tissue.

Cyst formation and development of PanIN in the ductal epithelium can occur.

The differential diagnosis includes (1) ampullary adenomyoma, which is histologically similar to class III pancreatic heterotopias, so knowledge of the site of biopsy is important. In general, ampullary adenomyoma is associated with more smooth muscle proliferation than usual pancreatic heterotopia. The presence of peribiliary glands indicates an ampullary location. (2) Pancreatic metaplasia is very rare in the small intestine and consists of small lobulated collection of pancreatic acinar glands confined to the mucosa; and (3) accessory pancreatic duct is found in the region of the ampulla and has a distinctive duct structure.

Lesions Characterised by Stromal Inflammation and Stromal Expansion (Box 7.1)

Box 7.1 Lesions Characterised by Stromal Inflammation and Stromal Expansion

Mucosal prolapse

Inflammatory fibroid polyp

Hamartomas—juvenile polyposis, Canada-Cronkhite syndrome

Inflammatory pseudopolyp

Pseudopolyp (Benign Mucosal Polyp, Inflammatory Pseudopolyp)

Local trauma or inflammation is most common. Inflammation may be related to Crohn's disease [6] or to medications, e.g. NSAID. Local mucosal ischaemia is a rare cause in the small intestine. It is discussed in more depth in the ileum section.

Mucosal Prolapse-Type Polyps

Mucosal prolapse polyps are a stromal and epithelial expansion induced by traction on the mucosa during peristalsis. Smooth muscle proliferation into the mucosa from a thickened muscularis mucosae is a characteristic feature. Prolapse-type polyps may be related to a submucosal lesion; anatomical abnormality, e.g. sharp angulation in the duodenum; or a mucosal tumour.

The characteristic histological features are crypt elongation and stromal expansion by fibrosis and smooth muscle proliferation from the muscularis mucosae. Inflammation and erosion can occur. Since mucosal prolapse changes may be accompanied by a mucosal-based neoplasm or overlie a submucosal lesion, so careful attention should be paid to these possibilities.

Sometimes the mucosa is normal, and the polyps are due to the expansion of the submucosa, a process akin to that described in the colon as colonic muco-submucosal elongated polyp [6]. The main differential diagnosis is with hamartomatous lesions discussed below. The clinical setting is of most help in separating these two lesions.

Overgrowth of Normal Elements (Hamartomas)

Hamartomas are benign tumour comprising a disorganised collection of tissue elements native to the site of occurrence. They may occur sporadically or as part of several tumour syndromes (discussed below). Solitary hamartomatous polyps of the small intestine are most frequently Peutz-Jeghers type, Brunner's gland type or neuromuscular and vascular type.

The microscopic features of Peutz-Jeghers-type polyp and Brunner's gland hamartoma are discussed below. Neuromuscular- and vascular-type hamartoma comprises an admixture of neural elements, both nerve bundles and ganglion cells, with smooth muscle proliferation. This is mostly within the submucosa and is associated with stricture rather than a discrete polyp. Ectatic vessels may also been seen, particularly at the edge of the areas of frequent mucosal ulceration. There is a clinical and histological overlap with nonsteroidal anti-inflammatory drug-related small bowel diaphragm disease [7]. The absence of a history of NSAID use helps exclude the latter. A well-developed smooth muscle proliferation in the lamina propria and the absence of granulomata are the most helpful features in excluding Crohn's disease (Figs. 7.5 and 7.6) [8].

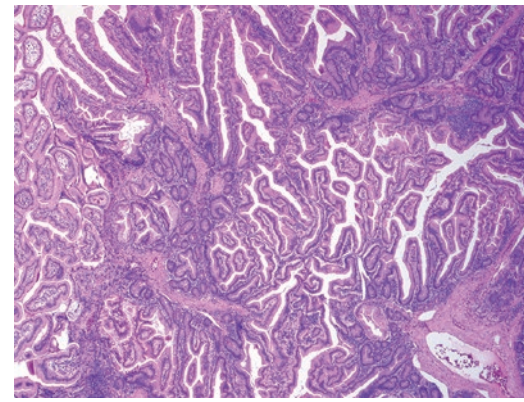

Fig. 7.5 Peutz-Jeghers polyp - arborising smooth muscle core and a proliferation of normal glandular elements

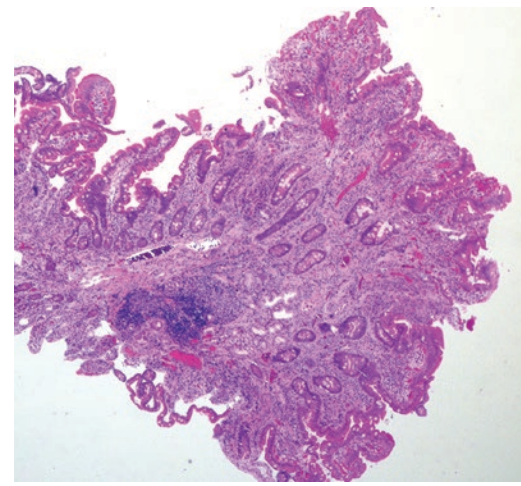

Fig. 7.6 Hamartomatous polyp in duodenum in a patient with Cowden syndrome. Note gland elongation and stromal expansion

Inflammatory Fibroid Polyp

(See page 251)

Cystic Lesions (Box 7.2)

Box 7.2 Cystic Lesions
Brunner's gland cyst
Pneumatosis
Cystic vascular lesions—lymphangiectasia, venous bleb
Post inflammatory

Brunner's Gland Cyst

Brunner's gland cyst is a benign cystic dilatation of a main duct draining the Brunner's glands of the duodenum. It is present in the submucosa but is usually amenable to partial endoscopic sampling (Fig. 7.7). The lesion is underrecognised and is a common cause for a proximal duodenal nodule. It is lined by a single layer of tall columnar mucinous epithelium with clear cytoplasm and basal nuclei. A pseudomicropapillary folded architecture is often present, at least focally (Fig. 7.8) [9]. There is no cytologic atypia, mitotic activity or dysplasia. The adjacent Brunner's gland appears normal. The cyst likely develops as a result of local duct obstruction.

Fig. 7.7 Brunner's gland cyst endoscopic resection picture

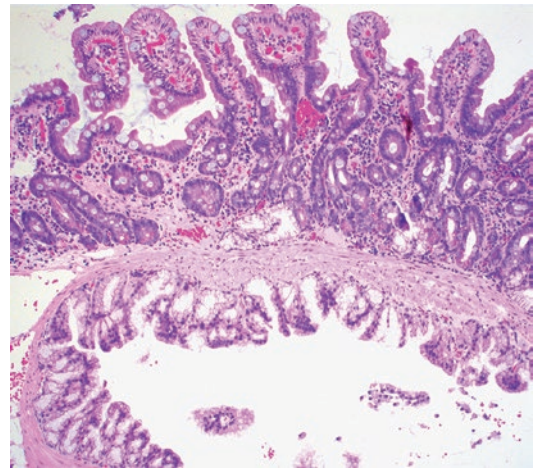

Fig. 7.8 Brunner's gland cyst

Other Cystic Lesions

- Pneumatosis (see page xx)
- Cystic vascular lesions—lymphangiectasia, venous bleb (see page xx)
- Post inflammatory

Glandular Proliferations with No Stromal Invasion

Epithelial Dysplasia

Flat epithelial dysplasia is very uncommon in the duodenum. When present histological features are identical to those described in the large intestine.

Adenoma

Brunner's Gland Adenoma (Syn. Brunneroma, Brunner's Gland Hamartoma)

This is a benign mass of unknown aetiology forming as a result of proliferation of Brunner's glands of the proximal duodenum. It may represent a hamartoma rather than a true neoplasm.

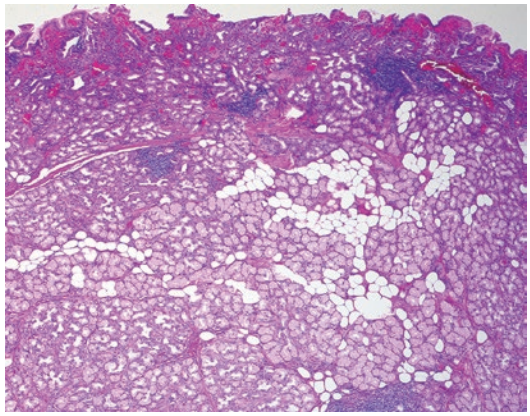

Fig. 7.9 Brunner's gland hamartoma - Brunners gland proliferation, lymphoid follicles and adipose tissue

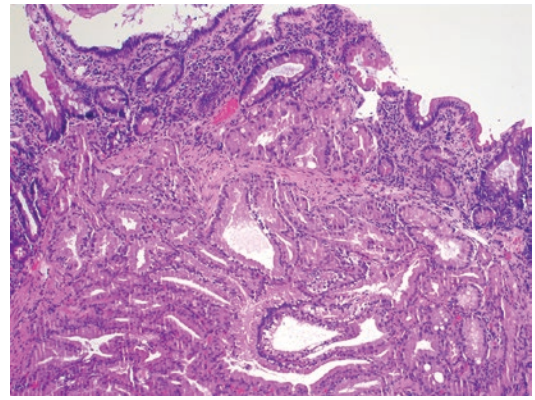

Fig. 7.10 Pyloric gland adenoma - glandular proliferation. The lining cells have clear to light eosinophilic cytoplasm

There is a lobulated proliferation of Brunner's glands within the submucosa and basal mucosa of the duodenum and rarely the proximal jejunum [10, 11]. The lining cells are uniform, cuboidal with pale cytoplasm containing neutral mucin. The gland architecture is regular, although cystic dilatation may occur. There may be admixed smooth muscle proliferation, adipose tissue (Fig. 7.9), lymphoid tissue and/or heterotopic pancreatic acini and ducts. Reactive epithelial changes are often present in the overlying mucosa, particularly in large lesions with surface erosion.

The main differential diagnosis is Brunner's gland hyperplasia resulting from peptic duodenitis. The finding of mucosal inflammation and the less organised architecture are the key distinguishing features. Pyloric gland adenoma is also a consideration; however, the lining cells typically exhibit atypia with prominent nucleoli. Cytoplasmic eosinophilia is usually appreciable in some cells in pyloric gland adenoma but is not found in Brunner's gland adenoma.

Pyloric Gland (Gastric gland-type) Adenoma

Pyloric gland adenoma is a neoplastic proliferation of cells with differentiation towards the gastric pyloric gland cells. Most cases are sporadic, although recent studies suggest an increased prevalence in both Lynch syndrome and familial adenomatous polyposis. Mutations in GNAS and KRAS are frequently found. In the absence of dysplasia, pyloric gland adenoma is characterised by a proliferation of regular, tubular glands lined by cuboidal cells that have clear to eosinophilic cytoplasm and a round nucleus with generally small nucleolus (Fig. 7.10) [12–14]. Development of dysplasia is characterised by architectural irregularity, increase in cell size, increase in nuclear size and increased prominence of nucleoli. Development of invasive carcinoma may be deceptive. A back-to-back gland pattern or infiltration by single tumour cells indicates malignancy.

Pyloric gland adenoma displays cytoplasmic expression of MUC6. Expression of MUC5ac may be found in cells near the luminal aspect of the tumour. Some examples have more extensive MUC5ac expression and the pattern is more of a gastric foveolar type adenoma. The general term of "gastric type adenoma" may be more appropriate for these cases. Differential diagnosis includes gastric heterotopias, which comprise the specialised gastric mucosa distinct from the neutral mucin-producing cells of pyloric gland adenoma. Brunner's gland hyperplasia/adenoma has less cytoarchitectural abnormality than pyloric gland adenoma. Well-differentiated adenocarcinoma may be difficult to separate and require additional tumour material to be examined. Persistent growth or large tumour size is a concerning feature for adenocarcinoma.

Intestinal-Type Adenoma

Intestinal-type adenomas are neoplastic, noninvasive proliferation of dysplastic intestinal lining

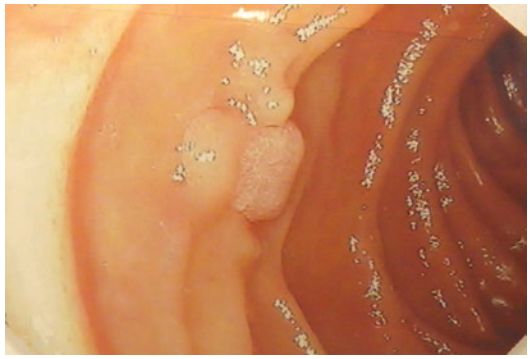

Fig. 7.11 Duodenal adenoma—endoscopic view

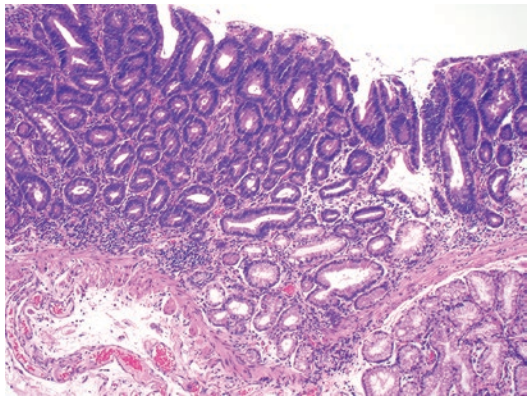

Fig. 7.12 Tubular adenoma of duodenum - morphology identical to the large intestinal counterpart

cells closely akin to their large intestinal counterparts. Most are sporadic; however, some arise in a syndromic setting such as familial adenomatous polyposis syndrome, Lynch syndrome and MutYH associated polyposis.

As with their more common large intestinal counterparts, they may have tubular (Figs. 7.11 and 7.12), tubulovillous or villous architecture, and accompanying dysplasia may be low grade or high grade. Serrated architecture, with a pattern resembling traditional serrated adenoma, may be seen in all or part of the lesion (discussed below; see Fig. 7.12). Gastric surface metaplasia is present in 40% of cases, and a distinctive clear cell change in the cytoplasm of the adenoma cells is present in some cases. Adenomas arising in Lynch syndrome, are likely to be larger, demonstrate tubulovillous architecture and exhibit high grade dysplasia. These generally show a loss of nuclear

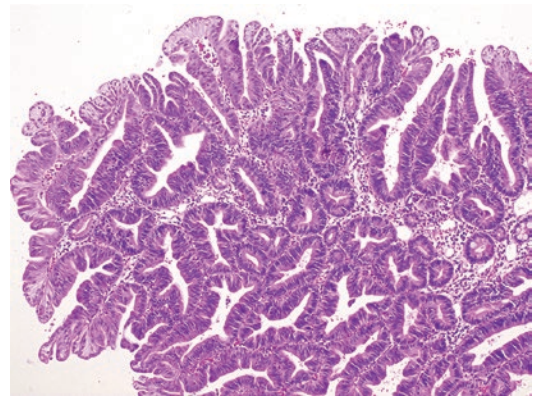

Fig. 7.13 Intestinal adenoma of duodenum with serrated architecture

immunohistochemical reaction for one or more of the mismatch repair proteins, MLH-1, MSH-2, MSH-6 and PMS-2.

Care should be taken to exclude reactive change, seen most commonly at the edge of an ulcer or with acute inflammation. An abrupt change from normal mucosa to the dysplastic epithelium of intestinal adenoma is a helpful feature in this distinction. Intestinal-type adenocarcinoma may arise from an adenoma and the distinction on a small biopsy rests on the finding of complex glandular architecture and stromal desmoplasia or infiltrating single cells. In the ampullary region, pancreatic or biliary tree neoplasia may mimic intestinal-type adenoma particularly on small biopsy.

Serrated Polyps

Serrated lesions of the small intestine remain poorly characterised compared to their colonic relatives (Fig. 7.13). A lesion resembling colonic hyperplastic polyp has been described but is rare [15, 16]. Lesions resembling traditional serrated adenoma of colon, either in pure form or as part of an otherwise conventional intestinal-type adenoma, are reported [17]. Mucosal regeneration after injury, e.g. NSAID induced, may acquire a serrated pattern. Usually there are associated stromal changes of fibrosis and inflammation.

Lesions resembling colonic hyperplastic polyps are innocuous and do not require further

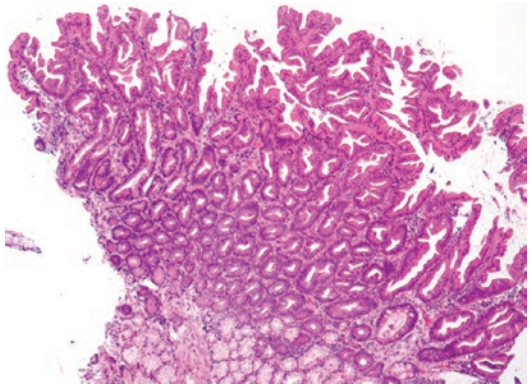

Fig. 7.14 Hyperplastic polyp of duodenum

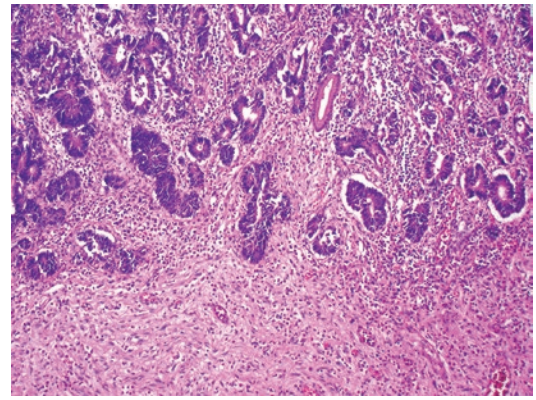

Fig. 7.15 Adenocarcinoma of intestinal type arising in neurofibromatosis with background neurofibroma

treatments (Fig. 7.14). Traditional serrated adenoma-like lesions most likely have a risk for development of malignancy similar to conventional adenomas. Hence, they should be treated and followed up accordingly.

Glandular Proliferations with Stromal Invasion

Blue Cell Pattern

Adenocarcinoma

Usual types of adenocarcinoma are described in Chap. 1. Unusual subtypes include sarcomatoid, choriocarcinoma and hepatoid variants.

Adenocarcinoma: Intestinal Type

This is a malignant neoplasm arising from the glandular epithelium of the small intestine. It is morphologically similar to its colonic counterpart (Fig. 7.15). There is an increased risk in the following conditions:

1. Common:
   - Polyposis syndromes—Familial adenomatous polyposis (FAP), Lynch syndrome (hereditary nonpolyposis colon cancer syndrome, HNPCC), juvenile polyposis syndrome, Peutz-Jeghers syndrome and neurofibromatosis type 1
   - Crohn's disease
2. Uncommon:
   - Celiac disease
   - Congenital abnormalities—Meckel diverticulum, heterotopic pancreas, duplication cysts
   - Chronic inflammation—Ileostomy, ileal pouch radiotherapy

Differential diagnosis of adenocarcinoma in the duodenum:

- Adenocarcinoma of intestinal type (most common).
- Adenocarcinoma of pancreaticobiliary type (see below).
- Adenocarcinoma of pyloric gland type (see below).
- Adenoma with high-grade dysplasia—The absence of clear evidence of lamina propria invasion indicates the lesion is still an adenoma.
- Peutz-Jeghers polyp with pseudoinvasion—Distinction lies in the recognition of the underlying polyp and the absence of cytological dysplasia.
- Adenomyoma of ampulla and heterotopic pancreas devoid of acinar structures. No cytologic atypia is seen.
- Endometriosis—The presence of endometrial stroma and the uniform benign cytology of the endometrial glands allow distinction. A panel of CK7, CK20, CDX-2 and PAX-8 can be applied to difficult cases.

Pink Cell Pattern

Adenocarcinoma of Pancreaticobiliary Type

It presents as a mass arising at the ampulla or periampullary region. In contrast to intestinal-type adenocarcinoma, the component cells are cuboidal and the glands smaller and without the "dirty necrosis" seen in intestinal type adenocarcinoma (Fig. 7.16). As the prognosis of intestinal-type adenocarcinoma is more favourable than pancreaticobiliary-type adenocarcinoma, it is important to make this distinction. A panel of immunohistochemical stains has been shown to be useful (Table 7.1) [18].

Adenocarcinoma of Pyloric Gland (Gastric gland-type) Type

It typically arises from a pre-existing pyloric gland adenoma. Invasion may be difficult to establish on biopsy. Suspicious features are a complex cribriform or small gland pattern. The tumour cells are cuboidal and have clear or lightly eosinophilic cytoplasm in contrast to the pencillate, brightly eosinophilic cells of intestinal-type adenocarcinoma. Immunohistochemical stains aid differentiation of pyloric gland adenocarcinoma (MUC2−, MUC6+, CDX-2−, CK20−) from intestinal adenocarcinoma (MUC2+, MUC6−, CDX-2+, CK20+).

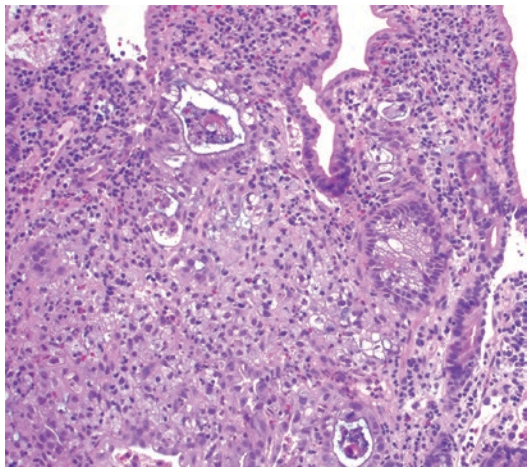

Fig. 7.16 Pancreatic adenocarcinoma in ampulla

Clear Cell Pattern

It is uncommon but may be seen in signet ring cell carcinoma, pyloric gland adenocarcinoma, clear cell sarcoma, metastatic clear cell renal cell carcinoma and clear cell patterns of biliary and pancreatic adenocarcinoma. Rarely neuroendocrine neoplasm may assume a clear cell pattern.

Neuroendocrine Neoplasm

Neuroendocrine neoplasm of the small intestine may be derived from neuroendocrine cells originating in the foregut (duodenum) or midgut (jejunum, ileum). A variety of terms are used for tumours in the small intestine that have in common the feature of neuroendocrine differentiation. For example, tumours are often designated based on their active hormone production or lack there of—gastrinoma, somatostatinoma and non-functional neuroendocrine neoplasm ("carcinoids") (Figs. 7.17 and 7.18). General features are listed in Table 7.2 [19, 20].

Neuroendocrine neoplasm in the proximal small intestine show morphological features of neuroendocrine differentiation as described in Chap. 1. There is a spectrum of cell size and of cytoplasmic characteristic with pink cyto-

Table 7.1 Immunohistochemical stains

	Immunohistochemical stain				
Adenocarcinoma type	MUC 1	MUC 2	CDX 2	CK7	CK20
Intestinal	−	+	+	±	+
Pancreaticobiliary	+	−	−	+	±

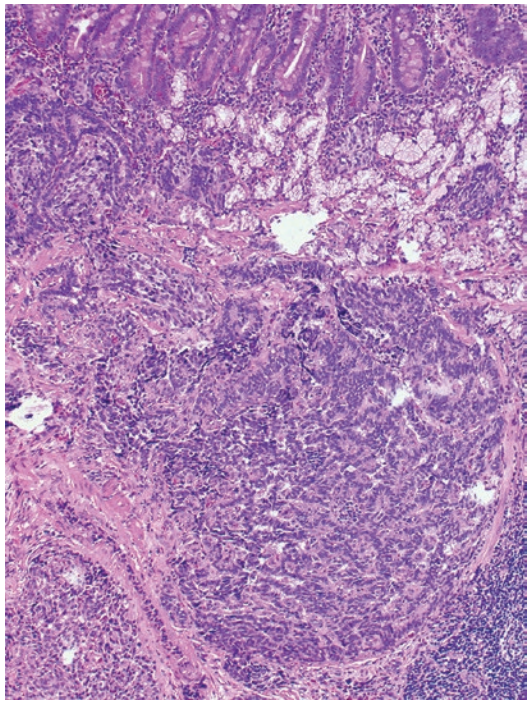

Fig. 7.17 "Carcinoid" tumour duodenum

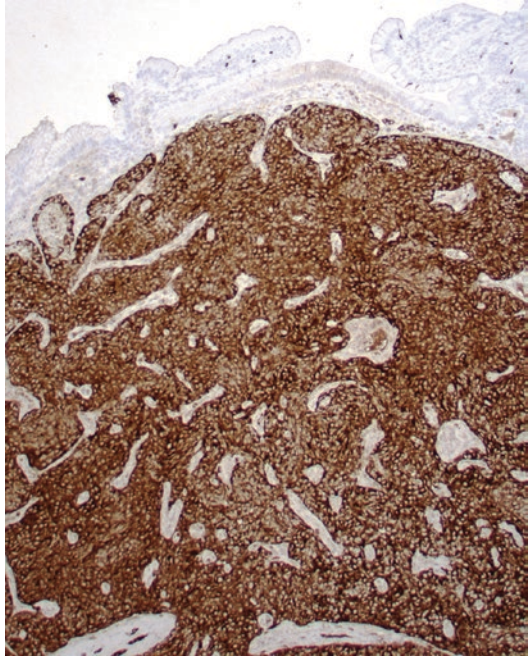

Fig. 7.18 "Carcinoid" tumour duodenum - chromogranin stain with positive reaction

Table 7.2 Neuroendocrine neoplasm of the proximal small intestine: summary features

• 20% of all GIT NENs
• 1–3% all primary duodenal neoplasms • M:F = 2:1 • Mean age sixth decade • Syndromic—MEN1, —6%; NF1, rare • 90% nonfunctional • 10%—functional (mostly gastrinoma producing Zollinger-Ellison syndrome. This is associated with MEN1 in 50%) • Multiple—10% • Periampullary/ampullary location in 20% • 75% are <2 cm (mucosa/submucosa) • Regional lymph node metastases in 50% (early) • Liver metastases in 10% • Prognosis 5-year survival I. Localised—80–95% II. Regional LN—65–75% III. Distant metastases—5–10%

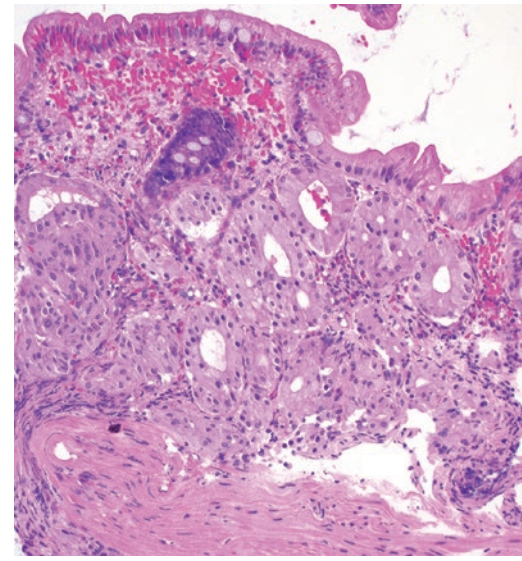

Fig. 7.19 Somatostatinoma - pseudoglandular architecture

plasm being most common but clear cell and the light base of the change are also seen. Pseudoglandular architecture and psammomatous-type dystrophic calcification may occur with somatostatinoma (Fig. 7.19), and amyloid deposition may be encountered in any functional tumour.

In addition to usual immunohistochemical markers of neuroendocrine differentiation, there may be specific hormone production in tumour cells (which does not necessarily correlate with release into the blood or with the production of a specific clinical syndrome), e.g. insulin, gastrin, glucagon and somatostatin. However, demonstration of this is not necessary for histological classification. Because of the variable appearance, duodenal neuroendocrine neoplasm may elicit a wide differential diagnosis. This includes melanoma, GIST, neuroectodermal tumour, lymphoma, paraganglioma (and gangliocytic paraganglioma) and clear cell sarcoma. A panel of immunohistochemical stains that includes neuroendocrine markers, keratin, CD117, S-100 and LCA will usually allow distinction.

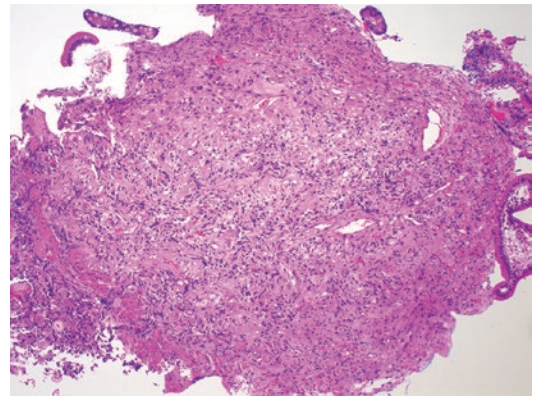

Fig. 7.20 Gangliocytic paraganglioma - note the admixture of elements

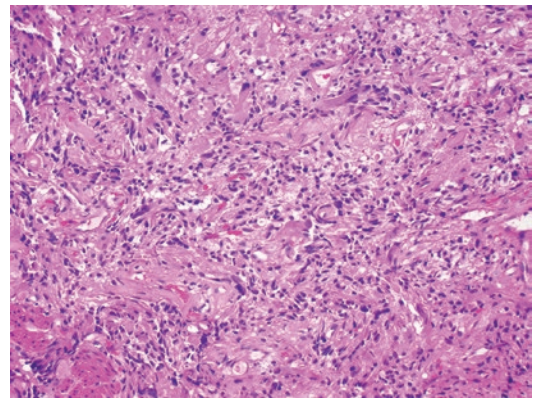

Fig. 7.21 Gangliocytic paraganglioma - neuroendocrine and schwann cell elements

Pseudoinvasion

Pseudoinvasion may be seen in intestinal-type adenoma and also in Peutz-Jeghers polyps. The absence of stromal desmoplasia is an important finding in favour of pseudoinvasion. In Peutz-Jeghers polyps, the lining epithelium will be bland and these will be associated prominent smooth muscle proliferation.

Mixed Epithelial and Stromal Pattern

See Box 7.3.

Box 7.3 Mixed Epithelial and Stromal Pattern
Gangliocytic paraganglioma
Synovial sarcoma
Metastases
Endometriosis

Gangliocytic Paraganglioma

Gangliocytic paraganglioma is a distinctive neuroendocrine neoplasm usually developing in the ampullary region of the duodenum and characterised by differentiation towards neuroendocrine cell, Schwann cell and ganglion cell lineages (Figs. 7.20, 7.21, 7.22, 7.23, and 7.24).

Histologically, the components are an admixture of:

1. Spindle-shaped Schwann cells forming background supporting stroma (S-100 positive).
2. Ganglion cells—either clustered or dispersed within the Schwann cell stroma—S-100 and synaptophysin positive.
3. Well-differentiated neuroendocrine cells in nested, trabecular or papillary arrangements—immunoreactive for keratin and neu-

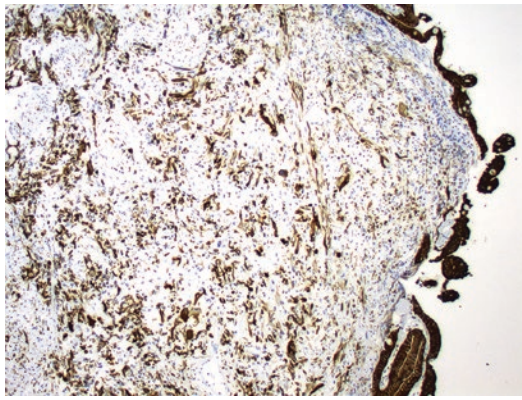

Fig. 7.22 Gangliocytic paraganglioma Keratin stain

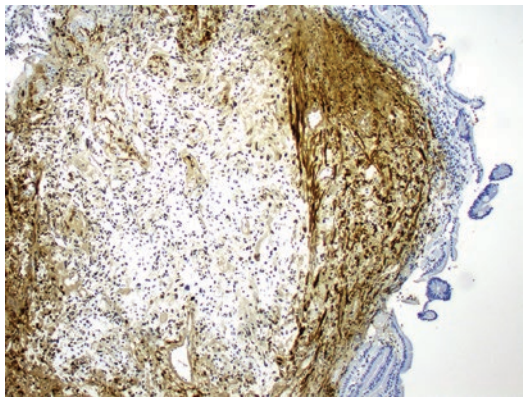

Fig. 7.23 Gangliocytic paraganglioma S-100 stain

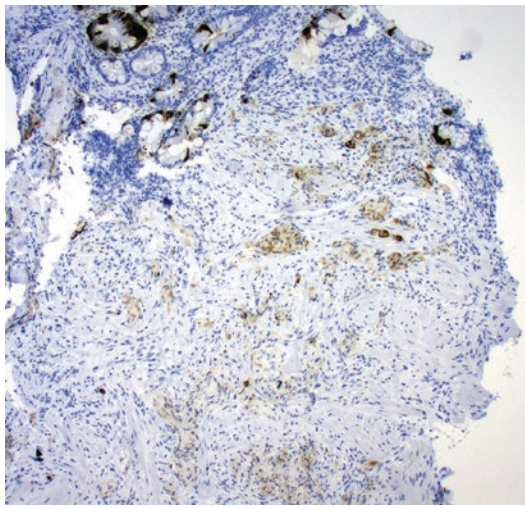

Fig. 7.24 Gangliocytic paraganglioma chromogranin stain

roendocrine stains (e.g. synaptophysin, chromogranin, CD56).

Spindle or epithelial elements might also dominate the appearance, and deeper levels can be useful in identifying other cell types. The differential diagnosis includes:

1. Spindle cell elements—nerve sheath tumour and GIST. GIST can be separated on the basis of immunohistochemical positivity for CD117 and/or DOG-1 stains.
2. Epithelial elements—neuroendocrine neoplasm, as discussed above, are devoid of other elements. Paraganglioma does not contain ganglion cells and exhibits a sustentacular pattern of S-100 reactive cells around the tumour cell nests. Adenocarcinoma should not be reactive for S-100 or neuroendocrine markers such as chromogranin and synaptophysin.
3. Ganglion cells—ganglioneuroma. The presence of neuroendocrine elements is important to this distinction.

Although rare reports of regional lymph node metastases exist [21], there have been no tumour-related deaths and the neoplasm is regarded as indolent.

Diffuse Round Cell Pattern

The causes of this pattern are described below in the following tables.

Blue Cell Pattern

See Table 7.3.

Pink Cell Pattern

See Table 7.4.

Clear Cell Pattern

See Table 7.5.

Table 7.3 Blue cell pattern

Diagnosis	Immunohistochemical profile
Lymphoma	LCA, CD3 or CD20
Plasma cell tumours	CD138
Leukaemia	MPO, CD43
Carcinoma—adenocarcinoma	AE1/AE3
Neuroendocrine neoplasm	AE1/AE3, neuroendocrine markers
Mastocytosis	CD117, CD25
Sarcoma—Ewing's/PNET	CD99
Metastasis	Variable pattern

PNET = primitive neuroectodermal tumour

Table 7.4 Pink cell pattern

Diagnosis	Immunohistochemical profile
GIST	CD117, DOG1
Histiocytic tumours	CD68
Glomus tumour	SMA
Granular cell tumour	S-100, SOX10
Langerhans cell histiocytosis	S-100, CD1a
Epithelioid smooth muscle tumour	SMA, desmin, H-caldesmon
Carcinoma—squamous	P63, High molecular weight CK
Metastasis	Variable pattern

GIST = gastrointestinal stromal tumour

Table 7.5 Clear cell pattern

Diagnosis	Immunohistochemical profile
GIST	CD117, DOG1
Carcinoma—any	AE1/AE3
Histiocytic lesions (xanthoma)	CD68
Lymphoma	LCA
Mastocytosis	CD117, CD25
Langerhans cell histiocytosis	S-100, CD1a
Clear cell sarcoma	S-100, HMB45
PEComa	HMB45
Epithelioid smooth muscle tumour	SMA, desmin, H-caldesmon
Metastasis—clear cell renal cell carcinoma	CD10

GIST = gastrointestinal stromal tumour

Table 7.6 Primary small intestine non-Hodgkin's lymphoma [22]

Tumour type	Frequency compared to all GIT lymphoma sites
Diffuse large B-cell lymphoma	38%
Follicular lymphoma	23%
Enteropathy-associated T-cell lymphoma	10%
Post-transplant lymphoproliferative disorder	10%
Burkitt's lymphoma	8%
MALT	5%

MALT = mucosa-associated lymphoid tissue

Table 7.7 Small and large cell patterns of lymphomas

Small cell pattern	Large cell pattern
Follicular lymphoma MALT lymphoma Chronic lymphocytic leukaemia IPSID	Diffuse large B-cell lymphoma Hodgkin's lymphoma Plasmablastic lymphoma Burkitt's lymphoma T-cell lymphoma
Usually B cell	B or T cell

MALT = mucosa-associated lymphoid tissue; IPSID = immunoproliferative small intestine disease

Lymphoma

The small intestine is a common site for gastrointestinal tract lymphoma. Follicular lymphoma and diffuse large B-cell lymphoma are most frequent (Table 7.6) [22].

It is useful for the initial workup to divide lymphomas of the small intestine in terms of predominant cell size. The differential diagnosis and required immunohistochemical panel can then be applied more effectively (Table 7.7).

In this chapter, Lymphomas that may be encountered in endoscopic biopsy material from the proximal small intestine are described below.

B-Cell Non-Hodgkin's Lymphoma

Follicular B-Cell Lymphoma of the Gastrointestinal Tract

It is a distinctive subset of B-cell follicular lymphoma with generally indolent behaviour, developing as a primary lesion in the gastrointestinal

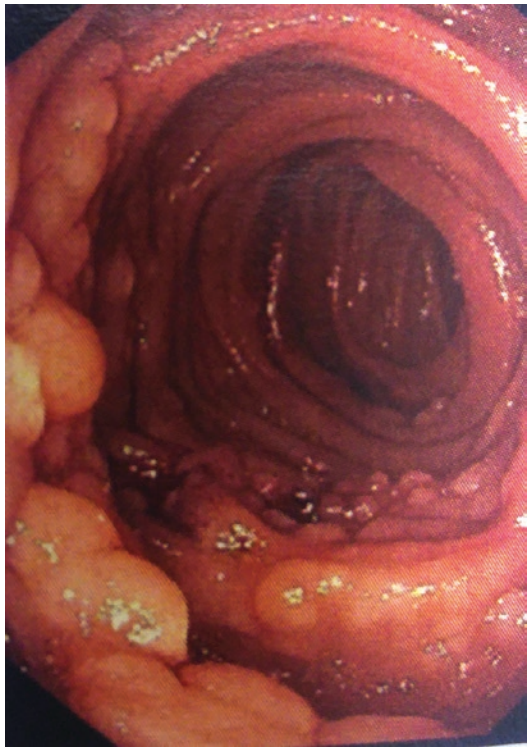

Fig. 7.25 Endoscopic picture of follicular lymphoma in duodenum

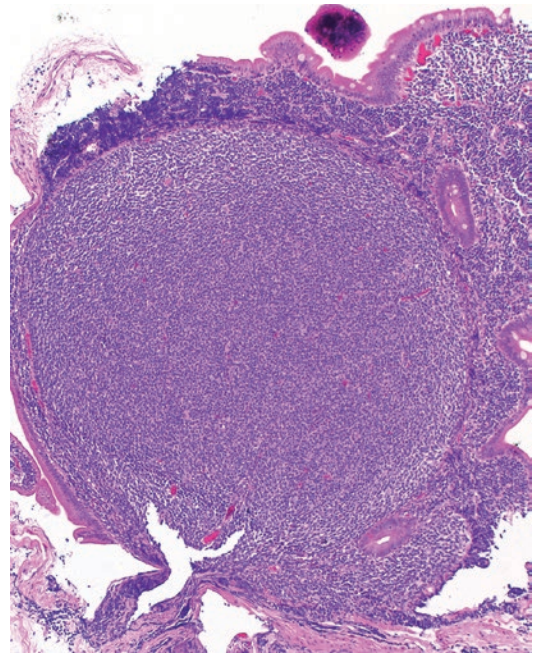

Fig. 7.26 Follicular lymphoma

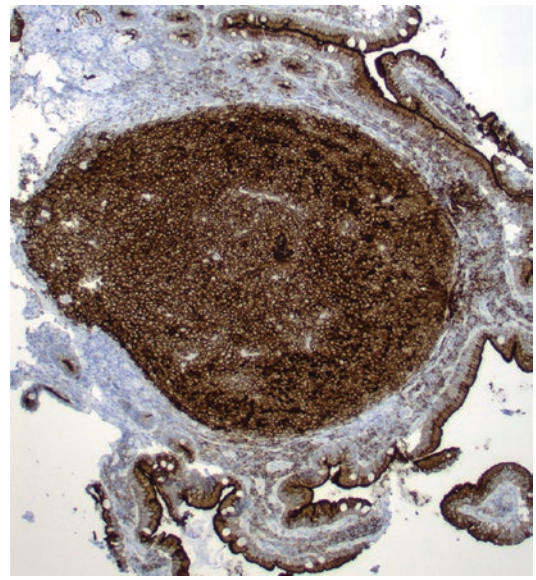

Fig. 7.27 Follicular lymphoma CD10

tract, in particular the second part of duodenum (Fig. 7.25). Follicular architecture is characteristic. The tumour cells are small with irregular nuclear outline resembling centrocytes (Figs. 7.26). Variable numbers of blastic cells resembling centroblasts may be seen; however, tingible body macrophages are conspicuously absent. Centrocyte-like cells may extend in a diffuse fashion into the adjacent lamina propria.

Duodenal follicular lymphoma exhibits the following:

1. Immunophenotype: CD10 (+) (Fig. 7.27), B-cell lymphoma 2 (BCL-2) (+) (Fig. 7.28), BCL-6 (+) and loose CD21 (+) follicular dendritic cell network (often located at the periphery of the follicle). CD10 (+) cells extending in a sheet-like pattern into the lamina propria are particularly suggestive of this lymphoma. It has recently been suggested that the cell of origin may be a memory B cell, although previously follicular lymphoma in the gastrointestinal tract was likened to mucosa-associated lymphoid tissue (MALT) lymphoma. The combination of (1) expression of α-4-β-7 integrin, which is a mucosal homing receptor, (2) VH gene deviation and (3) IgA production suggests that tumour cells are derived from mucosal B cells.

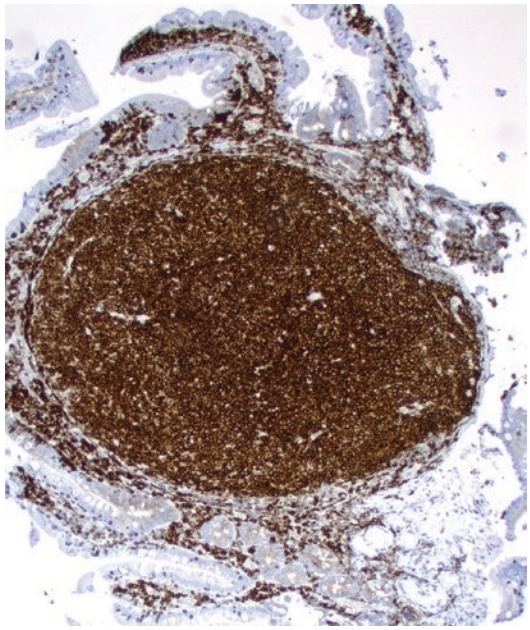

Fig. 7.28 Follicular lymphoma bcl2

2. Flow cytometry: See table (Chapter 1).
3. Molecular: Clonal restriction for Ig heavy and light chain genes. Bcl-2 rearrangement.

Follicular lymphoma should be distinguished from [23, 24]:

1. Reactive lymphoid hyperplasia—features of reactive lymphoid hyperplasia include the presence of tingible body macrophages; absence of Bcl-2 and CD10 confined to germinal centres only
2. MALT lymphoma. Follicular lymphoma differs by having CD10 positive B cells extending into the lamina propria; and no lymphoepithelial lesions

Extranodal Marginal Zone Mucosa-Associated Lymphoid Tissue (MALT) Lymphoma

May present as a primary lesion in the small intestine as a single mass or rarely as a lymphomatoid polyposis. Diagnostic features are discussed in the gastric tumour chapter. IPSID is a distinct subset presenting in the small intestine and is discussed below.

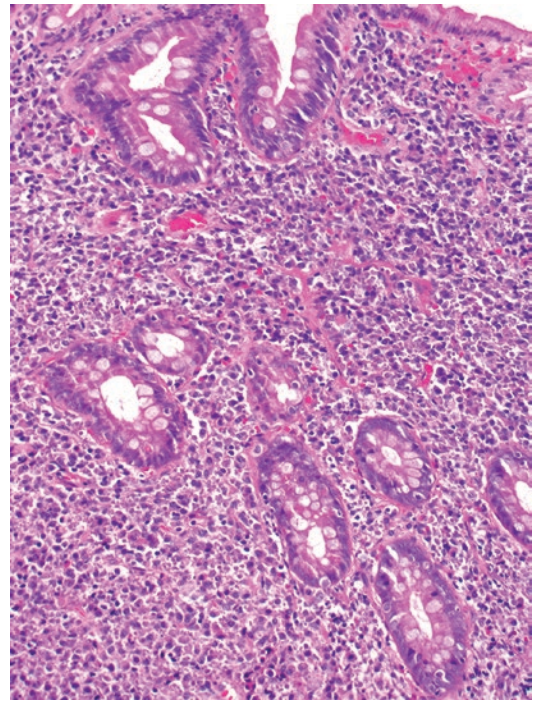

Fig. 7.29 IPSID - note plasmacytoid cell rich infiltrate

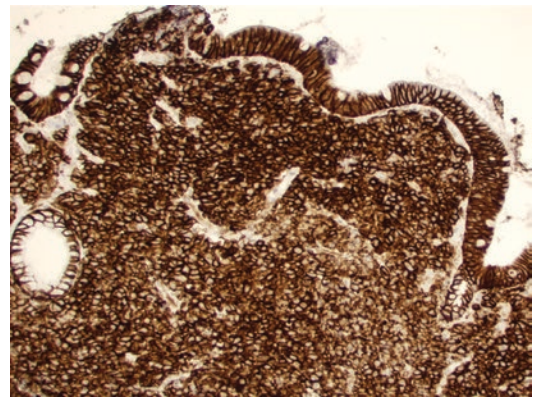

Fig. 7.30 IPSID positive reaction with CD138

Immunoproliferative Small Intestinal Disease (IPSID)/α Heavy Chain Disease (Syn. Mediterranean Lymphoma)

Is a subtype of small intestinal MALT lymphoma predominantly occurring in young adults of Middle Eastern or Mediterranean origin. IPSID is associated with *Campylobacter jejuni* infection and early stage disease may

respond to antibiotic therapy [25]. Poor sanitation, concurrent parasitic infection and low socioeconomic class are risk factors for disease development.

Three stages of disease are recognised. In stage A, there is an infiltrate of essentially normal appearing lymphocytes and plasma cells in the small intestinal mucosa without disturbance of villous architecture. In stage B, nodular collections of mildly atypical lymphoid cells expand the lamina propria and cause villous blunting. Lymphoepithelial lesions and follicular colonisation can be seen. Stage C disease is a fully developed malignancy with diffuse sheets of atypical, large cells, resembling immunoblasts or plasmablasts (Fig. 7.29). Reed-Sternberg-like cells may be seen.

Immunohistochemical and molecular features are summarised in Table. The fully developed malignancy is characterised by positive staining for CD20, CD138 (Fig. 7.30) and α-heavy chain (but no light chain staining). Early in the process, the combination of villous blunting and a plasma cell-rich infiltrate in the lamina propria can resemble coeliac disease or other similar enteropathy. The absence of intraepithelial lymphocytosis and the density of the infiltrate point to the correct diagnosis. Later, the process may be mistaken for diffuse large B-cell lymphoma or plasmablastic lymphoma. Early stage disease often responds to antibiotic therapy (30–70% remission). Untreated IPSID progresses to lymphoplasmacytic and immunoblastic diffuse large cell lymphoma that invades the intestinal wall, involves mesenteric lymph nodes and may metastasize to a distant organ [26]. Later stage disease requires radiotherapy and chemotherapy.

B-Chronic Lymphocytic Leukaemia/ Small Lymphocytic Lymphoma

This lymphoma is uncommon in the small intestine and is generally only seen in advanced disease with poorer prognosis. A diffuse small cell lymphoid infiltrate is seen. There may be single cell infiltration of the epithelium.

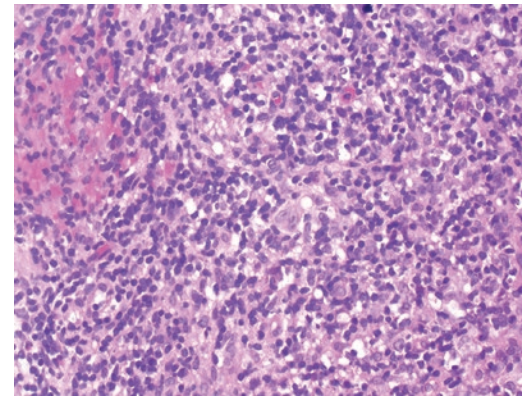

Fig. 7.31 PTLD in ileum range of cell sizes and a Reed Sternberg-like cell centrally. CMV was present in the endothelial cells

Post-transplant Lymphoproliferative Disorder

This is a lymphoproliferative disorder arising in immunosuppressed organ transplant recipients usually in association with EBV infection. Most cases are B-cell derived, although T-cell post-transplant lymphoproliferative disorder (PTLD) does exist (Fig. 7.31).

Immunosuppression required to prevent transplant rejection is the underlying cause. EBV infection is the main viral cofactor; however, it is not solely responsible for lymphomagenesis. Alterations in oncogenes and tumour suppressor genes and epigenetic changes, particularly, hypermethylation, are important. Plasmacytoid dendritic cells (PDCs) that are activated by viral infections probably play a pathogenetic role as do regulatory T cells (Treg cells), which modulate the immune reactions once incited by antigen [27].

There is a wide spectrum of histopathologic findings from B-cell (plasma cell-rich) hyperplasia to lymphoma. The attached table provides a classification scheme. The lymphoma is most often polymorphic characterised by an admixture of small lymphocytes, plasmacytoid cells, large immunoblastic cells and occasional multilobulated cells resembling Reed-Sternberg cells. Monomorphic lymphoma is usually a diffuse process with large immunoblastic or plasmoblastic cells. Geographic necrosis may be seen (Table 7.8).

Immunohistochemical and molecular features are tumour cells immunoreactive with pan B-cell

Table 7.8 Classification of PTLD [28]

(1) Early lesions
(a) Reactive plasmacytic hyperplasia
(b) Infectious mononucleosis-like lesions
(2) Polymorphic PTLD
(3) Monomorphic PTLD (classified according to lymphoma they resemble)
B-cell neoplasms
(a) Diffuse large B-cell lymphoma (DLBCL)
(b) Burkitt's lymphoma
(c) Plasma cell myeloma
(d) Plasmacytoma-like lesions
(e) Others
T-cell neoplasms
(a) Peripheral T-cell lymphoma not otherwise specified
(b) Hepatosplenic T-cell lymphoma
(c) Others
(4) Classical Hodgkin's lymphoma-type (HL-PTLD) and HL-like PTLD

PTLD = post-transplant lymphoproliferative disorder

markers CD19, CD20 and CD79a. EBV in situ hybridisation (EBV-ISH) is usually positive. Monoclonal expression of either kappa or lambda light chain is seen mostly in the monomorphic cases. PCR analysis of immunoglobulin gene rearrangement is often monoclonal. T-cell PTLD tumour cells are immunoreactive with the T-cell markers CD3 and CD5 and demonstrate clonal T-cell receptors αβ or γδ on PCR analysis. The differential diagnosis includes a broad range of B- and T-cell NHL and also Hodgkin's lymphoma, depending of the dominant morphologic pattern. In practice, the clinical setting generally provides the correct diagnosis.

T-Cell/NK-T-Cell Non-Hodgkin's Lymphoma

Ulcerative Jejunoileitis

Ulcerative jejunoileitis is a clinical syndrome of multiple intestinal ulcers, frequently complicated by haemorrhage, perforation or obstruction that is due to a coeliac disease-related clonal T-cell proliferation. This disease is infrequently sampled by routine endoscopic techniques, however, push enteroscopy may allow for biopsies to be taken. Histologically there is ulceration, acute and chronic inflammation, fibrosis and pseudopyloric gland metaplasia. Features of coeliac disease are usually evident in the adjacent small bowel mucosa. There may be collagenous sprue.

The intraepithelial lymphocytes demonstrate an aberrant immunophenotype identical to RCD2 in the majority of cases. TCR monoclonality is present.

Differential diagnosis includes other causes of multifocal ulceration:

- Drug injury, e.g. NSAIDs
- Vasculitis
- CMUSE
- Crohn's disease

These lack a history or serological evidence of coeliac disease and there are no coeliac disease enteropathy changes in non-ulcerated mucosa. Enteropathy-associated T-cell lymphoma forms a disease spectrum with UJ and separation is based on the identification of a mass lesion with ETTL.

Enteropathy-Associated T-Cell Lymphoma (Enteropathy-Type T-Cell Lymphoma, Intestinal T-cell Lymphoma)

This is a rare T-cell malignancy of the small intestine that usually, but not exclusively, arises in association with gluten-sensitive enteropathy. The association of this lymphoma with coeliac disease is based on the following evidence: (1) the presence of coeliac disease enteropathy in the adjacent mucosa, (2) history of long-standing coeliac disease in up to 10% of patients, (3) ETTL prevalence parallel coeliac disease prevalence and (4) high prevalence of HLA DQ2 haplotype in both diseases.

Two morphological variants are recognised (see Table 7.9). Prognosis is poor in both subtypes. Death is often as a result of severe malnutrition or as a complication of intestinal perforation [29, 30].

Extranodal NK-T-Cell Lymphoma, Nasal Type (ENKTL)

This is a mostly extranodal EBV infection-related lymphoma of NK-cell origin more often than T-cell origin. It is most commonly encountered in adult

Table 7.9 Two types of morphological variants

Type I or classical variant (Enteropathy associated T cell lymphoma)	Type 2 or monomorphic variant (monomorphic epitheliotropic T cell lymphoma)
• 80% to 90% of cases • Strong association with coeliac disease • Intermediate to large cells with abundant pale eosinophilic cytoplasm and round or slightly irregular central nuclei with prominent nucleoli • Associated inflammatory infiltrate of histiocytes and eosinophils • Adjacent coeliac enteropathy • CD3+, CD5−, CD7+, CD4−, CD8− (occasional +), CD103+, cytotoxic T-cell marker (TIA, granzyme, perforin) +, CD30 +/- and CD56− (rare +) • Gains 1q and 5q	• 10% to 20% • Asian populations, uncommon association with coeliac disease • Small to intermediate size cells with inconspicuous nucleoli and minimal cytoplasm (monomorphic) • No associated inflammation • Adjacent intraepithelial lymphocytosis (without villous atrophy) • CD3+, CD5−, CD8+, CD56+, CD30-, cytotoxic T-cell markers (TIA1+/−, granzyme B+, perforin+/−) • Gain 9q or deletion 16q, STAT5B mutation, MYC amplification

males of oriental or South American origin. The gastrointestinal tract is one of the more frequent sites of occurrence. The lymphoma is pleomorphic with an admixture of small and large malignant cells together with a background of eosinophils, plasma cells and histiocytes. Angioinvasive and angiodestructive growth are common leading to zones of necrosis and prominent karyorrhectic debris [31, 32]. In some tumours, there is predominance of small cells without necrosis.

Most cases have an NK-cell immunophenotype: CD2+, CD45RO+, CD43+ and CD56+. Clonality for T-cell receptor is αβ− and γδ−. Surface CD3 is usually absent, but cytoplasmic CD3 may be detected on paraffin sections because NK cells contain an epsilon (ε) chain of the CD3 molecular that is recognised by a CD3 immunohistochemical stain. T-cell cases are characterised by surface CD3 expression and clonal T-cell receptor αβ+ or γδ+. EBV genome is demonstrable in the tumour cells (EBV-ISH+). Differential diagnosis includes:

- Reactive/infectious process associated with extensive necrosis, e.g. mycobacterium tuberculosis infection. Attention to the finding of atypia in the lymphoid cells should allow distinction.
- Other large cell lymphomas, particularly those displaying angioinvasive growth. The immunophenotypic characterisation will separate most cases.
- Vasculitic processes—The finding of an extensive and atypical lymphoid infiltrate should alert to the possibility of lymphoma.
- NK-cell enteropathy [33]—An expanding range of benign NK-cell proliferations is recognised. These may involve the gastrointestinal tract and be sufficiently dense as to cause concern for lymphoma. EBV infection may be involved in the pathogenesis of some cases.

The tumour is aggressive with high mortality. Localised disease may respond to radiotherapy.

Hodgkin's Lymphoma

Hodgkin's lymphoma is overwhelmingly a nodal disease and is very unlikely to present in the small intestine in primary form. A primary enteric lymphoma containing Reed-Sternberg-like cells is more likely to represent a form of T-cell lymphoma or PTLD than to represent Hodgkin's lymphoma.

Haemopoietic Disorders with Plasmacytic Differentiation

Extramedullary Plasmacytoma (EMP)

Primary enteric plasmacytoma is rarely encountered in the small intestine. Well-differentiated lesions may mimic a primary plasma cell-rich inflammatory process (Fig. 7.32). The near absence of other inflammatory cells is a clue to a neoplastic process. Fortunately, immunohistochemical staining for kappa and lambda light chains is usually diagnostic, showing a clear light chain restriction. Plasma cell-rich MALT lymphoma and IPSID are other diagnostic possibilities. Absence of reaction with the B-cell marker CD20 is a clue the lesion is not a form of B-cell lymphoma. The plasma cell

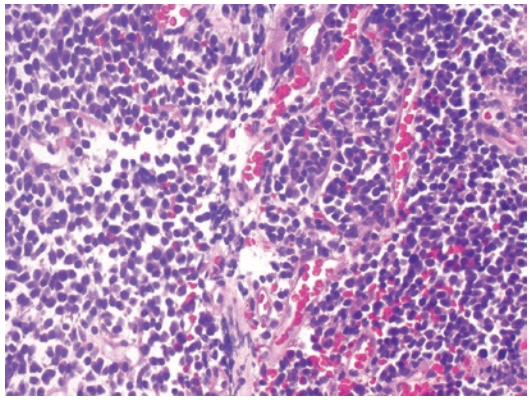

Fig. 7.32 Plasmacytoma duodenum - note the sheet like pattern of plasmacytic cells that can mimic an inflammatory process. The absence of other cell types is a clue to its neoplastic nature

nature of the tumour can be confirmed with plasma cell markers CD38 and CD138. Poorly differentiated lesions ("anaplastic plasmacytoma") have a broad differential diagnosis including high-grade lymphoma, metastatic melanoma and carcinoma. With respect to the latter, it should be remembered that some adenocarcinomas will express CD138 and many plasmacytomas express EMA.

Plasmablastic Lymphoma

Plasmablastic lymphoma (PBL) is a rare aggressive B-cell lymphoproliferative disorder that is most commonly encountered in the oral cavity of HIV-positive patients. Small intestinal location is uncommon. Cases of non-immunosuppressed, often elderly, patients are increasingly identified. Microscopically there is large cell lymphoma with plasmacytic differentiation (see Fig. 7.32). The immunophenotype is positive for CD79a (CD20 is negative), CD138, CD38, MUM-1 and CD10. EBV is often positive by in situ hybridisation. EMA may also be expressed. The Ki67 proliferation index is typically high [34].

Lymphoplasmacytic Lymphoma

Lymphoplasmacytic lymphoma is a B-cell lymphoma with plasmacytic differentiation that underlies most cases of Waldenstrom's macroglobulinaemia. The latter is characterised by deposition of IgM paraprotein producing eosinophilic, homogenous and strongly PAS+, begins within the villous lymphatics and eventually fills the lamina propria.

Other Haemopoietic Disorders

Extensive plasmacytic differentiation may be encountered in MALT lymphoma, IPSID and post-transplant lymphoproliferative disorder.

Leukaemia

Leukemic infiltration of the small intestine is rare. When present, there is generally evidence of systemic disease, although it may signal relapse of known disease. Chronic lymphocytic leukaemia, acute myeloid (myelogenous) leukaemia and acute lymphoblastic leukaemia are most commonly encountered.

Granulocytic sarcoma refers to an extramedullary tumour of myeloblasts and/or immature myeloid cells often a forerunner to the development of acute myelogenous leukaemia, but may also signal impending blast crisis in the setting of a myeloproliferative disorder or leukemic transformation in myelodysplastic syndrome. Intestinal involvement is sometimes a primary presentation of disease. The small intestine is the most common site of occurrence in the gastrointestinal tract. It tends to present as a polyp or larger ulcerated mass. Microscopically there is a diffusely infiltrating population of medium to large cells with occasional prominent nucleoli and minimal to moderate eosinophilic cytoplasm. A variable number of admixed maturing eosinophils and neutrophils are typically present in the more differentiated lesion. The immunophenotype is positive expression of CD43, in the absence of CD3 staining, lysozyme, CD34, CD117 and myeloperoxidase (MPO). Flow cytometry is also helpful. Characteristic cytogenetic abnormalities t(8;21)(q22;q22) and inv(16)(p13q22) are often found. Treatment should consist of systemic chemotherapy tailored to the treatment of AML, possibly in conjunction with surgical resection or radiation [35].

Table 7.10 Histiocytic infiltrates

Histiocytic disorders of the small intestine
Xanthogranulomatous inflammation
Infections rich in histiocytic cells, e.g. Whipple's disease, MAIC
Neoplasms, e.g. Rosai-Dorfman disease, Langerhans cell histiocytosis, juvenile xanthogranuloma, Erdheim-Chester disease, crystal storing histiocytosis, histiocytic sarcoma
Malakoplakia

Histiocytic Disorders

Xanthoma

Xanthoma is a collection of foamy histiocytes that forms single or multiple tumours. These may involve the mucosa only or the full thickness of the small intestinal wall. Multiple lesions may be present throughout the gastrointestinal tract. Hyperlipidaemia is an infrequent association in contradistinction to soft tissue xanthoma. A response to local mucosal injury is postulated as the aetiology in most cases. Confirmation of the histiocytic nature of the cells is via positive immunoreaction for histiocytic makers, e.g. CD68. The condition is benign and asymptomatic unless large. The main diagnostic considerations[2] are included in Table 7.10 [36, 37].

Malakoplakia

This is a reactive process caused by inadequate processing of bacterial products (usually derived from *E. coli*) by histiocytes. The resulting accumulation of histiocytes forms a tumour that often involves the mucosa. The terminal ileum is the most commonly involved small intestinal site. Malakoplakia is characterised by sheets of histiocytes with abundant granular eosinophilic that contain basophilic, periodic acid Schiff (PAS)-positive, diastase-resistant inclusions and diagnostic targetoid Michaelis-Gutmann bodies [38]. The latter are grey to blue with H&E and are positive for calcium von Kossa stain and iron Perls stain. The histiocytes are positive for CD68 antibody. Xanthogranulomatous inflammation is the main differential diagnosis but lacks the characteristic Michaelis-Gutmann bodies.

Langerhans Cell Histiocytosis

Gastrointestinal tract involvement by Langerhans cell histiocytosis is uncommon, and small intestinal involvement is rare. It may affect adults as well as children and mostly present as a polyp forming mucosal infiltrate measuring <10 mm diameter. Histologically, the lesion is mostly well circumscribed and contains sheets of polygonal cells with moderate pink slightly granular cytoplasm. The nuclei are characteristically grooved and are occasionally folded. An infiltrate, sometimes prominent, of eosinophils and lymphocytes may accompany the tumour. Mucosal ulceration, reactive mucosal changes, entrapped epithelial elements, focal necrosis and multinucleated giant cells can be seen [39]. By immunohistochemistry, the lesions express S-100 protein and CD1a. Adult cases are typically solitary polyps that are cured by polypectomy. In contrast, paediatric cases are usually associated with systemic disease and a poor prognosis.

Metastases to the Small Intestine Mucosa

Most originate from a remote, typically extraintestinal site. Spread is via direct invasion, transcoelomic spread or vascular/lymphatic permeation. Most small intestinal metastases are not diagnosed on endoscopic biopsies either because their complications such as obstruction, perforation or haemorrhage require emergent surgical intervention or because they are located within the deep submucosa or muscularis propria and are therefore not accessible to biopsy forceps. Mostly, metastases are readily distinguished by distinctive morphology and lack of an in situ component. Immunohistochemistry may be required to determine the site of origin.

Melanoma is the most common metastatic tumour and causes the most diagnostic difficulty because of variable morphology. The major differential diagnostic considerations include lymphoma, GIST and neuroendocrine carcinoma. Metastatic disease in the small intestine is a marker of advanced disease.

Multifocal Tumour

See Table 7.11.

Table 7.11 Multifocal tumour

Causes of multifocal tumour
Primary neoplasms—neuroendocrine, haematopoietic, e.g. lymphomatoid polyposis
Metastases
Others, e.g. infection-related tumours
Polyposis syndromes (see Chap. 1)

Spindle Cell Pattern: Benign Appearing

See Table 7.12.

Table 7.12 Spindle cell pattern: benign appearing (uniform cells with at most rare mitoses)

Leiomyoma
Schwannoma
Neurofibroma
Granular cell tumour
Solitary fibrous tumour
Inflammatory myofibroblastic tumour
Fibromatosis
Inflammatory fibroid polyp
Mastocytosis

Gastrointestinal Stromal Tumour (GIST)

GIST is a mesenchymal tumour mostly arising in the gastrointestinal tract. They are occasionally sampled in endoscopic biopsies, and establishment of the diagnosis is the most important aspect for the pathologist at this stage. GISTs originate from the interstitial cells of Cajal, a component of the gut autonomic nervous system. Most tumours harbour activating mutations of the tyrosine kinase receptors, c-KIT or platelet-derived growth factor receptor (PDGFR). Rarely mutations of exon 15 of BRAF and in genes encoding the enzyme complex of succinate dehydrogenase (SDH) have also been identified. Most GIST mutations are sporadic. Up to 5% have a hereditary basis or occur in a multi-tumour syndrome. These include (1) neurofibromatosis (NF-1)—lack both c-KIT and PDGRA mutation; (2) Carney's triad (gastric GIST, pulmonary chondroma and extraadrenal paraganglioma)—have dysfunction of SDH enzyme complex but do not have underlying gene mutation; (3) Carney-Stratakis syndrome (hereditary GIST and paraganglioma syndrome caused by germline mutations in succinate dehydrogenase (SDH)); and (4) familial GIST syndrome—have germline gain-of-function mutations in c-KIT (especially due to exon 11 mutation). PDGFRA mutation may also be found.

GISTs exhibit a wide variety of cellular and architectural patterns. (1) Cell type—this may be of spindle (70%), epithelioid (20%) or mixed (10%) type. Spindle cells range from plump smooth muscle-like cells to thin wavy neural-like cells, often with characteristic juxtanuclear vacuoles. Epithelioid cells are generally large and display cytoplasmic clearing (sometimes signet ring like). Nuclear variability and "floret"-like giant cells may be seen. (2) Architectural pattern includes short fascicles, palisading, nested (sometimes resembling neuroendocrine neoplasm), peritheliomatous, pseudovascular, pseudoglandular, haemangiopericytoma-like, linear streaming and sheeting/frankly sarcomatous patterns. (3) Stroma is also variable and includes hyalinised collagen, myxoid areas, microcystic stromal degeneration, lymphocytic infiltration and sometimes calcification and/or mature bone. Knowledge of the myriad cellular and architectural patterns is required to consider the correct diagnosis.

Routine mucosal biopsy specimens often contain little tumour submucosal-based GIST. Direct sampling of the tumour via TUNNEL or SINK procedures yields more materials.

Immunohistochemistry findings are tabulated in Table 7.13.

Gene mutation testing has potential diagnostic, prognostic and therapeutic value (see tables below) but is typically not requested on mucosal biopsy material. The differential diagnosis consists of other mesenchymal tumours of the gut. Predictive factors for progressive disease after primary resection are based on tumour size, site, mitotic activity and mutation background [40, 41]. These features are summarised in Tables 7.14, 7.15, 7.16, 7.17, and 7.18.

Table 7.13 Immunohistochemistry findings of gastrointestinal stromal tumours (GISTs)

1. CD117—positive in 95%. Pattern of reaction is at the cell membrane with a Golgi dot pattern of reaction in 45%. Negative staining may be seen in between 35% and 80% of PDGFRA mutation GIST and is more common in epithelioid tumours. Positive reaction is encountered in melanoma, seminoma and occasionally desmoid tumour
2. DOG-1—positive in >95%. Is as sensitive for c-KIT mutation spindle cell GISTs as CD117 and detects at least one third of the of the CD117 nonreactive tumours. It also reacts with a higher proportion of epithelioid and/or PDGFRA mutation GISTs
3. CD34—positive in 70%. This is more likely in gastric sites than the small intestine
4. SMA—positive in 30–40%
5. S-100—positive in 5% of all GIST but up to 1/3 of NF1-associated GIST
6. Desmin—positive in 1–2%
7. Keratin—positive in 1–2%
8. SDH subunits—SDHB is the common immunohistochemical stain used and may detect abnormalities in other subunits of the enzyme complex. There is loss of reaction in SDH mutation; hence, a good internal control (usually native gastric body mucosa) is required. SDH mutation is not expected in small intestinal GIST

Table 7.14 Risk of progressive disease in gastrointestinal stromal tumours (GISTs) according to mitotic index, size and site

Mitotic index, HPF	Size (cm)	Duodenum	Jejunum/ileum
≤5/50	≤2	None (0%)	None (0%)
≤5/50	2 to ≥5	Very low (3.8%)	Low (3.4%)
≤5/50	≥5 to >10	Insufficient data	Moderate (24%)
>5/50	>10	High (34%)	High (52%)
>5/50	≤2	Insufficient data	High (50%)
>5/50	2 to ≥5	High (50%)	High (73%)
>5/50	≥5 to >10	Insufficient data	High (85%)
>5/50	>10	High (86%)	High (90%)

Table 7.15 c-KIT

	Exon 9	Exon 11	Exon 13	Exon 17
Frequency (all GIST)	10–15%	65–70%	1%	1%
Histology	Usual pattern	Spindle > epithelioid		
Site predilection	Small intestine	Stomach	?	?
Imatinib response	++ (often requires higher dose)	+++	Variable	Variable
Progressive disease	17%	3%	?	?

GIST = gastrointestinal stromal tumours

Table 7.16 PDGFR

	Exon 12	Exon 14	Exon 18 (usually D842V)
Frequency (all GIST)	1.5%	0.5%	6%
Histopathology	Epithelioid, multinucleate giant cells, intermediate/high risk		
Site predilection	Stomach, omentum/peritoneal surface		
Imatinib response	Variable	Variable	Nil (D842V mutation is imatinib resistant)
Progressive disease	Overall less aggressive than c-kit mutant GIST		

GIST = gastrointestinal stromal tumours

Table 7.17 BRAF

	Exon 15 (V600E)
Frequency	Rare (<1%), female > male
Histopathology	Spindle cell
Site	Small intestine > stomach
Imatinib response	Nil (BRAF inhibitors may be useful in advanced disease)
Progressive disease	Insufficient data

Table 7.18 SDH deficiency

	SDHB (also SDHA, SDHC, SDHD)
Frequency	Rare (<1%), often familial, young females
Histopathology	Multinodular/plexiform; epithelioid cells
Site	Stomach only
Imatinib response	Nil (inhibition of insulin-like growth factor 1 receptor shows promise)
Progressive disease	20–25% develop liver metastases; however, long-term survival is still possible. 15% mortality (median 15 years of follow-up) Traditional risk assessment is poorly predictive of progression risk

Table 7.19 Other mesenchymal tumours encountered in mucosal biopsies of the small intestine

Mesenchymal cell of origin	Tumour type	Immunohisto-chemistry
Smooth muscle	Leiomyoma (rarely leiomyosarcoma)	SMA, Desmin
Neural	Schwannoma, neurofibroma, MPNST, perineurioma	S-100 EMA
Fibroblastic/ myofibroblastic	Solitary fibrous tumour, inflammatory myofibroblastic tumour, fibromatosis	CD34, STAT 6
Vascular	Glomus tumour, angiosarcoma	SMA CD31
Adipose	Lipoma, liposarcoma	CD34
Unknown	Synovial sarcoma, clear cell sarcoma, PEComa	EMA HMB-45

Inflammatory Fibroid Polyp

See terminal ileum chapter.

Other Mesenchymal Tumours

Other mesenchymal tumours that may be encountered in mucosal biopsies of the small intestine are included in Table 7.19.

Spindle Cell Pattern: Malignant Appearing (Hypercellular with cytological atypia and readily identified mitoses) (Box 7.4)

Box 7.4 Spindle Cell Pattern—Malignant Appearing

- Inflammatory myofibroblastic tumour
- Angiosarcoma
- Sarcomatoid carcinoma
- Follicular dendritic cell tumour
- Dedifferentiated liposarcoma
- GIST
- Leiomyosarcoma
- Kaposi sarcoma
- Synovial sarcoma

Lymphoid Hyperplasia

Small reactive lymphoid follicles may also be seen in the proximal small intestine mainly as a response to food allergy in children or in primary immunodeficiency disorder (e.g. CVID, IgA deficiency).

Non-neoplastic Vascular Lesions

Pyogenic Granuloma

Pyogenic granuloma is benign proliferation of capillary vessels originating from a feeding vessel. The aetiology is often unclear. Trauma is responsible for at least some cases. Medications such as retinoids, the protease inhibitor indinavir, 5-fluorouracil, capecitabine and some EGF receptor inhibitors have been implicated [42]. This lesion is also known as lobulated capillary haemangioma befitting its morphology. Typically, it is a raised, frequently ulcerated benign proliferation of capillary sized vessels in an oedematous stroma. Variable numbers of acute and chronic inflammatory cells may be present. The vessels show a branching pattern leading off a feeding vessel at the base. The major differential diagnoses are exuberant granulation tissue and

Kaposi sarcoma. Inflammatory fibroid polyp and inflammatory myofibroblastic tumour may sometimes enter the differential diagnosis. Attention to the clinical setting will aid the differential diagnosis.

Vascular Abnormalities

- These are non-neoplastic abnormalities in the vascular architecture or vessel anatomy. They often present as gastrointestinal tract bleeding.
  - Angiectasia [43]—This is characterised by dilated, thin-walled veins lacking an elastic lamina that results from a regional or generalised increase in venous pressure.
  - Haemodialysis-associated telangiectasia [43]—This is a generalised angiectasia of the gastrointestinal tract developing in patients on long-term haemodialysis. Changes in circulatory fluid volume may be a causative factor.
  - Portal hypertensive enteropathy [44, 45]—This is a form of generalised angiectasia resulting from portal hypertension. Thick-walled dilated vessels along with oedema of the lamina propria, fibromuscular proliferation, a decreased villous/crypt ratio and thickened muscularis mucosae form a characteristic picture of portal hypertensive enteropathy. Occasionally polyp formation or ulceration may occur.
  - Dieulafoy's lesion—This is a "calibre persistent" submucosal vein that projects in the overlying mucosa.
  - Arteriovenous malformation—This is characterised by an abnormal, frequently transmural collection of vessels displaying variable thickness of their vessel walls. An internal elastic lamina can be identified in some of the vessels.
  - Lymphangioma or acquired lymphangiectasia - contains proteinaceous fluid rather than blood within the vascular lumina (Fig. 7.33).

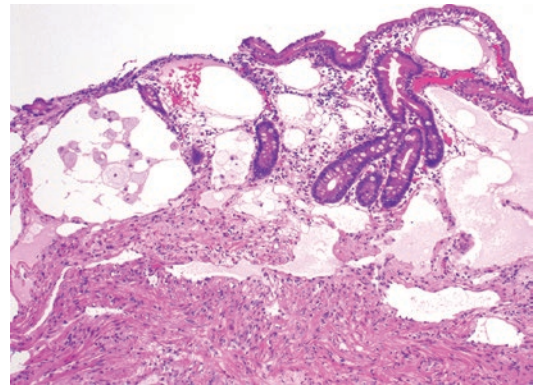

Fig. 7.33 Lymphangioma of duodenum - note proteinaceous content within dilated vascular spaces

Primary Lymphangiectasia

Primary lymphangiectasia is a rare condition of dilated intestinal lymphatics/lacteals with leakage of protein-rich material into the gut lumen leading to protein losing enteropathy and malabsorption. Dilated lymphatics appear through all layers of the intestine wall. They can appear empty or contain proteinaceous material with free floating histiocytes. There is no associated inflammation [46–48]. The main diagnostic considerations are lymphangioma, Whipple's disease, MAIC and pneumatosis intestinalis.

References

1. Genta RM, Kinsey S, Singhal A, Suterwala S. Gastric foveolar metaplasia and gastric heterotopia in the duodenum: no evidence of an etiologic role for Helicobacter pylori. Hum Pathol. 2010;41:1593–600.
2. Hoedemaeker PJ. Heterotopic gastric mucosa in the duodenum. Digestion. 1970;3:165–73.
3. Lessells AM, Martin DF. Heterotopic gastric mucosa in the duodenum. J Clin Pathol. 1982;35:591–5.
4. Yuan Z, Chen J, Zheng Q, Huang XY, Yang Z, Tang J. Heterotopic pancreas in the gastrointestinal tract. World J Gastroenterol. 2009;15(29):3701–3.
5. Bromberg SH, Camilo Neto C, Borges AF, Franco MI, França LC, Yamaguchi N. Pancreatic heterotopias: clinicopathological analysis of 18 patients. Rev Col Bras Cir. 2010;37(6):413–9.
6. Tan CL, Tan SH, So JB, Petersson F. Muco-submucosal elongated polyps of the gastrointesti-

nal tract: a case series and a review of the literature. World J Gastroenterol. 2013;19(11):1845–9.
7. de Sanctis S, Qureshi T, Stebbing JF. Clinical and pathological overlap in nonsteroidal anti-inflammatory drug-related small bowel diaphragm disease and the neuromuscular and vascular hamartoma of the small bowel. Am J Surg Pathol. 2001;25(4):539–41.
8. Shepherd NA, Jass JR. Neuromuscular and vascular hamartoma of the small intestine: is it Crohn's disease? Gut. 1987;28(12):1663–8.
9. Powers M, Sayuk GS, Wang HL. Brunner gland cyst: report of three cases. Int J Clin Exp Pathol. 2008;1(6):536–8.
10. Levine JA, Burgart LJ, Batts KP, Wang KK. Brunner's gland hamartomas: clinical presentation and pathological features of 27 cases. Am J Gastroenterol. 1995;90:290–4.
11. Gao YP, Zhu JS, Zheng WJ. Brunner's gland adenoma of duodenum: a case report and literature review. World J Gastroenterol. 2004;10(17):2616–7.
12. Vieth M, Kushima R, Borchard F, Stolte M. Pyloric gland adenoma: a clinico-pathological analysis of 90 cases. Virchows Arch. 2003;442(4):317–21.
13. Chen ZM, Scudiere JR, Abraham SC, Montgomery E. Pyloric gland adenoma: an entity distinct from gastric foveolar type adenoma. Am J Surg Pathol. 2009;33(2):186–93.
14. Khor TS, Brown I, Kattampallil J, Yusoff I, Kumarasinghe MP. Duodenal adenocarcinoma arising from a pyloric gland adenoma with a brief review of the literature. BMJ Case Rep. 2010;29.
15. Rosty C, Buchanan DD, Walters RJ, Carr NJ, Bothman JW, Young JP, Brown IS. Hyperplastic polyp of the duodenum: a report of 9 cases with immunohistochemical and molecular findings. Hum Pathol. 2011;42(12):1953–9.
16. Rubio CA. Serrated adenoma of the duodenum. J Clin Pathol. 2004;57(11):1219–21.
17. Rosty C, Campbell C, Clendenning M, Bettington M, Buchanan DD, Brown IS. Do serrated neoplasms of the small intestine represent a distinctive entity? Pathological findings and molecular alterations in a series of 13 cases. Histopathology. 2015;66:333.
18. Chu PG, Schwarz RE, Lau SK, Yen Y, Weiss LM. Immunohistochemical staining of pancreatobiliary and ampulla of Vater adenocarcinoma: application of CDX2, CK17, MUC1, and MUC2. Am J Surg Pathol. 2005;29(3):359–67.
19. Klöppel G, Rindi G, Anlauf M, Perren A, Komminoth P. Site-specific biology and pathology of gastroenteropancreatic neuroendocrine tumors. Virchows Arch. 2007;451(Suppl 1):S9–27.
20. Rindi G, Kloppel G, Alhman H, et al. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. Virchows Arch. 2006;449:395–401.
21. Sundararajan V, Robinson-Smith TM, Lowy AM. Duodenal gangliocytic paraganglioma with lymph node metastasis: a case report and review of the literature. Arch Pathol Lab Med. 2003;127(3):139–41.
22. O'Malley DP, Goldstein NS, Banks PM. The recognition and classification of lymphoproliferative disorders of the gut. Hum Pathol. 2014;45(5):899–916.
23. Misdraji J, Harris NL, Hasserjian RP, Lauwers GY, Ferry JA. Primary follicular lymphoma of the gastrointestinal tract. Am J Surg Pathol. 2011;35(9):1255–63.
24. Takata K, Sato Y, Nakamura N, Tokunaka M, Miki Y, Yukie Kikuti Y, Igarashi K, Ito E, Harigae H, Kato S, Hayashi E, Oka T, Hoshii Y, Tari A, Okada H, Al-Kader LA, Maeda Y, Tanimoto M, Kinoshita T, Yoshino T. Duodenal follicular lymphoma lacks AID but expresses BACH2 and has memory B-cell characteristics. Mod Pathol. 2013;26(1):22–31.
25. Lecuit M, Abachin E, Martin A, Poyart C, Pochart P, Suarez F, Bengoufa D, Feuillard J, Lavergne A, Gordon JI, Berche P, Guillevin L, Lortholary O. Immunoproliferative small intestinal disease associated with Campylobacter jejuni. N Engl J Med. 2004;350(3):239–48.
26. Al-Saleem T, Al-Mondhiry H. Immunoproliferative small intestinal disease (IPSID): a model for mature B-cell neoplasms. Blood. 2005;105(6):2274–80.
27. Ibrahim HA, Naresh KN. Post-transplant lymphoproliferative disorders. Adv Hematol. 2012;2012:230173.
28. Ho-Yen C, Chang F, van der Walt J, Mitchell T, Ciclitira P. Recent advances in refractory celiac disease: a review. Histopathology. 2009;54(7):783–95.
29. Arps DP, Smith LB. Classic versus type II enteropathy-associated T-cell lymphoma: diagnostic considerations. Arch Pathol Lab Med. 2013;137(9):1227–31.
30. Shroff S, Ganapathi KA. Enteropathy associated T cell lymphoma: a review of diagnostic findings and therapeutic strategies. Diagn Histopathol. 2014;20:151–5.
31. Ferry JA. Extranodal Lymphoma. Arch Pathol Lab Med. 2008;132:565–78.
32. Mansoor A, Pittaluga S, Beck PL, Wilson WH, Ferry JA, Jaffe ES. NK-cell enteropathy: a benign NK-cell lymphoproliferative disease mimicking intestinal lymphoma: clinicopathologic features and follow-up in a unique case series. Blood. 2011;117(5):1447–52.
33. Banks PM. Gastrointestinal lymphoproliferative disorders. Histopathology. 2007;50(1):42–54.
34. Wang HW, Yang W, Sun JZ, Lu JY, Li M, Sun L. Plasmablastic lymphoma of the small intestine: case report and literature review. World J Gastroenterol. 2012;18(45):6677–81.
35. Kohl SK, Aoun P. Granulocytic sarcoma of the small intestine. Arch Pathol Lab Med. 2006;130(10):1570–4.
36. Nielsen SL, Ingeholm P, Holck S, Talbot I. Xanthomatosis of the gastrointestinal tract with focus on small bowel involvement. J Clin Pathol. 2007;60(10):1164–6.
37. Detlefsen S, Fagerberg CR, Ousager LB, Lindebjerg J, Marcussen N, Nathan T, Sørensen FB. Histiocytic disorders of the gastrointestinal tract. Hum Pathol. 2013;44(5):683–96.

38. De Petris G, Leung ST. Pseudoneoplasms of the gastrointestinal tract. Arch Pathol Lab Med. 2010;134(3):378–92.
39. Singhi AD, Montgomery EA. Gastrointestinal tract langerhans cell histiocytosis: a clinicopathologic study of 12 patients. Am J Surg Pathol. 2011;35(2):305–10.
40. Miettinen M, Lasota J. Gastrointestinal stromal tumors. Gastroenterol Clin North Am. 2013;42(2):399–415.
41. Doyle LA, Hornick JL. Gastrointestinal stromal tumors: from KIT to succinate dehydrogenase. Histopathology. 2014;64(1):53–67.
42. Shirakawa K, Nakamura T, Endo M, Suzuki K, Fujimori T, Terano A. Pyogenic granuloma of the small intestine. Gastrointest Endosc. 2007;66(4):827–8.
43. Yano T, Yamamoto H. Vascular, polypoid, and other lesions of the small bowel. Best Pract Res Clin Gastroenterol. 2009;23(1):61–74.
44. Rondonotti E, Villa F, Signorelli C, de Franchis R. Portal hypertensive enteropathy. Gastrointest Endosc Clin N Am. 2006;16(2):277–86.
45. Misra V, Misra SP, Dwivedi M, Gupta SC. Histomorphometric study of portal hypertensive enteropathy. Am J Clin Pathol. 1997;108(6):652–7.
46. Abramowsky C, Hupertz V, Kilbridge P, et al. Intestinal lymphangiectasia in children: a study of upper gastrointestinal endoscopic biopsies. Pediatr Pathol. 1989;9:289.
47. Aoyagi K, Iida M, Yao T, et al. Characteristic endoscopic features of intestinal lymphangiectasia: correlation with histological findings. Hepatogastroenterology. 1997;44:133.
48. Riemann JF, Schmidt H. Synopsis of endoscopic and other morphological findings in intestinal lymphangiectasia. Endoscopy. 1981;13:60.