# Gastric polyps and dysplasia

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## Abstract

Gastric polyps are not uncommonly encountered at endoscopy and their discovery will normally precipitate a biopsy to determine the nature of the lesion. The foundation for arriving at the correct diagnosis is to be aware of the entities that exist and to this end we offer a classification based on histogenesis to aid the diagnostic endeavour. The vast majority of polyps encountered are epithelial in origin and so this review will focus mainly on epithelial polyps. Like elsewhere in the gastrointestinal tract, epithelial polyps can be associated with dysplasia which can be challenging to diagnose and grade. Dysplasia in the upper gastrointestinal tract has undergone recent reclassification and so we provide update and discussion on this neoplastic process as it applies to the stomach.

**Keywords** adenoma; dysplasia; fundic gland polyp; hyperplastic polyp; neuroendocrine tumour; polyp; stomach

## Introduction

The term gastric polyp usually refers to any lesion which projects above the mucosal plane into the lumen of the stomach. Polyps are identified during 2–6% of upper GI endoscopies, mainly as incidental findings.[1–5] Although there may be some endoscopic clues as to the subtype, histological examination is necessary to evaluate the wide and varied differential diagnosis.

This review aims to offer the reader a succinct and practical classification system for diagnosing gastric polyps. A detailed description of all gastric polyps is however beyond the scope of this article and in this respect the reader is referred to a number of excellent texts.[5,6] Instead, we will focus the discussion on the more common entities, particularly epithelial polyps, and those for which new morphological data as emerged in recent years. Dysplasia can also occur as a polypoid lesion and will also be discussed herein.

## Classification of gastric polyps

In the simplest classification, gastric polyps can be divided into neoplastic and non-neoplastic categories. Although simple at first glance, this scheme still requires further subclassification to allow consideration of all entities. We feel that a more practical classification relies on the pathologist recognizing and assigning the histogenesis of the polyp in the first instance, which can be followed by assessment for neoplastic potential. This classification is summarized in Table 1.

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## Epithelial polyps

Epithelial polyps represent the most prevalent type of gastric polyps. These can be further subdivided into non-neoplastic and neoplastic polyps, the latter of which includes adenomas that by definition exhibit dysplasia. Fundic gland polyps have traditionally been regarded as hamartomatous lesions but increasing evidence suggests that these may be neoplastic. Consideration should also be given to adenocarcinoma and metastatic tumours, both of which can present as a polyp endoscopically.

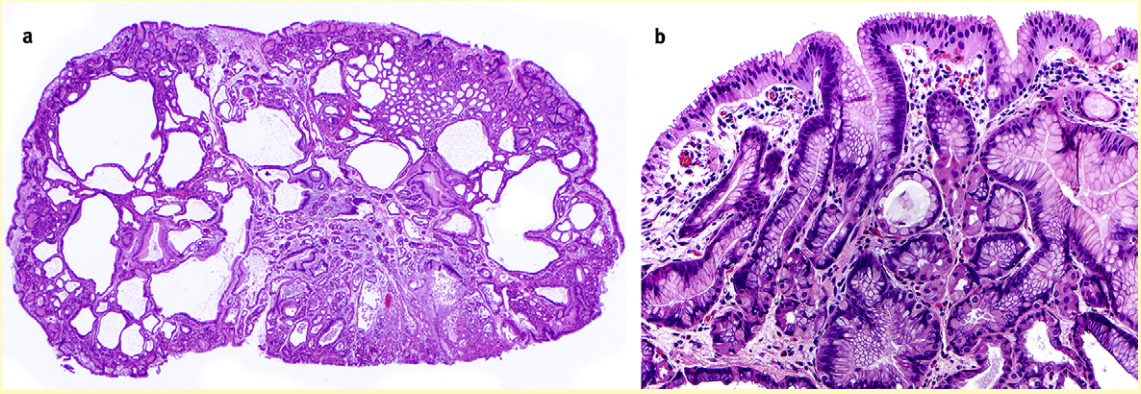
### Fundic gland polyps

FGPs are now recognized as the most common type of gastric polyp, accounting for 77% of all polyps in a recent large study with an overall prevalence in the general population of 3–11%.[5] They occur either sporadically or in the setting of Familial Adenomatous

**Histogenetic classification of gastric polyps**

| Cell of origin | Entity |
|---|---|
| Epithelial | Fundic gland polyp |
| | Hyperplastic polyp |
| | Adenoma including pyloric gland adenoma |
| | Neuroendocrine tumour |
| | Polyp cancer |
| | Metastatic carcinoma |
| Mesenchymal | Inflammatory fibroid polyp |
| | Gastrointestinal stromal tumour |
| | Inflammatory myofibroblastic tumour |
| | Smooth muscle tumours |
| | Glomus tumour |
| | Neural tumours |
| | Schwannoma |
| | Ganglioneuroma |
| | Granular cell tumour |
| | Adipocytic tumours |
| | Vascular tumours |
| Lymphoid/inflammatory | Polypoid gastritis |
| | Lymphoid hyperplasia |
| | Lymphoma |
| Miscellaneous | Xanthoma |
| | Pancreatic heterotopia |
| | Brunner gland adenoma |
| | Granuloma |
| | Amyloid |
| | Histiocytosis X |
| | Non-epithelial metastatic tumour e.g. malignant melanoma |

**Table 1**




**a** Typical fundic gland polyp at low power showing numerous cystically-dilated oxyntic glands with overlying foveolar-type epithelium. **b** Surface of fundic gland polyp lined by bland foveolar epithelium.

**Figure 1**

Polyposis (FAP). Sporadic FGPs are much more common, and their increased prevalence probably relates to their putative association with proton pump inhibitors. There has been some debate whether or not there is a negative association with *Helicobacter pylori* infection.[7] Most patients with FGPs are asymptomatic although non-specific gastrointestinal symptoms may occur in association with larger lesions. Endoscopically, FGPs appear as smooth, translucent, circumscribed mucosal elevations located in the body-fundic oxyntic mucosa. They can be single but are more commonly multiple (<10), and most measure less than 5 mm. Histology shows one or more cystically dilated fundic-type glands lined by flattened parietal cells with a degree of architectural distortion. The surface comprises foveolar-type epithelium which may appear atrophic (Figure 1). Assessment of the surrounding oxyntic glands may show parietal cell hyperplasia, hypertrophy and vacuolation which imparts a somewhat serrated appearance, all features which are suggestive of PPI drug use.[8] In the setting of PPI therapy, one may also see ECL cell hyperplasia; antral tissue sampled may show evidence of G cell hyperplasia. The finding of multiple FGPs (>10) in a young person should prompt both the pathologist and clinician to consider the possibility of FAP. In this scenario, follow-up with colonoscopy or flexible sigmoidoscopy may have some merit.[9]

FGPs were previously considered hamartomatous lesions but the association of genetic alterations in both sporadic and FAP-associated polyps suggests that both may be neoplasms. Mutations in the *APC — β-catenin* pathway have been encountered in both types of FGP however, in FAP, the polyps are more frequently demonstrate *adenomatous polyposis coli* (APC) gene (90%) mutations, compared to *β-catenin* mutations (10%).[10] The converse is true in sporadic FGPs, which more often harbour activating mutations in the *β-catenin* gene.[11]

Dysplasia is rare in sporadic FGPs but is encountered in a significant number of FAP-associated polyps. Interestingly, sporadic FGPs found to harbour dysplastic foci are more frequently associated with *APC* gene mutations, suggesting that this subgroup is phenotypically akin to FAP-associated FGPs (Figure 2).[12]

Regression of FGPs has been noted to occur despite evidence accruing that these are neoplastic. If clinically appropriate, such as in the setting of large sporadic polyps, PPI therapy may be discontinued. Some studies have suggested however, that PPI therapy may be protective against dysplasia in FAP-associated FGPs.[2,13] The risk of dysplasia in sporadic polyps is very low and although polypectomy is not necessary, biopsy is useful in order to exclude dysplasia; endoscopic surveillance is not recommended.[2,9] Follow-up guidelines for patients with FAP are not well established but in this setting, annual screening and surveillance is probably advisable as their risk of dysplasia is greater.

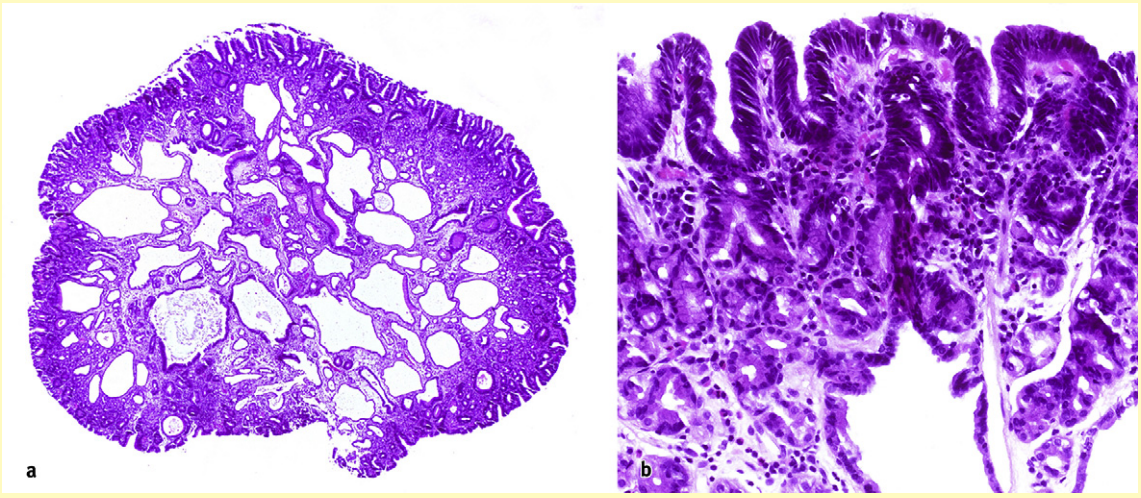
### Hyperplastic polyps and variants

Hyperplastic polyps comprise approximately 17% of all gastric polyps, although a wide variation has been reported.[2,5,6,14] This variation likely reflects prescribing practices for proton pump inhibitors, surgical practice and the prevalence of *Helicobacter* infection.

Hyperplastic polyps occur against a background of chronic gastritis and it is considered that these lesions develop as the result of an exaggerated mucosal response to injury.[15] An association with *H. pylori* infection has been reported but hyperplastic polyps can also be associated with autoimmune gastritis and bile reflux.[9] Solid organ transplant has also been reported as a risk factor.[16,17]

Hyperplastic polyps are typically observed in the antrum and are often multiple. Less often they are noted in the cardia, where there is an association with reflux disease. Multiple hyperplastic polyps can be found in patients with Menetrier's disease. Macroscopically, they are smooth, dome-shaped and usually measure between 0.5 and 1.5 cm but may exceed 2 cm. Larger lesions are prone to surface erosion which can result in chronic blood loss and possibly iron-deficiency anaemia. Gastric outlet obstruction is a rare complication of large hyperplastic polyps.[18–20]

Histologically, hyperplastic polyps comprise variably elongated, distorted and branching foveolae lying within an oedematous and inflamed stroma (Figure 3). The foveolae are lined by a single layer of foveolar-type epithelium. Pyloric-type glands and foci of intestinal metaplasia may be seen but in general the gastric



**a** Fundic gland polyp with increased surface epithelial density. **b** Higher power shows cytonuclear atypia, consistent with low-grade dysplasia.

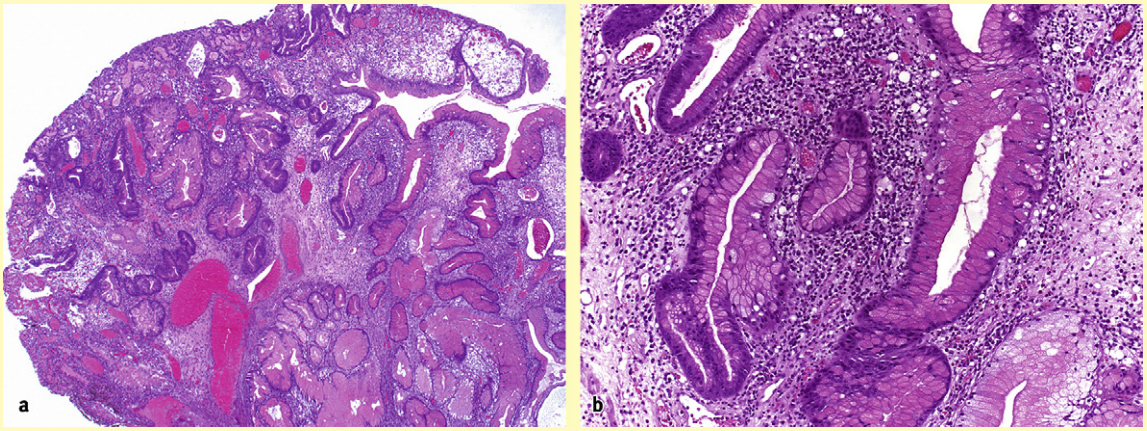
**Figure 2**

glands are not present. A rich vasculature is also common and can contribute to profuse bleeding during removal. Wisps of smooth muscle derived from the muscularis mucosa are usually seen.[8] The presence of thickened and splayed muscle fibres in the core of the polyp should lead one to consider an alternative lesion such as a prolapse polyp[21] (Figure 4) or Peutz–Jegher-type polyp.

In most cases, the diagnosis of a hyperplastic polyp is straightforward. However, a challenge can be to differentiate between florid regenerative changes on the surface of an eroded polyp from a dysplastic or neoplastic process. To this end, one should carefully assess that the atypia observed is confined to an area of surface damage, where it is more likely to be reactive. It is pertinent to remind the reader that foci of dysplasia or intramucosal carcinoma can be encountered in up to 4% of hyperplastic polyps, and more commonly in large polyps (>2 cm).[22–25] For this reason, it is important to assess all of the available material and liaise with the clinician if a dysplasia is identified, particularly if the polyp is large or there has been subtotal removal. Since there is also a not infrequent association with neoplasia elsewhere in the stomach (noted in 4–6% of cases), dysplastic changes in hyperplastic polyps should prompt endoscopic assessment of the surrounding mucosa.[4,9,25]

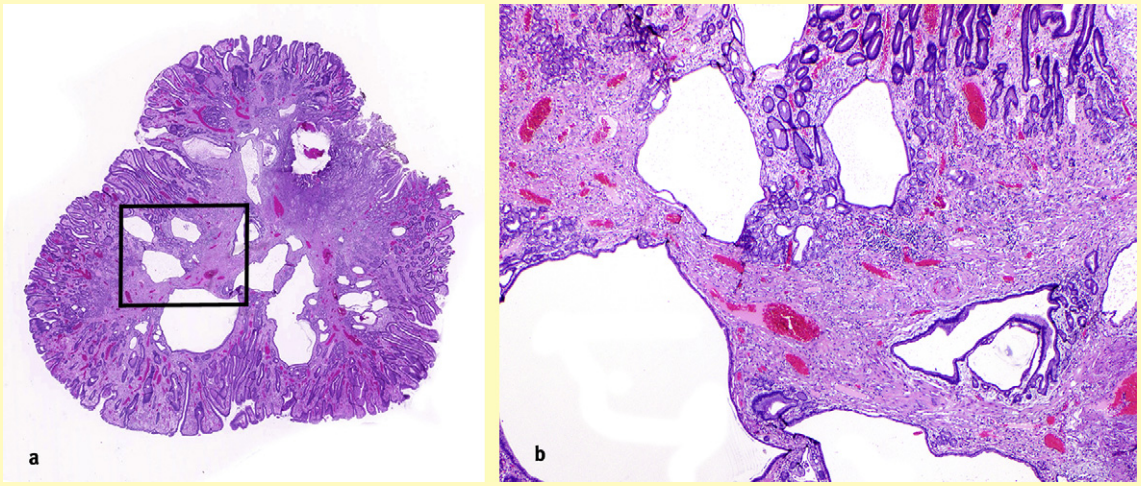
## Variants of hyperplastic polyps

***Polypoid foveolar hyperplasia*** – is regarded as a precursor lesion to hyperplastic polyps and shares a common aetiology in



**a** Hyperplastic polyp comprising irregular, cystically dilated glands lined by foveolar cells set within an inflamed and oedematous stroma. There is evidence of surface erosion at the bottom of the field associated with a degree of reactive atypia. **b** The characteristic inflammatory cell infiltrate is evident adjacent to tortuous and distended glands.

**Figure 3**




**a** At low power, the configuration of a prolapse-type gastric polyp is similar to a hyperplastic polyp. **b** On higher power thickened and splayed muscle fibres are more conspicuous and are associated with dilated and congested vascular channels, characteristic of trauma-induced changes. Cystically dilated misplaced glands are also noted, reminiscent of gastric cystica, are also associated with prolapsing mucosa.

**Figure 4**

the form of chronic mucosal injury. Typically, the lesions are between 1 and 2 mm and exhibit simple hyperplasia of the gastric foveolae without cystic change and gland distortion. Both regression and progression to hyperplastic polyps has been described, depending on the persistence of the underlying stimulus.

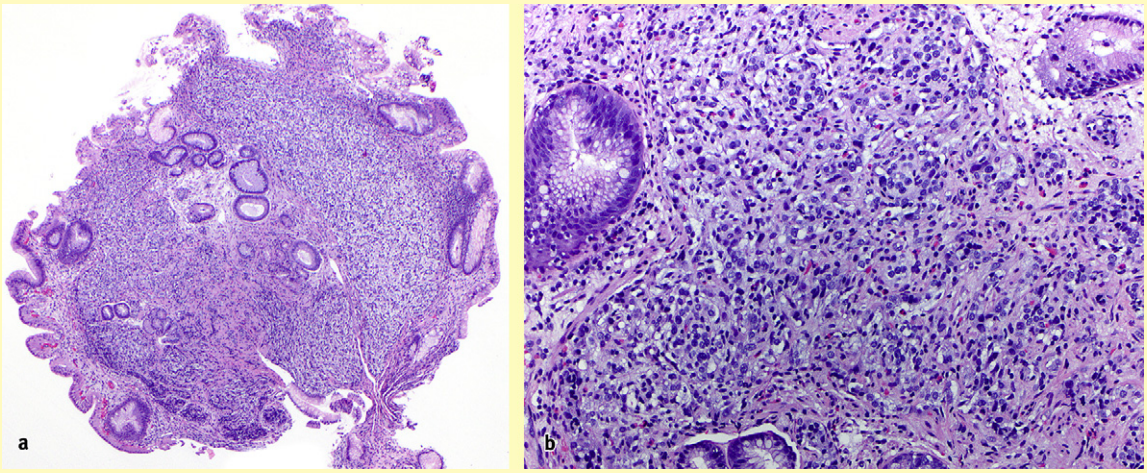
***Gastritis cystica polyposa/profunda*** – is defined as a hyperplastic polyp is which there is epithelial misplacement in the muscularis mucosa or more deeply in the submucosa or muscularis propria. The application of the term polyposa refers to when the lesion is mainly intraluminal; profundus is the preferred term when most of the lesion is intramural.[6] Like elsewhere in the gastrointestinal tract, it is generally held that epithelial misplacement is a result of trauma-induced entrapment of glands in the deeper compartments of the stomach wall. The main diagnostic difficulty lies in distinguishing a well differentiated adenocarcinoma. Bland cytomorphology, low or absent mitotic activity and lack of desmoplasia serve as indicators of benign misplaced epithelium.

### Neuroendocrine tumours – so called "carcinoid" tumours

The term "neuroendocrine tumour" (NET) has now been adopted in preference to "carcinoid" and these comprise less than 2% of gastric polypoid lesions with a trend towards an increasing incidence. Several different types of neuroendocrine cells are present in the stomach but at least 70% of all gastric NETs derive from enterochromaffin-like (ECL) cells.[2,5,6,26,27] In the current WHO system, gastrointestinal NETs are further assessed and subclassified to establish malignant potential using several parameters including site of origin, size, angioinvasion, proliferative activity, metastasis and association with clinical hormonal syndromes.[27,28]

ECL cell NETs may arise sporadically, or against a background of ECL cell hyperplasia induced by hypergastrinaemia. Four types of gastric NET exist (Type I–IV) and differ according to aetiology and morphology.[27,28] Both type I and II tumours are associated with hypergastrinaemia and arise in the body or fundus. Type I tumours are associated with a background of chronic autoimmune atrophic gastritis which results in loss of negative feedback to the G cells in the gastric antrum, secondary to destruction of parietal cells. Type II gastric NETs are associated with gastrinomas in the context of Zollinger–Ellison syndrome and multiple endocrine neoplasia type I (3–15% of tumours).[29] Consequently, the background mucosa will appear different in type II tumours and will demonstrate parietal cell hypertrophy and hyperplasia. Type III tumours are sporadic and generally do not have signature changes in the background mucosa; these are typically larger and exhibit more aggressive behaviour. Tumours associated with hypergastrinaemia are usually smaller, broad based and multifocal, while those that are sporadic (Type III) tend to be unifocal and larger. Type IV gastric NETs are rare, solitary and correspond to undifferentiated solid carcinomas that show early metastasis and poor outcome; there is no association with atrophic gastritis or ZES.[28]

Histologically, the most common forms of gastric NETs adopt ribbon and trabecular patterns. Insular patterns can also be seen. The cytomorphology is bland and similar to typical "carcinoid" tumours occurring elsewhere in the gastrointestinal tract (Figure 5). The cells are usually chromogranin A positive but negative for chromogranin B. Synaptophysin is positive in 50% of cases. In addition, if a biopsy displays features of atrophic gastritis or hypertrophy, assessment should include examination of the NE cell compartments, as precursor lesions of type I and II gastric NETs, namely hyperplasia, dysplasia and micro-NETs, can also be recognized histologically and may give rise to polypoid lesions at endoscopy. A three-tier system for grading NETs of the gastrointestinal tract has been proposed based on assessment of mitotic activity and proliferative activity (as measured by Ki67 or MIB1). This has been somewhat controversial but has been included in British and European guidelines for management.[27] The presence of anaplasia and necrosis is also



**a** Small well-differentiated gastric neuroendocrine tumour can be seen against a background of atrophic gastritis (Type I ECL cell NET). Typical nests of ECL cells are seen at the bottom left of the field. **b** Higher power shows ill-defined nests of ECL cells in the lamina propria. The cells have bland epithelioid nuclei with typical "salt and pepper" chromatin.

**Figure 5**

suggestive of higher grade and more likely to be found in sporadic NETs.[2]

Management of the gastric NETs depends on assessment of the parameters discussed above as well as tumour subtype (I–IV) and grade (1–3).[27] Type I NETs are nearly always benign and can be managed by endoscopic resection and surveillance; those that are difficult to control may require antrectomy to remove the stimulus from antral G cells. Treatment of associated vitamin B12 deficiency is also requisite. It is usual for type II tumours to remain indolent and as such local excision following treatment of underlying ZES suffices. Type II tumours may be larger than their Type I counterpart, and lymph node metastases have been reported. Type III tumours are fundamentally different, are more aggressive are best treated by partial or total gastrectomy. Due to the advanced stage of disease at presentation, Type IV NETs may have more limited treatment options.

### Adenomas

Gastric adenomas are defined by the WHO as circumscribed polypoid lesions composed of tubular and/or villous structures lined by dysplastic epithelium.[8,30] They can occur spontaneously or in the context of Familial Adenomatosis Polyposis (FAP). Many surgical pathologists use the terms [flat] dysplasia (such as that occurring against a background of chronic atrophic gastritis and intestinal metaplasia) and adenoma interchangeably. We do not subscribe to the opinion that the term adenoma should be reserved to denote polypoid dysplastic lesions developing without associated chronic atrophic gastritis or intestinal metaplasia[7] since in most cases the lack of associated pathology is related to limited sampling of the surrounding mucosa. Moreover, dysplasia occurring in completely normal gastric mucosa is exceptionally rare.

The prevalence of gastric adenomas is reported to be between 0.65% and 3.75% in Western countries and between 9 and 27% in countries such as Japan and China, where there is a higher incidence of gastric carcinoma.[5,14,25,31] Most adenomas are solitary, exophytic lesions which can be sessile (more common) or pedunculated and usually measure less than 2 cm, although they can reach up to 4 cm in size. The risk of malignancy is related to size, grade of dysplasia and villosity of the growth pattern. Larger adenomas are more frequently associated with a component of high-grade dysplasia, and a significant proportion contains foci of malignant transformation, the incidence of which is 40–50% for lesions measuring greater than 2 cm. Smaller adenomas should not be dismissed with little more than a cursory assessment as these too can contain carcinomatous foci.[8,30,32]

As preinvasive lesions, it is recommended that adenomas are excised in total when it is safe to do so, either by endoscopic polypectomy or by endoscopic mucosal resection (EMR). As there is a risk of synchronous carcinomas in patients with an adenomatous polyp,[2] thorough evaluation of the entire stomach should be recommended and undertaken. Follow-up surveillance is also recommended when gastric adenomas are excised.[9]

Please refer to the Gastric dysplasia section for review of the microscopic features of adenomas/dysplasia.

### Polyposis syndromes

A number of polyposis syndromes can affect the stomach including FAP, Juvenile polyposis, Peutz–Jeghers syndrome, Cronkite–Canada syndrome and Cowden disease and are associated with hamartomatous polyps. These conditions are relatively rare and the patients may present clinically with manifestations unrelated to the stomach. Fundic gland polyps, which are the most common type of gastric polyp are also associated with FAP (see above). A detailed discussion of these syndromes is beyond the scope of this review.

### Malignant epithelial polyps and metastatic tumours

As is the case elsewhere in the gastrointestinal tract, carcinomas can appear endoscopically as polyps. After establishing that one

is dealing with an invasive adenocarcinoma as opposed to dysplasia, it is necessary to evaluate whether the tumour is primary or metastatic. If primary, one should evaluate if it is superficial (i.e. an early gastric cancer) or more deeply invasive. Usually biopsies from primary gastric carcinomas will be associated with background changes of dysplasia. Diffuse-type gastric carcinoma may not have obvious surrounding dysplasia and it is usually pertinent to consider the differential diagnosis of metastatic carcinoma, in particular metastatic lobular carcinoma from the breast. In cases where there is little or no evidence of an origin, correlation with all available clinical information, including the patient's past medical history is important.

Non-epithelial malignant tumours such as malignant melanomas should also be considered in the differential diagnosis of poorly differentiated carcinoma.

## Non-epithelial polyps

The various mesenchymal and stromal elements of the stomach can give rise to nodular proliferations and tumours that manifest endoscopically as polyps. This heterogeneous group of lesions is listed in Table 1. In our practice, other than glomus tumours, most lesions in this category morphologically comprise spindle cells and frequently immunohistochemistry is required to establish the final diagnosis. Several entities should be considered in the differential diagnosis of a gastric spindle cell lesion including inflammatory fibroid polyp (IFP), gastrointestinal stromal tumour (GIST) and inflammatory myofibroblastic tumour (IMT). Less common spindle cells lesions that may be sampled in an endoscopic biopsy include nerve sheath tumours such as schwannomas and ganglioneuromas and smooth muscle tumours. Only IFPs will be discussed further here and the reader is referred to other papers with respect to GISTs[33–35] and IMTs.[36]

### Inflammatory fibroid polyp

IFPs comprise between 1 and 3% of all gastric polyps.[5,14] They arise in the submucosa of the antropyloric region and appear as solitary, sessile or pedunculated lesions that are frequently ulcerated. Histologically, they comprise bland spindle cells lying within a vascularized stroma that has an associated inflammatory infiltrate that is strikingly rich in eosinophils. Classically, the spindle cells are concentrically arranged around blood vessels but this is not always the rule (Figure 6). We have also seen variants of IFP which have a myxoid appearance, reminiscent of a nerve sheath myxoma. The spindle cells are usually CD34 positive and CD117 negative. It is wise to perform a wider panel of immunohistochemistry in difficult cases as CD34 positivity is also a feature of GISTs; since GISTs may also be CD117 negative, it may also be pertinent to include DOG-1 in the immunopanel.

In the past, IFPs were generally considered reactive lesions as there was an association with hypochlorhydria and achlorhydria. An allergic aetiology also seemed plausible due to the characteristic finding of eosinophils. A familial tendency has been noted following the discovery of a family in the UK, whose female members have a high incidence of the polyps.[37] More recently studies have demonstrated gain-of-function mutations in the *PDGFR-α* gene in IFPs, similar to those found in *kit*-negative GISTS, thereby alluding to a neoplastic process.[38,39]

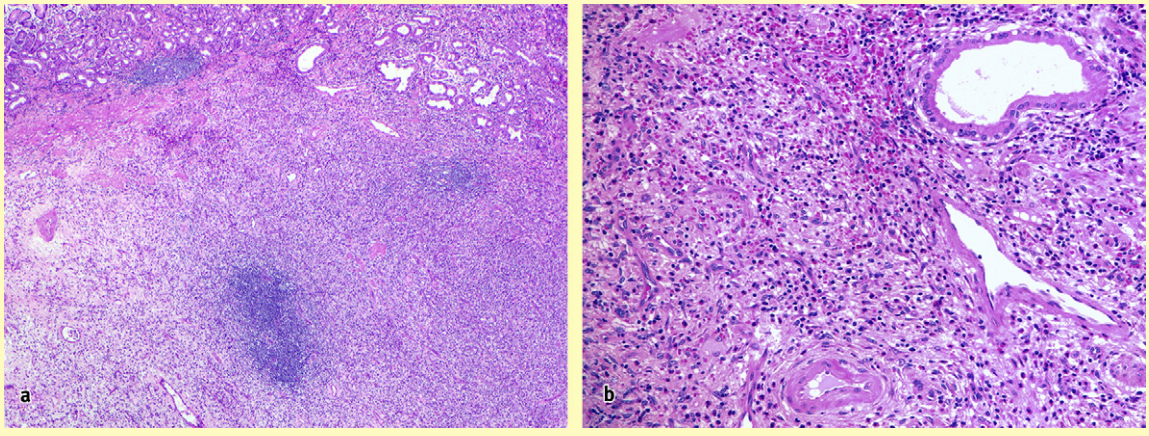
In management terms, most IFPs are found incidentally and do not recur after excision. Further treatment is not usually undertaken and patients do not require surveillance.[5]

## Miscellaneous lesions presenting as polyps

A range of other lesions can present as polyps as demonstrated in Table 1. Of these xanthomata and pancreatic heterotopia will be discussed.

### Xanthomata

These commonly appear as yellow plaques at endoscopy as opposed to well-defined polyps and are found in the body and fundus. They are thought to develop in association with chronic gastritis, especially after gastric resection and thus are believed to represent a reaction pattern to tissue injury. They are small




**a** Inflammatory fibroid polyp appearing as a moderately cellular submucosal tumour with limited extension into the lamina propria. Lymphoid aggregates are also present. **b** The characteristic morphology is more evident at higher power. Bland spindle cells are more conspicuous and there is evidence of perivascular "whorling". The stroma is rich in inflammatory cells, in particular eosinophils, which is typical.

**Figure 6**

lesions, usually measuring less than 3 mm, and histologically appear as loose collections of lipid-laden macrophages in the lamina propria. Diagnosis is normally straightforward and their main diagnostic significance is related to the differential diagnosis which includes diffuse-type (signet ring) carcinoma and granular cell tumour. A combination of histology, histochemistry (periodic-acid Schiff, mucicarmine) and immunohistochemistry (CD68, S100, cytokeratin) will allow differentiation of these entities.

### Pancreatic heterotopia

Pancreatic heterotopia presents in two settings. The first refers to the gastro-oesophageal junction where small nodules of pancreatic acinar tissue may be noted. This is reported in up to 15% of people undergoing endoscopy for gastro-oesophageal reflux disease and it is plausible that it forms part of a metaplastic process. "True" pancreatic heterotopia usually occurs in the prepyloric region of the stomach. The polypoid lesion may appear umbilicated, due to the presence of a pancreatic duct. The histological appearance is essentially of submucosally-based normal pancreatic tissue. Of note, in some cases pancreatic ductal tissue may predominate or be the only tissue recognized. There may be prominence of somewhat disorganized smooth muscle fibres admixed with the pancreatic tissue which engenders the alternative term of "adenomyoma" for pancreatic heterotopia.

Unless symptomatic, the patient does not require further therapy. Neoplastic transformation (i.e. pancreatic ductal adenocarcinoma or pancreatic neuroendocrine tumour) has been described but is sufficiently rare that there is no need for surgical excision or endoscopic surveillance.

The main differential diagnoses are well-differentiated adenocarcinoma and gastritis cystica polyposa/profundus. Resolving the differential diagnosis with well-differentiated adenocarcinoma may be difficult, particularly as pancreatic acini and islets may not be apparent in some cases of heterotopia. In this situation it is useful to note the bland cytology and the vaguely organoid or lobular appearance of heterotopia that can be appreciated on low power examination.

## Lymphoid proliferations

The main lesions to consider are:

- Polypoid gastritis
- Lymphoid hyperplasia
- Gastric lymphoma

Both polypoid gastritis and lymphoid hyperplasia are benign conditions, have preponderance for occurring in the antrum and are associated with *H. pylori* infection. Consistent with this is that both lesions can regress with successful eradication of the bacteria. The histology is similar as nodular lymphoid aggregates are noted in both however, in the former, the inflammatory infiltrate is more mixed and may be accompanied by overlying epithelial changes. The histological finding of lymphoid rich lesions in the stomach should prompt the pathologist to consider gastric lymphoma. A finding of destructive infiltrates of atypical lymphoid cells should raise suspicion of lymphoma followed by judicious use of immunohistochemistry to establish the diagnosis. A second opinion from a haematopathologist may also be advisable.

## The absent polyp

Up to 16% of gastric biopsies taken from endoscopically identified polyps disclose no histological features that pertain to a recognized gastric polyp. Indeed many such biopsies will either be normal or show variable degrees of inflammation.[5] Occasionally, there may be oedema or mild foveolar hyperplasia, which may account for a polypoid endoscopic appearance but this is non-specific. In such cases, it may be pertinent to liaise with the endoscopist or add a comment that the biopsy may not be representative of the lesion seen, or a more deeply seated lesion. However, care should be taken not to elevate the clinical concerns unnecessarily. It is good practice for endoscopic pictures to be included with the biopsy.[2]

## Gastric dysplasia

Diagnosing and grading gastric dysplasia continues to be a source of difficulty. In the first instance, it is relatively infrequently encountered in routine practice, particularly in Western countries. Second, and not infrequently, there can be great difficulty in distinguishing florid regenerative atypia from dysplasia.

### Diagnosing and grading gastric dysplasia and differentiation from regenerative atypia

Historically, criteria used to classify dysplasia and early invasive carcinoma in the upper gastrointestinal tract has differed between Western and Japanese pathologists, leading to difficulty in comparing prevalence data. Presently, there is a greater degree of consensus opinion, which has led to the development of several similar classification systems that in common adopt the two-tier grading system of low- and high-grade dysplasia. The classification systems in use are illustrated in Table 2.

***Low grade dysplasia*** shows only slight architectural deviation from non-neoplastic glandular epithelium and comprises multiple small glandular tubules with little branching or irregularity. Cytologically, there is a mild to moderate degree of atypia, with elongate or ovoid (so called "pencil-shaped") hyperchromatic nuclei. There is nuclear crowding and pseudostratification but in

**Classification schemes for evaluating dysplasia and invasive adenocarcinoma in the upper gastrointestinal tract**

| WHO classification | Vienna classification |
|---|---|
| Negative for dysplasia | 1. Negative for dysplasia |
| Indefinite for dysplasia | 2. Indefinite for dysplasia |
| Low-grade dysplasia | 3. Non-invasive, low grade dysplasia |
| High-grade dysplasia | 4. Non-invasive neoplasia |
| | 4.1 High-grade dysplasia |
| | 4.2 Non-invasive carcinoma |
| | 4.3 Suspicious for invasive carcinoma |
| Invasive adenocarcinoma* | 5. Invasive neoplasia |
| | 5.1 Intramucosal carcinoma |
| | 5.2 At least submucosal carcinoma |

* Includes intramucosal carcinoma.

**Table 2**

general the nuclei retain a tendency for basal orientation. The cells may appear mucin depleted. An important diagnostic feature is that the atypical features described extend to mucosal surface indicating lack of maturation (Figure 7).

***High-grade dysplasia*** displays more pronounced architectural aberrations with a greater degree of glandular crowding and gland irregularity. Typical patterns include prominent branching, budding and cribriforming (Figure 8). Small amounts of necrotic material or degenerate cell debris may be noted within glandular lumina and if extensive, one should search for evidence of intramucosal carcinoma. The constituent cells may appear cuboidal as opposed to columnar. There is generally a greater degree of nuclear pseudostratification with extension of nuclei towards the apical portion of the cell. The nuclei may be oval and hyperchromatic as for low-grade dysplasia but more often will appear rounded, with vesicular chromatin and prominent nucleoli. Irregular, thickened nuclear membranes may be seen and may impart the appearance of "boulder-shaped" nuclei. Mitoses are more numerous and may be noted in the surface epithelium; atypical mitoses be also be noted more frequently.[40]

***Regenerative atypia***, particularly when florid, can be difficult to distinguish from dysplasia. In contrast to dysplastic mucosa, regenerating or reactive mucosa generally does not exhibit the same degree of architectural atypia or disorganization as a dysplastic process. Glands tend to respect their relative spaces and may be patulous with a corkscrew appearance, reminiscent of foveolar hyperplasia. To discern a reactive process, one should carefully examine the surrounding mucosa and assess the changes therein as features such as inflammation, oedema and vascular congestion may point to a benign process. In regeneration, the cells present often appear immature and cuboidal with reduced amounts of cytoplasm. The nuclei may be slightly larger than in normal epithelium, but in general terms they are more monomorphic, evenly spaced without significant crowding or pseudostratification and tend to remain basally orientated. It is inferred that the nuclear to cytoplasmic ratio will be increased but this is less marked than in dysplasia. Nucleoli may be seen

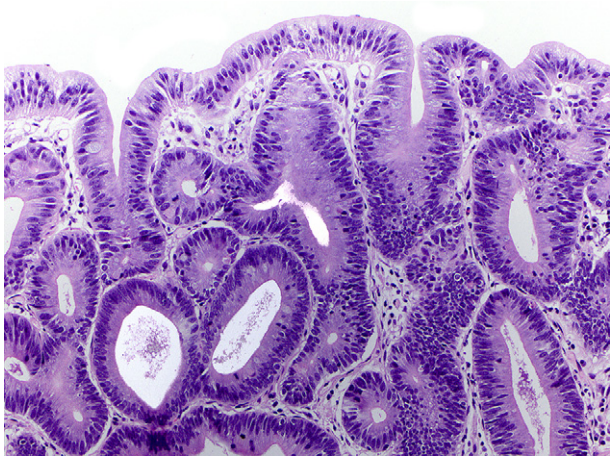


**Figure 7** Low-grade adenomatous (Type I) dysplasia. The normal architecture is largely maintained but there is cellular and nuclear crowding. The hyperchromatic nuclei are pencil-shaped and show pseudostratification. The abnormalities can be seen within deep glands and on the surface indicating failure of maturation. This feature helps to establish a diagnosis of dysplasia over regenerative atypia.

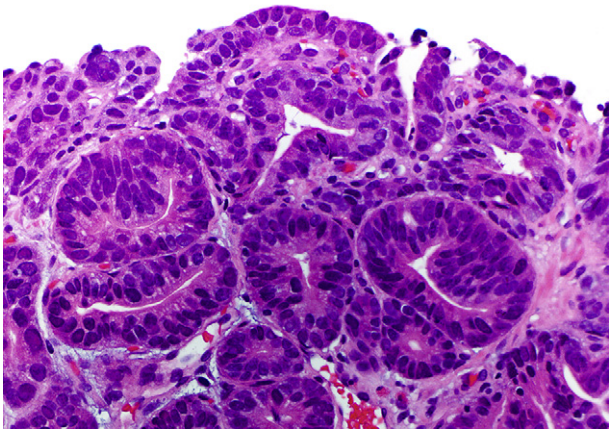
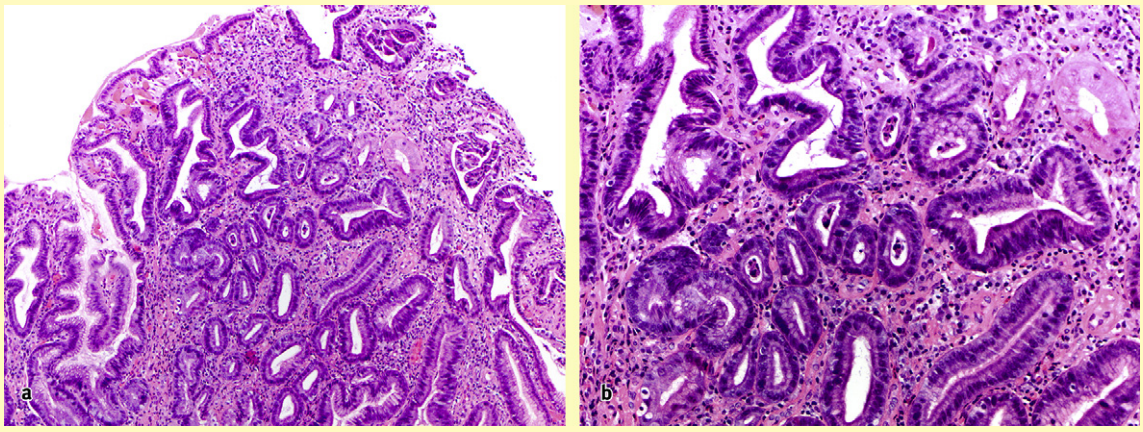


**Figure 8** High-grade adenomatous (Type I) dysplasia characterized by a greater degree of architectural changes such as crowding and back-to-back glandular arrangements. The nuclei are more pleomorphic and have boulder-like outlines.

but tend to be much smaller and may be multiple. Mitotic activity is usually increased but is confined to the proliferative "neck" zone and should not be present in surface epithelial cells. A key finding to appreciate is maturation and cellular differentiation as cells move from the proliferative zone to the surface[40] (Figure 9). Another useful finding is the lack of abrupt transition from benign epithelium to atypical epithelium, as is more commonly noted in dysplasia.[41]

Ancillary techniques such as p53 and Ki67 immunohistochemistry have been used to assist in distinguishing between florid reactive atypia and dysplasia. Strong, nuclear staining for p53 is thought to be a marker of neoplasia and can be detected in approximately one-third of gastric dysplasia. The finding of an area of strong p53 staining in conjunction with Ki67 labelling, especially at the surface (and hence distant from the normal proliferative zone), is suggestive of dysplasia. However, this staining pattern is not specific and it should be noted that p53 staining has been detected in *H. pylori* gastritis and in up to 30% of cases of intestinal metaplasia. Therefore the results of immunohistochemistry should be correlated closely with the morphological impression gained from thorough H&E examination, and should never be used in isolation to render a diagnosis of dysplasia.

***Indefinite for dysplasia*** is used in many of the current classification systems. It is not a biological entity but a reflection of a diagnostic difficulty. From a clinical standpoint, the term essentially indicates a need for close surveillance and repeat biopsy of the patient. The diagnosis can be used in a limited number of settings such as when there is a genuine difficulty in discerning reactive epithelial changes from dysplasia, when worrisome atypia is noted but is confined to a very small area or when the tissue is limited in amount or quality. When strict criteria are applied, this represents an uncommon diagnosis in our experience. In addition, a proffered diagnosis of "indefinite for dysplasia" should be accompanied by an explanatory note to the clinician regarding the diagnostic dilemma. Importantly, this category should not serve as a wastebasket group for all cases of regenerative atypia, as in most cases, an underlying inflammatory condition can be recognized.



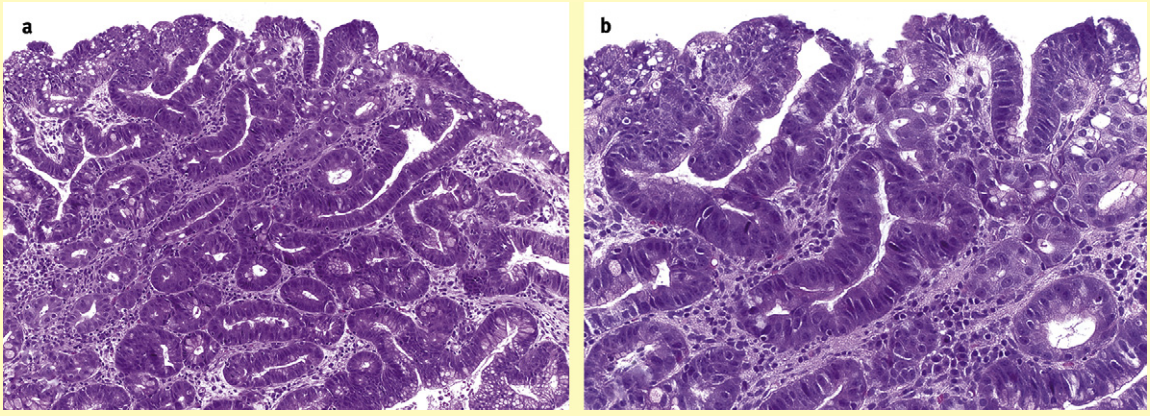

Regenerative atypia. Although cells exhibit mild nuclear enlargement and mucin depletion, there is uniformity amongst all the atypical cells with no evidence of an abrupt transition to normal appearing epithelium, which is more typical of dysplasia. Note also the foveolar hyperplasia at the left side of the field and maturation of cells towards the surface. When all the features are taken together, a diagnosis of regenerative or reactive atypia can be rendered.

**Figure 9**

### Types of gastric dysplasia

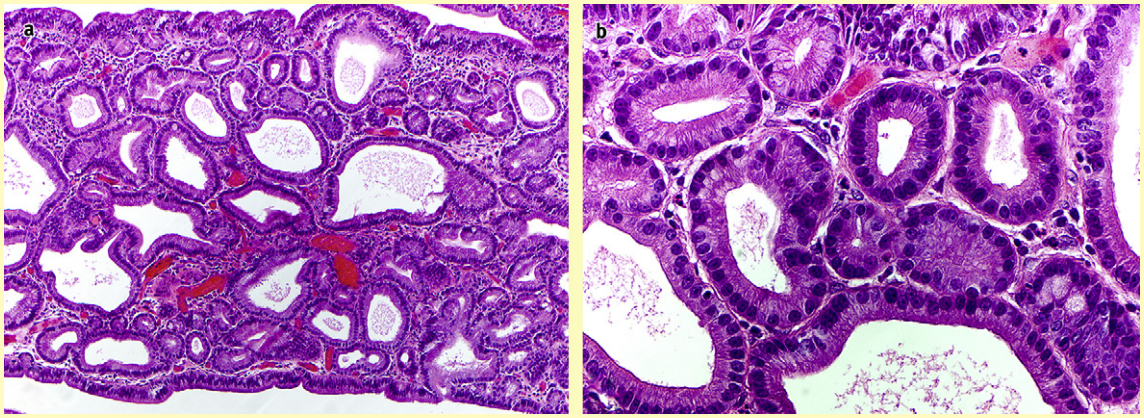
Four types of gastric dysplasia are recognized. The most common form of gastric dysplasia has an intestinal phenotype, resembling colonic adenomas. This is classified as Type I or "adenomatous" dysplasia (Figures 7 and 8). Type II (hyperplastic/foveolar) dysplasia is less common, and typically resembles foveolar epithelium. In a series of 69 cases of gastric dysplasia, foveolar-type accounted for approximately 22% of the cases.[42] The morphological features of low-grade foveolar dysplasia can be deceptively bland and it may be difficult to differentiate from reactive foveolar atypia. This may explain why foveolar dysplasia is reported to be more commonly high grade than intestinal-type dysplasia. The constituent glands tend to show variation in size and shape with occasional cystic change and gland branching. Papillary in-folding and gland serrations may be seen and are reminiscent of colonic hyperplastic polyps or serrated adenomas. The cells tend to have a cuboidal configuration with clear to faintly eosinophilic cytoplasm and vesicular nuclei and prominent nucleoli (Figure 10).[7,40]

The third type of dysplasia represents the pyloric gland adenoma (Figure 11). The characteristics of pyloric gland adenomas were first described by Borchard in 1990.[43] These lesions commonly arise against a background of autoimmune gastritis or *H. pylori* infection, and are more prevalent in elderly patients. They are composed of tightly packed pyloric-type glands lined by bland appearing low columnar mucus-secreting epithelium with fine granular cytoplasm but the normal apical




**a** Foveolar (Type II) dysplasia. Irregular gland contours can be appreciated with short papillations and serrations. The lining epithelium resembles gastric foveolar epithelium. **b** At this power, nuclear atypia can be appreciated allowing a diagnosis of dysplasia.

**Figure 10**

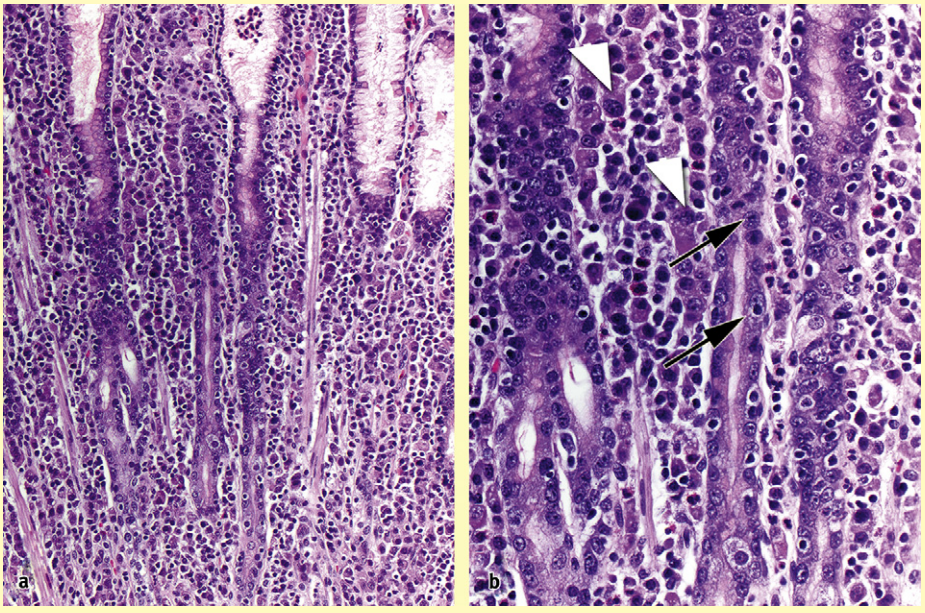


**a** Pyloric gland adenoma. Tightly packed glands are present which are lined by pyloric-type epithelium. There is minimal atypia. **b** At higher power, mild nuclear enlargement can be appreciated along with small nucleoli. Despite the bland morphology, these lesions are considered to be dysplastic.

**Figure 11**

mucin cap is absent. The immunohistochemical stain MUC6 characteristically decorates the constituent cells. Assigning the grade of dysplasia can be difficult in pyloric gland adenomas and there is a significant risk of malignant transformation.[44,45] Thus, in light of the reported risks with these lesions, complete removal is necessary.

Tubule neck (or globoid) dysplasia represents the fourth type of dysplasia and is believed to be a precursor to sporadic diffuse-type gastric carcinoma. It occurs in neck region of non-metaplastic gastric epithelium and the typical appearance is of as enlarged clear cells, of which some have signet-ring morphology (Figure 12). By definition, the atypical cells are confined by the



**a** Tubule neck dysplasia in a case of sporadic diffuse-type carcinoma of the stomach. At this power only pit elongation and sharp transition with normal foveolar cells is noted. **b** The gastric pit (arrow) shows elongation and is lined by mucin-depleted cells showing nuclear pleomorphism. The adjacent lamina propria contains mononuclear inflammatory cells as well as individual malignant epithelial cells (arrowhead). This latter population shares features in common with the adjacent pit allowing one to interpret the atypia as representing tubule neck dysplasia. It is extremely rare and difficult to diagnose tubule neck.

**Figure 12**

basement membrane. It is rare to make a diagnosis of tubule neck dysplasia as it is extremely subtle and difficult to recognize; in many cases, the diagnosis is only made on resection specimens of diffuse-type gastric carcinoma.[7,40,41] Accordingly, it is rarely seen on endoscopic biopsies and this point should be considered if one is contemplating the diagnosis on such material. Occasionally, clearing of neck cells, believed to be related to PPI effects, can mimic tubule neck dysplasia (personal observation GYL). These lesions ought to be differentiated from those seen in familial diffuse-type gastric cancer.

### Management of gastric dysplasia

Both low- and high-grade dysplasia are variably associated with an increased risk of malignant transformation. Rendering either of these diagnoses thus has significance for the patient in terms of further management and follow-up.

It is reported that low-grade dysplasia persists in 19–50% of cases but regresses in 38–75%.[46–48] The risk of progression to high-grade dysplasia is suggested to be 17%.[49] There has also been variation in figures quoted for progression to adenocarcinoma but more recent studies suggest that this is in the order of 0–9%.[49,50] Follow-up of low-grade dysplasia is recommended in the form of annual endoscopic surveillance and re-biopsy; advances in endoscopic techniques such as the introduction of chromoendoscopy, narrow band imaging and confocal microscopy now allows improved surveillance with detection and sampling of previously undetectable lesions.[41]

A diagnosis of high-grade dysplasia places the patient in a different clinical category associated with higher rates of persistence (14–58%) and progression (60–85%). Similarly, regression is less often observed being documented in 0–16% cases.[49–52] With more advanced techniques available for management, rendering a diagnosis of HGD (as well as intramucosal carcinoma) is no longer an indication for gastrectomy. Instead, following exclusion a more deeply infiltrative lesion by endoscopic ultrasound and adequate sampling, it is now possible to employ endoscopic mucosal resection for definitive management.

## Conclusion

A huge variety of lesions may present incidentally at endoscopy as gastric polyps. Unfortunately, it is often the case that the biopsy specimen is submitted with little or no details as to the endoscopic impression of the lesion and thus the pathologist is asked to make a diagnosis in a vacuum based on limited clinical information and material. Rendering the correct diagnosis first requires knowledge of the individual entities that may exist and to this end establishing the histogenesis of the lesion is a good starting point. Dysplasia can involve a number of different epithelial polyps and despite improved consensus in classifying and grading dysplasia, this remains challenging for many pathologists at the sign-out bench. Unfortunately, despite the range of ancillary tests that can be employed in histopathology, there is no substitute for careful H&E examination. Double reporting of upper gastrointestinal tract dysplasia is being increasingly used and is to be welcomed. In cases were diagnostic doubt persists we advocate a low threshold for seeking a second opinion. ◆

## REFERENCES


1 Dekker W. Clinical relevance of gastric and duodenal polyps. *Scand J Gastroenterol* 1990; **25**(suppl 178)**:** 7–12.
2 Carmack SW, Genta RM, Graham DY, Lauwers GY. Management of gastric polyps: a pathology-based guide for gastroenterologists. *Nat Rev Gastroenterol Hepatol* 2009; **6:** 331–41.
3 Ghazi A, Ferstenberg H, Shinya H. Endoscopic gastroduodenal polypectomy. *Ann Surg* 1984; **200:** 175–80.
4 Laxen F, Sipponen P, Ihamaki T, Hakkiluoto A, Dortscheva Z. Gastric polyps; their morphological and endoscopical characteristics and relation to gastric carcinoma. *Acta Pathol Microbiol Immunol Scand A* 1982; **90:** 221–8.
5 Carmack SW, Genta RM, Schuler CM, Saboorian MH. The current spectrum of gastric polyps: a 1-year national study of over 120,000 patients. *Am J Gastroenterol* 2009; **104:** 1524–32.
6 Odze RD, Goldblum JR. Surgical pathology of the GI tract, liver, biliary tract and pancreas. Philadelphia: Saunders Elsevier, 2009.
7 Yantiss RK, O.R.. Neoplastic precursor lesions in the upper gastrointestinal tract. *Diagnostic Histoplathology* 2008; **14:** 437–52.
8 Park do Y, Lauwers GY. Gastric polyps: classification and management. *Arch Pathol Lab Med* 2008; **132:** 633–40.
9 Goddard AF, Badreldin R, Pritchard DM, Walker MM, Warren B. The management of gastric polyps. *Gut* 2010; **59:** 1270–6.
10 Abraham SC, Nobukawa B, Giardiello FM, Hamilton SR, Wu TT. Fundic gland polyps in familial adenomatous polyposis: neoplasms with frequent somatic adenomatous polyposis coli gene alterations. *Am J Pathol* 2000; **157:** 747–54.
11 Abraham SC, Nobukawa B, Giardiello FM, Hamilton SR, Wu TT. Sporadic fundic gland polyps: common gastric polyps arising through activating mutations in the beta-catenin gene. *Am J Pathol* 2001; **158:** 1005–10.
12 Abraham SC, Park SJ, Mugartegui L, Hamilton SR, Wu TT. Sporadic fundic gland polyps with epithelial dysplasia: evidence for preferential targeting for mutations in the adenomatous polyposis coli gene. *Am J Pathol* 2002; **161:** 1735–42.
13 Bianchi LK, Burke CA, Bennett AE, Lopez R, Hasson H, Church JM. Fundic gland polyp dysplasia is common in familial adenomatous polyposis. *Clin Gastroenterol Hepatol* 2008; **6:** 180–5.
14 Stolte M, Sticht T, Eidt S, Ebert D, Finkenzeller G. Frequency, location, and age and sex distribution of various types of gastric polyp. *Endoscopy* 1994; **26:** 659–65.
15 Dirschmid K, Platz-Baudin C, Stolte M. Why is the hyperplastic polyp a marker for the precancerous condition of the gastric mucosa? *Virchows Arch* 2006; **448:** 80–4.
16 Amaro R, Neff GW, Karnam US, Tzakis AG, Raskin JB. Acquired hyperplastic gastric polyps in solid organ transplant patients. *Am J Gastroenterol* 2002; **97:** 2220–4.
17 Jewell KD, Toweill DL, Swanson PE, Upton MP, Yeh MM. Gastric hyperplastic polyps in post transplant patients: a clinicopathologic study. *Mod Pathol* 2008; **21:** 1108–12.
18 Abraham SC, Singh VK, Yardley JH, Wu TT. Hyperplastic polyps of the stomach: associations with histologic patterns of gastritis and gastric atrophy. *Am J Surg Pathol* 2001; **25:** 500–7.
19 Cerwenka H, Bacher H, Mischinger HJ. Pyloric obstruction caused by prolapse of a hyperplastic gastric polyp. *Hepatogastroenterology* 2002; **49:** 958–60.
20 Chen HW, Lu CH, Shun CT, Lin MT, Tsang YM. Gastric outlet obstruction due to giant hyperplastic gastric polyps. *J Formos Med Assoc* 2005; **104:** 852–5.

**21** Gonzalez-Obeso E, Fujita H, Deshpande, V, et al. Gastric "hyperplastic polyps": a heterogeneous clinicopathological group including a distinct subset best categorized as mucosal prolapse polyp. *Am J Surg Pathol*., in press.

**22** Daibo M, Itabashi M, Hirota T. Malignant transformation of gastric hyperplastic polyps. *Am J Gastroenterol* 1987; **82:** 1016–25.

**23** Dirschmid K, Walser J, Hugel H. Pseudomalignant erosion in hyperplastic gastric polyps. *Cancer* 1984; **54:** 2290–3.

**24** Han AR, Sung CO, Kim KM, et al. The clinicopathological features of gastric hyperplastic polyps with neoplastic transformations: a suggestion of indication for endoscopic polypectomy. *Gut Liver* 2009; **3:** 271–5.

**25** Hattori T. Morphological range of hyperplastic polyps and carcinomas arising in hyperplastic polyps of the stomach. *J Clin Pathol* 1985; **38:** 622–30.

**26** Gilligan CJ, Lawton GP, Tang LH, West AB, Modlin IM. Gastric carcinoid tumors: the biology and therapy of an enigmatic and controversial lesion. *Am J Gastroenterol* 1995; **90:** 338–52.

**27** Williams GT. Endocrine tumours of the gastrointestinal tract-selected topics. *Histopathology* 2007; **50:** 30–41.

**28** Kloppel G, Perren A, Heitz PU. The gastroenteropancreatic neuroendocrine cell system and its tumors: the WHO classification. *Ann N Y Acad Sci* 2004; **1014:** 13–27.

**29** Kloppel G, Heitz PU, Capella C, Solcia E. Pathology and nomenclature of human gastrointestinal neuroendocrine (carcinoid) tumors and related lesions. *World J Surg* 1996; **20:** 132–41.

**30** Watanabe H, J.J., Sobin LH, eds. Histological typing of oesophageal and gastric tumors. Berlin: Springer-Verlag, 1990.

**31** Nakamura T, Nakano G. Histopathological classification and malignant change in gastric polyps. *J Clin Pathol* 1985; **38:** 754–64.

**32** Park DI, Rhee PL, Kim JE, et al. Risk factors suggesting malignant transformation of gastric adenoma: univariate and multivariate analysis. *Endoscopy* 2001; **33:** 501–6.

**33** Agaimy A. Gastrointestinal stromal tumors (GIST) from risk stratification systems to the new TNM proposal: more questions than answers? A review emphasizing the need for a standardized GIST reporting. *Int J Clin Exp Pathol* 2010; **3:** 461–71.

**34** Miettinen M, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. *Arch Pathol Lab Med* 2006; **130:** 1466–78.

**35** Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. *Am J Surg Pathol* 2005; **29:** 52–68.

**36** Coffin CM, Hornick JL, Fletcher CD. Inflammatory myofibroblastic tumor: comparison of clinicopathologic, histologic, and immunohistochemical features including ALK expression in atypical and aggressive cases. *Am J Surg Pathol* 2007; **31:** 509–20.

**37** Allibone RO, Nanson JK, Anthony PP. Multiple and recurrent inflammatory fibroid polyps in a Devon family ('Devon polyposis syndrome'): an update. *Gut* 1992; **33:** 1004–5.

**38** Schildhaus HU, Buttner R, Binot E, Merkelbach-Bruse S, Wardelmann E. Inflammatory fibroid polyps are true neoplasms with PDGFRA mutations. *Pathologe* 2009; **30**(Suppl. 2)**:** 117–20.

**39** Schildhaus HU, Cavlar T, Binot E, Buttner R, Wardelmann E, Merkelbach-Bruse S. Inflammatory fibroid polyps harbour mutations in the platelet-derived growth factor receptor alpha (PDGFRA) gene. *J Pathol* 2008; **216:** 176–82.

**40** Misdraji J, Lauwers GY. Gastric epithelial dysplasia. *Semin Diagn Pathol* 2002; **19:** 20–30.

**41** Srivastava A, Lauwers GY. Gastric epithelial dysplasia: the western perspective. *Dig Liver Dis* 2008; **40:** 641–9.

**42** Park do Y, Srivastava A, Kim GH, et al. Adenomatous and foveolar gastric dysplasia: distinct patterns of mucin expression and background intestinal metaplasia. *Am J Surg Pathol* 2008; **32:** 524–33.

**43** Borchard F, Ghanei A, Koldovsky U, et al. Gastrale Differenzierung in Adenomen der Magenschleimkaut Immunohistochemische und elec-kronenmikroskopische Untersuchungen. *Verh Dtsch Ges Pathol* 1990; **74:** 528.

**44** 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:** 186–93.

**45** Vieth M, Kushima R, Borchard F, Stolte M. Pyloric gland adenoma: a clinico-pathological analysis of 90 cases. *Virchows Arch* 2003; **442:** 317–21.

**46** Bearzi I, Brancorsini D, Santinelli A, Rezai B, Mannello B, Ranaldi R. Gastric dysplasia: a ten-year follow-up study. *Pathol Res Pract* 1994; **190:** 61–8.

**47** Burke AP, Sobin LH, Shekitka KM, Helwig EB. Dysplasia of the stomach and Barrett esophagus: a follow-up study. *Mod Pathol* 1991; **4:** 336–41.

**48** Lansdown M, Quirke P, Dixon MF, Axon AT, Johnston D. High grade dysplasia of the gastric mucosa: a marker for gastric carcinoma. *Gut* 1990; **31:** 977–83.

**49** Rugge M, Cassaro M, Di Mario F, et al. The long term outcome of gastric non-invasive neoplasia. *Gut* 2003; **52:** 1111–6.

**50** Yamada H, Ikegami M, Shimoda T, Takagi N, Maruyama M. Long-term follow-up study of gastric adenoma/dysplasia. *Endoscopy* 2004; **36:** 390–6.

**51** Di Gregorio C, Morandi P, Fante R, De Gaetani C. Gastric dysplasia. A follow-up study. *Am J Gastroenterol* 1993; **88:** 1714–9.

**52** Saraga EP, Gardiol D, Costa J. Gastric dysplasia. A histological follow-up study. *Am J Surg Pathol* 1987; **11:** 788–96.


## Practice points

- Gastric polyps can derive from any of the component cells of the stomach wall and therefore assigning histiogenesis to a lesion forms a useful starting point for diagnosis.
- Dysplasia can involve a number of "benign" gastric polyps, so all material should be carefully examined.
- Gastric dysplasia is relatively rare in routine practice and remains challenging to diagnose and grade. Rendering this diagnosis has implications for patient follow-up and management.
- Increasingly double reporting is being utilized in the diagnosis of dysplasia and is to be welcomed.