8 Drugs-Induced Injury, Infections, Vascular, Congenital, and Miscellaneous Disorders

Vishal S. Chandan

Drug-Induced Injury

Medication-associated gastric injuries have been known for decades. The first report on aspirin-associated gastric injury was published in 1938 [1]. In the recent years, the number of different drug-associated gastric injuries has significantly increased. Some of the injury patterns are nonspecific but generate a differential diagnosis which could be narrowed to a specific drug by incorporating the clinical history and patient's medication list. However, specific patterns of injury can also be seen which are typically associated with a particular drug. A surgical pathologist's familiarity with the general and specific patterns of drug-induced injury to the stomach can be an invaluable tool to pathologic interpretation. Recognition and reporting of drug-induced injury by pathologists can alert clinicians to this under-recognized condition that can usually be easily corrected.

Iron Pill-Associated Gastric Injury

Oral iron medication is commonly used to treat and prevent iron deficiency anemia. Ferrous sulfate is the most common iron medication associated with gastric injury. Iron overdose can cause severe corrosive injury to the stomach and result in ulceration and hemorrhagic necrosis which can even lead to gastric perforation in severe cases [2, 3]. However, a small subset of patients can also develop localized gastric mucosal injury from iron tablet ingestion at the therapeutic level due to impaction of iron material [4, 5]. Iron pill-associated gastric injury can cause various endoscopic abnormalities such as erythema, erosion, ulceration, subepithelial hemorrhages, flat black dots, and even dark brown appearance of gastric mucosa. Rarely, iron-induced gastric ulceration can also mimic gastric carcinoma both radiologically and endoscopically [6]. The pathogenesis of mucosal injury related to therapeutic iron medication is not well understood. However, it is most likely a combined effect of dysmotility or preexisting mucosal damage and prolonged contact of trapped iron pill material.

Identification of iron deposition in the gastric mucosa is usually straightforward. Iron pill material shows a characteristic brown crystalline and clumpy fibrillary material which is refractile but not polarizable (Fig. 8.1a). This material represents oxidized inorganic iron and is generally extracellular. Most of the time, this brown crystalline material is luminal, seen adjacent to the surface epithelium and admixed with luminal inflammatory exudate (Fig. 8.1b). It can be also seen deposited within the lamina propria, either covered by intact epithelium or adjacent to superficial erosions or even within granulation tissue. A small subset of cases may show iron-containing thrombi in mucosal blood vessels or iron deposition within mucosal vessel walls.

The adjacent gastric mucosa can show reactive foveolar hyperplasia with mucin depletion and elongated tortuous gastric pits (Fig. 8.2). The gastric epithelium can show marked epithelial atypia with prominent nucleoli, retained mucosal architecture, low nuclear to cytoplasmic ratio, and lack of nuclear hyperchromasia and should be differentiated from dysplasia.

Hemosiderin deposition can also be frequently seen within the surface epithelium and/or the gastric glands. On an iron stain, the crystalline iron pill material can be easily distinguished from hemosiderin pigment, despite positive staining for both on the iron stain (Fig. 8.3).

Proton Pump Inhibitors

Proton pump inhibitors (PPIs) are very commonly used for treatment of reflux esophagitis and gastric peptic ulcer dis-

V. S. Chandan (✉)
Department of Pathology, University of California – Irvine, Irvine, CA, USA
e-mail: vchandan@uci.edu

L. Zhang et al. (eds.), *Surgical Pathology of Non-neoplastic Gastrointestinal Diseases*,
https://doi.org/10.1007/978-3-030-15573-5_8

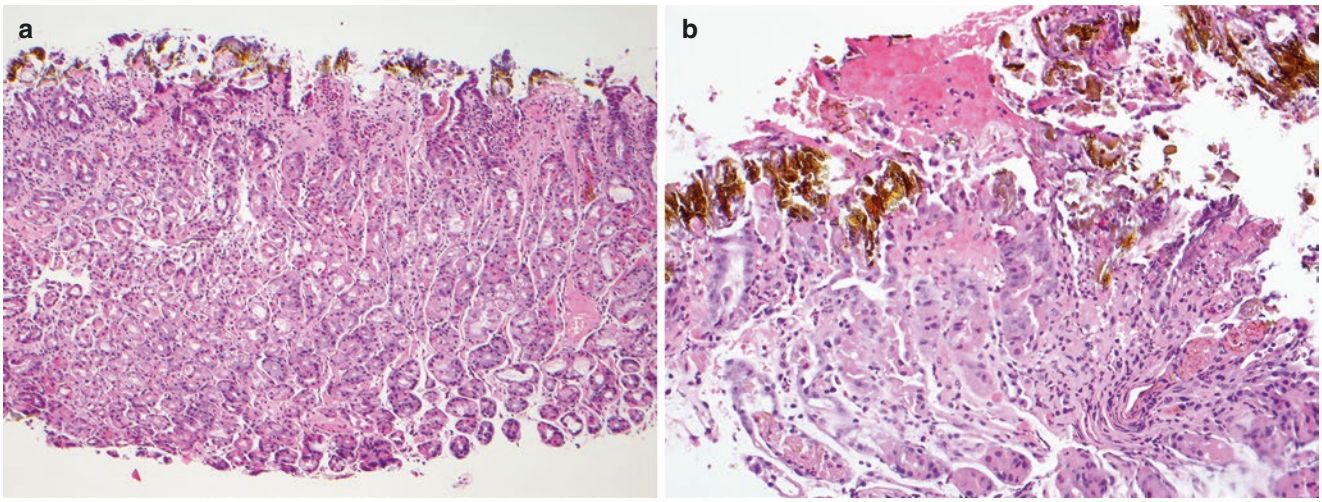

Fig. 8.1 Iron pill-associated gastric injury. Brown crystalline and clumpy fibrillary iron pill material encrusted on the surface epithelium with erosive injury (**a**). Refractile iron pill material is admixed with luminal inflammatory exudate (**b**)

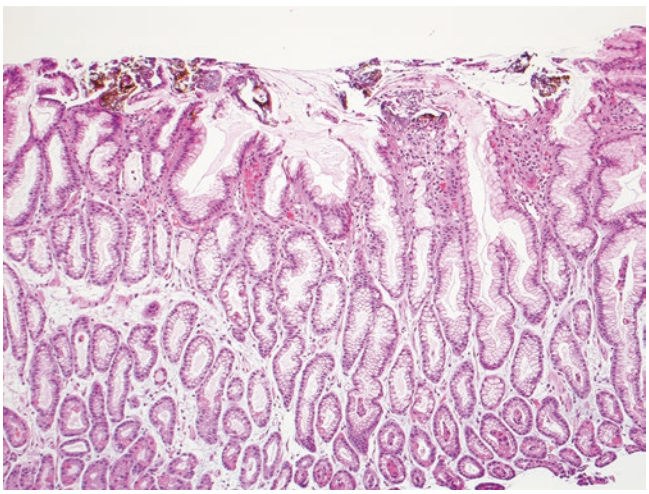

Fig. 8.2 Reactive epithelial changes in iron pill-associated injury. Gastric mucosa shows reactive foveolar hyperplasia and elongated tortuous gastric pits

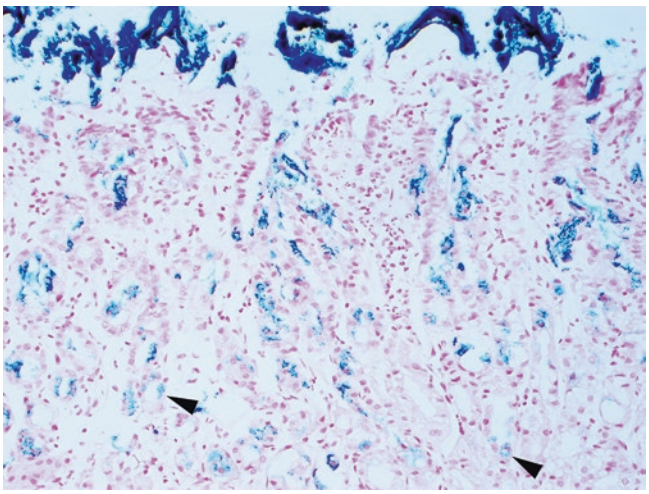

Fig. 8.3 The crystalline iron pill material is positive on the iron stain. There is also iron deposition within the crypt lumen and occasional within the gastric epithelial cells (arrowheads)

ease. These medications are freely available over the counter and are very effective in reducing gastric acidity. However, there is some concern about their long-term usage leading to gastric polyps, atrophic gastritis, and even gastric endocrine cell hyperplasia.

A subset of patients develop gastric parietal cell hyperplasia within the body, characterized by enlarged and increased parietal cells protruding into the gastric glands and even imparting a serrated appearance to the glandular lumen (Fig. 8.4). The obstruction of the acid flow by the hypertrophic parietal cells presumably leads to fundic gland cysts and fundic gland polyps. Several studies have confirmed prolonged use of PPIs with development of fundic gland polyps [7–9]. A study has also shown disappearance of the fundic gland polyps with discontinuation of PPIs and recurrence with resumed use of PPIs, further supporting the relationship between PPIs and fundic gland polyps [10]. However, some authors disputed this association [11, 12].

Long-term PPI usage has also been associated with two- to fourfold increase in serum gastrin levels in some patients [13–16]. Similarly, due to increased gastrin levels, endocrine cell hyperplasia has also been seen in some patients on long-term PPI usage [16–18]. However, no increased risk of gastric neuroendocrine tumors has been reported with long-term PPI usage. PPI usage among *H. pylori*-infected patients has also been associated with aggravation of gastritis and atrophy of gastric corpus [13, 17–21]. Hence, there has been suggestion about patients being tested for *H. pylori* before long-term PPI therapy [19].

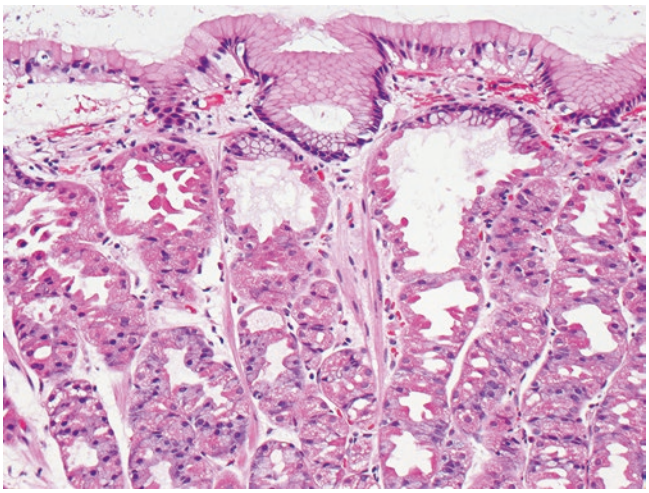

Fig. 8.4 Proton pump inhibitors' effects. Enlarged and increased parietal cells protruding into the gastric glands with a serrated appearance to the glandular lumen in body and fundus

OsmoPrep-Associated Gastritis

OsmoPrep is a tablet form of osmotic laxative sometimes used for bowel preparation as a colon preparatory agent. It is usually used in patients who cannot tolerate the large chalky fluid which constitutes the more commonly prescribed liquid sodium phosphate agent. The active ingredient is sodium phosphate and has been associated with risk of acute phosphate nephrotoxicity.

In a recent study, a subset of patients who were prescribed OsmoPrep showed purple to black inorganic deposits in the superficial lamina propria of the stomach [22]. The deposits varied in size (<100 m) and showed irregular contour with the appearance of crushed pill fragments. The gastric mucosa showed features of reactive gastropathy with marked reactive epithelial changes, including mucin loss and nuclear hyperchromasia. No erosions or ulcers were seen. However, in some cases congestion and mild edema were seen adjacent to these deposits. The differential for these deposits included iron pill material and mucosal calcinosis. However, these OsmoPrep deposits were positive on von Kossa stain but negative on alizarin red (a calcium chelating dye) arguing against mucosal calcinosis. The deposits were also negative on Perl's iron stain.

Mycophenolate Mofetil

Mycophenolate mofetil (MMF) is an immunosuppressant used in solid organ and bone marrow as well as stem cell transplant patients to prevent allograft rejection and graft versus host disease (GVHD), respectively. It is also used to treat some autoimmune and inflammatory diseases such as psoriasis, lupus nephritis, and myasthenia gravis. The histological hallmark of MMF-associated injury is increased apoptosis, characterized by condensation and fragmentation of blue nuclear and pink cytoplasmic material with an empty space surrounding the degenerated cell components. Gastric biopsies can show a range of histological changes varying from severe reactive gastropathy, Crohn's-like features including granulomatous inflammation, to nonspecific changes [23, 24]. A small subset of patients can also show ballooning degeneration of the parietal cells characterized by enlarged parietal cell to more than twice its normal size and clearing of the cytoplasm [24].

Medications Associated with Mitotic Arrest (Colchicine and Taxol)

Colchicine is an alkaloid used for treatment of gout and other medical conditions including immune/rheumatologic disorders. Colchicine exhibits antimitotic activity due to its ability to bind to tubulin and preventing the polymerization of tubulin into microtubules. Patients with renal and/or hepatic failure may develop colchicine toxicity. The most noticeable feature of colchicine toxicity is mitotic arrest in metaphase with absent mitotic spindles and bizarre chromatin patterns, especially ring mitosis (Fig. 8.5) [25, 26]. The mucous neck region of the stomach usually shows the prominent mitosis with colchicine toxicity. The gastric foveolar epithelium may also show enlarged hyperchromatic nuclei with loss of polarity and epithelial stratification. Increased apoptosis may also be seen. It is important for the pathologists to recognize the epithelial atypia to be related to colchicine toxicity in order to avoid confusion with high-grade

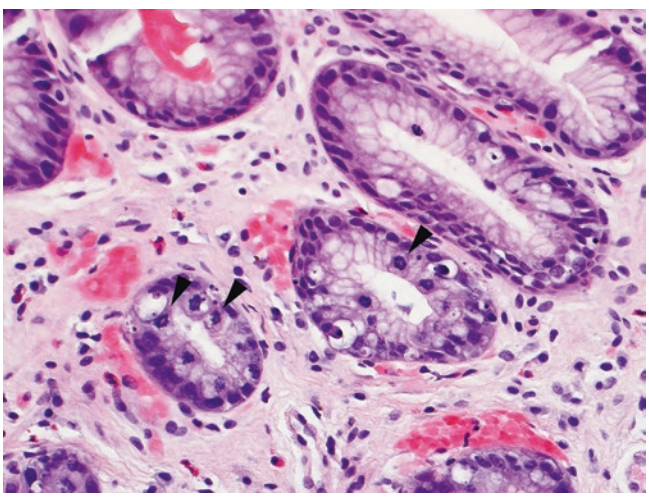

Fig. 8.5 Colchicine toxicity. Gastric biopsy from a chronic renal failure patients taking colchicine shows mitotic arrest in metaphase (ring mitosis, arrowheads) and increased apoptosis

dysplasia. These changes are not seen in patients taking colchicine who do not have clinical evidence of toxicity. Hence when these changes are identified by the pathologists, it is important to reconcile with the patient's medication list, since if colchicine is the offending agent, then the patient is probably toxic. Of note, even therapeutic doses of colchicine may rarely cause ring mitosis, especially in colorectal polyps [27]. The histological findings of colchicine toxicity regress on cessation of the drug.

Taxol (paclitaxel) is a chemotherapy drug used to treat malignancies of lung, esophagus, and breast. Taxol binds to the microtubules of the mitotic spindle causing metaphase arrest. Like colchicine, Taxol causes increased and arrested mitotic activity including ring mitosis [25, 28]. The mitotic figures are predominantly seen in the proliferative zone of the gastric mucosa. Taxol effects are histologically identical to those of colchicine toxicity and morphologically indistinguishable. However, the histological features of Taxol effect can be seen in any patient undergoing chemotherapy with this drug, and unlike colchicine, mitotic arrest and ring mitosis after Taxol administration do not indicate Taxol toxicity. Rarely, patients with telomere-mediated disorders may also show ring mitosis and apoptosis [29].

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs are widely used for their analgesic and anti-inflammatory effects. They prevent prostaglandin synthesis by inhibiting cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). The decreased prostaglandin synthesis results in mucosal ischemia and decreased mucosal integrity within the gastrointestinal tract due to decreased production of mucosal protectants. Within the stomach, three major histologic types of gastric injuries are noted: acute hemorrhagic gastritis (described in detail in Chap. 6), ulcers, and reactive gastropathy (described in detail in Chap. 6) [30, 31]. NSAID-related erosions frequently develop in the gastric body, whereas NSAIDs ulcers are often large, multiple, and painless and develop in the antrum [32, 33].

Chemotherapy and Radiation-Associated Changes

Chemotherapeutic agents, such as 5-fluoro-2-deoxuridin (FUDR) and mitomycin C when used for hepatic arterial infusion chemotherapy, have been associated with erosions and ulcers within the distal stomach [34, 35]. In some patients, chemotherapy-related gastric ulcers may show marked epithelial atypia that can be mistaken for gastric dysplasia or even early carcinoma [36, 37]. These changes can be distinguished from "true" dysplasia by its patchy distribution, absence of a mass lesion, surface maturation, lack of intestinal metaplasia, lack of infiltrative pattern, open nuclear chromatin with prominent nucleoli, retained nuclear polarity, lack of atypical mitosis, and cytoplasmic eosinophilia and/or vacuolization [38].

Yttrium-90 microspheres injected for selective internal radiation can be associated with gastric ulceration and presence of black microspheres within the mucosal capillaries [39, 40]. This occurs when the Yttrium-90-labeled microspheres accidentally enter the arteries supplying the stomach, causing unintended radiation damage. The stomach shows lamina propria hyalinization, atypical stromal and endothelial cells, as well as damaged ectatic vessels (Fig. 8.6a). The microspheres are basophilic and uniform and measure about 30–40 m in diameter (Fig. 8.6b) [40, 41].

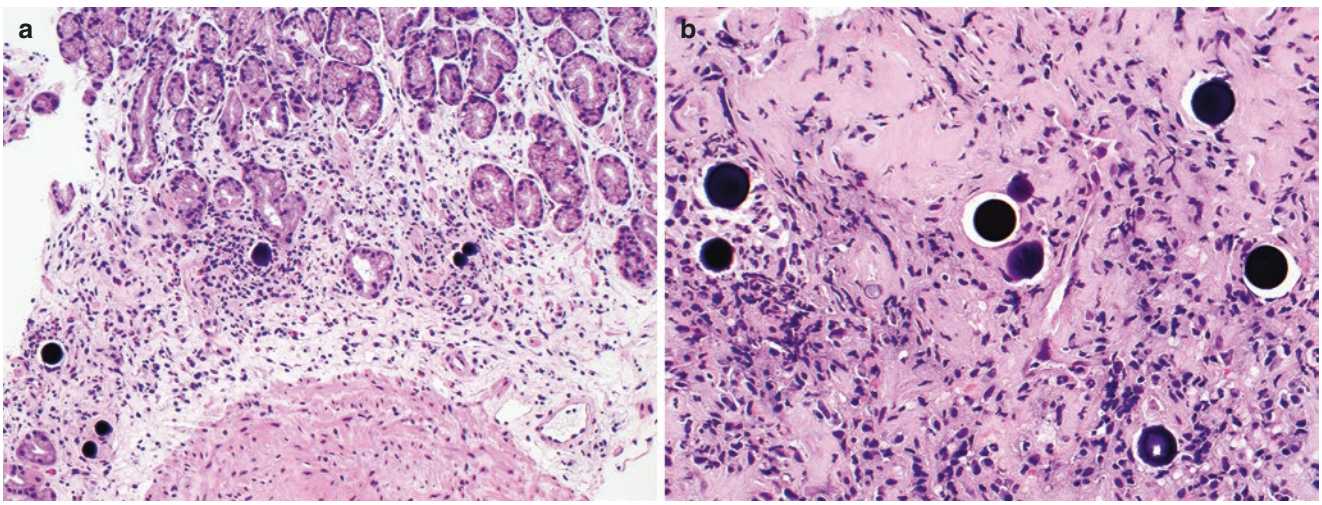

Fig. 8.6 Yttrium-90-induced gastric mucosal injury. The stomach shows lamina propria hyalinization and basophilic, uniform Yttrium-90 microspheres within lamina propria (**a**) and granulation tissue (**b**)

Resins (Kayexalate-Sorbitol, Cholestyramine, Colesevelam, Colestipol, and Sevelamer)

Resins are nonabsorbable medications which act as platforms for ion exchange in the gastrointestinal tract. The commonly used resins include Kayexalate (sodium polystyrene sulfonate), sevelamer, and bile acid sequestrants (BAS).

Kayexalate-sorbitol enemas are used for treatment of hyperkalemia in patients with renal insufficiency. Kayexalate is a cation exchange resin that picks up excess potassium ions in exchange for sodium ions within the large intestine. The resin and excess potassium ions are then excreted in the stool. Sorbitol is a laxative agent which is administered with Kayexalate, as it can cause constipation and bezoar formation. However, as a result of vascular shunting due to osmotic load, a subset of patients with uremia can develop gastrointestinal tract ischemia and even necrosis [42–44]. There is also some suggestion that Kayexalate can itself directly inflict mucosal injury [43]. Within the stomach, hemorrhagic gastritis, serpiginous ulcers, and erosions have been described to be related to Kayexalate-sorbitol (Fig. 8.7a) [42, 44, 45]. Kayexalate crystals are rhomboid or triangular in shape and deeply basophilic on hematoxylin and eosin (H&E) stain (Fig. 8.7b). They also can be highlighted on PAS-D (the crystals are magenta color), Diff-Quik, and acid-fast stains (the crystals are black). They exhibit a distinctive internal mosaic pattern that resembles fish scales [42]. These crystals are refractile but do not polarize. The crystals remain attached to the intact mucosa or can be seen admixed with the inflammatory exudates in cases with ulcers or erosions.

Cholestyramine is a bile acid sequestrant which is clinically used in treatment of hyperlipidemia. Cholestyramine crystals are irregularly shaped and have a near black to deep red to bright orange color on H&E stain depending on the tissue thickness and stain variability [46–48]. They also lack the fish-scale pattern of Kayexalate and appear to have a smooth glassy texture (Fig. 8.8). Large cholestyramine crystals may occasionally show irregular cracking lines but still would lack the geometric fish scale pattern. They appear dull yellow on acid-fast stain and variable gray or hot pink on PAS-D stain [48, 49]. Cholestyramine is probably not directly harmful to the gastrointestinal tract mucosa, but it can potentiate preexisting lesions, thereby increasing the risk of bleeding [49]. However, in the stomach, it has been associated with superficial erosions to ulcerations [50].

Colesevelam and colestipol are also bile acid sequestrants that are used to treat diarrhea, hypercholesteremia, and dyslipidemia. They probably lack the ability to cause significant

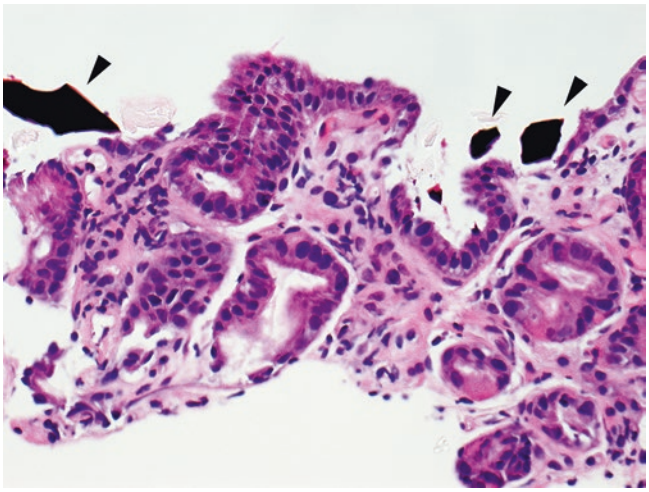

Fig. 8.8 Cholestyramine crystals. Cholestyramine crystals (arrowheads) are irregularly shaped and have a near black to deep-red to bright orange color with smooth glassy texture and no fish scale on H&E stain

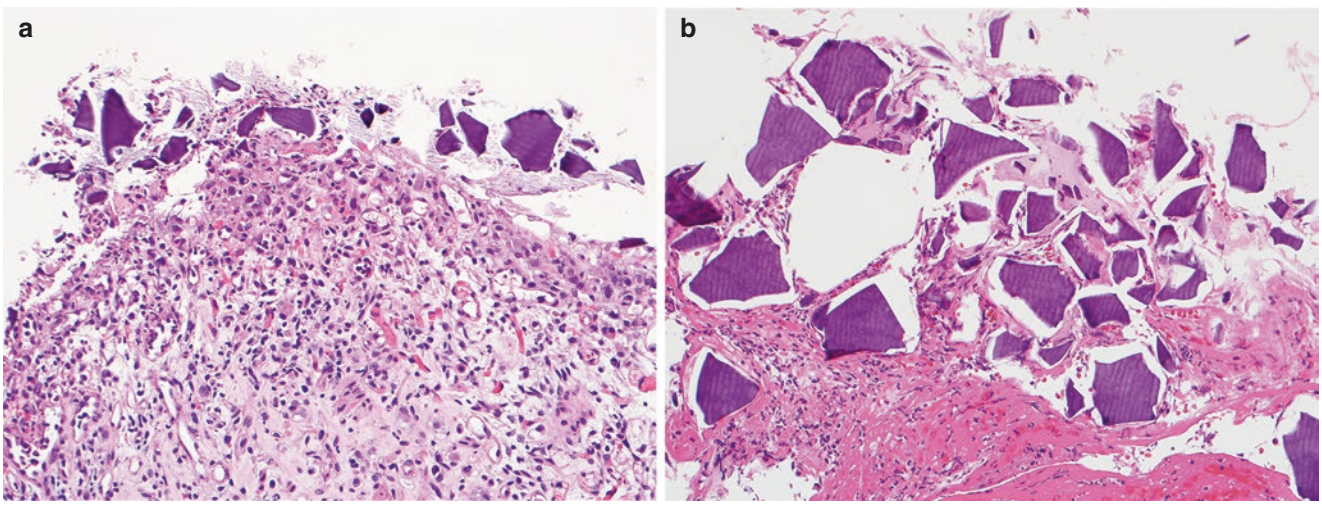

Fig. 8.7 Kayexalate-sorbitol-associated gastric injury. Kayexalate crystals present in gastric ulcer (**a**). Kayexalate crystals are rhomboid or triangular in shape and deeply basophilic with mosaic pattern that resembles fish scales on H&E stain (**b**)

direct mucosal injury to the gastrointestinal tract [48]. However, crystals can be seen occasionally within stomach biopsies. Morphologically the crystals of colesvelam and colestipol are identical to cholestyramine crystals and cannot be distinguished from one another.

Sevelamer carbonate is another anion exchange resin which is a phosphate binder. It is used in patients with chronic renal failure to treat hyperphosphatemia. It has been associated with gastric mucosal injury, but its exact etiological role remains unclear as it may just be an innocent bystander [47]. On the H&E stain the crystals of sevelamer appear broad, curved, and irregularly spaced (Fig. 8.9). Like Kayexalate, they also show fish-scale pattern. However, they also show a characteristic two-toned color imparted by bright pink linear accentuations with a rusty yellow background. Some crystals embedded in an area of ulcer, necrosis, or ischemia may acquire a deep eosinophilic or rusty brown color [47]. On the PAS-D stain, the sevelamer crystals acquire a violet color. These crystals are exclusively identified in patients with chronic kidney disease, and this is an important clue toward their diagnosis.

Lanthanum

Lanthanum carbonate (Fosrenol) is used in patients with chronic renal failure for treatment of hyperphosphatemia. It is a rare alkaline earth metal that binds with phosphate in the gastrointestinal tract and has a poor absorption from the gastrointestinal tract. However, a small subset of patients taking this drug develops lanthanum deposition within mucosal histiocytes (Fig. 8.10a–c) [51–53]. Small foreign body granulomas may also be seen [54]. The histiocytes show a fine to coarse granular material that varies in color from brown, gray, to violet. These histiocytes may stain positive with Prussian blue and toluidine blue in some cases. Lanthanum can be identified in the histiocytes by electron microscopy, but the diagnosis is usually confirmed by correlation with the clinical history. There are some reports suggesting that this accumulation reverses after stopping lanthanum, but in rare cases, the deposits are seen even years after the discontinuation of lanthanum [55, 56].

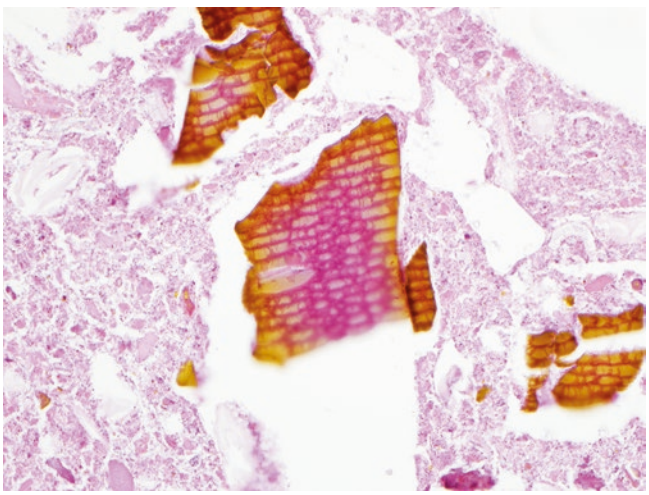

Fig. 8.9 Sevelamer crystals. Sevelamer crystals have broad, curved, and irregularly spaced fish-scale pattern and a characteristic two-toned color imparted by bright pink linear accentuations with a rusty yellow background on the H&E stain

Olmesartan

Angiotensin II receptor antagonists such as olmesartan (Benicar) are commonly used for treatment of hypertension. A subset of patients taking olmesartan may show lymphocytic gastritis (Fig. 8.11), collagenous gastritis, or chronic gastritis [57].

Tetracycline/Doxycycline

Doxycycline is an oral tetracycline antibiotic. Recently, there have been reports of doxycycline causing superficial gastric mucosal necrosis with a peculiar form of vascular degeneration [58, 59]. Endoscopy showed white to yellow plaque-like lesions or non-bleeding ulcers. Histologically, the superficial mucosal necrosis was characterized by hyperplastic foveolar cells, inflamed lamina propria, and sloughing of the superficial epithelial cells. They also show vascular degeneration of the capillaries characterized by eosinophilic necrosis of the vessel wall creating a ringlike deeply eosinophilic granular structure, sometimes even creating a halo effect due to separation from the surrounding tissue. These vessels often show intraluminal neutrophils and microthrombi [58]. This pattern of injury is unique and its presence should alert the pathologists to the possibility of doxycycline-induced gastric injury.

Crospovidone and Microcrystalline Cellulose

Crospovidone and microcrystalline cellulose are biologically inert pharmaceutical fillers incorporated into medications to facilitate drug delivery. They can sometimes be seen in stomach biopsies. Awareness of their morphology would be helpful for the pathologists to differentiate them from parasites, calcifications, and other medications associated with mucosal injuries. In a recent study by Shaddy et al., the overall filler incidence in gastric biopsies was about 3% [60]. Their presence outside the luminal bowel may be an indicator of perforation. On H&E stain crospovidone appears non-birefringent, coral, or sponge shaped with pink core and purple coat and measures 0.4–1.5 mm in diameter

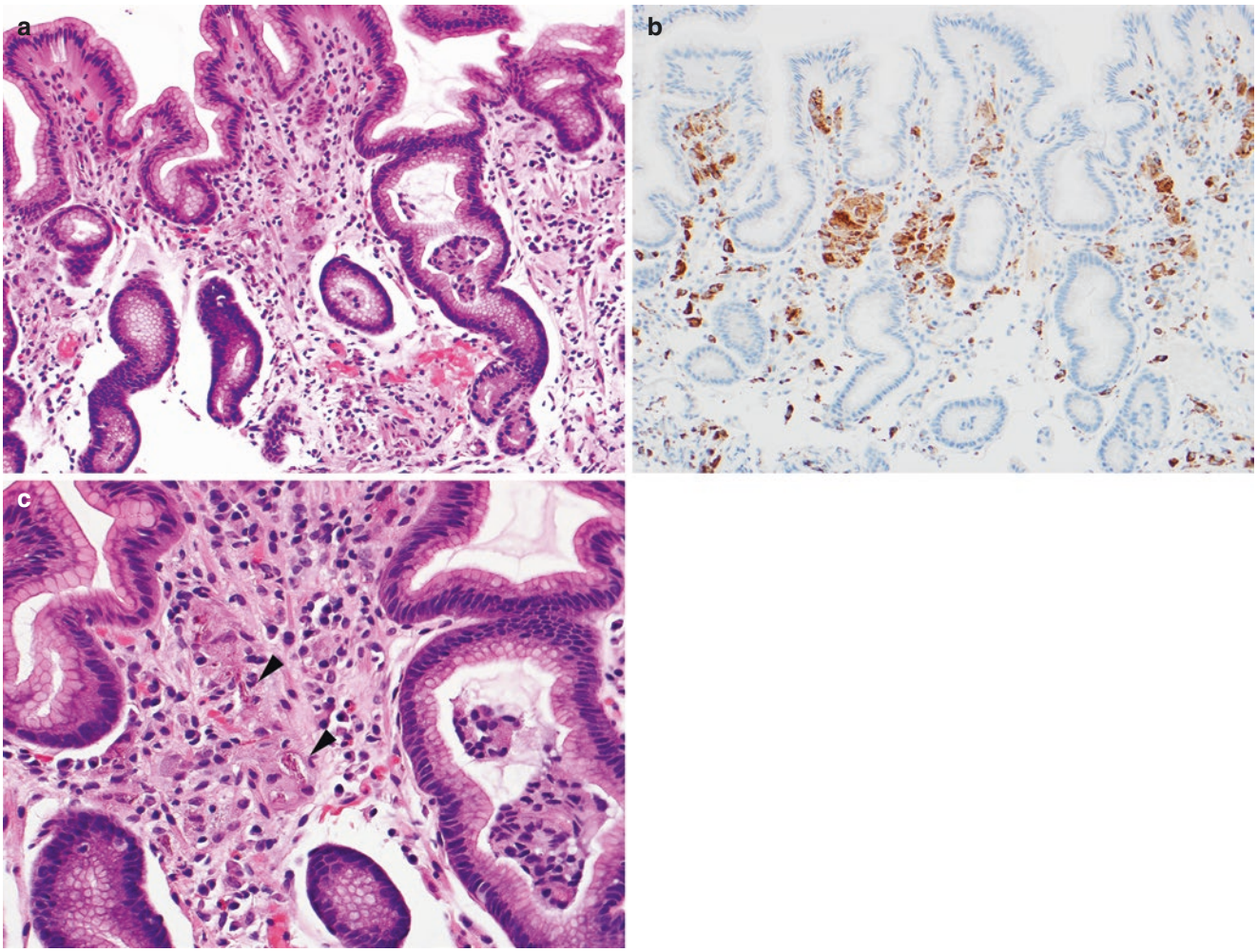

Fig. 8.10 Lanthanum deposition. Antral mucosal biopsy from a chronic renal failure patient receiving lanthanum carbonate for hyperphosphatemia shows histiocytic aggregates within lamina propria (**a**). The histiocytes within the lamina propria are positive for CD68 by immunohistochemical stain (**b**). There are cytoplasmic coarse inclusion-like brownish materials with irregular branching (arrowheads) present within the histiocytes (**c**)

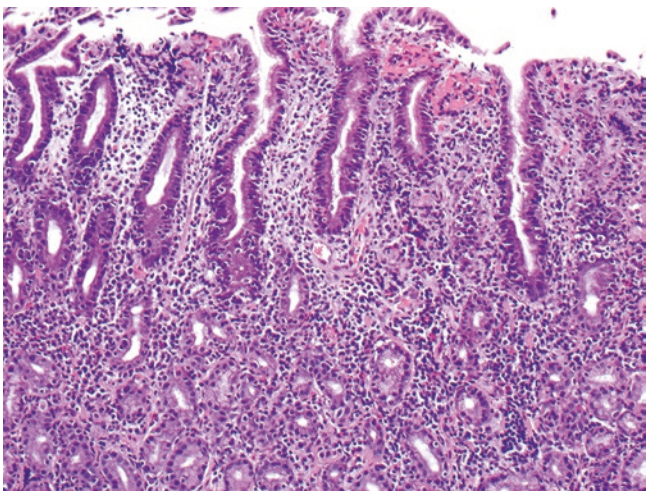

Fig. 8.11 Olmesartan-associated gastric injury. Lymphocytic gastritis pattern in a patient with olmesartan-associated enteropathy

(Fig. 8.12). Microcrystalline cellulose on H&E stain appears transparent with a rod or matchstick shape (Fig. 8.13a) and is brightly birefringent under polarized light (Fig. 8.13b) [60].

Infections

Phlegmonous (Suppurative) Gastritis

Definition

Phlegmonous gastritis is a rare form of rapidly progressive suppurative bacterial infection that affects the stomach. Its hallmarks are necrosis and gangrene.

Clinical Features

Patients usually have an underlying condition, such as immunocompromised status or debilitating condition such as

malignancy, human immunodeficiency virus (HIV) infection, or alcoholism. The exact pathogenesis is not known but is often caused by a variety of bacteria including *Staphylococcus*, *Streptococcus*, *Enterococcus, Escherichia coli*, *Proteus*, and *Clostridium* species [61–63]. Presenting symptoms include fever, abdominal pain, nausea, vomiting, and hematemesis [61]. Computed tomography (CT) scan may show diffuse thickening of the gastric wall with intramural low density. Endoscopy may show ulcers, thickened gastric folds, mass effect, or necrotic material.

Pathological Features

Grossly the stomach wall may appear thickened and necrotic. Microscopy shows suppurative necrosis of the mucosa and submucosa with acute inflammation. Transmural necrosis may be seen in severe cases. A Gram stain may show bacteria. Of note, a superficial mucosal biopsy may be unremarkable if the findings are confined to the submucosa or deeper structures.

Differential Diagnosis

Differential diagnosis includes gastric lymphoma, gastrointestinal stromal tumor, linitis plastic, and superinfected malignancy. These conditions can be differentiated by careful histological review and use of special stains as needed.

Treatment and Prognosis

Treatment includes medical and surgical intervention. Broad-spectrum antibiotics are useful. Surgical resection is also an option and may offer better survival. Mortality is low (~10%) for localized disease but can be higher (>50%) for cases with diffuse gastric involvement. Early diagnosis and treatment are the key for improved survival [61, 62].

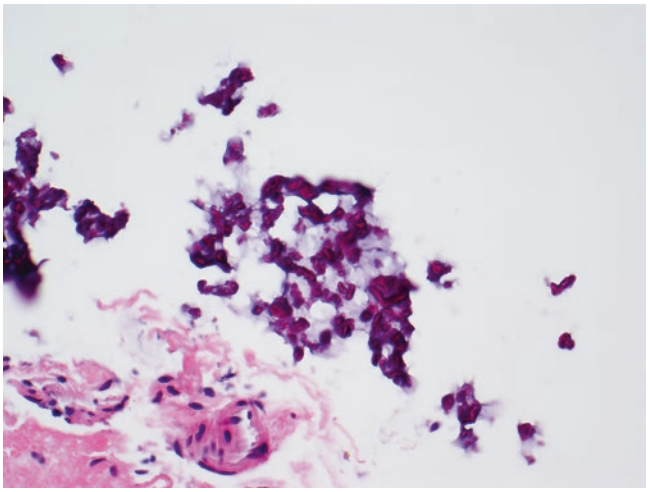

Fig. 8.12 Crospovidone. This filler material appears non-birefringent, coral, or sponge shaped with pink core and purple coat on H&E stain

Sarcina ventriculi

Definition

Sarcina ventriculi is a Gram-positive anaerobic coccus that can be identified within the stomach, especially in patients with delayed gastric emptying.

Clinical Features

It occurs mainly in adults but can also be seen in children, more commonly in females than males [64]. More than half of the patients have a history of gastric outlet obstruction, gastroparesis, and/or gastrointestinal surgery. It has also been associated with gastric perforation and emphysematous gastritis [65, 66]. Most patients present with abdominal pain, nausea, and vomiting. In some patients, it may just be an

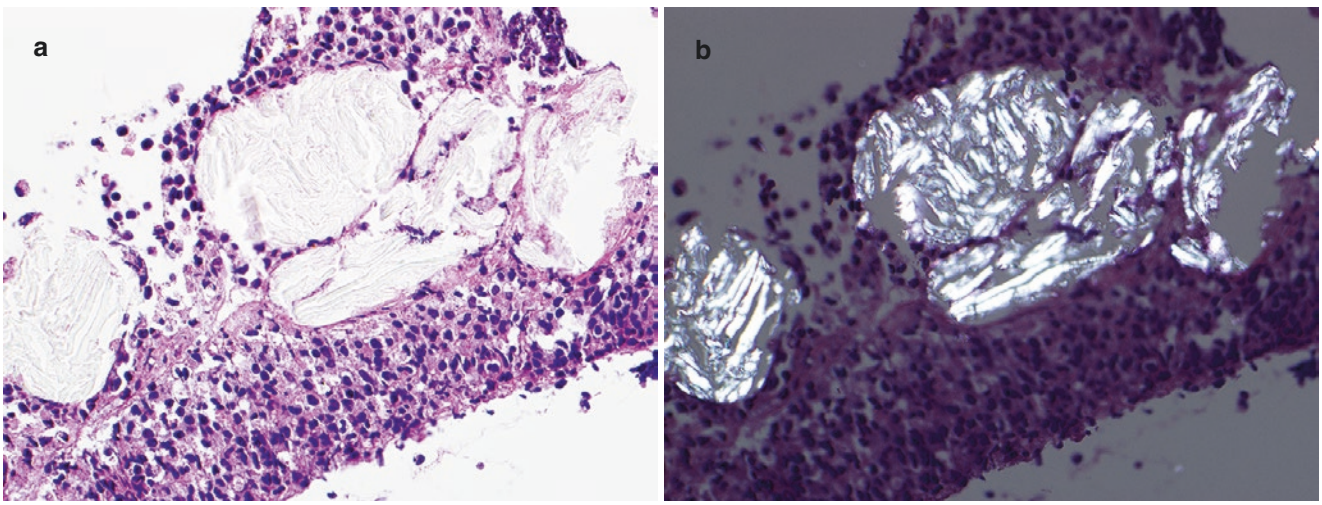

Fig. 8.13 Microcrystalline cellulose. This filler material appears transparent with a rod or matchstick shape in background of inflammatory exudates on H&E stain (**a**) and is brightly birefringent under polarized light (**b**)

incidental finding and the patient may be asymptomatic [67]. Endoscopy may show gastric bezoar, retained food residue, erosions, and ulcerations [64].

Pathological Features

The organisms are not invasive and generally seen near the mucosal surface in the gastric mucin. On H&E stain, *Sarcina ventriculi* appear as basophilic cuboid-shaped organisms measuring 1.8–3 m and arranged in tetrad packet arrangement (Fig. 8.14a). There may be flattening of the cell walls in areas of contact with adjacent organism and it may even be refractile in nature [64]. On Gram stain, the organisms are strongly positive. The organism can also be confirmed by molecular methods using polymerase chain reaction (PCR) and sequencing of the 16S ribosomal RNA gene and pyruvate decarboxylase gene. The adjacent gastric mucosa is usually unremarkable, but, in some cases, it may show diffuse hemorrhagic gastritis with ulceration (Fig. 8.14b) [68]. The exact mechanism of mucosal injury caused by *Sarcina* is not entirely clear. There has been a suggestion that it may simply be a bystander in an underlying disease process. The organism has also been reported in feces of healthy people, especially those on vegetarian diet [69]. It can also be found in the soil and air [70]. However, identification of Sarcina in gastric biopsies is important for surgical pathologists due to its strong association with gastric stasis and rare cases of life-threatening emphysematous gastritis. Its presence in a gastric biopsy should raise a consideration for gastric outlet obstruction and delayed gastric emptying.

Differential Diagnosis

The main differential is *Micrococcus* species, a Gram-positive coccus that occurs in tetrads or packets. However, the *Micrococcus* is considerably smaller measuring 0.5 m and unlike *Sarcina* species, the *Micrococcus* species tend to form tightly packed clusters [68]. In addition, the *Micrococcus* bacterium is aerobic and catalase positive and does not form spores, while *Sarcina ventriculi* is anaerobic, catalase negative, and spore forming [71]. *Staphylococcus* species can also be in the differential, and they are also Gram-positive. However, *Staphylococcus* bacteria are smaller in size, measuring around 1 m in diameter, and arranged in grape-like clusters, rather than a tetrad pattern.

Treatment and Prognosis

There is no standard regimen for treatment. Antibiotics such as metronidazole are successful in eradication of the organism. There is also suggestion to omit treatment if the patient is healthy and asymptomatic, as the organism can occur commensally [64].

Syphilis Gastritis

Definition

It is a gastric infection caused by spirochete *Treponema pallidum*, which is mostly a sexually transmitted disease.

Clinical Features

Median age is 39 years, more common in males and black race [72]. Epigastric or abdominal pain is the most common presenting symptom, followed by vomiting and weight loss. Only a small subset of patients may have a history of syphilis but many of them may have prior or concurrent clinical manifestations of the disease. Majority of cases have positive serological tests for syphilis (Venereal Disease Research Laboratory (VDRL), Rapid Plasma Reagin (RPR), and/or Kolmer). Endoscopy may show gastric ulceration, erosion, nodular mucosa, thickened folds, or rarely even a mass lesion [72].

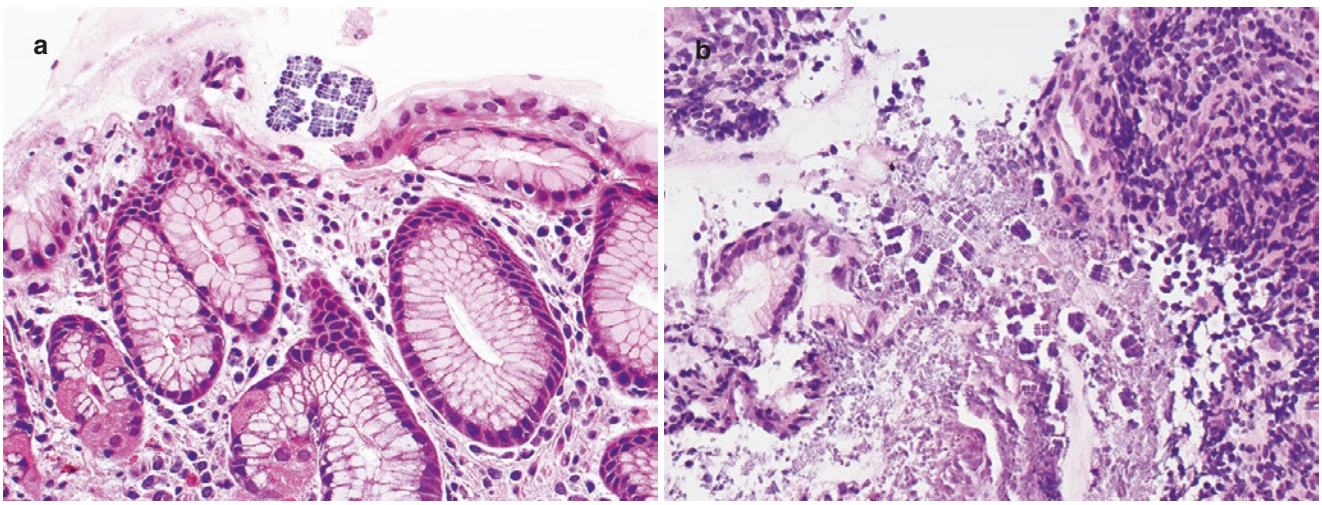

Fig. 8.14 *Sarcina ventriculi*. Basophilic, cuboid-shaped organisms in tetrad packet arrangement on luminal surface of gastric mucosa with mild chronic inflammation (**a**) and in foci of ulceration with inflammatory exudates (**b**)

Pathological Features

Microscopy shows gastritis with a prominent plasma cell infiltrate, admixed lymphocytes, and varying number of neutrophils. The dense plasmacytic infiltrate may show a perivascular distribution. Vasculitis is seen in the form of proliferative endoarteritis; however, endophlebitis may also be seen in occasional cases. Rare cases may also show atrophic gastritis [72]. *T. pallidum* immunostain can be used to highlight the organisms and confirm the diagnosis. Silver stains such as Warthin-Starry can also be useful in detecting the organisms, but it can be difficult to read and is also not highly sensitive [73]. Immunofluorescence microscopy and PCR testing is also available [74]. *Treponema pallidum* is a Gram-negative spirochete measuring 8–15 m in length and 0.1–0.2 m in diameter. The organisms are usually present in the lamina propria and between the glandular epithelial cells.

Differential Diagnosis

Helicobacter pylori and *Helicobacter heilmannii* enter the differential as they share some morphological similarity with *Treponema pallidum*. *Helicobacter pylori* are much smaller and measure 1–3 m in length and 0.5–1 m in diameter. *Helicobacter heilmannii* is longer and wider than *Helicobacter pylori* but shorter and plumper than *Treponema pallidum* with 4–6 helical turns giving a corkscrew-like appearance [75, 76]. Immunostains for *Helicobacter pylori* and *Treponema pallidum* can be useful in their distinction. The *Treponema* immunostain has recently been reported to show crossed reactivity with *Helicobacter heilmannii* [77].

Treatment and Prognosis

Antibiotics like penicillin usually resolve the infection. The clinical symptoms usually disappear in a week and the endoscopy findings return to normal in about 10 days. Rare patients may develop complications such as gastric perforation or obstruction and may need surgical resection.

Viral Infections

Cytomegalovirus (CMV)

Cytomegalovirus (CMV) gastritis is usually seen in immunocompromised patients, such as those with malignancies, HIV infection, and post-transplant or on steroids [78]. Symptoms include fever and abdominal pain. Endoscopy may show erythema, erosions, and ulceration. Rare cases may show hypertrophic gastritis resembling Menetrier's disease [79]. Histopathology shows characteristically enlarged endothelial, stromal, or rarely epithelial cells with an owl's eye intranuclear inclusions and/or granular basophilic cytoplasmic inclusions (Fig. 8.15). CMV immunostain can be used to confirm the diagnosis.

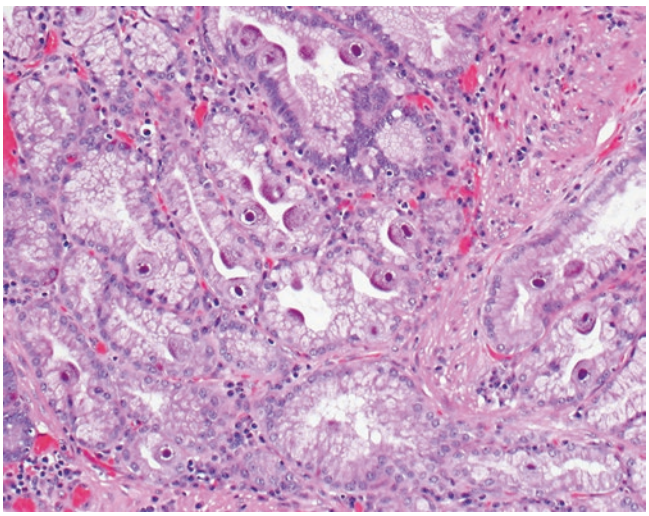

Fig. 8.15 CMV gastritis. Antral mucosa with multiple owl's eye intranuclear inclusions and granular basophilic cytoplasmic inclusions within epithelial cells

Herpesvirus (HSV)

Gastric infection by herpesvirus (HSV) and varicella zoster virus (VZV) is rare but can be seen in immunosuppressed patients [80, 81]. The epithelial cells typically show ground glass nuclei and eosinophilic inclusion surrounded by a clear halo, demonstrating margination, multinucleation, and molding.

Epstein-Barr Virus (EBV)

Rare cases of Epstein-Barr virus (EBV) gastritis (Fig 8.16a, b) have been reported with associated prominent lymphoid hyperplasia simulating a lymphoma [82, 83].

Fungal Infections

Candida infection is usually seen in immunocompromised individuals, alcoholics, or those who have ingested corrosive liquids. Mucosa shows erosions or ulcers. On microscopy, yeasts and pseudohyphae can be identified using silver stain or PAS-D stain. Large gastric ulcers with cancer can also show fungal contamination by *Candida* [84]. A rare fatal case of invasive mucormycosis associated with emphysematous gastritis has also been reported [85].

Parasites

Gastric infection by parasites is rare. However, *Schistosoma ova* can be seen within the stomach [86]. Cryptosporidiosis has been reported in AIDS patients, presenting as subtotal gastric obstruction due to stricturing [87, 88]. Gastric invasive anisakiasis has also been reported after consumption of fish [89].

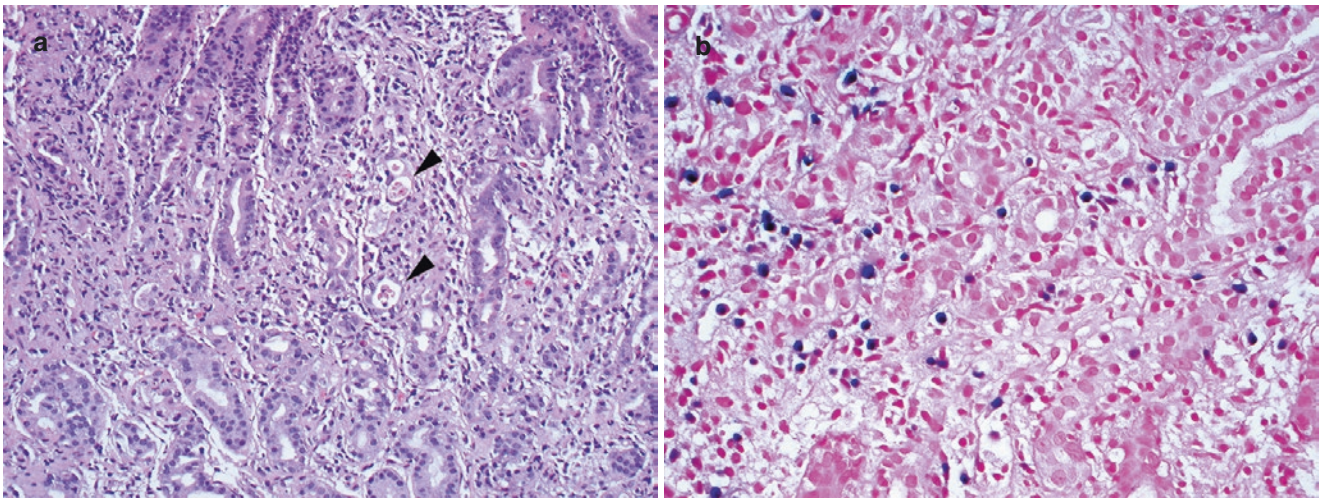

Fig. 8.16 EBV gastritis. Gastric biopsy shows lymphocytic infiltrates in lamina propria and foci of epithelial necrosis (arrowheads) (**a**). EBV in situ hybridization showing numerous EBER-positive lymphocytes in the lamina propria (**b**)

Vascular Gastropathies

Gastric Antral Vascular Ectasia (GAVE)

Definition

It is also known as "watermelon stomach," characterized by marked veno-capillary ectasia involving the gastric antrum and converging on pylorus at endoscopy.

Clinical Features

GAVE was first described in 1953 by Rider et al. [90] in a patient with severe chronic iron-deficiency anemia. The term "watermelon stomach" was coined by Jabbari et al. [91] based on the characteristic endoscopic appearance of hyperemic stripes radiating from the pylorus. GAVE is mainly an endoscopic diagnosis based on its typical appearance. It is a relatively common finding at endoscopy and a cause of gastrointestinal bleeding, accounting for around 4% of all upper gastrointestinal bleeding [92]. The exact pathophysiological changes leading to GAVE are not well defined but may be a combination of abnormal gastric motility, mechanical stress, and mucosal prolapse [93, 94]. Some authors have also linked GAVE with low levels of pepsinogen, achlorhydria, and elevated gastrin levels [94, 95]. It is typically seen in elderly patients, more common in females, and many suffer from chronic medical conditions. About 30% of patients with GAVE have cirrhosis [96]. In non-cirrhotic patients, autoimmune conditions such as connective tissue disorders and Raynaud's syndrome are common [95]. Other conditions such as bone marrow transplantation, chronic renal failure, ischemic heart disease, diabetes mellitus, and hypertension have also been associated with GAVE [95, 97, 98]. Most patients present with anemia due to chronic blood loss. Acute bleeding is less common. Endoscopy shows raised, intensely red, nearly parallel, longitudinal mucosal stripes traversing the gastric antrum and converging on the pylorus, simulating the appearance of a watermelon (Fig. 8.17a). Raised mucosal elevations may give the appearance of polypoid lesion [99]. In severe form, gastric hemorrhage may also be seen.

Pathological Features

The characteristic histological findings of GAVE include prominent dilated capillaries which often contain fibrin thrombi (in ~50% of cases) involving the mucosa of the gastric antrum (Fig. 8.17b). The surrounding tissue may show reactive gastropathy, edema, interstitial hemorrhage, and mild chronic inflammation. The dilated capillaries are often surrounded by fibrohyalinosis and fibromuscular hyperplasia of the lamina propria. The gastric body and fundus are usually spared; however, the cardia may be involved in a small subset of patients.

Differential Diagnosis

Histologic differential includes gastric varices which are seen at the gastroesophageal junction in patients with portal hypertension. Portal hypertensive gastropathy is an important differential and these lesions are compared in Table 8.1.

Treatment and Prognosis

Endoscopic ablation is the first choice of treatment. Pharmacological therapy with estrogen, progesterone, and tranexamic acid is used if endoscopic measures fail. Surgical antrectomy is reserved for unresponsive cases [100].

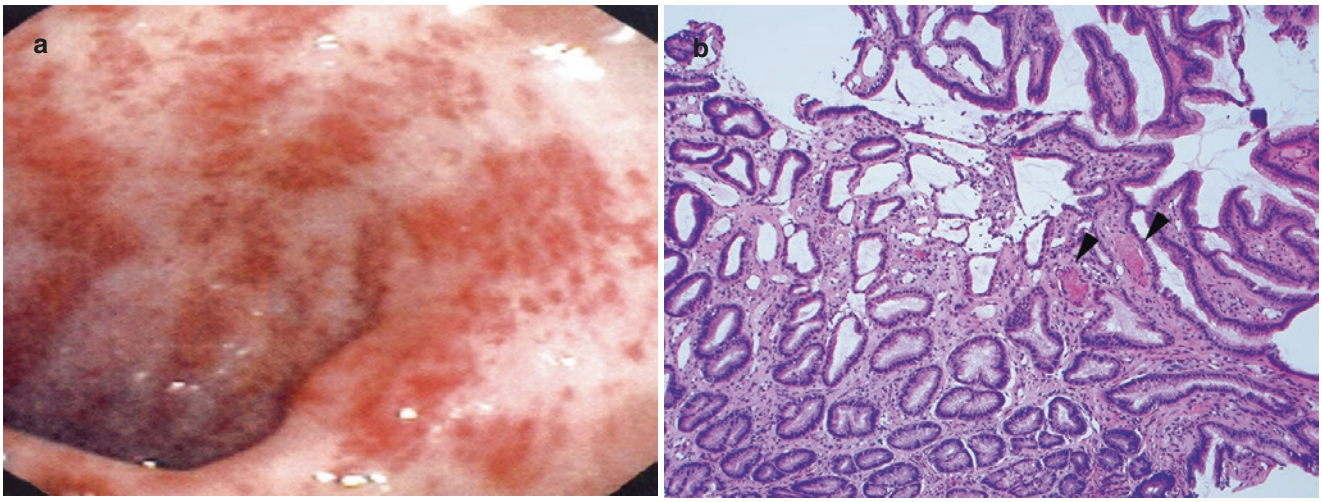

Fig. 8.17 Gastric antral vascular ectasia. Endoscopy shows red, nearly parallel, longitudinal mucosal stripes traversing the gastric antrum with the appearance of a watermelon (**a**). Prominent dilated capillaries with fibrin thrombi (arrowheads) involving the mucosa of the gastric antrum (**b**)

Table 8.1 Differences between portal hypertensive gastropathy and gastric antral vascular ectasia

Features	Portal hypertensive gastropathy	Gastric antral vascular ectasia
Sex	More common in males	More common in females
Age	Any age, including children	Typically, elderly (>70 years)
Associated conditions	Portal hypertension, cirrhosis	Cirrhosis, autoimmune disorders, connective tissue diseases
Endoscopy	Snake skin appearance with red spots	Tortuous columns of ectatic vessels in watermelon or diffuse pattern
Location	Fundus, body	Antrum
Degree of ectasia	Mild	Prominent
Fibrin thrombi	Absent	Present
Fibrohyalinosis	Absent	Present

Portal Hypertensive Gastropathy

Definition

This is gastric mucosal vasculopathy and injury that occurs in patients with portal hypertension.

Clinical Features

The term "portal hypertensive gastritis" was coined by Sarfeh et al. in 1984 where they described a distinct form of gastric mucosal hemorrhage in patients who had portal hypertension [101]. It can occur at any age and has been reported both in pediatric and adult patients and is more common in males. Portal hypertension and cirrhosis are the two main associations for this condition [102–105]. The reported prevalence in portal hypertensive patients varies from 20% to 75% and in cirrhotic patients from 35% to 80%. Portal hypertensive gastropathy can also occur in patients with non-cirrhotic portal fibrosis, extrahepatic portal vein obstruction, and hepatic veno-occlusive disease [102, 106, 107]. The hemodynamic instabilities in the gastric mucosal blood flow associated with passive congestion of the portal system play a role in its pathogenesis [108, 109]. Many patients may be asymptomatic but the most common presenting symptoms are gastrointestinal hemorrhage and anemia. Endoscopy shows a snake skin-type mosaic pattern or a diffuse erythematous and reticular cobblestone pattern with red punctate spots predominantly within the gastric mucosa of the body and fundus [102, 108, 110, 111].

Pathological Features

Characteristic histological findings include dilated ectatic capillaries and venules within the reactive gastric mucosa (Fig. 8.18a) accompanied by markedly congested and tortuous venules in the submucosa [112]. The lamina propria may also show stromal fibrosis and edema (Fig. 8.18b). Fibrin thrombi are usually absent.

Differential Diagnosis

GAVE is an important differential and these lesions are compared in Table 8.1.

Treatment and Prognosis

Treatment is aimed at reducing the portal pressure using medical therapy (propranolol), endoscopic therapy (argon plasma coagulation), radiologic intervention (transjugular intrahepatic portosystemic shunt), and surgical shunting [113].

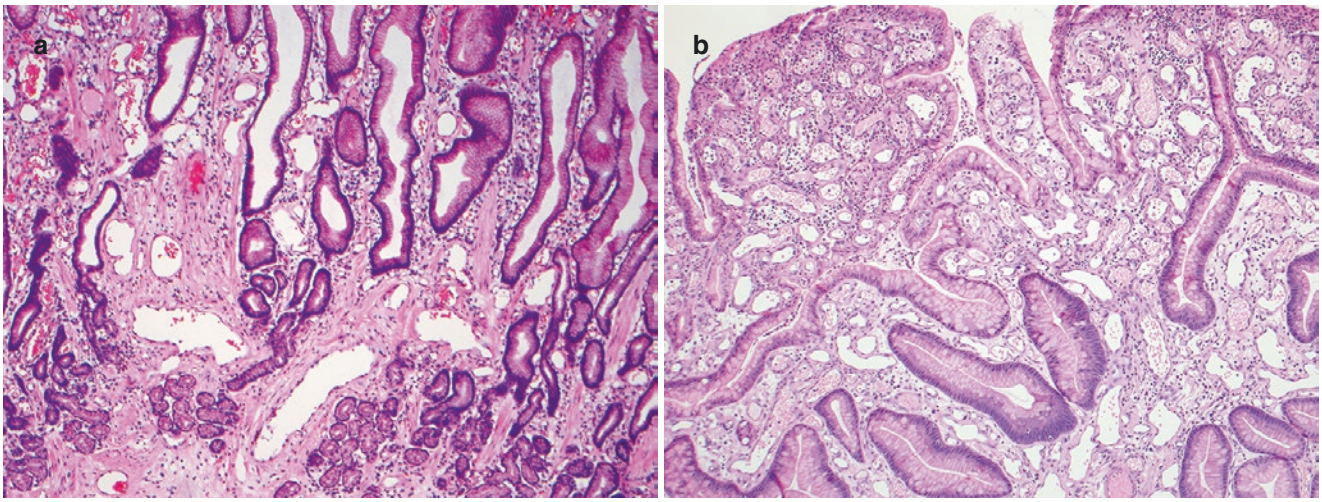

Fig. 8.18 Portal hypertensive gastropathy. Dilated ectatic capillaries and venules within the gastric mucosa (**a**). The lamina propria shows stromal edema and prominent dilated capillaries, and absence of fibrin thrombi (**b**)

Dieulafoy Lesion

Definition

Dieulafoy lesion is defined as large abnormal caliber artery in the submucosa protruding through a small defect within the overlying mucosa, potentially responsible for life-threatening bleeding. It is also known as cirsoid aneurysm, caliber-persistent artery, and submucosal arterial malformation.

Clinical Features

Dieulafoy lesion was first described in 1884 by Gallard as "military aneurysms of the stomach" in two autopsy cases [114, 115]. This condition was more accurately described in 1898 by the French surgeon Georges Dieulafoy in his study of fatal gastric hemorrhage in three asymptomatic men [115, 116]. It is now believed to be congenital developmental malformation in nature. It can be seen in any age group including children, but is most common in elderly (>50 years) males, accounting for 1–6% of upper gastrointestinal bleeding [115–117]. Many patients have comorbidities such as cardiopulmonary dysfunction, hypertension, and chronic renal failure. Patients typically present with acute painless massive gastrointestinal bleeding resulting in hemodynamic shock. A small subset of patients may also present as iron deficiency anemia. The exact pathogenesis is not known, but it is suggested that pulsations in large submucosal vessel causes damage of the overlying mucosa, leading to localized ischemia, erosion, and rupture. Another theory suggests gastric mechanical forces predispose to arterial thrombosis leading to overlying mucosal injury and necrosis [114, 118, 119]. Endoscopy may show active bleeding within the stomach from an isolated protruding vessel surrounded by normal mucosa or a clot without an ulcer [114, 120]. The lesion is most commonly seen on the lesser curvature of the stomach within 6 cm of the gastroesophageal junction.

Pathological Features

Microscopy would show a luminally exposed ruptured artery within the superficial submucosa (Fig. 8.19). A fibrin thrombus may be seen covering the arterial defect. The artery usually appears normal in architecture with no aneurysm or atherosclerosis. The adjacent mucosa may show fibrinoid necrosis but is usually devoid of significant inflammation away from the lesion [121].

Differential Diagnosis

GAVE can be distinguished from Dieulafoy lesion by presence of dilated mucosal capillaries containing fibrin thrombi with intact mucosa showing foveolar hyperplasia. Gastric varices typically occur at the gastroesophageal junction in patients with portal hypertension, and microscopy shows blood-filled dilated veins. Arteriovenous malformation can also come in the differential but typically shows a mixture of thick- and thin-walled irregular vessels. Erosive gastritis secondary to *H. pylori* or NSAIDs generally shows more inflammation and absence of ruptured artery.

Treatment and Prognosis

Advances in endoscopy have increased its detection rate and markedly reduced the associated mortality from 90% to less than 5% [122–125]. Endoscopic hemostatic methods are the treatment of choice. However, the risk of rebleeding has been reported between 10% and 40% after endoscopic therapies. Hence, few cases may require angioembolization or surgical resection [115].

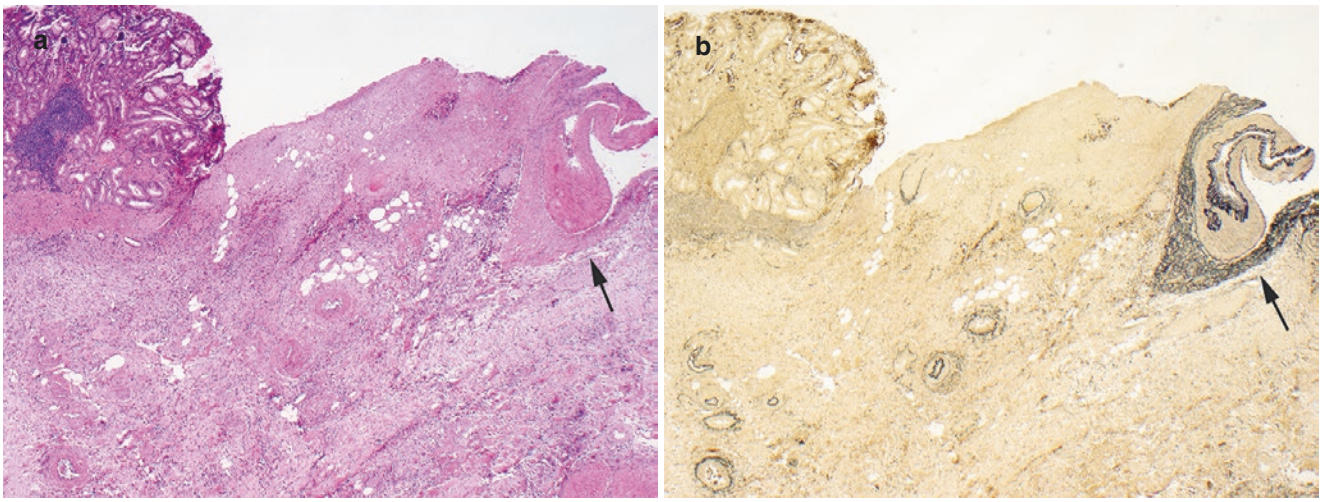

Fig. 8.19 Dieulafoy lesion. A large abnormal caliber artery in submucosa beneath a defect of the overlying mucosa on the H&E stain (**a**) and elastic stain (**b**)

Congenital Disorders

Duplication Cyst

Definition

Gastric duplication cyst is a complete or partial replica of a gastric segment.

Clinical Features

Duplication cysts of the gastrointestinal tract are rare and considered to be congenital in nature. They probably represent a cystic developmental malformation of the primitive foregut vestiges [126, 127]. They constitute around 2–9% of all gastrointestinal duplications and often coexist with other anomalies like esophageal duplications, rotational disorders, cloacal anomalies, urinary tract anomalies, and cardiovascular malformations. They are usually detected early in life, and most patients present during neonatal years. Presenting symptoms include abdominal pain, distention, palpable mass, nausea, and vomiting. Computed tomography (CT) and magnetic resonance imaging (MRI) would reveal a cystic mass connected or adjacent to the stomach. Sometimes the preoperative CT and MRI imaging findings of a gastric duplication cyst may be interpreted as consistent with a gastrointestinal stromal tumor (GIST) or sarcoma [128].

Pathological Features

Most gastric duplication cysts involve the anterior or posterior walls of the greater curvature. A subset may adhere to the pancreas (Fig. 8.20a) and may even communicate with the pancreatic duct. Grossly they appear as cylindrical or oval cystic masses ranging in size from a few millimeters to 12 centimeters [128]. Three microscopic criteria are needed for diagnosis of a duplication cyst and they include: (1) connecting attachment to the stomach (however, a luminal connection is not necessary); (2) smooth muscle layer that fuses with the gastric muscle layer; and (3) a mature or primitive gastrointestinal lining epithelium [129]. The presence of a muscle coat is needed to define a duplication cyst. The absence of a muscle coat defines an enterogenous cyst. The lining epithelium of the gastric duplication cyst may resemble normal gastric epithelium but may also coexist with small bowel or colonic epithelium (Fig. 8.20b, c). A subset may also show a component of respiratory mucosa, ceruminous glands, and cartilage. Bleeding and ulcer can develop within a gastric duplication cyst.

Differential Diagnosis

Pericardial cysts are in the differential, but they are lined by flattened mesothelium with absence of muscularis propria. Lymphangiomas are also in the differential, but microscopy would show large lymphatic channels in loose connective tissue stroma.

Treatment and Prognosis

Surgical excision is the treatment of choice [130]. There are rare reported cases of malignancies such as adenocarcinomas and neuroendocrine carcinoma developing within gastric duplication cysts [128, 131].

Pancreatic Heterotopia

Definition

Pancreatic heterotopia is defined as presence of pancreatic tissue outside the boundaries of the pancreas that lacks ana-

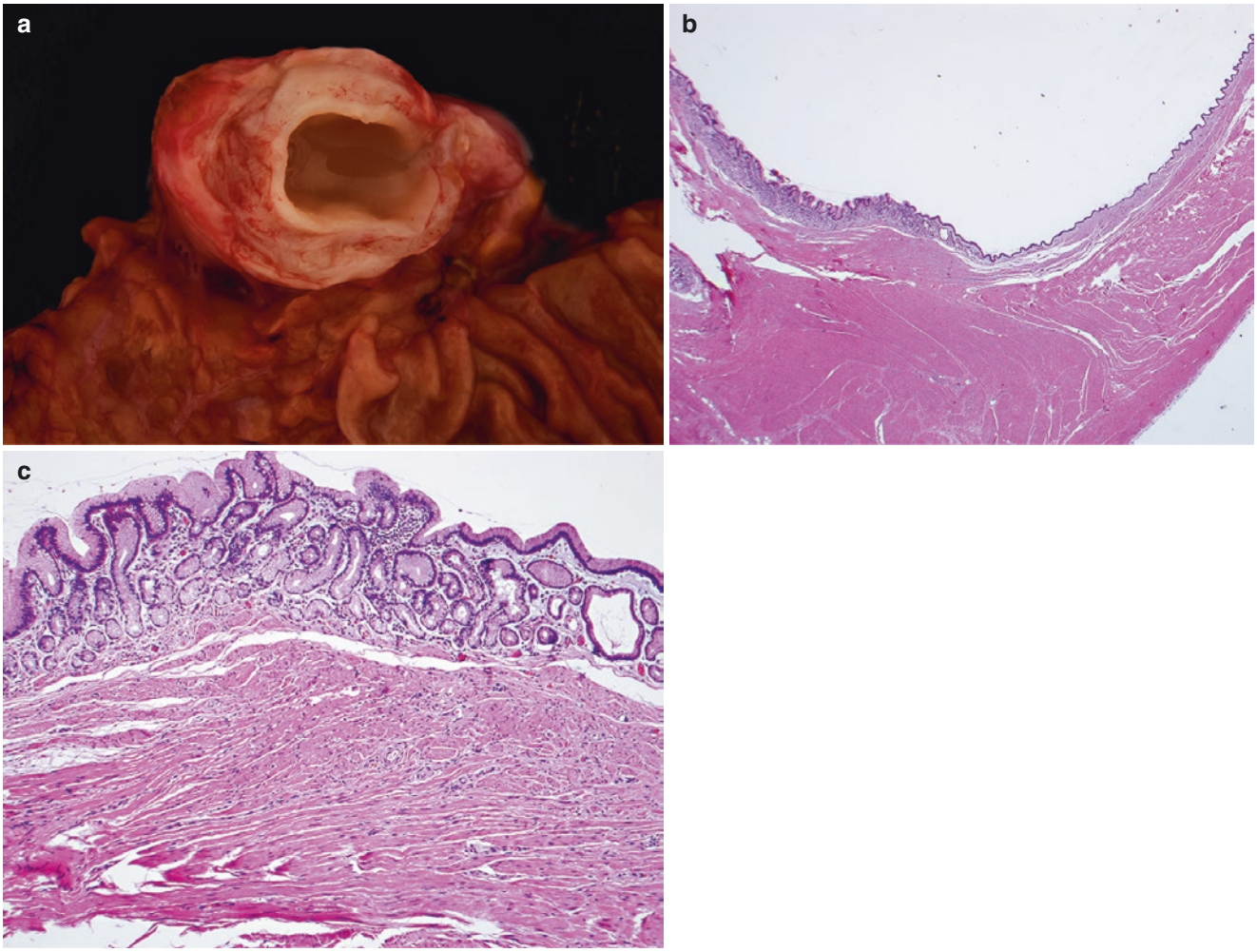

Fig. 8.20 Gastric duplication cyst. The duplication cyst is adhered to the pancreas (**a**). Muscular propria is present within the cyst wall (**b**), and the lining epithelium shows normal gastric epithelium (**c**)

tomic, functional, and vascular connection with the original organ.

Clinical Features

In general, pancreatic heterotopia is a relatively infrequent lesion, with an autopsy frequency ranging between 0.6% and 13% [132, 133]. Stomach is the most frequent site of pancreatic heterotopia. It can be associated with other congenital anomalies such as gastrointestinal atresia and duplication. The exact pathogenesis of this lesion is unknown. It is believed to arise during embryonic development of the gastrointestinal tract. During embryogenesis, if one or more evaginations from developing pancreas remain entrapped, then it may be carried away from the remainder of the gland by the developing gastrointestinal tract and may give rise to heterotopic pancreas. The other theory proposes pancreatic metaplasia of endodermal tissues that end up in the submucosa during embryonic life. Majority of the patients remain asymptomatic and the lesion is found incidentally during endoscopy, surgery, or autopsy. A small subset of patients may present with abdominal pain, bleeding, nausea, and vomiting [134].

Pathological Features

Grossly it appears as a single, well-circumscribed, solid, or cystic tan mass within the submucosa. Endoscopically the lesion may appear as a mucosal polyp with central umbilication and normal-appearing overlying mucosa. Occasionally, it may also be seen within the muscularis propria or serosa. It varies in size from 0.2 cm to 6 cm. Rare cases can be multiple or pedunculated. Histologically, it contains a mixture of tissues that may be found in the normal pancreas. Most consists primarily of ducts and surrounding simple mucin-producing glands. Special stains are usually not needed but trypsin immunostain can be used to confirm the presence of pancreatic acini. Cytokeratin 7 immunostain has also been shown to facilitate recognition of pancreatic heterotopia in gastric biopsies [135]. Ectopic pancreas can be classified

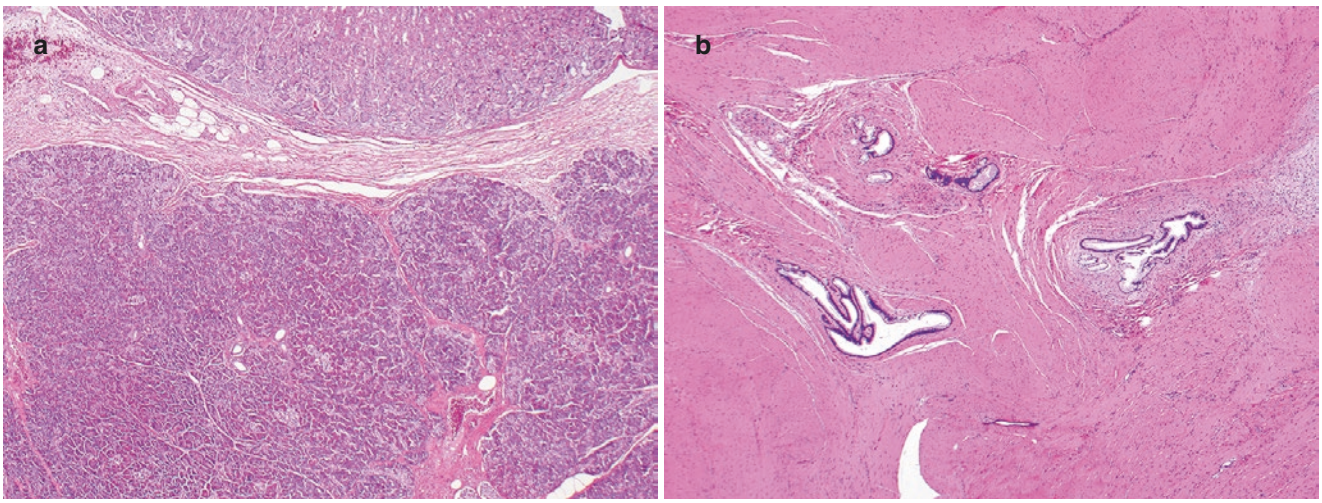

Fig. 8.21 Gastric pancreatic heterotopia. Pancreatic heterotopia comprising of all cell types, including exocrine cells, endocrine cells, and ductal epithelium present within gastric submucosa (**a**). Pancreatic heterotopia composed of ducts only in muscularis propria of stomach (**b**)

into three types according to Heinrich based on the types of the pancreatic cells present: type I with all three components of pancreatic tissues (acini, ducts, and islet cells) (Fig. 8.21a); type II with exocrine components of pancreatic tissues (acini and ducts, but no islet cells); and type III with mainly ducts but no acini or islet cells (Fig. 8.21b) [136]. Occasionally, pancreatic heterotopia can be composed of islet cells only (endocrine heterotopia) (Fig. 8.22a, b) [137]. A subset of cases can show secondary changes such as pancreatitis, abscess formation, fibrosis, or fat necrosis, distorting the histology of the heterotopic tissue. Rarely, endocrine and/or glandular neoplasms as well as pancreatic cysts can also develop within pancreatic heterotopia [138, 139].

Differential Diagnosis

If only pancreatic acinar cells are present, especially in the gastroesophageal junction region, then it may represent pancreatic acinar metaplasia [140]. Cases of autoimmune atrophic gastritis can also show pancreatic acinar metaplasia in the stomach [141]. Purely endocrine heterotopic pancreas may mimic a well-differentiated neuroendocrine tumor (Fig. 8.22a, b). Both show monomorphic neuroendocrine cells arranged in small nests or microtubules. However, the scattered nature of the lesion, small size of the nests, and absence of stromal reaction argue against a neuroendocrine tumor and favor an endocrine pancreatic heterotopia. Immunostains may also help in making this distinction as cases of endocrine pancreatic heterotopia would show majority of cells expressing insulin (Fig. 8.22c), mostly in the center of the nodules, with fewer peripheral cells showing somatostatin (Fig. 8.22d) and glucagon (Fig. 8.22e) positivity [142].

Treatment and Prognosis

Asymptomatic cases do not need treatment unless complications develop. Localized surgical resection is usually the treatment of choice.

Congenital Pyloric Stenosis

Definition

Congenital pyloric stenosis is defined as narrowing of the stomach due to abnormal thickening of the pylorus resulting in gastric outlet obstruction.

Clinical Features

Congenital pyloric stenosis is the most common cause of gastric outlet obstruction and surgical cause of vomiting in infants. Incidence ranges from 1 to 6 per 1000 live births [143, 144]. Commonly occurs in whites, first-born child, and males. Congenital pyloric stenosis can be associated with other anomalies like esophageal atresia, intestinal malrotation, and urinary tract defects [145]. The etiology remains unknown but probably is multifactorial involving genetic predisposition and perinatal as well as environmental factors [146]. However, it has been associated with several chromosomal aneuploidy syndromes such as deletion 11q, duplica-

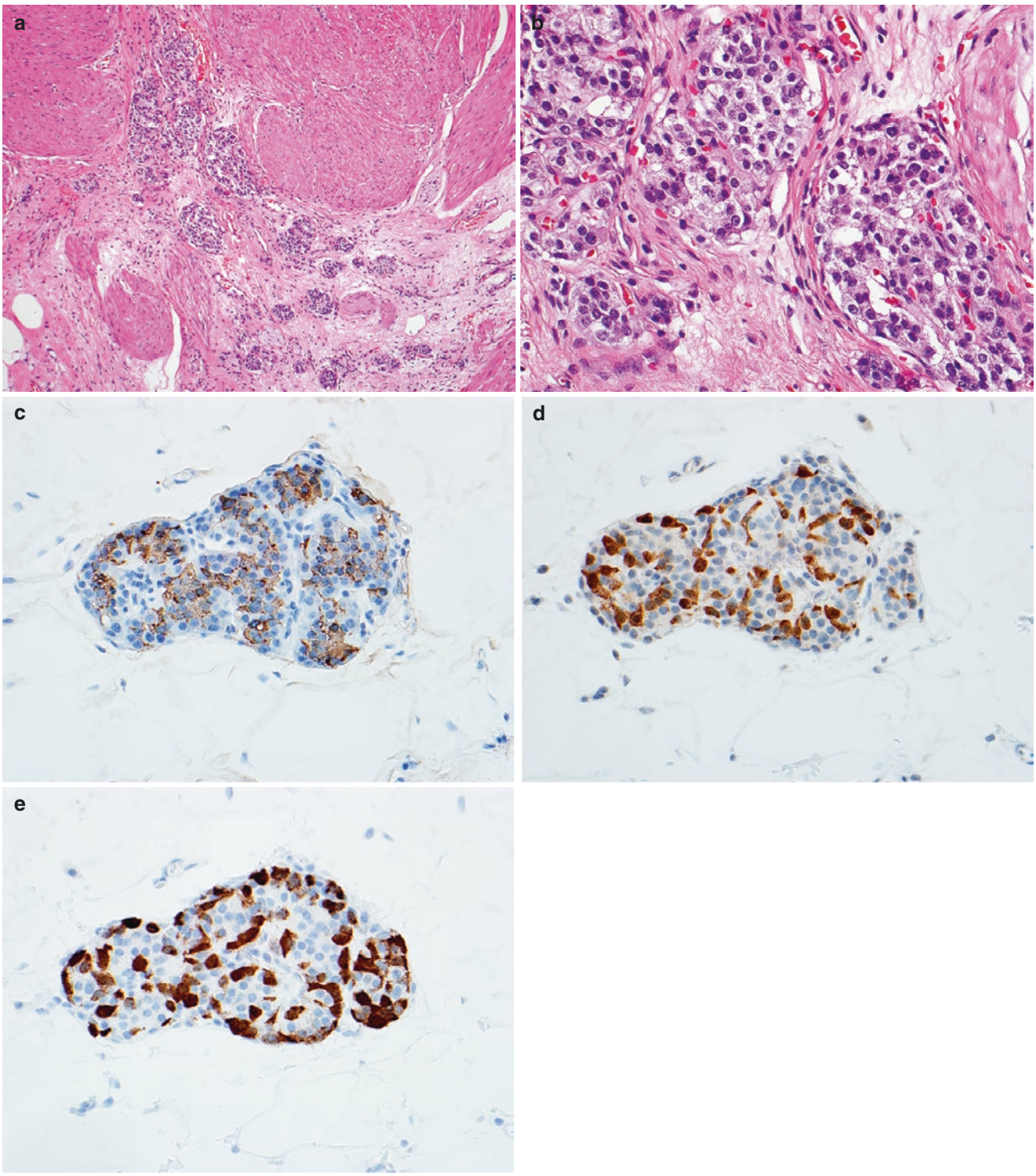

Fig. 8.22 Gastric pancreatic endocrine heterotopia. Pancreatic heterotopia comprising islet cells only in muscularis propria of stomach (**a**). The neuroendocrine cells arranged in small nests and absence of stromal reaction (**b**) and the majority of cells, mostly in the center of the nodules expressing insulin (**c**), with fewer peripheral cells expressing somatostatin (**d**) and glucagon (**e**) by immunostains

tion 14q, duplication 9q, trisomy 18, and trisomy 21 [147]. Formula feeding and azithromycin have also been associated with increased risk of developing hypertrophic pyloric stenosis [148, 149]. Clustering of cases has been seen within families [147]. Patients typically present with progressive projectile nonbilious vomiting between the second and eighth weeks of life [150, 151]. If untreated, the infant may develop hypochloremic and hypokalemic metabolic alkalosis. The clinical diagnosis can be made by feeling the thickened pylorus as an olive-shaped mass in the mid-epigastrium and observing the gastric peristaltic waves. Abdominal ultrasound can confirm the diagnosis [152, 153].

Pathological Features

The characteristic finding on gross is concentrically enlarged gastric pylorus with thickness of more than 1 cm and two to four times its usual length. The pylorus becomes very hard due to the hypertrophy of the muscle and elastic tissue in the submucosa. The proximal stomach dilates with hypertrophy of the antrum and gastric outlet obstruction at the pylorus. Microscopically, there will be hyperplasia and hypertrophy of both the circular and longitudinal muscle fibers of the muscularis propria. The vessels in the submucosa may appear dilated. The nerve fibers may be reduced or absent and the ganglion cells may also disappear. Interstitial cells of Cajal may also be reduced in number [154].

Treatment and Prognosis

Extramucosal pyloromyotomy is the treatment of choice [155, 156]. Age below 2 weeks, delayed presentation, and prolonged preoperative hospital stay are predictors of poor outcome [157]. However, majority of the infants undergoing pyloromyotomy have an excellent prognosis with no long-term sequelae.

Polypoid Lesions

Gastric polyp is any lesion that protrudes into the gastric lumen above the mucosal surface. They are identified mostly as an incidental finding during about 1–6% of upper endoscopies [158–160]. A small subset of large polys may present with abdominal pain, bleeding, anemia, or gastric outlet obstruction [161]. The endoscopic appearance of gastric polyps is not specific for a particular subtype and hence histopathological examination is necessary for their accurate pathological diagnosis. The role of the pathologists is to identify a specific subtype of gastric polyp as it may have prognostic implications with a central goal of identifying whether the polyp is dysplastic or not. Many subtypes of gastric polyps arise in a background of chronic gastritis or association with polyposis syndromes. Hence, accurate identification of a particular subtype of gastric polyp may provide useful clues about its etiology as well as abnormalities in the background gastric mucosa.

Gastric Xanthoma

Definition

Gastric xanthoma is composed of benign aggregate of foamy lipid-laden histiocytes. It is also known as gastric xanthelasma or gastric lipid islands.

Clinical Features

Reported incidence varies between 1% and 6% in non-operated stomachs, most commonly seen in the stomach but can also be seen in small bowel, colon, and esophagus [162]. The etiology has not yet been established. However, it is probably a response to initial localized destruction of cells caused by inflammatory and degenerative changes, which leads to accumulation of cholesterol or fat [163]. Gastric xanthomas are commonly seen in patients after Billroth resection. They may be associated with hyperlipidemia, *H. pylori* infection, or gastric dysplasia; however, the evidence is not consistent [164–166]. It is usually an incidental finding as most patients are asymptomatic. On endoscopy, they appear as single or multiple, yellow to white plaques that are typically well demarcated, round to flat and vary from 1 to 10 mm. They are usually antral and near the lesser curvature but occasionally are located in the body or fundus and may be multiple.

Pathological Features

Histologically, they consist of numerous foamy macrophages usually within the lamina propria (Fig. 8.23a), particularly its upper half. The foamy cells do not show nuclear atypia or mitosis. The adjacent gastric mucosa may show chronic gastritis, intestinal metaplasia, or even atrophic gastritis. The foamy histiocytes are positive for CD68 (Fig. 8.23b) and CD163, and are negative for mucicarmine and cytokeratin (Fig. 8.23c).

Differential Diagnosis

The major differential diagnosis is signet ring cell adenocarcinoma, which would show nuclear atypia and positive staining for mucicarmine and cytokeratin. Metastatic clear cell renal cell carcinoma may also enter the differential, but it would be positive for keratin and PAX8. Whipple disease and *Mycobacterium avium*-intracellulare are rare infections of the stomach that also enter into consideration, and they can be evaluated by special stains (PAS-D and acid-fast bacilli).

Treatment and Prognosis

No treatment or follow-up is needed. However, recent studies have shown a high prevalence rate of gastric xanthoma in

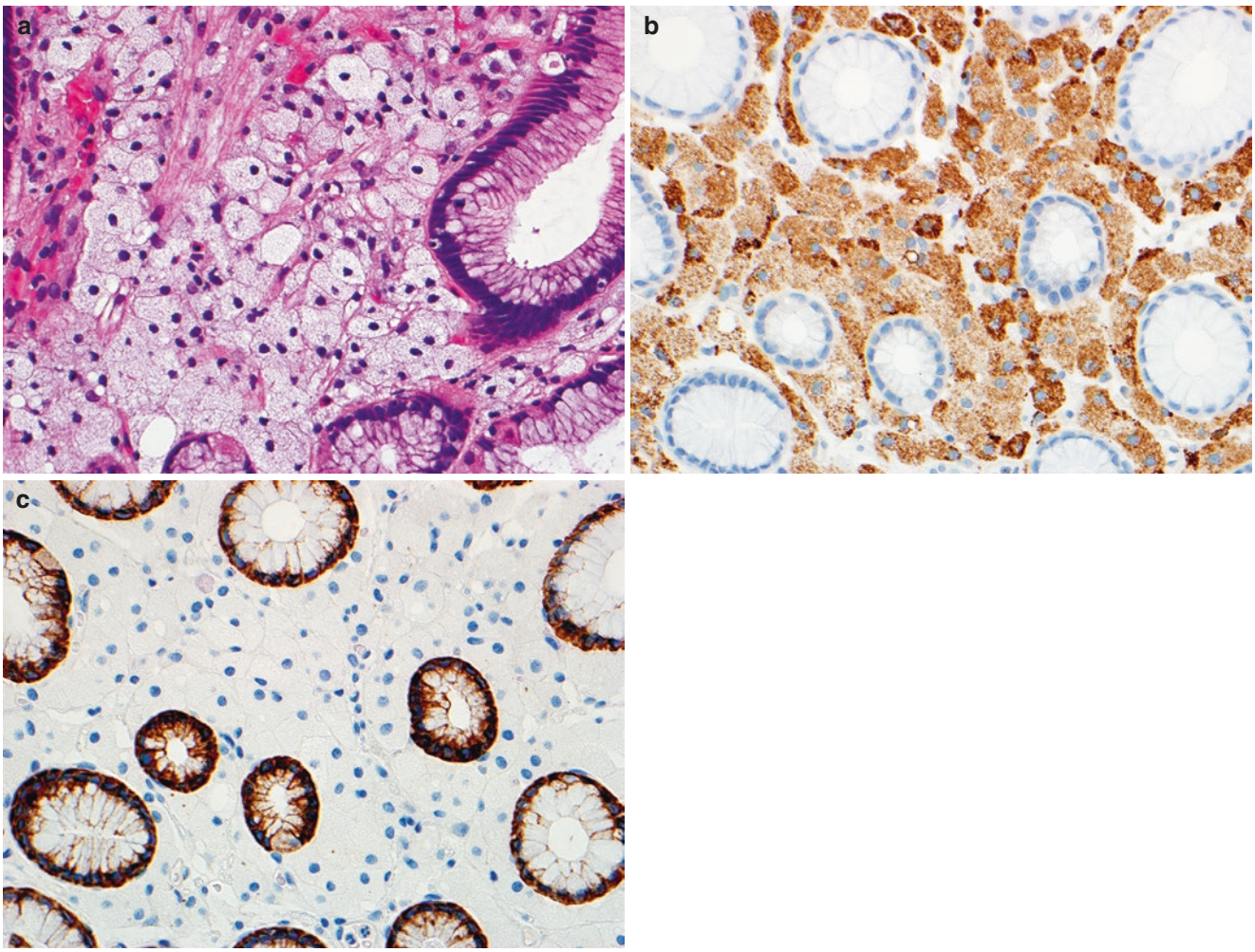

Fig. 8.23 Gastric xanthoma. Numerous foamy histiocytes within the lamina propria of gastric mucosa (**a**). The foamy histiocytes are positive for CD68 (**b**) and are negative for cytokeratin (**c**) by immunostains

gastric cancer cases with its presence as a predictive marker for metachronous and synchronous gastric cancer [167, 168].

Hyperplastic Polyp

Definition

Hyperplastic polyp is a benign polyp lined by gastric foveolar epithelium composed of elongated and distorted gastric pits with an inflamed and edematous stroma. It is also known as regenerative polyp and hyperplasiogenous polyp.

Clinical Features

It is the second most common type (about 15%) of gastric polyp after fundic gland polyp in the western populations [158, 161]. It can be found at any age but commonly seen in adults with a mean age range of 65–75 years. They are usually asymptomatic, most commonly seen in the gastric antrum, but can be seen throughout the stomach [169]. They can be single or multiple and range in size from a few millimeters to a few centimeters with a majority being less than 2 cm. They tend to arise in response to a variety of mucosal injuries and are strongly associated with chronic gastritis related to *H. pylori*, chemical, or autoimmune gastritis [169, 170]; hence evaluation of the background gastric mucosa is important in cases of hyperplastic polyps due to clinical consequences. Multiple hyperplastic polyps can be found in Menetrier's disease. Solid organ transplant has also been reported as a risk factor for development of hyperplastic polyps [171, 172]. Endoscopically, hyperplastic polyps may show superficial ulceration and a broad pedicle.

Pathological Features

Histologically, hyperplastic polyps are composed of elongated and dilated gastric pits with an edematous inflamed lamina propria and lined by reactive foveolar epithelium (Figs. 8.24a, b). A rich vasculature is common. The surface may be eroded or ulcerated with prominent reactive atypia within the foveolar epithelium (Fig. 8.24c). Pyloric-type

glands and foci of intestinal metaplasia may be seen (Fig. 8.24d). Wisps of smooth muscle originating from the muscularis mucosa may be seen in larger polyps.

Differential Diagnosis

Polypoid foveolar hyperplasia is considered a precursor of gastric hyperplastic polyp by some and measures less than 1 cm. It differs slightly from hyperplastic polyp with absence of cystically dilated gastric pits and normal or only slightly swollen lamina propria and mild inflammatory component. Considering the concept of a continuum between these two entities, a definitive distinction may be not important [173].

Gastric mucosal prolapse polyp can show varying degree of elongation and cystic dilatation of the pit region (Fig. 8.25). However, it contains thick-walled vessels and prominent bundles of arborizing smooth muscle. The glandular component is usually compact with back to back glands [173].

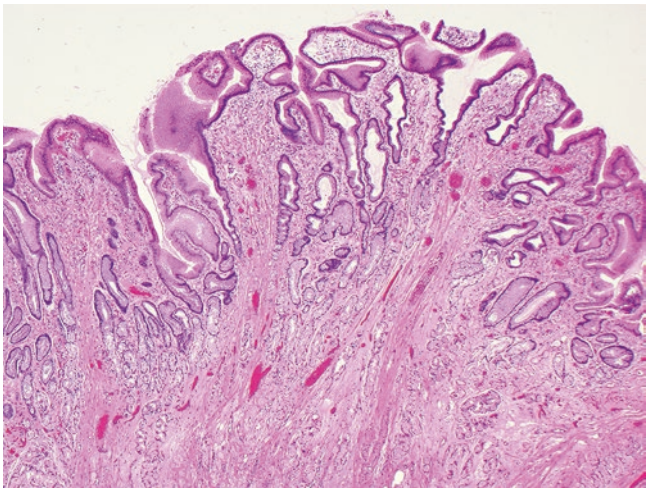

Fig. 8.25 Mucosal prolapse polyp. Antral mucosa with elongation and cystic dilatation of the pit region and prominent bundles of smooth muscle in lamina propria

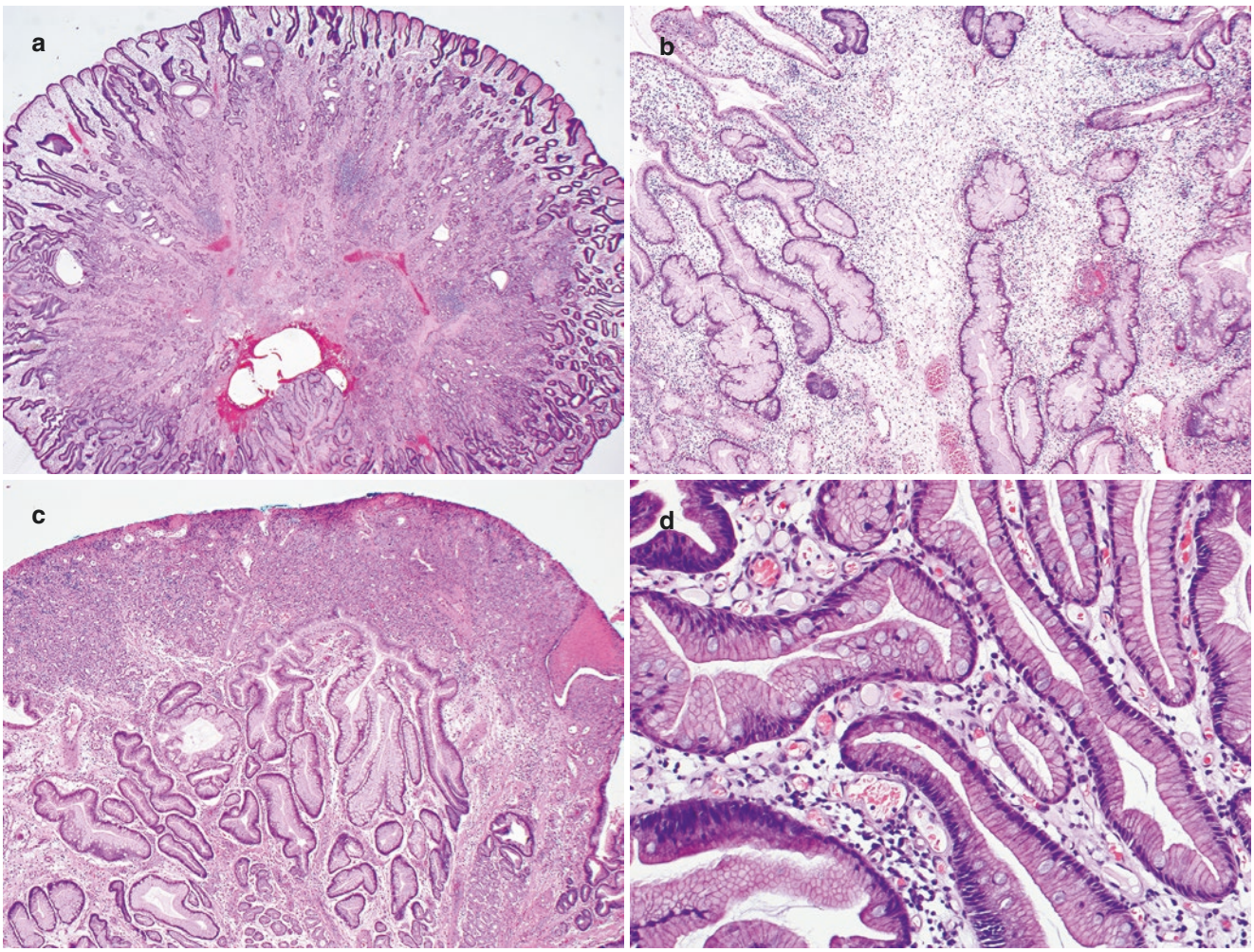

Fig. 8.24 Hyperplastic polyp. Gastric hyperplastic polyp is composed of elongated and dilated gastric pits (**a**) with an edematous inflamed lamina propria (**b**), erosion and granulation tissue in lamina propria (**c**), and foci of intestinal metaplasia (**d**)

Patients with Menetrier's disease can have multiple hyperplastic polyps. However, Menetrier's disease is usually limited to the gastric body and fundus. It shows prominent foveolar hyperplasia with lesser degree of inflammation. There is absence of intervening normal gastric mucosa between the polyps.

Morphological differentiation of hyperplastic polyps from hamartomatous polyps seen in Cronkhite-Canada syndrome and juvenile polyposis can be very difficult as they share significant morphologic overlap. Communication with the clinical colleagues to see if the patient has other features to support a particular syndrome is usually helpful in such situations to establish a correct diagnosis. However, a useful distinguishing feature of Cronkhite-Canada syndrome is the presence of inflammatory and edematous changes in the non-polypoid areas similar to those seen in the polypoid areas. In contrast, the inflammatory changes in juvenile polyposis are limited to the polypoid areas only with intervening normal mucosa.

Circumscribed foci of pseudosignet ring cell changes can occur in a small subset of hyperplastic polyps related to gland degeneration from torsion or ischemic injury and results in epithelial sloughing, and the epithelial cells assume a signet ring-like appearance (Fig. 8.26). The distinction from signet ring cell adenocarcinoma can be made by appreciating the lack of usual high-grade cytologic atypia and absence of infiltrative growth pattern within these sloughed epithelial cells showing pseudosignet ring cell change as well as ischemic/degenerative changes within the surrounding mucosa. E-cadherin and Ki-67 immunostain as well as reticulin stain may be useful adjuncts in such situations. E-cadherin is usually positive in the sloughed pseudosignet ring cells while it would be negative in signet ring cell adenocarcinoma. Reticulin stain would highlight the confinement of the pseudosignet ring cells within the gland basement membrane and the absence of an infiltrative pattern. The Ki-67 labeling in pseudosignet ring cells would be low (<2% staining), while the Ki-67 labeling would be increased in signet ring cell adenocarcinoma [174].

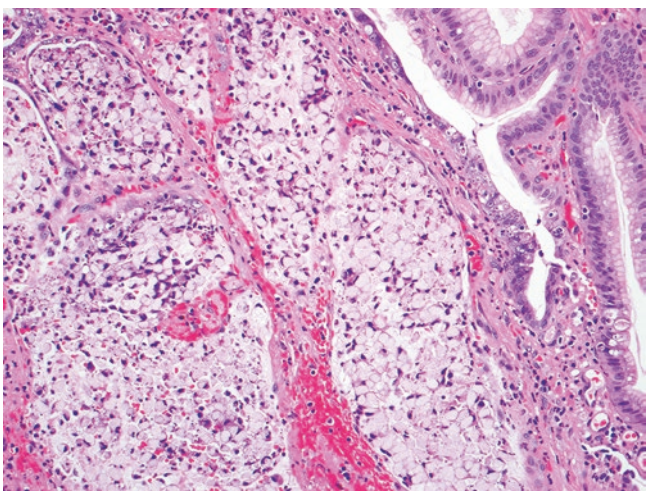

Fig. 8.26 Gastric hyperplastic polyp with pseudosignet ring cell changes. Circumscribed foci of epithelial sloughing assuming a signet ringlike appearance related to gland degeneration from torsion or ischemic injury in a gastric hyperplastic polyp

Treatment and Prognosis

Up to 80% of hyperplastic polyps have been reported to regress after eradication of *H. pylori* before endoscopic removal [175, 176]. Hence, testing for *H. pylori* infection and its eradication are important in patients with hyperplastic polyps. They rarely undergo neoplastic change, and dysplasia in hyperplastic polyps is rare, ranging from 1.5% to 4%. It is more common in polyps measuring >2 cm [169, 177–179]. Adenocarcinoma is even rarer with a reported range of up to 2%. However, hyperplastic polyps are associated with an increased risk of synchronous cancer occurring elsewhere in the gastric mucosa [180]. Hence, endoscopic and microscopic assessment of the surrounding gastric mucosa is important. There is controversy regarding whether they should be simply biopsied or whether they should be entirely removed by polypectomy. Some recommend performing polypectomy for all small polyps and periodic biopsy of larger hyperplastic polyps that are too big for polypectomy. Others recommend polypectomy for only large hyperplastic polyps as they have the highest risk for neoplastic change.

Peutz-Jeghers Polyp

Definition

Peutz-Jeghers polyp is a hamartomatous polyp arising in patients with Peutz-Jeghers syndrome (PJS).

Clinical Features

PJS is an autosomal dominant syndrome caused by a germline mutation of the *LKB1/STK11* gene. WHO criteria for clinical diagnosis of PJSs are: (1) detection of three or more histologically confirmed Peutz-Jeghers polyps; or (2) the presence of any number of Peutz-Jeghers polyps in a patient with a family history of the syndrome; or (3) detection of characteristic, prominent mucocutaneous pigmentation in the patient with a family history of the syndrome; or (4) detection of any number of Peutz-Jeghers polyps in a patient with prominent mucocutaneous pigmentation [181]. Patients with PJS have gastrointestinal polyposis, perioral pigmentation, and overtime cancer risk of >80% by the age 70 years [182, 183]. About 25% of patients with PJS develop gastric polyps [184].

Pathological Features

The polyps usually vary in size between 0.1 cm and 5 cm and they are often sessile. The gastric polyps commonly arise in the antrum. Microscopically, they are composed of promi-

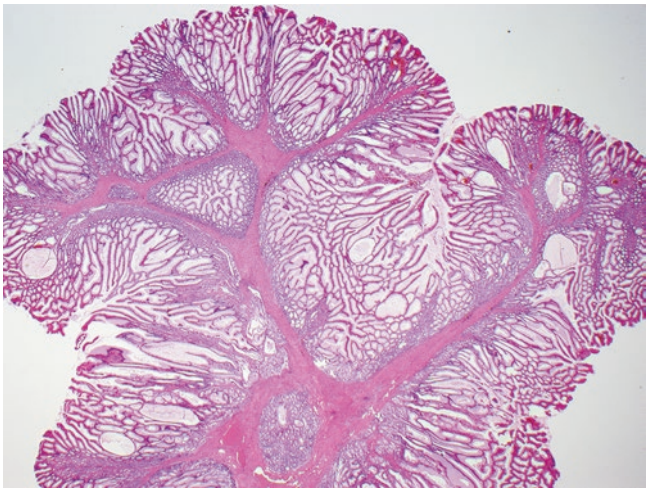

Fig. 8.27 Peutz-Jeghers polyp. A hamartomatous polyp composed of prominent, dilated, or branching mucin-filled gastric pits lined by foveolar epithelium and variable number of deep glands. Some arborizing smooth muscle bundles are present in this gastric Peutz-Jeghers polyp

nent dilated or branching mucin-filled gastric pits lined by foveolar epithelium and variable number of deep glands (Fig. 8.27). The surfaces of polyps may be superficially eroded and acutely inflamed. They usually lack an arborizing architecture with prominent bands of smooth muscle as seen in small bowel or colonic Peutz-Jeghers polyps; however, a subset of them may show some degree of smooth muscle proliferation. The background gastric mucosa is usually unremarkable. A subset of large polyps may show displaced benign glands and mucinous cysts within the submucosa, muscularis propria, or even the serosa. The benign histologic appearance of the epithelium differentiates these areas from invasive adenocarcinoma.

Differential Diagnosis

Gastric Peutz-Jeghers polyps are often difficult to distinguish from gastric hyperplastic polyps and juvenile polyps [185]. They are best distinguished by correlation with the clinical history and other features that characterize each syndrome to establish the correct diagnosis. A subset of large gastric hyperplastic polyps may develop prominent smooth muscle bundles within the polyp due to mucosal prolapse. Therefore, the identification of prominent smooth muscle bundles is also not diagnostic of Peutz-Jeghers polyps in the stomach. Hence, one should be cautious in making a new diagnosis of Peutz-Jeghers syndrome while evaluating gastric polyps in isolation of the clinical context.

Treatment and Prognosis

These patients are at an increased risk for a variety of extraintestinal and gastrointestinal malignancies including gastric, small bowel, and colorectal cancers. Patients with PJS have a 29% lifetime risk of gastric cancer [186, 187]. Dysplasia in gastric Peutz-Jeghers polyp is rare. It has been proposed that Peutz-Jeghers polyps are not malignant precursors but in fact just an epiphenomenon to cancer prone condition [188]. The gastric mucosa of PJS patients has yet not been studied for pre-tumor progression [189]. Surveillance guidelines for PJS patients recommend upper gastrointestinal endoscopy and colonoscopy be done first at the age of 8 years. If polyps are found, it should be repeated every 3 years. If no polyps are found, then a second baseline examination should be done at the age of 18 years and then every 3 years, or earlier if symptoms occur [182]. It has also been suggested that gastric Peutz-Jeghers polyps larger than 1 cm should be resected endoscopically, and patients should receive annual surveillance [170].

Juvenile Polyp

Definition

Juvenile polyp is a hamartomatous polyp arising in patients with juvenile polyposis syndrome (JPS).

Clinical Features

JPS is an autosomal dominant syndrome and is the most common of the hamartomatous polyposis syndromes. Synonyms for this syndrome include generalized juvenile polyposis, juvenile polyposis of infancy, and gastric juvenile polyposis. It is caused by mutations of the *SMAD4* gene (also called the *MADH4* gene) or the *BMPR1A* gene in 20% and 25% of patients, respectively [190–192]. *SMAD4* mutation is associated with the greatest risk factor for upper-gastrointestinal tract involvement, as more than 80% of patients with a germline *SMAD4* mutation will have extra-colonic involvement [193, 194]. The early childhood presentation has been associated with *ENG* germline mutations [195]. Majority of the patients have a family history of JPS; however, about 25% of newly diagnosed cases represent new or de novo mutations and hence they are sporadic [196]. WHO criteria for the clinical diagnosis of JPS include: (1) more than three to five juvenile polyps of the large bowel; or (2) multiple juvenile polyps throughout the gastrointestinal tract; or (3) any number of juvenile polyps with a family history of JPS [197]. JPS patients develop hamartomatous polyps in the colon, the stomach, and less commonly in the small bowel. More than 80% of JPS patients have lesions in the stomach. Most develop polyps before the age of 20 years; hence, the diagnosis can be made much later in life in late adulthood (the word "juvenile" signifies the type of polyp and not the age of diagnosis or onset of the polyp). The clinical manifestations can vary in severity, as a subset of patients developing only a few polyps, whereas others have extensive polyposis, presenting with diarrhea or malabsorption.

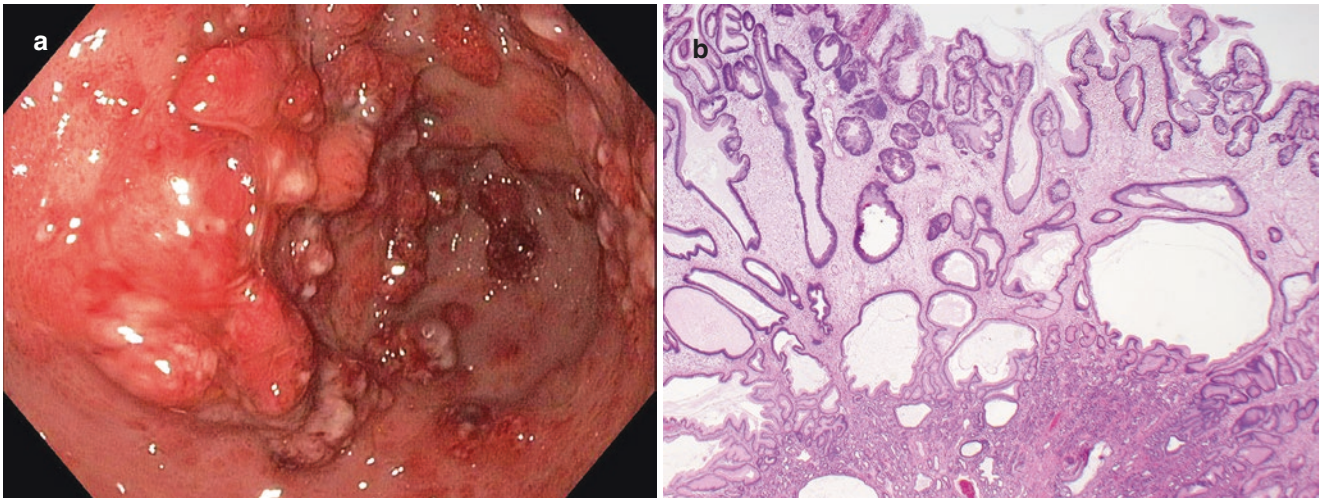

Fig. 8.28 Juvenile polyposis syndrome. Multiple polyps in stomach affecting the antrum, body, and fundus in a patient with juvenile polyposis syndrome on upper endoscopy (**a**). The polyp shows abundant distorted and mucus-filled dilated gastric glands with prominent edema in lamina propria (**b**)

Pathological Features

Grossly juvenile polyps are usually multiple polyps ranging from 0.1 cm to 5 cm affecting the antrum and extending to the fundus/body (Fig. 8.28a). They usually have spherical shape with a smooth surface. The larger polyps can be multilobated or may show a villiform architecture. Microscopically, they show abundant distorted and mucus-filled dilated gastric glands with excess of lamina propria showing edema and inflammatory cells (Fig. 8.28b). The stroma/epithelium ratio is abnormally greater than normal. Smooth muscle is rarely seen within the lamina propria. Dysplasia can be found in 15% of gastric juvenile polyps [198]. A subset of patients with JPS may develop massive gastric juvenile polyposis showing total or near-total carpeting of the gastric mucosa by innumerable polyps, ranging from a few millimeters to 10 cm [199, 200].

Differential Diagnosis

Gastric juvenile polyps share resemblance with hyperplastic polyps or other hamartomatous gastric polyps such as PJS, Cronkhite-Canada syndrome, and Cowden syndrome [185]; hence, they are difficult to almost impossible to differentiate on morphology alone. One clue may be the abnormal intervening mucosa seen in Cronkhite-Canada syndrome polyps but not in JPS. The polyps in JPS are usually more extensive and densely distributed, and they also have more abundant inflamed stroma and less foveolar hyperplasia than hyperplastic polyps.

JPS polyps should be distinguished from sporadic juvenile polyps unassociated with a syndrome, which are typically single incidental lesions in the antrum, with a prevalence of about 2% of the pediatric and adult population. In contrast, JPS gastric polyps are typically multiple with involvement of both gastric antrum and body. There are no morphological features that can help separate syndromic from non-syndromic polyps.

Treatment and Prognosis

Patients with JPS have a 20% risk of developing gastric carcinoma [201]. Upper gastrointestinal endoscopy is recommended between the age of 12 and 15 years, and it should be repeated annually if polyps are found and every 1–3 years if no polyps are found [182].

Cronkhite-Canada Syndrome

Definition

Cronkhite-Canada syndrome is a rare non-congenital protein-losing enteropathy characterized by diffuse gastrointestinal tract polyposis and ectodermal changes such as alopecia and nail dystrophy.

Clinical Features

Majority of the patients manifest in middle to late adulthood, and >80% of patients are over 50 years at the time of diagnosis with a mean age at presentation of 59 years. Abdominal pain, diarrhea, and weight loss are the common presenting symptoms. Patients may also present with protein-losing enteropathy and peripheral edema due to malabsorption. Almost all patients also show ectodermal manifestations such as alopecia (of the body and scalp), nail dystrophy, and skin hyperpigmentation. Its exact cause is unknown but an autoimmune etiology has been suggested [202].

Pathological Features

The polyposis in Cronkhite-Canada syndrome involves the entire gastrointestinal tract except the esophagus [203, 204]. The polyps range in size from a few millimeters to 1.5 cm. The polyps may involve the entire stomach (Fig. 8.29a).

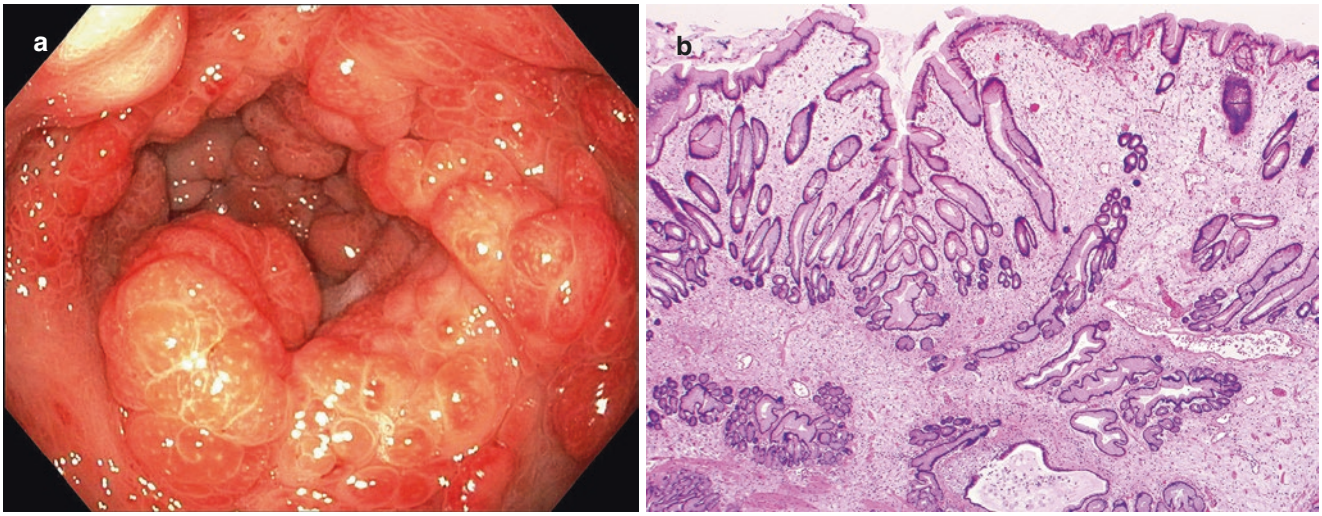

Fig. 8.29 Cronkhite-Canada syndrome. Numerous polypoid lesions present in the entire stomach on upper endoscopy in a patient with Cronkhite-Canada syndrome (**a**). The polyps have a hamartomatous appearance with cystically dilated gastric glands and edematous lamina propria (**b**)

Occasionally, there may be selective sparing of the stomach [204]. Microscopically, the Cronkhite-Canada syndrome polyps have a hamartomatous appearance. They show cystically dilated gastric glands and edematous lamina propria with mild mononuclear inflammation (Fig. 8.29b). Oxyntic, chief, Paneth, and endocrine cells are usually inconspicuous. A prominent mast cell, eosinophils, or IgG4 positive plasma cell infiltrate may be seen [203, 205–207]. The most important microscopic finding that distinguishes Cronkhite-Canada syndrome from other polyposis syndromes is the presence of lamina propria edema, gland/crypt architectural distortion, and inflammation in the intervening endoscopically/macroscopically normal-appearing non-polypoid gastric mucosa.

Differential Diagnosis

Gastric Cronkhite-Canada syndrome polyps share resemblance with hyperplastic polyps or other hamartomatous gastric polyps such as PJS, JPS, and Cowden syndrome [202]. Hence, they are very difficult to differentiate on morphology alone. One clue may be the abnormal intervening mucosa seen in Cronkhite-Canada syndrome polyps but not in others.

An infiltrative or infectious etiology may also be in the differential especially if endoscopy shows a diffusely thickened or atrophic appearance rather than a polypoid mucosa. Careful histopathological evaluation will easily exclude neoplasia as well as infection and confirm the characteristic architectural distortion and lamina propria changes of Cronkhite-Canada syndrome. Special stains for infectious etiology can also be helpful.

Menetrier's disease can also present as polypoid gastric mucosa on endoscopy, and Cronkhite-Canada syndrome is clinically associated with peripheral edema, diarrhea, and protein-losing enteropathy. However, the hyperplastic changes on microscopy are virtually always limited to the proximal stomach with an endoscopically and histologically unremarkable antral mucosa. Moreover, the duodenal mucosa would also be normal in Menetrier's disease [208].

Treatment and Prognosis

Cronkhite-Canada syndrome polyps are considered nonneoplastic with controversial malignant potential. However, carcinomas of the stomach have been described in patients with Cronkhite-Canada syndrome [209–211]. Due to its rarity, it is debatable if the patients with Cronkhite-Canada syndrome are truly at risk for gastrointestinal cancers. Variety of treatment approaches such as nutritional support, antibiotics, immune suppression, and surgery have been tried, often in different combinations and they have had variable success [202]. Less than 5% of patients have a complete remission and the overall outcome remains poor [212]. The 5-year disease-related mortality is reported as high as 55% and is most frequently related to gastrointestinal hemorrhage, infection, malnutrition, or congestive heart failure [204, 213].

Cowden Syndrome

Definition

Cowden syndrome is a rare autosomal dominant condition characterized by multiple hamartomatous lesions. It is included in the spectrum of *PTEN* hamartoma tumor syndromes. Recent studies have shown a prevalence of 25–35% for *PTEN* mutations in Cowden syndrome patients [214–216].

Clinical Features

It is characterized by pathognomonic mucocutaneous lesions (facial trichilemmoma, acral keratoses, papillomatous papules, and mucosal lesions), increased cancer risk (breast, thyroid, endometrial, colorectal, kidney, and melanoma), benign hamartomatous overgrowth of tissues (including gastrointestinal polyposis), and macrocephaly. Gastrointestinal polyposis involving the entire gastrointestinal tract is a common manifestation in patients with Cowden syndrome. Almost all patients with Cowden syndrome have gastric polyps. Most of the patients with Cowden syndrome manifest the phenotype by the second decade. Consensus-based diagnostic criteria for Cowden syndrome has been established by the International Cowden Consortium [217, 218].

Pathological Features

Gastric polyps are usually numerous and range in size from 0.1 cm to 2 cm (Fig. 8.30a). Microscopically, the polyps are hyperplastic or hamartomatous (Fig. 8.30b) as seen in other polyposis syndromes such as Cronkhite-Canada syndrome and JPS. Dysplasia is extremely rare.

Differential Diagnosis

Gastric polyps in Cowden syndrome share resemblance with hyperplastic polyps or other hamartomatous gastric polyps such as PJS, JPS, and Cronkhite-Canada syndrome. Hence, they are very difficult to differentiate on morphology alone.

Treatment and Prognosis

It is unclear if patients with Cowden syndrome have an increased risk for gastric cancer. However, there are a few reported cases of gastric cancer in patients with Cowden syndrome [219, 220]. Endoscopic upper gastrointestinal tract surveillance is recommended in patients with Cowden syndrome every 2–3 years starting at 15 years of age [182].

Miscellaneous Disorders

Pancreatic Acinar Metaplasia

Definition

Pancreatic acinar metaplasia (PAM) is defined as nests or lobules of pancreatic acinar tissue composed of cells with coarse apical eosinophilic granules with or without mucous cells. Synonyms include pancreatic cell metaplasia and pancreatic metaplasia.

Clinical Features

Usually an incidental finding that can be seen in children and adults with no gender preference. It is may represent a congenital rest or a type of metaplasia [140, 221–225]. Studies have shown PAM in up to 11% of investigated subjects [140, 141, 221]. It is commonly seen in the gastric cardia and antrum without any significant association with inflammation, atrophy, or intestinal metaplasia. However, PAM in the gastric body has been associated with autoimmune atrophic gastritis [141]. A study has also shown PAM located above the gastroesophageal junction to be associated with *H. pylori* gastritis and gastroesophageal reflux [226].

Pathological Features

On H&E-stained sections, PAM appears as pancreatic acinar-like cells with abundant cytoplasm that is eosinophilic and granular in the apical and middle portions and basophilic in the basal area (Fig. 8.31). The nuclei are basally situated, small,

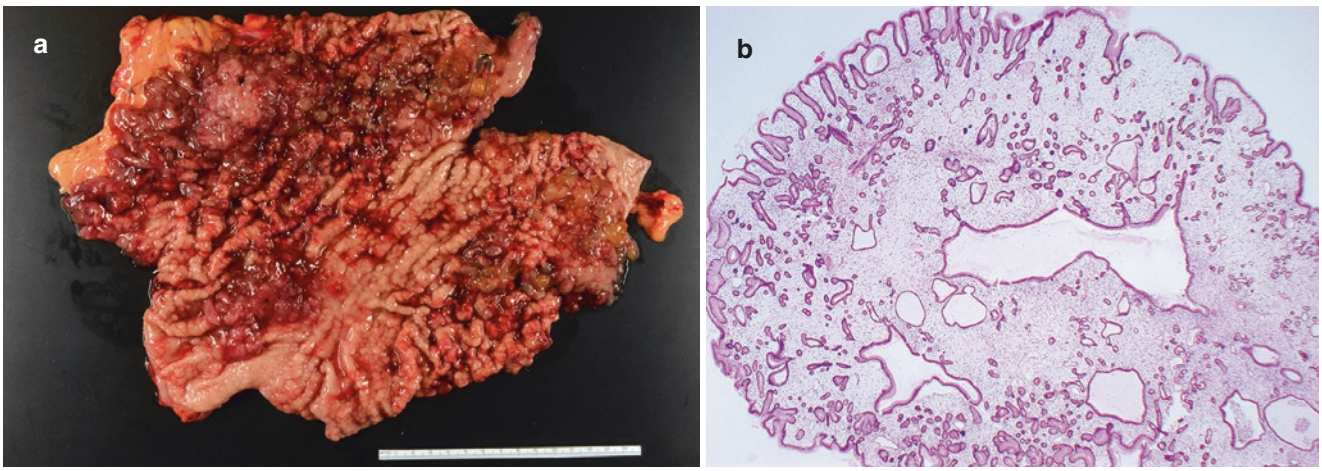

Fig. 8.30 Cowden syndrome. A gastrectomy specimen shows numerous polyps in the antrum, body, and fundus in a patient with Cowden syndrome (**a**). The polyps have hyperplastic or hamartomatous appearance similar to the histological features of juvenile polyp or Cronkhite-Canada syndrome (**b**)

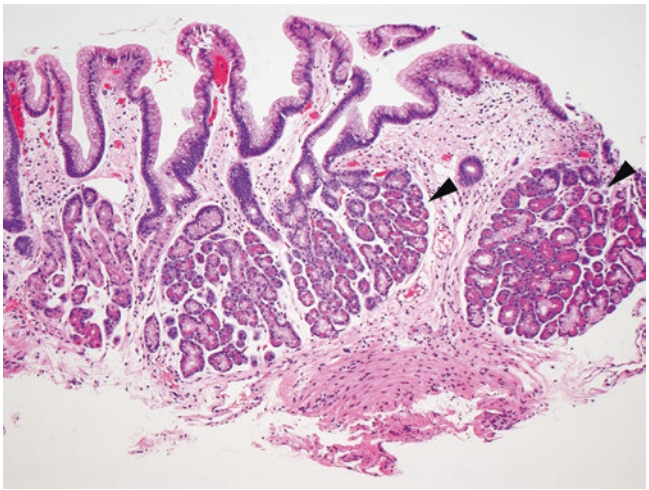

Fig. 8.31 Pancreatic acinar metaplasia. A few foci of well-circumscribed pancreatic acinar cells (arrowheads) present in a biopsy from gastric cardia with mild chronic inflammation in lamina propria

round, and uniform with inconspicuous nucleoli. Mucous cells may be intermingled with acinar-like cells within the lobules or could line tubules or small cystic spaces. The foci of PAM may be in continuity with the adjacent gastric glands or may be separated from them by smooth muscle or fibrous tissue. Immunohistochemically, PAM is positive for pancreatic lipase, amylase, and trypsinogen [140, 221]. However, immunostains are usually not required for diagnosis. Rare cells in PAM may be positive for chromogranin, synaptophysin, or gastrin.

Differential Diagnosis

Pancreatic heterotopia is differentiated from PAM by presence of ductal elements and/or well-defined islets. Paneth cells may also come in the differential, but the presence of large refractile granules within Paneth cells helps to distinguish them from PAM in which the zymogen granules are much smaller and eosinophilic. Immunostains for trypsin or lipase may be helpful in difficult cases.

Treatment and Prognosis

No treatment is needed as it is an incidental finding. However, its presence in adult gastric mucosa from the body or fundus should raise a suspicion for autoimmune atrophic gastritis especially if there is presence of associated chronic inflammation and/or atrophy of the oxyntic glands.

Gastritis Cystica Polyposa or Profunda

Definition

Gastritis cystica polyposa is a rare pseudotumor of the stomach characterized by benign growth of deep gastric glands through the muscularis mucosa into the submucosa or beyond. A polypoid lesion is known as polyposa, and when it is predominantly inverted, forming a submucosal lesion or mass, it is referred to as profunda.

Clinical Features

Gastritis cystica polyposa is usually seen in adults in the 5th or 6th decades of life. Patients may remain asymptomatic or present with abdominal pain, gastrointestinal bleed, and rarely gastric outlet obstruction. Endoscopy may show a nodular mucosa. It is commonly seen in patients who have undergone gastric surgery such as gastroenterostomy [227–229]. However, it can also be seen in non-operated stomachs [230–232]. Chronic inflammation, gastric surgery, and ischemia are considered to be the most important factors in its pathogenesis [233]. Epithelial displacement and implantation into the submucosa or beyond occurs following mucosal ulceration, herniation, iatrogenic mucosal defect (due to surgery, biopsy or polypectomy), or microdiverticula. Standard endoscopic biopsy is usually less helpful in making the diagnosis as it seldom offers information about the submucosa. In many cases, the preoperative diagnosis of this entity can be challenging and the patient may have to undergo gastric resection for definitive diagnosis.

Pathological Features

Histology shows dilated glands extending through the muscularis mucosa into the submucosa, muscularis propria, and even into the serosa (Fig. 8.32). These glands are lined by bland foveolar epithelium with absence of nuclear atypia or mitotic activity. The glands are surrounded by a rim of normal lamina propria and absence of desmoplastic stromal reaction. The surrounding stroma may be edematous with varying degrees of mixed inflammation, hemosiderin deposition, and fibrosis. The overlying gastric mucosa may show active chronic inflammation, ulceration, glandular atrophy, or intestinal metaplasia.

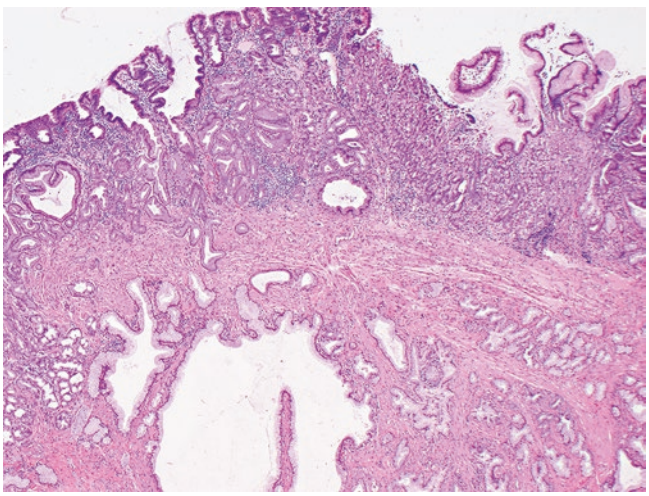

Fig. 8.32 Gastritis cystica profunda. Dilated gastric glands with absence of nuclear atypia extend through the muscularis mucosa into the submucosa. The glands present in the submucosa are surrounded by a rim of normal lamina propria and are without desmoplastic stromal reaction

Differential Diagnosis

Invasive well-differentiated adenocarcinoma is the main differential, and its distinction can be challenging [234]. However, careful attention to the absence of invasive growth pattern, lack of cytologic atypia, absence of desmoplastic stromal reaction, presence of lamina propria around the glands, and history of prior surgical procedure helps in distinguishing invasive adenocarcinoma from gastritis cystica polyposa or profunda (Table 8.2). Endometriosis may also come in the differential, but the presence of endometrial stroma and its positivity for estrogen receptor immunostain can help in making this distinction.

Treatment and Prognosis

Localized surgical excision including endoscopic submucosal dissection and endoscopic mucosal resection are usually curative [231]. However, recurrence can be rarely seen after surgical resection [235]. There has been a suggestion that gastritis cystica profunda/polyposa may be a precancerous condition, but this is controversial and not universally accepted [236–238]. However, there are rare cases of gastritis cystica profunda/polyposa reported in association with gastric adenocarcinoma in unoperated stomach [239, 240].

Table 8.2 Differences between gastritis cystica profunda/polyposa and invasive adenocarcinoma

Features	Gastritis cystica profunda/polyposa	Invasive adenocarcinoma
Overlying dysplastic epithelium	Absent	Present
Rim of lamina propria around the glands	Present	Absent
Desmoplastic stromal reaction around the glands	Absent	Present
Mitosis	Absent to rare	Present
Contour of glands	Smooth, regular, and lobular	Irregular and distorted
Cytologic atypia	Absent	Present

Mucosal Calcinosis

Definition

Gastric mucosal calcinosis is defined as deposition of calcium salts within the gastric mucosa.

Clinical Features

Gastric mucosal calcinosis is typically seen in adults with a female predominance. Usually asymptomatic but occasional patients can present with dyspepsia, nausea, vomiting, and epigastric pain. Most examples are detected at autopsy or due to the use of bone-seeking radiopharmaceuticals such as technetium-99 m methylene diphosphate. In routine practice, gastric calcifications are rare and seen in less than 0.1% of gastric biopsies [241]. However, up to 33% of gastric biopsies in transplant patients and up to 60% of chronically uremic, dialyzed patients can have calcinosis in their gastric biopsies [242, 243]. Gastric mucosal calcinosis has been associated with a number of etiological conditions such as hypercalcemia and/or hyperphosphatemia (related to chronic renal disease, uremia, dialysis, and secondary hyperparathyroidism), antacids, sucralfate, citrate-containing blood products, and organ transplantation [241]. Endoscopy may show 1–5 mm white flat plaques or nodules in the gastric fundus, body, and/or antrum [244, 245]. Rarely, it may appear as a large ulcerative lesion mimicking malignancy [246].

Pathological Features

Histological findings include amorphous irregular basophilic deposits in the lamina propria usually just below the epithelium or foveolar tips (Fig. 8.33a). These deposits may

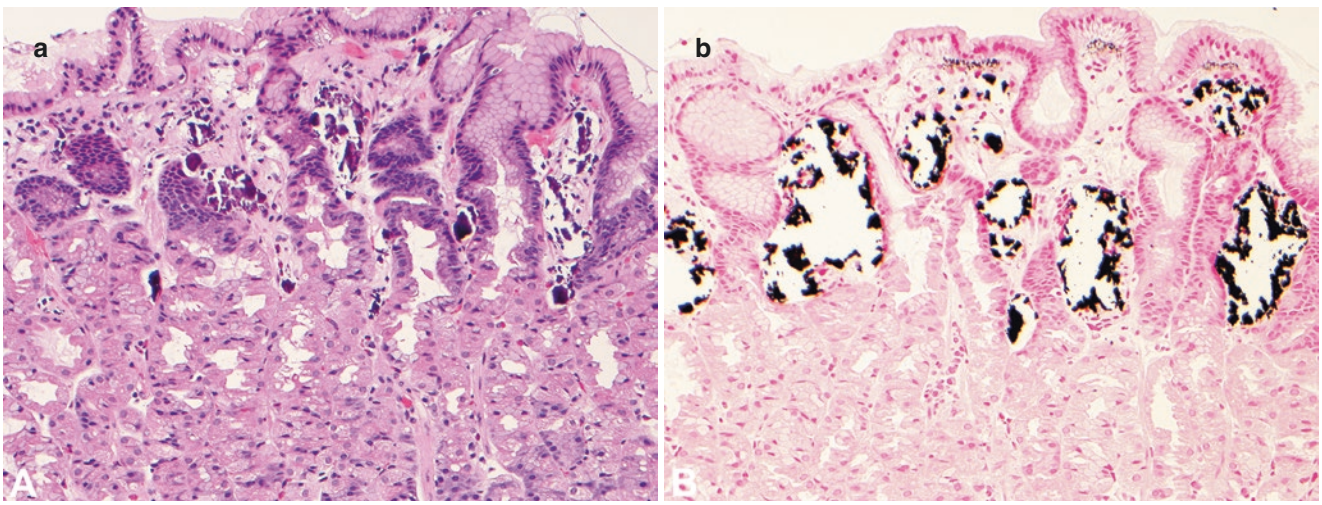

Fig. 8.33 Mucosal calcinosis. Amorphous irregular basophilic deposits in the lamina propria below the gastric surface epithelium or foveolar tips (**a**). These deposits are positive on Von Kossa stain (**b**)

also be found in the deeper lamina propria or muscularis mucosa. The deposits may be slightly refractile but do not polarize. Von Kossa (Fig. 8.33b) and alizarin red stains are positive. There is no predilection for any particular part of the stomach as they can be found in the fundus, body, and/or antrum. In severe cases, the calcinosis may also be seen in the submucosal vessels with associated luminal stenosis. In majority of cases, the background gastric mucosa may be unremarkable (metastatic calcification). However, about 30% of cases may show some background changes such as inflammation, edema, ulceration, atrophy, and foveolar hyperplasia (dystrophic calcification). There is no significant association between gastric mucosal calcinosis and *H. pylori*.

Differential Diagnosis

Kayexalate crystals may come in the differential but are rhomboid or triangular in shape, deeply basophilic on H&E stain, and exhibit a distinctive internal mosaic pattern that resembles fish scales [42]. Schistosomal eggs and strongyloides worm can undergo calcification and be in the differential. However, identification of parasitic structures within the areas of calcifications and presence of eosinophils and Charcot-Leyden crystals can help make the differentiation. OsmoPrep deposits can mimic mucosal deposits, but they are purple to black in color. They are also positive on von Kossa stain but negative with alizarin red helping to make the distinction [22].

Treatment and Prognosis

The presence of mucosal calcinosis in gastric biopsies should be reported as its presence serves as a marker for the presence of metastatic calcifications in organs such as the heart, where it may be fatal [243]. Some cases of mucosal calcification are reversible with normalization of the biochemical parameters [241].

Amyloidosis

Definition

Gastric amyloidosis is defined as deposition of amyloid protein within the stomach.

Clinical Features

In patients with systemic amyloidosis, gastric involvement is seen in around 8% of cases by biopsy and 12% at autopsy [247] and is commonly seen in male adults in the 6th and 7th decades. Presenting symptoms include nausea, vomiting, weight loss, abdominal pain, gastrointestinal bleeding, and gastric outlet obstruction [248–252]. However, only about 1% of patients with gastric amyloidosis are symptomatic. Endoscopy may show varying appearances including thickened gastric folds, loss of rugal folds, ulcers, hematomas, granular mucosa, gastroparesis, nodular appearance, mass lesion, and plaque-like lesions [247, 253]. Up to a third of patients may show unremarkable gastric mucosa suggesting that a gastric biopsy is essential for diagnosis of gastric amyloidosis [249].

Pathological Features

Histologically, amyloid deposits appear pale eosinophilic and acellular on H&E stain (Fig. 8.34a). Congo red stain is positive exhibiting an apple green birefringence (Fig. 8.34b, c). Amyloid deposition can be seen within the body/fundus and/or antrum. Muscularis mucosae is the most common location for amyloid deposition, followed by the lamina propria, and submucosa [249]. The blood vessels also commonly show amyloid deposition. The surrounding gastric mucosa may show changes of reactive gastropathy, gastritis, intestinal metaplasia, and *H. pylori* infection. A recent series on gastric amyloidosis showed AL (amyloid light chain) type to be the most common subtype of amyloid involving the stomach, followed by the ATTR (transthyretin amyloidosis), AA (acquired amyloidosis), and AApo A1 (Apolipoprotein A1 amyloidosis) types [249].

Differential Diagnosis

Differential diagnosis includes extracellular deposits that can mimic amyloidosis on H&E stain such as collagen deposits, light chain deposition disease, and elastosis (Fig. 8.35a). Collagen fibers tend to be brighter and more eosinophilic than amyloid on H&E stain. Trichrome stain will show strong positivity for collagen, in comparison amyloid tends to be negative or very weakly positive. Congo red stain can also help, as collagen is not congophilic. Under polarizing light, the collagen does not show the apple green birefringence but shows a silvery white birefringence. Light chain deposition disease is rare in the stomach [254, 255]. They will be negative on Congo red stain. The monoclonal light chains are usually kappa light chain restricted. Elastosis will be negative on Congo red stain. Acid orcein-Giemsa and Verhoeff-van Gieson stains (Fig. 8.35b) can be used to highlight the elastic fibers.

Treatment and Prognosis

The treatment and prognosis of amyloidosis depends on the underlying disease. Hence, accurate subtyping of amyloid deposits by mass spectrometry is important for therapeutic purposes and prognosis. In AL amyloidosis, treatment focuses on the underlying plasma cell dyscrasia. While in AA amyloidosis, cure is aimed at the underlying inflammatory or infectious disorder.

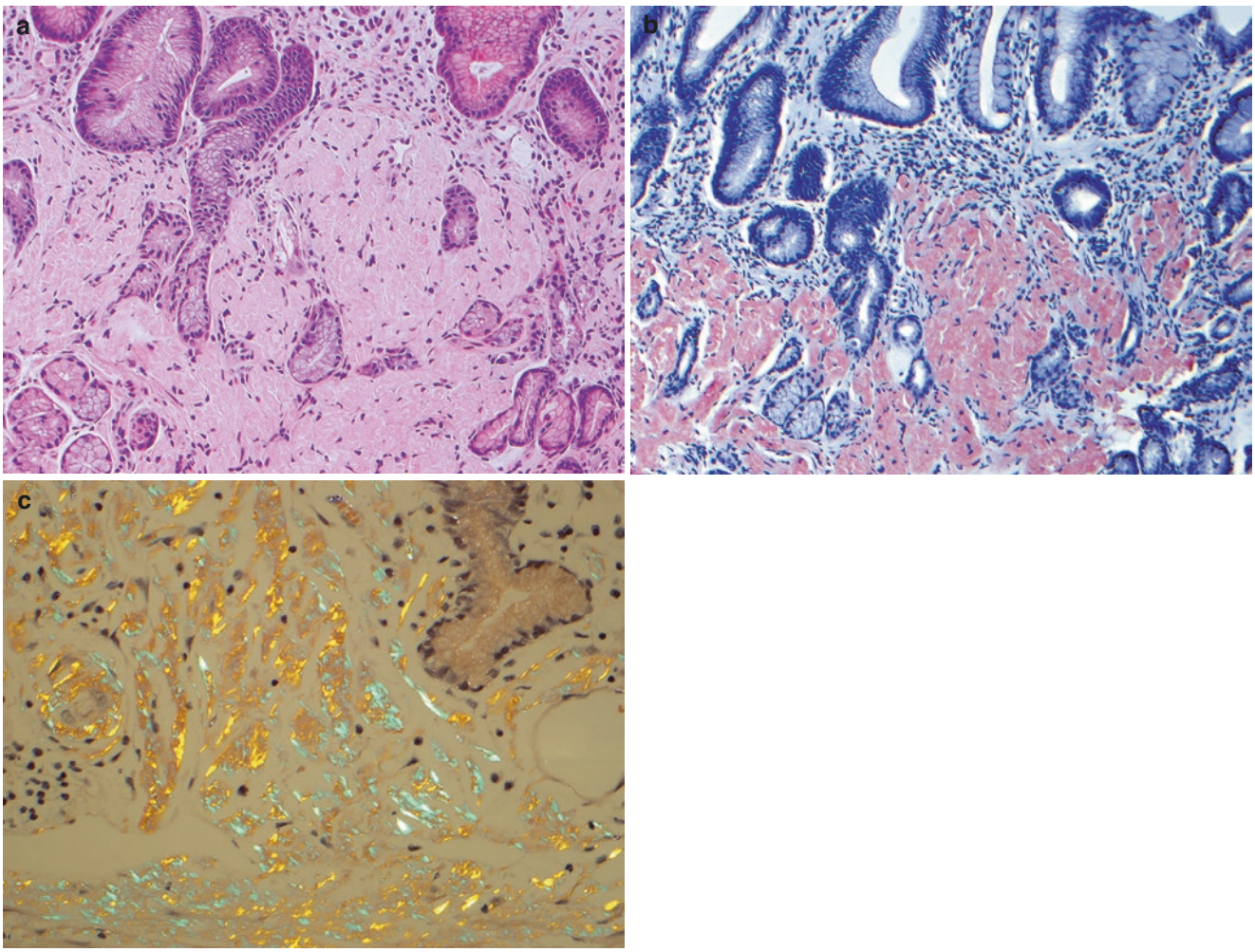

Fig. 8.34 Gastric amyloidosis. Pale eosinophilic and acellular amyloid deposits within lamina propria on H&E stain (**a**). The amyloid deposits are positive on Congo red stain (**b**) and show an apple green birefringence under polarized light (**c**)

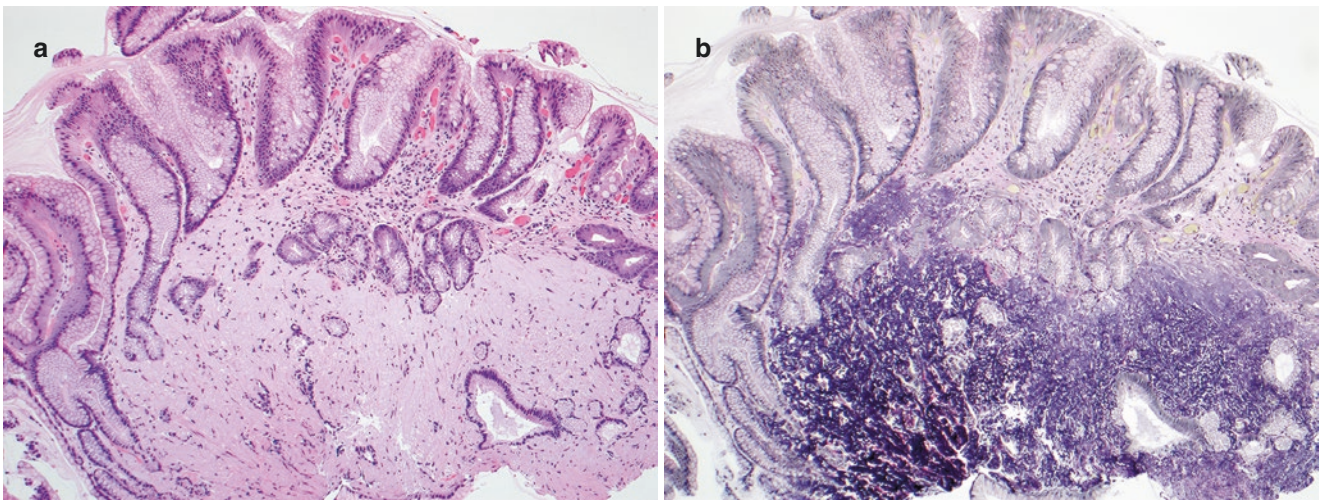

Fig. 8.35 Elastosis. Gastric antral biopsy with pale pink eosinophilic amorphous deposition within the lamina propria on H&E stain (**a**). The pale pink eosinophilic amorphous depositions are elastic fibers and positive on Verhoeff-van Gieson stain (**b**)

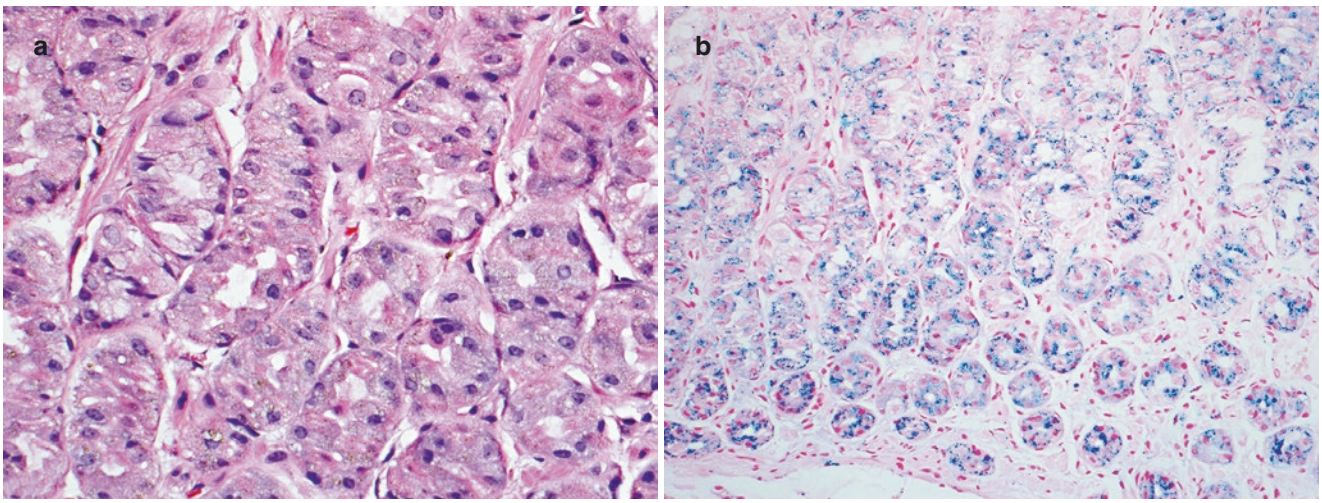

Fig. 8.36 Gastric siderosis. Brownish iron deposition in the fundic glandular epithelium (**a**) and is positive on Prussian blue stain (**b**)

Gastric Siderosis

Definition

Gastric siderosis is defined as iron deposition within the gastric mucosa.

Clinical Features

Gastric siderosis is typically seen in adults with no gender predominance and is usually seen in patients with iron overload/hemochromatosis, heavy alcohol abusers, or patients taking iron medications. One study showed gastric siderosis in 50–69% of gastric biopsies from patients with hemochromatosis or alcoholics [256]. However, overall it is an uncommon condition with a prevalence of 3.6% in gastric biopsies [257]. This condition is usually asymptomatic and the patients may present with symptoms related to the underlying disorder. Laboratory tests can show an elevated ferritin. Endoscopy may show speckled areas of brown pigmentation within the stomach [258].

Pathological Features

Iron deposits appear as brown granules that are consistent with hemosiderin. Sometimes it may form large coarse clumps with a fibrillary appearance. Three patterns of gastric siderosis have been described. [257]. First and the most common pattern shows predominant iron deposition in the stromal cells and macrophages, and it is most likely a result of gastric inflammation or prior trauma or hemorrhage. The second pattern shows predominantly extracellular iron deposition with associated mild gastritis and reactive gastropathy. This pattern is associated with oral iron medication use. The third pattern shows predominant iron deposition in the antral and fundic glandular epithelium and may be associated with systemic iron overload/hemochromatosis (Fig.8.36a). Prussian blue (iron) stain can highlight the iron in cases of gastric siderosis (Fig. 8.36b).

Differential Diagnosis

Iron pill-associated gastritis may come in the differential. However, iron pill material shows a characteristic brown crystalline and clumpy fibrillary material which is refractile (Fig. 8.1). Most of the time, this brown crystalline material is luminal, seen adjacent to the surface epithelium and admixed with luminal inflammatory exudate. The adjacent gastric mucosa can show reactive foveolar hyperplasia with mucin depletion and elongated tortuous gastric pits. On an iron stain, the crystalline iron pill material can be easily distinguished from hemosiderin pigment, despite positive staining for both on the iron stain.

Treatment and Prognosis

Treatment depends on the underlying disorder. When gastric siderosis is identified, it should be an indication for further workup to rule out iron overload/hemochromatosis and portal hypertension within the patient.

References

1. Douthwaite AH, Lintott GAM. Gastroscopic observation of the effect of aspirin and certain other substances of the stomach. Lancet. 1938;232(6013):1225. https://doi.org/10.1016/S0140–6736(00)78970–7.
2. Banner W Jr, Tong TG. Iron poisoning. Pediatr Clin N Am. 1986;33(2):393–409.
3. McGuigan MA. Acute iron poisoning. Pediatr Ann. 1996;25(1):33–8.
4. Eckstein RP, Symons P. Iron tablets cause histopathologically distinctive lesions in mucosal biopsies of the stomach and esophagus. Pathology. 1996;28(2):142–5.
5. Abraham SC, Yardley JH, Wu TT. Erosive injury to the upper gastrointestinal tract in patients receiving iron medication: an underrecognized entity. Am J Surg Pathol. 1999;23(10):1241–7.
6. Smith IM, Bryson G, Glen P. Iron-induced gastric ulceration with radiological and endoscopic appearance of carcinoma. BMJ Case Reports. 2015;2015 https://doi.org/10.1136/bcr-2015–211997.

7. Jalving M, Koornstra JJ, Wesseling J, Boezen HM, De Jong S, Kleibeuker JH. Increased risk of fundic gland polyps during long-term proton pump inhibitor therapy. Aliment Pharmacol Ther. 2006;24(9):1341–8. https://doi.org/10.1111/j.1365–2036.2006.03127.x.
8. Ally MR, Veerappan GR, Maydonovitch CL, Duncan TJ, Perry JL, Osgard EM, et al. Chronic proton pump inhibitor therapy associated with increased development of fundic gland polyps. Dig Dis Sci. 2009;54(12):2617–22. https://doi.org/10.1007/s10620–009–0993-z.
9. Zelter A, Fernández JL, Bilder C, Rodríguez P, Wonaga A, Dorado F, et al. Fundic gland polyps and association with proton pump inhibitor intake: a prospective study in 1,780 endoscopies. Dig Dis Sci. 2011;56(6):1743–8. https://doi.org/10.1007/s10620–010–1493-x.
10. Choudhry U, Boyce HW Jr, Coppola D. Proton pump inhibitor-associated gastric polyps: a retrospective analysis of their frequency, and endoscopic, histologic, and ultrastructural characteristics. Am J Clin Pathol. 1998;110(5):615–21.
11. Declich P, Ambrosiani L, Bellone S, Tavani E, Prada A, Bortoli A, et al. Fundic gland polyps under omeprazole treatment [1] (multiple letters). Am J Clin Pathol. 1999;112(4):576–7.
12. Declich P, Tavani E, Porcellati M, Bellone S, Grassini R. Long-term omeprazole treatment and fundic gland polyps: a very authoritative proof against a link? [7]. Am J Gastroenterol. 2001;96(5):1650.
13. Berstad AE, Hatlebakk JG, Maartmann-Moe H, Berstad A, Brandtzaeg P. Helicobacter pylori gastritis and epithelial cell proliferation in patients with reflux oesophagitis after treatment with lansoprazole. Gut. 1997;41(6):740–7.
14. Klinkenberg-Knol EC, Festen HPM, Jansen JBMJ, Lamers CBHW, Nelis F, Snel P, et al. Long-term treatment with omeprazole for refractory reflux esophagitis: efficacy and safety. Ann Intern Med. 1994;121(3):161–7.
15. McCloy RF, Arnold R, Bardhan KD, Cattan D, Klinkenberg-Knol E, Maton PN, et al. Pathophysiological effects of long-term acid suppression in man. Dig Dis Sci. 1995;40(2 Supplement):96S–120S. https://doi.org/10.1007/BF02214874.
16. Lamberts R, Creutzfeldt W, Strüber HG, Brunner G, Solcia E. Long-term omeprazole therapy in peptic ulcer disease: gastrin, endocrine cell growth, and gastritis. Gastroenterology. 1993;104(5):1356–70.
17. Lamberts R, Brunner G, Solcia E. Effects of very long (up to 10 years) proton pump blockade on human gastric mucosa. Digestion. 2001;64(4):205–13. https://doi.org/10.1159/000048863.
18. Kuipers EJ, Lundell L, Klinkenberg-Knol EC, Havu N, Festen HPM, Liedman B, et al. Atrophic gastritis and helicobacter pylori infection in patients with reflux esophagitis treated with omeprazole or fundoplication. N Engl J Med. 1996;334(16):1018–22. https://doi.org/10.1056/NEJM199604183341603.
19. Kuipers EJ, Uyterlinde AM, Pena AS, Hazenberg HJA, Bloemena E, Lindeman J, et al. Increase of helicobacter pylori-associated corpus gastritis during acid suppressive therapy: implications for long-term safety. Am J Gastroenterol. 1995;90(9):1401–6.
20. Meining A, Kiel G, Stolte M. Changes in helicobacter pylori-induced gastritis in the antrum and corpus during and after 12 months of treatment with ranitidine and lansoprazole in patients with duodenal ulcer disease. Aliment Pharmacol Ther. 1998;12(8):735–40. https://doi.org/10.1046/j.1365–2036.1998.00370.x.
21. Kuipers EJ, Lee A, Klinkenberg-Knol EC, Meuwissen SGM. The development of atrophic gastritis—helicobacter pylori and the effects of acid suppressive therapy. Aliment Pharmacol Ther. 1995;9(4):331–40. https://doi.org/10.1111/j.1365–2036.1995.tb00391.x.
22. Matsukuma K, Gui D, Olson KA, Tejaswi S, Clayton EF, Thai A. OsmoPrep-associated gastritis. Am J Surg Pathol. 2016;40(11):1550–6. https://doi.org/10.1097/PAS.0000000000000706.
23. Parfitt JR, Jayakumar S, Driman DK. Mycophenolate Mofetil-related gastrointestinal mucosal injury: variable injury patterns, including graft-versus-host disease-like changes. Am J Surg Pathol. 2008;32(9):1367–72. https://doi.org/10.1097/PAS.0b013e31816bf3fe.
24. Nguyen T, Park JY, Scudiere JR, Montgomery E. Mycophenolic acid (cellcept and myofortic) induced injury of the upper gi tract. Am J Surg Pathol. 2009;33(9):1355–63. https://doi.org/10.1097/PAS.0b013e3181a755bd.
25. Iacobuzio-Donahue CA, Lee EL, Abraham SC, Yardley JH, Wu TT. Colchicine toxicity: distinct morphologic findings in gastrointestinal biopsies. Am J Surg Pathol. 2001;25(8):1067–73. https://doi.org/10.1097/00000478–200108000–00012.
26. Al-Daraji WI, Al-Mahmoud RM, Ilyas M. Gastric changes following colchicine therapy in patients with FMF. Dig Dis Sci. 2008;53(8):2079–82. https://doi.org/10.1007/s10620–007–0132–7.
27. Torbenson M, Montgomery EA, Iacobuzio-Donahue C, Yardley JH, Wu TT, Abraham SC. Colchicine effect in a colonic hyperplastic polyp: a lesion mimicking serrated adenoma. Arch Pathol Lab Med. 2002;126(5):615–7.
28. Daniels JA, Gibson MK, Xu L, Sun S, Canto MI, Heath E, et al. Gastrointestinal tract epithelial changes associated with taxanes: marker of drug toxicity versus effect. Am J Surg Pathol. 2008;32(3):473–7. https://doi.org/10.1097/PAS.0b013e3181582331.
29. Jonassaint NL, Guo N, Califano JA, Montgomery EA, Armanios M. The gastrointestinal manifestations of telomere-mediated disease. Aging Cell. 2013;12(2):319–23. https://doi.org/10.1111/acel.12041.
30. Taha AS. Histopathological aspects of mucosal injury related to non-steroidal anti-inflammatory drugs. Ital J Gastroenterol. 1996;28(SUPPL. 4):12–5.
31. Quinn CM, Bjarnason I, Price AB. Gastritis in patients on non-steroidal anti-inflammatory drugs. Histopathology. 1993;23(4):341–8. https://doi.org/10.1111/j.1365–2559.1993.tb01217.x.
32. Hirschowitz BI, Lanas A. Atypical and aggressive upper gastrointestinal ulceration associated with aspirin abuse. J Clin Gastroenterol. 2002;34(5):523–8. https://doi.org/10.1097/00004836–200205000–00008.
33. Sung JJY, Russell RI, Yeomans N, Chan FKL, Chen SL, Fock KM, et al. Non-steroidal anti-inflammatory drug toxicity in the upper gastrointestinal tract. J Gastroenterol Hepatol. 2000;15(SUPPL. OCTOBER):G58–68. https://doi.org/10.1046/j.1440–1746.2000.02267.x.
34. Jewell LD, Fields AL, Murray CJW, Thomson ABR. Erosive gastroduodenitis with marked epithelial atypia after hepatic arterial infusion chemotherapy. Am J Gastroenterol. 1985;80(6):421–4. https://doi.org/10.1111/j.1572–0241.1985.tb02136.x.
35. Wells JJ, Nostrant TT, Wilson JAP, Gyves JW. Gastroduodenal ulcerations in patients receiving selective hepatic artery infusion chemotherapy. Am J Gastroenterol. 1985;80(6):425–9. https://doi.org/10.1111/j.1572–0241.1985.tb02137.x.
36. Weidner N, Smith JG, LaVanway JM. Peptic ulceration with marked epithelial atypia following hepatic arterial infusion chemotherapy. A lesion initially misinterpreted as carcinoma. Am J Surg Pathol. 1983;7(3):261–8.
37. Petras RE, Hart WR, Bukowski RM. Gastric epithelial atypia associated with hepatic arterial infusion chemotherapy. Its distinction from early gastric carcinoma. Cancer. 1985;56(4):745–50. https://doi.org/10.1002/1097–0142(19850815)56:4<745::AID-CNCR2820560408>3.0.CO;2-Q.
38. Brien TP, Farraye FA, Odze RD. Gastric dysplasia-like epithelial atypia associated with chemoradiotherapy for esophageal cancer: a clinicopathologic and immunohistochemical study of 15 cases. Mod Pathol. 2001;14(5):389–96. https://doi.org/10.1038/modpathol.3880323.

39. Lim LC, Gibbs P, Yip D, Shapiro JD, Dowling R, Smith D, et al. A prospective evaluation of treatment with selective internal radiation therapy (SIR-spheres) in patients with unresectable liver metastases from colorectal cancer previously treated with 5-FU based chemotherapy. BMC Cancer. 2005;5 https://doi.org/10.1186/1471–2407–5-132.
40. Ogawa F, Mino-Kenudson M, Shimizu M, Ligato S, Lauwers GY. Gastroduodenitis associated with yttrium 90-microsphere selective internal radiation: an iatrogenic complication in need of recognition. Arch Pathol Lab Med. 2008;132(11):1734–8. https://doi.org/10.1043/1543-2165-132.11.1734.
41. Crowder CD, Grabowski C, Inampudi S, Sielaff T, Sherman CA, Batts KP. Selective internal radiation therapy-induced extrahepatic injury an emerging cause of iatrogenic organ damage. Am J Surg Pathol. 2009;33(7):963–75. https://doi.org/10.1097/PAS.0b013e31817ed787.
42. Abraham SC, Bhagavan BS, Lee LA, Rashid A, Wu TT. Upper gastrointestinal tract injury in patients receiving Kayexalate (sodium polystyrene sulfonate) in sorbitol: clinical, endoscopic, and histopathologic findings. Am J Surg Pathol. 2001;25(5):637–44. https://doi.org/10.1097/00000478–200105000–00011.
43. Harel Z, Harel S, Shah PS, Wald R, Perl J, Bell CM. Gastrointestinal adverse events with sodium polystyrene sulfonate (Kayexalate) use: a systematic review. Am J Med. 2013;126(3):264 .e9–e.e24. https://doi.org/10.1016/j.amjmed.2012.08.016.
44. Rashid A, Hamilton SR. Necrosis of the gastrointestinal tract in uremic patients as a result of sodium polystyrene sulfonate (kayexalate) in sorbitol: an underrecognized condition. Am J Surg Pathol. 1997;21(1):60–9. https://doi.org/10.1097/00000478–199701000–00007.
45. Roy-Chaudhury P, Meisels IS, Freedman S, Steinman TI, Steer M. Combined gastric and ileocecal toxicity (serpiginous ulcers) after oral Kayexalate in sorbital therapy. Am J Kidney Dis. 1997;30(1):120–2. https://doi.org/10.1016/S0272–6386(97)90574–6.
46. Chen Z, Scudiere JR, Montgomery E. Medication-induced upper gastrointestinal tract injury. J Clin Pathol. 2009;62(2):113–9. https://doi.org/10.1136/jcp.2008.058263.
47. Swanson BJ, Limketkai BN, Liu TC, Montgomery E, Nazari K, Park JY, et al. Sevelamer crystals in the gastrointestinal tract (GIT): a new entity associated with mucosal injury. Am J Surg Pathol. 2013;37(11):1686–93. https://doi.org/10.1097/PAS.0b013e3182999d8d.
48. Arnold MA, Swanson BJ, Crowder CD, Frankel WL, Lam-Himlin D, Singhi AD, et al. Colesevelam and colestipol: novel medication resins in the gastrointestinal tract. Am J Surg Pathol. 2014;38(11):1530–7. https://doi.org/10.1097/PAS.0000000000000260.
49. Vieth M, Montgomery E. Medication-associated gastrointestinal tract injury. Virchows Arch. 2017;470(3):245–66. https://doi.org/10.1007/s00428–017–2077–3.
50. Seminerio J, McGrath K, Arnold CA, Voltaggio L, Singhi AD. Medication-associated lesions of the GI tract. Gastrointest Endosc. 2014;79(1):140–50. https://doi.org/10.1016/j.gie.2013.08.027.
51. Goto K, Ogawa K. Lanthanum deposition is frequently observed in the gastric mucosa of dialysis patients with lanthanum carbonate therapy: a clinicopathologic study of 13 cases, including 1 case of lanthanum granuloma in the colon and 2 nongranulomatous gastric cases. Int J Surg Pathol. 2016;24(1):89–92. https://doi.org/10.1177/1066896915613434.
52. Rothenberg ME, Araya H, Longacre TA, Pasricha PJ. Lanthanum-induced gastrointestinal histiocytosis. ACG Case Rep J. 2015;2:187–9.
53. Yasunaga C, Haratake J, Ohtani A. Specific accumulation of lanthanum carbonate in the gastric mucosal histiocytes in a dialysis patient. Ther Apher Dial. 2015;19(6):622–4. https://doi.org/10.1111/1744–9987.12325.
54. Yabuki K, Shiba E, Harada H, Uchihashi K, Matsuyama A, Haratake J, et al. Lanthanum deposition in the gastrointestinal mucosa and regional lymph nodes in dialysis patients: analysis of surgically excised specimens and review of the literature. Pathol Res Pract. 2016;212(10):919–26. https://doi.org/10.1016/j.prp.2016.07.017.
55. Hoda RS, Sanyal S, Abraham JL, Everett JM, Hundemer GL, Yee E, et al. Lanthanum deposition from oral lanthanum carbonate in the upper gastrointestinal tract. Histopathology. 2017;70(7):1072–8. https://doi.org/10.1111/his.13178.
56. Davis RL, Abraham JL. Lanthanum deposition in a dialysis patient. Nephrol Dial Transplant. 2009;24(10):3247–50. https://doi.org/10.1093/ndt/gfp364.
57. Rubio-Tapia A, Herman ML, Ludvigsson JF, Kelly DG, Mangan TF, Wu TT, et al. Severe spruelike enteropathy associated with olmesartan. Mayo Clin Proc. 2012;87(8):732–8. https://doi.org/10.1016/j.mayocp.2012.06.003.
58. Shih AR, Lauwers GY, Mattia A, Schaefer EA, Misdraji J. Vascular injury characterizes doxycycline-induced upper gastrointestinal tract mucosal injury. Am J Surg Pathol. 2017;41(3):374–81. https://doi.org/10.1097/PAS.0000000000000792.
59. Xiao SY, Zhao L, Hart J, Semrad CE. Doxycycline-induced gastric and esophageal mucosal injuries with vascular degeneration. Am J Surg Pathol. 2013;37(7):1115–6. https://doi.org/10.1097/PAS.0b013e31828f5b3a.
60. Shaddy SM, Arnold MA, Shilo K, Frankel WL, Harzman AE, Stanich PP, et al. Crospovidone and microcrystalline cellulose. Am J Surg Pathol. 2017;41(4):564–9. https://doi.org/10.1097/PAS.0000000000000790.
61. Rada-Palomino A, Muñoz-Duyos A, Pérez-Romero N, Vargas-Pierola H, Puértolas-Rico N, Ruiz-Campos L, et al. Phlegmonous gastritis: a rare entity as a differential diagnostic of an acute abdomen. Description of a case and a bibliographic review. Revista Espanola de Enfermedades Digestivas. 2014;106(6):418–24.
62. Kim GY, Ward J, Henessey B, Peji J, Godell C, Desta H, et al. Phlegmonous gastritis: case report and review. Gastrointest Endosc. 2005;61(1):168–74. https://doi.org/10.1016/S0016–5107(04)02217–5.
63. Guo J, Young SK, Lorenzo CR, Lee CM, Kanel GC, Brynes RK, et al. Phlegmonous gastritis in a patient with myeloid sarcoma: a case report. Appl Immunohistochem Mol Morphol. 2009;17(5):458–62. https://doi.org/10.1097/PAI.0b013e31819f86e2.
64. Al Rasheed MR, Senseng CG. Sarcina ventriculi : review of the literature. Arch Pathol Lab Med. 2016;140(12):1441–5. https://doi.org/10.5858/arpa.2016–0028-RS.
65. Laass MW, Pargac N, Fischer R, Bernhardt H, Knoke M, Henker J. Emphysematous gastritis caused by Sarcina ventriculi. Gastrointest Endosc. 2010;72(5):1101–3. https://doi.org/10.1016/j.gie.2010.02.021.
66. Tolentino LF, Kallichanda N, Javier B, Yoshimori R, French SW. A case report of gastric perforation and peritonitis associated with opportunistic infection by Sarcina ventriculi. Lab Med. 2003;34(7):535–7. https://doi.org/10.1309/CDFF-04HE-9FHD-QPAN.
67. Haroon Al Rasheed MR, Kim GJ, Senseng C. A rare case of Sarcina ventriculi of the stomach in an asymptomatic patient. Int J Surg Pathol. 2016;24(2):142–5.
68. Lam-Himlin D, Tsiatis AC, Montgomery E, Pai RK, Brown JA, Razavi M, et al. Sarcina organisms in the gastrointestinal tract: a clinicopathologic and molecular study. Am J Surg Pathol. 2011;35(11):1700–5. https://doi.org/10.1097/PAS.0b013e31822911e6.
69. Crowther JS. Sarcina ventriculi in human faeces. J Med Microbiol. 1971;4(3):343–50.

70. Lowe SE, Pankratz HS, Zeikus JG. Influence of pH extremes on sporulation and ultrastructure of Sarcina ventriculi. J Bacteriol. 1989;171(7):3775–81.
71. Canale-Parola E. Biology of the sugar-fermenting Sarcinae. Bacteriol Rev. 1970;34(1):82–97.
72. Mylona EE, Baraboutis IG, Papastamopoulos V, Tsagalou EP, Vryonis E, Samarkos M, et al. Gastric syphilis: a systematic review of published cases of the last 50 years. Sex Transm Dis. 2010;37(3):177–83. https://doi.org/10.1097/OLQ.0b013e3181c0d51f.
73. Martín-Ezquerra G, Fernandez-Casado A, Barco D, Jucglà A, Juanpere-Rodero N, Manresa JM, et al. Treponema pallidum distribution patterns in mucocutaneous lesions of primary and secondary syphilis: an immunohistochemical and ultrastructural study. Hum Pathol. 2009;40(5):624–30. https://doi.org/10.1016/j.humpath.2008.10.017.
74. Chen CY, Chi KH, George RW, Cox DL, Srivastava A, Rui Silva M, et al. Diagnosis of gastric syphilis by direct immunofluorescence staining and real-time PCR testing. J Clin Microbiol. 2006;44(9):3452–6. https://doi.org/10.1128/JCM.00721–06.
75. Neafie RC, Marty AM. Unusual infections in humans. Clin Microbiol Rev. 1993;6(1):34–56.
76. Rank EL, Goldenberg SA, Hasson J, Cartun RW, Grey N. Treponema pallidum and helicobacter pylori recovered in a case of chronic active gastritis. Am J Clin Pathol. 1992;97(1):116–20.
77. Fernandez-Flores A, Garcia Varona A. Anti-Treponema antibody also stains helicobacter heilmannii. Appl Immunohistochem Mol Morphol. 2016;24(3):e20–1. https://doi.org/10.1097/PAI.0000000000000266.
78. Hinnant KL, Rotterdam HZ, Bell ET, Tapper ML. Cytomegalovirus infection of the alimentary tract: a clinicopathological correlation. Am J Gastroenterol. 1986;81(10):944–50.
79. Xiao SY, Hart J. Marked gastric foveolar hyperplasia associated with active cytomegalovirus infection. Am J Gastroenterol. 2001;96(1):223–6. https://doi.org/10.1111/j.1572–0241.2001.03480.x.
80. Nohr EW, Itani DM, Andrews CN, Kelly MM. Varicella-zoster virus gastritis: case report and review of the literature. Int J Surg Pathol. 2017;25(5):449–52. https://doi.org/10.1177/1066896917696751.
81. Rivera-Vaquerizo PA, Gomez-Garrido J, Vicente-Gutierrez M, Blasco-Colmenarejo M, Mayor-Lopez J, Perez-Flores R. Varicella zoster gastritis 3 years after bone marrow transplantation for treatment of acute leukemia. Gastrointest Endosc. 2001;53(7):809–10.
82. Chen ZM, Shah R, Zuckerman GR, Wang HL. Epstein-Barr virus gastritis: an underrecognized form of severe gastritis simulating gastric lymphoma. Am J Surg Pathol. 2007;31(9):1446–51. https://doi.org/10.1097/PAS.0b013e318050072f.
83. Kitayama Y, Honda S, Sugimura H. Epstein-Barr virus-related gastric pseudolymphoma in infectious mononucleosis. Gastrointest Endosc. 2000;52(2):290–1. https://doi.org/10.1067/mge.2000.107715.
84. Loffeld RJ, Loffeld BC, Arends JW, Flendrig JA, van Spreeuwel JP. Fungal colonization of gastric ulcers. Am J Gastroenterol. 1988;83(7):730–3.
85. Cherney CL, Chutuape A, Fikrig MK. Fatal invasive gastric mucormycosis occurring with emphysematous gastritis: case report and literature review. Am J Gastroenterol. 1999;94(1):252–6. https://doi.org/10.1111/j.1572–0241.1999.00809.x.
86. Mohamed AE, Ghandour ZM, Al-Karawi MA, Yasawy MI, Sammak B. Gastrointestinal parasites presentations and histological diagnosis from endoscopic biopsies and surgical specimens. Saudi Med J. 2000;21(7):629–34.
87. Forester G, Sidhom O, Nahass R, Andavolu R. AIDS-associated cryptosporidiosis with gastric stricture and a therapeutic response to paromomycin. Am J Gastroenterol. 1994;89(7):1096–8.
88. Garone MA, Winston BJ, Lewis JH. Cryptosporidiosis of the stomach. Am J Gastroenterol. 1986;81(6):465–70.
89. Sohn WM, Na BK, Kim TH, Park TJ. Anisakiasis: report of 15 gastric cases caused by Anisakis type I larvae and a brief review of Korean Anisakiasis cases. Korean J Parasitol. 2015;53(4):465–70. https://doi.org/10.3347/kjp.2015.53.4.465.
90. Rider JA, Klotz AP, Kirsner JB. Gastritis with venocapillary ectasia as a source of massive gastric hemorrhage. Gastroenterology. 1953;24(1):118–23. https://doi.org/10.1016/S0016–5085(53)80070–3.
91. Jabbari M, Cherry R, Lough JO, Daly DS, Kinnear DG, Goresky CA. Gastric antral vascular ectasia: the watermelon stomach. Gastroenterology. 1984;87(5):1165–70. https://doi.org/10.1016/S0016–5085(84)80080–3.
92. Dulai GS, Jensen DM, Kovacs TOG, Gralnek IM, Jutabha R. Endoscopic treatment outcomes in watermelon stomach patients with and without portal hypertension. Endoscopy. 2004;36(1):68–72. https://doi.org/10.1055/s-2004–814112.
93. Charneau J, Petit R, Cales P, Dauver A, Boyer J. Antral motility in patients with cirrhosis with or without gastric antral vascular ectasia. Gut. 1995;37(4):488–92.
94. Quintero E, Pique JM, Bombi JA, Bordas JM, Sentis J, Elena M, et al. Gastric mucosal vascular ectasias causing bleeding in cirrhosis. A distinct entity associated with hypergastrinemia and low serum levels of pepsinogen I. Gastroenterology. 1987;93(5):1054–61.
95. Gostout CJ, Viggiano TR, Ahlquist DA, Wang KK, Larson MV, Balm R. The clinical and endoscopic spectrum of the watermelon stomach. J Clin Gastroenterol. 1992;15(3):256–63.
96. Ward EM, Raimondo M, Rosser BG, Wallace MB, Dickson RD. Prevalence and natural history of gastric antral vascular ectasia in patients undergoing orthotopic liver transplantation. J Clin Gastroenterol. 2004;38(10):898–900. https://doi.org/10.1097/00004836–200411000–00013.
97. Tobin RW, Hackman RC, Kimmey MB, Durtschi B, Hayashi A, Malik R, et al. Bleeding from gastric antral vascular ectasia in marrow transplant patients. Gastrointest Endosc. 1996;44(3):223–9. https://doi.org/10.1016/S0016–5107(96)70155–4.
98. Smith E, Tekola B, Patrie J, Cornella S, Caldwell S. Clinical characterization of gastric antral vascular ectasia: a potential manifestation of the metabolic syndrome. Am J Med. 2016;129(12):1329 e19–23. https://doi.org/10.1016/j.amjmed.2016.07.007.
99. Hudson C, Fontenot E, Landreneau S. Gastric antral vascular ectasia presenting as a polypoid mass in a patient with cirrhosis. Gastrointest Endosc. 2017; https://doi.org/10.1016/j.gie.2017.08.002.
100. Selinger CP, Ang YS. Gastric antral vascular ectasia (GAVE): an update on clinical presentation, pathophysiology and treatment. Digestion. 2008;77(2):131–7. https://doi.org/10.1159/000124339.
101. James Sarfeh I, Tarnawski A. Portal hypertensive gastritis. Gastroenterology. 1984;86(3):592. https://doi.org/10.1016/S0016–5085(84)80052–9.
102. Sarin SK, Sreenivas DV, Lahoti D, Saraya A. Factors influencing development of portal hypertensive gastropathy in patients with portal hypertension. Gastroenterology. 1992;102(3):994–9.
103. Parikh SS, Desai SB, Prabhu SR, Trivedi MH, Shankaran K, Bhukhanwala FA, et al. Congestive Gastropathy: factors influencing development, endoscopic features, helicobacter pylori infection, and microvessel changes. Am J Gastroenterol. 1994;89(7):1036–42. https://doi.org/10.1111/j.1572–0241.1994.tb03219.x.
104. Primignani M, Carpinelli L, Preatoni P, Battaglia G, Carta A, Prada A, et al. Natural history of portal hypertensive gastropathy in patients with liver cirrhosis. Gastroenterology. 2000;119(1):181–7. https://doi.org/10.1053/gast.2000.8555.

105. Thuluvath PJ, Yoo HY. Portal hypertensive gastropathy. Am J Gastroenterol. 2002;97(12):2973–8. https://doi.org/10.1016/S0002–9270(02)05511–9.
106. Sogaard KK, Astrup LB, Vilstrup H, Gronbaek H. Portal vein thrombosis; risk factors, clinical presentation and treatment. BMC Gastroenterol. 2007;7 https://doi.org/10.1186/1471–230X-7–34.
107. Kamath PS, Lacerda M, Ahlquist DA, McKusick MA, Andrews JC, Nagorney DA. Gastric mucosal responses to intrahepatic portosystemic shunting in patients with cirrhosis. Gastroenterology. 2000;118(5):905–11. https://doi.org/10.1016/S0016–5085(00)70176–4.
108. Cubillas R, Rockey DC. Portal hypertensive gastropathy: a review. Liver Int. 2010;30(8):1094–102. https://doi.org/10.1111/j.1478–3231.2010.02286.x.
109. Ohta M, Yamaguchi S, Gotoh N, Tomikawa M. Pathogenesis of portal hypertensive gastropathy: a clinical and experimental review. Surgery. 2002;131(1):S165–S70. https://doi.org/10.1067/msy.2002.119499.
110. Ohta M, Higashi MHH, Ueno K, Tomikawa M, Kishihara F, Kawanaka H, et al. Portal and gastric mucosal hemodynamics in cirrhotic patients with portal-hypertensive gastropathy. Hepatology. 1994;20(6):1432–6. https://doi.org/10.1002/hep.1840200609.
111. Massoni F, Ricci L, Pelosi M, Ricci S. The portal hypertensive Gastropathy: a case and review of literature. J Clin Diagn Res. 2016;10(6):HD01–2. https://doi.org/10.7860/JCDR/2016/14489.7942.
112. McCormack TT, Sims J, Eyre-Brook I, Kennedy H, Goepel J, Johnson AG, et al. Gastric lesions in portal hypertension: inflammatory gastritis or congestive gastropathy? Gut. 1985;26(11):1226–32. https://doi.org/10.1136/gut.26.11.1226.
113. Han S, Chaudhary N, Wassef W. Portal hypertensive gastropathy and gastric antral vascular ectasia. Curr Opin Gastroenterol. 2015;31(6):506–12. https://doi.org/10.1097/MOG.0000000000000214.
114. Chaer RA, Helton WS. Dieulafoy's disease. J Am Coll Surg. 2003;196(2):290–6. https://doi.org/10.1016/S1072–7515(02)01801-X.
115. Nguyen DC, Jackson CS. The Dieulafoy's lesion: an update on evaluation, diagnosis, and management. J Clin Gastroenterol. 2015;49(7):541–9. https://doi.org/10.1097/MCG.0000000000000321.
116. Baxter M, Aly EH. Dieulafoy's lesion: current trends in diagnosis and management. Ann R Coll Surg Engl. 2010;92(7):548–54. https://doi.org/10.1308/003588410X12699663905311.
117. Marangoni G, Cresswell AB, Faraj W, Shaikh H, Bowles MJ. An uncommon cause of life-threatening gastrointestinal bleeding: 2 synchronous Dieulafoy lesions. J Pediatr Surg. 2009;44(2):441–3. https://doi.org/10.1016/j.jpedsurg.2008.09.033.
118. Juler GL, Labitzke HG, Lamb R, Allen R. The pathogenesis of Dieulafoy's gastric erosion. Am J Gastroenterol. 1984;79(3):195–200. https://doi.org/10.1111/j.1572–0241.1984.tb05118.x.
119. Miko TL, Thomázy VA. The caliber persistent artery of the stomach: a unifying approach to gastric aneurysm, Dieulafoy's lesion, and submucosal arterial malformation. Hum Pathol. 1988;19(8):914–21. https://doi.org/10.1016/S0046–8177(88)80006–6.
120. Stark ME, Gostout CJ, Balm RK. Clinical features and endoscopic management of Dieulafoy's disease. Gastrointest Endosc. 1992;38(5):545–50. https://doi.org/10.1016/S0016–5107(92)70513–6.
121. Senger JL, Kanthan R. The evolution of Dieulafoy's lesion since 1897: then and now-a journey through the Lens of a pediatric lesion with literature review. Gastroenterol Res Pract. 2012;2012:432517. https://doi.org/10.1155/2012/432517.
122. Chung IK, Kim EJ, Lee MS, Kim HS, Park SH, Lee MH, et al. Bleeding Dieulafoy's lesions and the choice of endoscopic method: comparing the hemostatic efficacy of mechanical and injection methods. Gastrointest Endosc. 2000;52(6):721–4. https://doi.org/10.1067/mge.2000.108040.
123. Matsui S, Kamisako T, Kudo M, Inoue R. Endoscopic band ligation for control of nonvariceal upper GI hemorrhage: comparison with bipolar electrocoagulation. Gastrointest Endosc. 2002;55(2):214–8. https://doi.org/10.1067/mge.2002.121337.
124. Park CH, Sohn YH, Lee WS, Joo YE, Choi SK, Rew JS, et al. The usefulness of endoscopic hemoclipping for bleeding Dieulafoy lesions. Endoscopy. 2003;35(5):388–92. https://doi.org/10.1055/s-2003–38780.
125. Park CH, Joo YE, Kim HS, Choi SK, Rew JS, Kim SJ. A prospective, randomized trial of endoscopic band ligation versus endoscopic hemoclip placement for bleeding gastric Dieulafoy's lesions. Endoscopy. 2004;36(8):677–81. https://doi.org/10.1055/s-2004–825661.
126. Khoury T, Rivera L. Foregut duplication cysts: a report of two cases with emphasis on embryogenesis. World J Gastroenterol. 2011;17(1):130–4. https://doi.org/10.3748/wjg.v17.i1.130.
127. Sharma S, Nezakatgoo N, Sreenivasan P, Vanatta J, Jabbour N. Foregut cystic developmental malformation: new taxonomy and classification—unifying embryopathological concepts. Indian J Pathol Microbiol. 2009;52(4):461–72. https://doi.org/10.4103/0377–4929.56119.
128. Horne G, Ming-Lum C, Kirkpatrick AW, Parker RL. High-grade neuroendocrine carcinoma arising in a gastric duplication cyst: a case report with literature review. Int J Surg Pathol. 2007;15(2):187–91. https://doi.org/10.1177/1066896906295777.
129. Rowling JT. Some observations on gastric cysts. Br J Surg. 1959;46(199):441–5.
130. Holcomb Iii GW, Gheissari A, O'Neill JA Jr, Shorter NA, Bishop HC. Surgical management of alimentary tract duplications. Ann Surg. 1989;209(2):167–74.
131. Kuraoka K, Nakayama H, Kagawa T, Ichikawa T, Yasui W. Adenocarcinoma arising from a gastric duplication cyst with invasion to the stomach: a case report with literature review. J Clin Pathol. 2004;57(4):428–31. https://doi.org/10.1136/jcp.2003.013946.
132. Dolan RV, Remine WH, Dockerty MB. The fate of heterotopic pancreatic tissue: a study of 212 cases. Arch Surg. 1974;109(6):762–5. https://doi.org/10.1001/archsurg.1974.01360060032010.
133. Martinez NS, Morlock CG, Dockerty MB, Waugh JM, Weber HM. Heterotopic pancreatic tissue involving the stomach. Ann Surg. 1958;147(1):1–12.
134. Chen HL, Chang WH, Shih SC, Bair MJ, Lin SC. Changing pattern of ectopic pancreas: 22 years of experience in a medical center. J Formos Med Assoc. 2008;107(12):932–6. https://doi.org/10.1016/S0929–6646(09)60016–4.
135. Lindtner RA, Schreiber F, Langner C. Cytokeratin 7 immunostaining facilitates recognition of pancreatic heterotopia in gastric biopsies. Pathol Int. 2007;57(8):548–50. https://doi.org/10.1111/j.1440–1827.2007.02138.x.
136. Distler M, Ruckert F, Aust D, Saeger HD, Grutzmann R. Pancreatic heterotopia of the duodenum: anatomic anomaly or clinical challenge? J Gastrointest Surg. 2011;15(4):631–6. https://doi.org/10.1007/s11605–011–1420–2.
137. Gaspar Fuentes A, Campos Tarrech JM, Fernández Burgui JL, Castells Tejón E, Ruíz Rossello J, Gómez Pérez J, et al. Pancreatic ectopias. Revista Espanola de las Enfermedades del Aparato Digestivo. 1973;39(3):255–68.
138. Osanai M, Miyokawa N, Tamaki T, Yonekawa M, Kawamura A, Sawada N. Adenocarcinoma arising in gastric heterotopic pancreas: clinicopathological and immunohistochemical study with

genetic analysis of a case. Pathol Int. 2001;51(7):549–54. https://doi.org/10.1046/j.1440–1827.2001.01240.x.
139. Chetty R, Weinreb I. Gastric neuroendocrine carcinoma arising from heterotopic pancreatic tissue. J Clin Pathol. 2004;57(3):314–7. https://doi.org/10.1136/jcp.2003.013557.
140. Wang HH, Zeroogian JM, Spechler SJ, Goyal RK, Antonioli DA. Prevalence and significance of pancreatic acinar metaplasia at the gastroesophageal junction. Am J Surg Pathol. 1996;20(12):1507–10.
141. Jhala NC, Montemor M, Jhala D, Lu L, Talley L, Haber MM, et al. Pancreatic acinar cell metaplasia in autoimmune gastritis. Arch Pathol Lab Med. 2003;127(7):854–7. https://doi.org/10.1043/1543–2165(2003)127<854:PACMIA>2.0.CO;2.
142. Hammock L, Jorda M. Gastric endocrine pancreatic heterotopia: report of a case with histologic and immunohistochemical findings and review of the literature. Arch Pathol Lab Med. 2002;126(4):464–7.
143. To T, Wajja A, Wales PW, Langer JC. Population demographic indicators associated with incidence of pyloric stenosis. Arch Pediatr Adolesc Med. 2005;159(6):520–5. https://doi.org/10.1001/archpedi.159.6.520.
144. Mullassery D, Perry D, Goyal A, Jesudason EC, Losty PD. Surgical practice for infantile hypertrophic pyloric stenosis in the United Kingdom and Ireland-a survey of members of the British Association of Paediatric Surgeons. J Pediatr Surg. 2008;43(6):1227–9. https://doi.org/10.1016/j.jpedsurg.2007.12.075.
145. Applegate MS, Druschel CM. The epidemiology of infantile hypertrophic pyloric stenosis in New York state: 1983 to 1990. Arch Pediatr Adolesc Med. 1995;149(10):1123–9. https://doi.org/10.1001/archpedi.1995.02170230077011.
146. Zhu J, Zhu T, Lin Z, Qu Y, Mu D. Perinatal risk factors for infantile hypertrophic pyloric stenosis: a meta-analysis. J Pediatr Surg. 2017;52(9):1389–97. https://doi.org/10.1016/j.jpedsurg.2017.02.017.
147. Peeters B, Benninga MA, Hennekam RC. Infantile hypertrophic pyloric stenosis—genetics and syndromes. Nat Rev Gastroenterol Hepatol. 2012;9(11):646–60. https://doi.org/10.1038/nrgastro.2012.133.
148. Wayne C, Hung JH, Chan E, Sedgwick I, Bass J, Nasr A. Formula-feeding and hypertrophic pyloric stenosis: is there an association? A case-control study. J Pediatr Surg. 2016;51(5):779–82. https://doi.org/10.1016/j.jpedsurg.2016.02.021.
149. Eberly MD, Eide MB, Thompson JL, Nylund CM. Azithromycin in early infancy and pyloric stenosis. Pediatrics. 2015;135(3):483–8. https://doi.org/10.1542/peds.2014–2026.
150. Poon TS, Zhang AL, Cartmill T, Cass DT. Changing patterns of diagnosis and treatment of infantile hypertrophic pyloric stenosis: a clinical audit of 303 patients. J Pediatr Surg. 1996;31(12):1611–5.
151. Panteli C. New insights into the pathogenesis of infantile pyloric stenosis. Pediatr Surg Int. 2009;25(12):1043–52. https://doi.org/10.1007/s00383–009–2484-x.
152. Taylor ND, Cass DT, Holland AJA. Infantile hypertrophic pyloric stenosis: has anything changed? J Paediatr Child Health. 2013;49(1):33–7. https://doi.org/10.1111/jpc.12027.
153. Hernanz-Schulman M. Infantile hypertrophic pyloric stenosis. Radiology. 2003;227(2):319–31. https://doi.org/10.1148/radiol.2272011329.
154. Rolle U, Piaseczna-Piotrowska A, Puri P. Interstitial cells of Cajal in the normal gut and in intestinal motility disorders of childhood. Pediatr Surg Int. 2007;23(12):1139–52. https://doi.org/10.1007/s00383–007–2022–7.
155. Aspelund G, Langer JC. Current management of hypertrophic pyloric stenosis. Semin Pediatr Surg. 2007;16(1):27–33. https://doi.org/10.1053/j.sempedsurg.2006.10.004.
156. Perger L, Fuchs JR, Komidar L, Mooney DP. Impact of surgical approach on outcome in 622 consecutive pyloromyotomies at a pediatric teaching institution. J Pediatr Surg. 2009;44(11):2119–25. https://doi.org/10.1016/j.jpedsurg.2009.02.067.
157. Chalya PL, Manyama M, Kayange NM, Mabula JB, Massenga A. Infantile hypertrophic pyloric stenosis at a tertiary care hospital in Tanzania: a surgical experience with 102 patients over a 5-year period. BMC Res Notes. 2015;8:690. https://doi.org/10.1186/s13104–015–1660–4.
158. 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(6):1524–32. https://doi.org/10.1038/ajg.2009.139.
159. Cao H, Wang B, Zhang Z, Zhang H, Qu R. Distribution trends of gastric polyps: an endoscopy database analysis of 24121 northern Chinese patients. J Gastroenterol Hepatol. 2012;27(7):1175–80. https://doi.org/10.1111/j.1440–1746.2012.07116.x.
160. Archimandritis A, Spiliadis C, Tzivras M, Vamvakousis B, Davaris P, Manika Z, et al. Gastric epithelial polyps: a retrospective endoscopic study of 12974 symptomatic patients. Ital J Gastroenterol. 1996;28(7):387–90.
161. Islam RS, Patel NC, Lam-Himlin D, Nguyen CC. Gastric polyps: a review of clinical, endoscopic, and histopathologic features and management decisions. Gastroenterol Hepatol. 2013;9(10):640–51.
162. Gencosmanoglu R, Sen-Oran E, Kurtkaya-Yapicier O, Tozun N. Xanthelasmas of the upper gastrointestinal tract. J Gastroenterol. 2004;39(3):215–9. https://doi.org/10.1007/s00535–003–1288–3.
163. Chandan VS, Wang W, Landas SK. Gastric lipid islands. Arch Pathol Lab Med. 2004;128(8):937–8. https://doi.org/10.1043/1543–2165(2004)128<937:GLI>2.0.CO;2.
164. Hori S, Tsutsumi Y. Helicobacter pylori infection in gastric xanthomas: Immunohistochemical analysis of 145 lesions. Pathol Int. 1996;46(8):589–93.
165. Isomoto H, Mizuta Y, Inoue K, Matsuo T, Hayakawa T, Miyazaki M, et al. A close relationship between helicobacter pylori infection and gastric xanthoma. Scand J Gastroenterol. 1999;34(4):346–52. https://doi.org/10.1080/003655299750026344.
166. Yi SY. Dyslipidemia and H pylori in gastric xanthomatosis. World J Gastroenterol. 2007;13(34):4598–601.
167. Shibukawa N, Ouchi S, Wakamatsu S, Wakahara Y, Kaneko A. Gastric xanthoma is a predictive marker for metachronous and synchronous gastric cancer. World J Gastrointest Oncol. 2017;9(8):327–32. https://doi.org/10.4251/wjgo.v9.i8.327.
168. Kitamura S, Muguruma N, Okamoto K, Tanahashi T, Fukuya A, Tanaka K, et al. Clinicopathological assessment of gastric xanthoma as potential predictive marker of gastric Cancer. Digestion. 2017;96(4):199–206. https://doi.org/10.1159/000481346.
169. 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(4):500–7. https://doi.org/10.1097/00000478–200104000–00010.
170. Goddard AF, Badreldin R, Pritchard DM, Walker MM, Warren B. The management of gastric polyps. Gut. 2010;59(9):1270–6. https://doi.org/10.1136/gut.2009.182089.
171. Amaro R, Neff GW, Karnam US, Tzakis AG, Raskin JB. Acquired hyperplastic gastric polyps in solid organ transplant patients. Am J Gastroenterol. 2002;97(9):2220–4. https://doi.org/10.1016/S0002–9270(02)04332–0.
172. Jewell KD, Toweill DL, Swanson PE, Upton MP, Yeh MM. Gastric hyperplastic polyps in post transplant patients: a clinicopathologic study. Mod Pathol. 2008;21(9):1108–12. https://doi.org/10.1038/modpathol.2008.87.
173. Gonzalez-Obeso E, Fujita H, Deshpande V, Ogawa F, Lisovsky M, Genevay M, et al. Gastric hyperplastic polyps: a heterogeneous clinicopathologic group including a distinct subset best categorized

as mucosal prolapse polyp. Am J Surg Pathol. 2011;35(5):670–7. https://doi.org/10.1097/PAS.0b013e3182127d2b.
174. Boncher J, Bronner M, Goldblum JR, Liu X. Reticulin staining clarifies florid benign signet ring cell change with mitotic activity in a penetrating gastric ulcer. Am J Surg Pathol. 2011;35(5):762–6. https://doi.org/10.1097/PAS.0b013e318213f833.
175. Ohkusa T, Takashimizu I, Fujiki K, Suzuki S, Shimoi K, Horiuchi T, et al. Disappearance of hyperplastic polyps in the stomach after eradication of helicobacter pylori: a randomized, controlled trial. Ann Intern Med. 1998;129(9):712–5.
176. Ljubičić N, Banić M, Kujundžić M, Antić Z, Vrkljan M, Kovačević I, et al. The effect of eradicating helicobacter pylori infection on the course of adenomatous and hyperplastic gastric polyps. Eur J Gastroenterol Hepatol. 1999;11(7):727–30.
177. Daibo M, Itabashi M, Hirota T. Malignant transformation of gastric hyperplastic polyps. Am J Gastroenterol. 1987;82(10):1016–25.
178. Han AR, Sung CO, Kim KM, Park CK, Min BH, Lee JH, et al. The clinicopathological features of gastric hyperplastic polyps with neoplastic transformations: a suggestion of indication for endoscopic polypectomy. Gut Liver. 2009;3(4):271–5. https://doi.org/10.5009/gnl.2009.3.4.271.
179. Hattori T. Morphological range of hyperplastic polyps and carcinomas arising in hyperplastic polyps of the stomach. J Clin Pathol. 1985;38(6):622–30.
180. 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(1):80–4. https://doi.org/10.1007/s00428–005–0068–2.
181. Offerhaus GJA, Billaud M, Gruber SB. Peutz-Jehgers syndrome. Tumours of the Digestive System. Editors Bosman FT, Carneiro F, Hruban RH and Theise ND, IARC, Lyon, 2010:166–70.
182. Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW. ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015;110(2):223–62. https://doi.org/10.1038/ajg.2014.435.
183. Brosens LAA, van Hattem WA, Jansen M, de Leng WWJ, Giardiello FM, Offerhaus GJA. Gastrointestinal polyposis syndromes. Curr Mol Med. 2007;7(1):29–46. https://doi.org/10.2174/156652407779940404.
184. McGarrity TJ, Kulin HE, Zaino RJ. Peutz-Jeghers syndrome. Am J Gastroenterol. 2000;95(3):596–604. https://doi.org/10.1016/S0002–9270(99)00890–4.
185. Lam-Himlin D, Park JY, Cornish TC, Shi C, Montgomery E. Morphologic characterization of syndromic gastric polyps. Am J Surg Pathol. 2010;34(11):1656–62. https://doi.org/10.1097/PAS.0b013e3181f2b1f1.
186. Van Lier MGF, Westerman AM, Wagner A, Looman CWN, Wilson JHP, De Rooij FWM, et al. High cancer risk and increased mortality in patients with Peutz—Jeghers syndrome. Gut. 2011;60(2):141–7. https://doi.org/10.1136/gut.2010.223750.
187. Giardiello FM, Brensinger JD, Tersmette AC, Goodman SN, Petersen GM, Booker SV, et al. Very high risk of cancer in familial Peutz-Jeghers syndrome. Gastroenterology. 2000;119(6):1447–53. https://doi.org/10.1053/gast.2000.20228.
188. Jansen M, De Leng WWJ, Baas AF, Myoshi H, Mathus-Vliegen L, Taketo MM, et al. Mucosal prolapse in the pathogenesis of Peutz-Jeghers polyposis. Gut. 2006;55(1):1–5. https://doi.org/10.1136/gut.2005.069062.
189. Langeveld D, Jansen M, De Boer DV, Van Sprundel M, Brosens LAA, Morsink FH, et al. Aberrant intestinal stem cell lineage dynamics in Peutz-Jeghers syndrome and familial adenomatous polyposis consistent with protracted clonal evolution in the crypt. Gut. 2012;61(6):839–46. https://doi.org/10.1136/gutjnl-2011–300622.
190. Howe JR, Roth S, Ringold JC, Summers RW, Järvinen HJ, Sistonen P, et al. Mutations in the SMAD4/DPC4 gene in juvenile polyposis. Science. 1998;280(5366):1086–8. https://doi.org/10.1126/science.280.5366.1086.
191. Howe JR, Ringold JC, Summers RW, Mitros FA, Nishimura DY, Stone EM. A gene for familial juvenile polyposis maps to chromosome 18q21.1. Am J Hum Genet. 1998;62(5):1129–36. https://doi.org/10.1086/301840.
192. Howe JR, Bair JL, Sayed MG, Anderson ME, Mitros FA, Petersen GM, et al. Germline mutations of the gene encoding bone morphogenetic protein receptor 1A in juvenile polyposis. Nat Genet. 2001;28(2):184–7. https://doi.org/10.1038/88919.
193. Aretz S, Stienen D, Uhlhaas S, Stolte M, Entius MM, Loff S, et al. High proportion of large genomic deletions and a genotype-phenotype update in 80 unrelated families with juvenile polyposis syndrome. J Med Genet. 2007;44(11):702–9. https://doi.org/10.1136/jmg.2007.052506.
194. Sayed MG, Ahmed AF, Ringold JR, Anderson ME, Bair JL, Mitros FA, et al. Germline SMAD4 or BMPR1A mutations and phenotype of juvenile polyposis. Ann Surg Oncol. 2002;9(9):901–6.
195. Sweet K, Willis J, Zhou XP, Gallione C, Sawada T, Alhopuro P, et al. Molecular classification of patients with unexplained hamartomatous and hyperplastic polyposis. J Am Med Assoc. 2005;294(19):2465–73. https://doi.org/10.1001/jama.294.19.2465.
196. Schreibman IR, Baker M, Amos C, McGarrity TJ. The hamartomatous polyposis syndromes: a clinical and molecular review. Am J Gastroenterol. 2005;100(2):476–90. https://doi.org/10.1111/j.1572–0241.2005.40237.x.
197. Offerhaus GJA, Howe JR. Juvenile polyposis. WHO Classification of Tumours of the Digestive System 2010:166–7.
198. Ma C, Giardiello FM, Montgomery EA. Upper tract juvenile polyps in juvenile polyposis patients: dysplasia and malignancy are associated with foveolar, intestinal, and pyloric differentiation. Am J Surg Pathol. 2014;38(12):1618–26.
199. Gonzalez RS, Adsay V, Graham RP, Shroff SG, Feely MM, Drage MG, et al. Massive gastric juvenile-type polyposis: a clinicopathological analysis of 22 cases. Histopathology. 2017;70(6):918–28. https://doi.org/10.1111/his.13149.
200. Lawless ME, Toweill DL, Jewell KD, Jain D, Lamps L, Krasinskas AM, et al. Massive gastric juvenile polyposis: a clinicopathologic study using SMAD4 immunohistochemistry. Am J Clin Pathol. 2017;147(4):390. https://doi.org/10.1093/ajcp/aqx015.
201. Howe JR, Mitros FA, Summers RW. The risk of gastrointestinal carcinoma in familial juvenile polyposis. Ann Surg Oncol. 1998;5(8):751–6.
202. Slavik T, Montgomery EA. Cronkhite-Canada syndrome six decades on: the many faces of an enigmatic disease. J Clin Pathol. 2014;67(10):891–7. https://doi.org/10.1136/jclinpath-2014–202488.
203. Ward EM, Wolfsen HC. Review article: the non-inherited gastrointestinal polyposis syndromes. Aliment Pharmacol Ther. 2002;16(3):333–42. https://doi.org/10.1046/j.1365–2036.2002.01172.x.
204. Daniel ES, Ludwig SL, Lewin KJ, Ruprecht RM, Rajacich GM, Schwabe AD. The cronkhite-Canada syndrome: an analysis of clinical and pathologic features and therapy in 55 patients. Medicine (United States). 1982;61(5):293–309.
205. Riegert-Johnson DL, Osborn N, Smyrk T, Boardman LA. Cronkhite-Canada syndrome hamartomatous polyps are infiltrated with IgG4 plasma cells [1]. Digestion. 2007;75(2–3):96–7. https://doi.org/10.1159/000102963.
206. Sweetser S, Ahlquist DA, Osborn NK, Sanderson SO, Smyrk TC, Chari ST, et al. Clinicopathologic features and treatment outcomes in Cronkhite-Canada syndrome: support for autoimmunity. Dig Dis Sci. 2012;57(2):496–502. https://doi.org/10.1007/s10620–011–1874–9.

207. Burke AP, Sobin LH. The pathology of Cronkhite-Canada polyps. A comparison to juvenile polyposis. Am J Surg Pathol. 1989;13(11):940–6. https://doi.org/10.1097/00000478–198911000–00004.
208. Wolfsen HC, Carpenter HA, Talley NJ. Menetrier's disease: a form of hypertrophic gastropathy or gastritis? Gastroenterology. 1993;104(5):1310–9. https://doi.org/10.1016/0016–5085(93)90339-E.
209. Isobe T, Kobayashi T, Hashimoto K, Kizaki J, Miyagi M, Aoyagi K, et al. Cronkhite-Canada syndrome complicated with multiple gastric cancers and multiple colon adenomas. Am J Case Rep. 2013;14:120–8. https://doi.org/10.12659/AJCR.889083.
210. Egawa T, Kubota T, Otani Y, Kurihara N, Abe S, Kimata M, et al. Surgically treated Cronkhite-Canada syndrome associated with gastric cancer. Gastric Cancer. 2000;3(3):156–60.
211. Watanabe T, Kudo M, Shirane H, Kashida H, Tomita S, Orino A, et al. Cronkhite-Canada syndrome associated with triple gastric cancers: a case report. Gastrointest Endosc. 1999;50(5):688–91.
212. Chadalavada R, Brown DK, Walker AN, Sedghi S. Cronkhite-Canada syndrome: sustained remission after corticosteroid treatment. Am J Gastroenterol. 2003;98(6):1444–6. https://doi.org/10.1111/j.1572–0241.2003.07509.x.
213. Goto A. Cronkhite-Canada syndrome: epidemiological study of 110 cases reported in Japan. Archiv fur Japanische Chirurgie. 1995;64(1):3–14.
214. Pilarski R, Stephens JA, Noss R, Fisher JL, Prior TW. Predicting PTEN mutations: an evaluation of cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome clinical features. J Med Genet. 2011;48(8):505–12. https://doi.org/10.1136/jmg.2011.088807.
215. Pilarski R, Burt R, Kohlman W, Pho L, Shannon KM, Swisher E. Cowden syndrome and the PTEN hamartoma tumor syndrome: systematic review and revised diagnostic criteria. J Natl Cancer Inst. 2013;105(21):1607–16. https://doi.org/10.1093/jnci/djt277.
216. Ngeow J, Sesock K, Eng C. Clinical implications for Germline PTEN Spectrum disorders. Endocrinol Metab Clin N Am. 2017;46(2):503–17. https://doi.org/10.1016/j.ecl.2017.01.013.
217. Eng C. Will the real Cowden syndrome please stand up: revised diagnostic criteria. J Med Genet. 2000;37(11):828–30.
218. Pilarski R, Eng C. Will the real Cowden syndrome please stand up (again)? Expanding mutational and clinical spectra of the PTEN hamartoma tumour syndrome. J Med Genet. 2004;41(5):323–6.
219. Al-Thihli K, Palma L, Marcus V, Cesari M, Kushner YB, Barkun A, et al. A case of Cowden's syndrome presenting with gastric carcinomas and gastrointestinal polyposis. Nat Clin Pract Gastroenterol Hepatol. 2009;6(3):184–9. https://doi.org/10.1038/ncpgasthep1359.
220. Hamby LS, Lee EY, Schwartz RW. Parathyroid adenoma and gatric carcinoma as manifestations of cowden's disease. Surgery. 1995;118(1):115–7. https://doi.org/10.1016/S0039–6060(05)80018–2.
221. Doglioni C, Laurino L, Dei Tos AP, De Boni M, Franzin G, Braidotti P, et al. Pancreatic (acinar) metaplasia of the gastric mucosa: histology, ultrastructure, immunocytochemistry, and clinicopathologic correlations of 101 cases. Am J Surg Pathol. 1993;17(11):1134–43. https://doi.org/10.1097/00000478–199311000–00006.
222. Krishnamurthy S, Dayal Y. Pancreatic metaplasia in Barrett's esophagus: an immunohistochemical study. Am J Surg Pathol. 1995;19(10):1172–80.
223. Integlia MJ. Pancreatic metaplasia of the gastric mucosa in pediatric patients. Am J Gastroenterol. 1997;92(9):1553–6.
224. Krishnamurthy S, Integlia MJ, Grand RJ, Dayal Y. Pancreatic acinar cell clusters in pediatric gastric mucosa. Am J Surg Pathol. 1998;22(1):100–5. https://doi.org/10.1097/00000478–199801000–00013.
225. Jhala N, Jhala D, West B, Atkinson BF, Haber MH. Pancreatic (acinar cell) metaplasia or early pancreatic heterotopia? Am J Clin Pathol. 1994;101:385.
226. Johansson J, Hakansson HO, Mellblom L, Kempas A, Kjellen G, Brudin L, et al. Pancreatic acinar metaplasia in the distal oesophagus and the gastric cardia: prevalence, predictors and relation to GORD. J Gastroenterol. 2010;45(3):291–9. https://doi.org/10.1007/s00535–009–0161–4.
227. Littler ER, Gleibermann E. Gastritis cystica polyposa. (Gastric mucosal prolapse at gastroenterostomy site, with cystic and infiltrative epithelial hyperplasia). Cancer. 1972;29(1):205–9. https://doi.org/10.1002/1097–0142(197201)29:1<205::AID-CNCR2820290130>3.0.CO;2-J.
228. Qizilbash AH. Gastritis cystica and carcinoma arising in old gastrojejunostomy stoma. Can Med Assoc J. 1975;112(12):1432–3.
229. Tomizuka T, Mazaki T, Mado K, Henmi A, Ishii Y, Masuda H, et al. A case of gastritis cystica profunda. Surgery. 2008;143(3):449–50. https://doi.org/10.1016/j.surg.2007.02.009.
230. Béchade D, Desramé J, Algayres JP. Gastritis cystica profunda in a patient with no history of gastric surgery. Endoscopy. 2007;39(Suppl 1):E80–1. https://doi.org/10.1055/s-2006–945070.
231. Xu G, Peng C, Li X, Zhang W, Lv Y, Ling T, et al. Endoscopic resection of gastritis cystica profunda: preliminary experience with 34 patients from a single center in China. Gastrointest Endosc. 2015;81(6):1493–8. https://doi.org/10.1016/j.gie.2014.11.017.
232. Yu XF, Guo LW, Chen ST, Teng LS. Gastritis cystica profunda in a previously unoperated stomach: a case report. World J Gastroenterol. 2015;21(12):3759–62. https://doi.org/10.3748/wjg.v21.i12.3759.
233. Franzin G, Novelli P. Gastritis cystica profunda. Histopathology. 1981;5(5):535–47. https://doi.org/10.1111/j.1365–2559.1981.tb01817.x.
234. Odze RD, Greenson J, Lauwers G, Goldblum J. Gastritis cystica profunda versus invasive adenocarcinoma. Am J Surg Pathol. 2012;36(2):316. https://doi.org/10.1097/PAS.0b013e31823edb3b.
235. Wang L, Yan H, Cao DC, Huo L, Huo HZ, Wang B, et al. Gastritis cystica profunda recurrence after surgical resection: 2-year follow-up. World J Surg Oncol. 2014;12(1) https://doi.org/10.1186/1477–7819–12–133.
236. Fonde EC, Rodning CB. Gastritis cystica profunda. Am J Gastroenterol. 1986;81(6):459–64. https://doi.org/10.1111/j.1572–0241.1986.tb01523.x.
237. Franzin G, Musola R, Zamboni G, Manfrini C. Gastritis cystica polyposa: a possible precancerous lesion. Tumori. 1985;71(1):13–8.
238. Choi MG, Jeong JY, Kim KM, Bae JM, Noh JH, Sohn TS, et al. Clinical significance of gastritis cystica profunda and its association with Epstein-Barr virus in gastric cancer. Cancer. 2012;118(21):5227–33. https://doi.org/10.1002/cncr.27541.
239. Park CH, Park JM, Jung CK, Kim DB, Kang SH, Lee SW, et al. Early gastric cancer associated with gastritis cystica polyposa in the unoperated stomach treated by endoscopic submucosal dissection. Gastrointest Endosc. 2009;69(6):e47–50. https://doi.org/10.1016/j.gie.2008.10.020.
240. Deery S, Yates R, Hata J, Shi C, Parikh AA. Gastric adenocarcinoma associated with gastritis cystica profunda in an unoperated stomach. Am Surg. 2012;78(8):E379–E80.
241. Gorospe M, Fadare O. Gastric mucosal calcinosis: clinicopathologic considerations. Adv Anat Pathol. 2007;14(3):224–8. https://doi.org/10.1097/PAP.0b013e31805048ea.
242. Greenson JK, Trinidad SB, Pfeil SA, Brainard JA, McBride PT, Colijn HO, et al. Gastric mucosal calcinosis: calcified aluminum phosphate deposits secondary to aluminum-containing antacids or sucralfate therapy in organ transplant

patients. Am J Surg Pathol. 1993;17(1):45–50. https://doi.org/10.1097/00000478–199301000–00005.
243. Kuzela DC, Huffer WE, Conger JD, Winter SD, Hammond WS. Soft tissue calcification in chronic dialysis patients. Am J Pathol. 1977;86(2):403–24.
244. Ou Tim L, Hurwitz S, Tuch P. The endoscopic diagnosis of gastric calcification. J Clin Gastroenterol. 1982;4(3):213–5.
245. Saab S, Venkataramani A, Behling CA, Savides TJ. Gastric mucosal calcinosis in a patient with dyspepsia. J Clin Gastroenterol. 1996;22(2):156–7. https://doi.org/10.1097/00004836–199603000–00020.
246. Nayak HK, Mohindra S, Iqbal S, Saraswat VA, Agarwal V, Pande G. Gastric mucosal calcinosis mimicking malignancy. Am J Gastroenterol. 2016;111(10):1380. https://doi.org/10.1038/ajg.2016.274.
247. Ebert EC, Nagar M. Gastrointestinal manifestations of amyloidosis. Am J Gastroenterol. 2008;103(3):776–87. https://doi.org/10.1111/j.1572–0241.2007.01669.x.
248. Menke DM, Kyle RA, Fleming CR, Wolfe JT III, Kurtin PJ, Oldenburg WA. Symptomatic gastric amyloidosis in patients with primary systemic amyloidosis. Mayo Clin Proc. 1993;68(8):763–7. https://doi.org/10.1016/S0025–6196(12)60634-X.
249. Said SM, Grogg KL, Smyrk TC. Gastric amyloidosis: clinicopathological correlations in 79 cases from a single institution. Human Pathology. 2015;46(4):491–8. Original contribution. https://doi.org/10.1016/j.humpath.2014.12.009.
250. Seon CS, Park YS, Jung YM, Choi JH, Son BK, Ahn SB, et al. Gastric outlet obstruction due to gastric amyloidosis mimicking malignancy in a patient with ankylosing spondylitis. Clin Endosc. 2013;46(6):651–5. https://doi.org/10.5946/ce.2013.46.6.651.
251. Khan Z, Darr U, Renno A, Tiwari A, Sofi A, Nawras A. Massive upper and lower GI bleed from simultaneous primary (AL) amyloidosis of the stomach and transverse colon in a patient with multiple myeloma. Case Rep Gastroenterol. 2017;11(3):625–31. https://doi.org/10.1159/000480073.
252. Rivera R, Kaul V, DeCross A, Whitney-Miller C. Primary gastric amyloidosis presenting as an isolated gastric mass. Gastrointest Endosc. 2012;76(1):186–7. https://doi.org/10.1016/j.gie.2012.02.059.
253. Tada S, Lida M, Iwashita A, Matsui T, Fuchigami T, Yamamoto T, et al. Endoscopic and biopsy findings of the upper digestive tract in patients with amyloidosis. Gastrointest Endosc. 1990;36(1):10–4. https://doi.org/10.1016/S0016–5107(90)70913–3.
254. Jimenez-Zepeda VH, Vajpeyi R, John R, Trudel S. Light chain deposition disease affecting the gastrointestinal tract in the setting of post-living donor kidney transplantation. Int J Hematol. 2012;96(1):125–31. https://doi.org/10.1007/s12185–012–1090–1.
255. Kwon JH, Jeong SH, Kim JW, Bang SM, Kim H, Kim YH, et al. Case report: a case of light chain deposition disease involving liver and stomach with chronic hepatitis C virus infection and hepatocellular carcinoma. J Med Virol. 2011;83(5):810–4. https://doi.org/10.1002/jmv.22050.
256. Conte D, Velio P, Brunelli L, Mandelli C, Cesana M, Ferrario L, et al. Stainable Iron in gastric and duodenal mucosa of primary hemochromatosis patients and alcoholics. Am J Gastroenterol. 1987;82(3):237–40. https://doi.org/10.1111/j.1572–0241.1987.tb05298.x.
257. Marginean EC, Bennick M, Cyczk J, Robert ME, Jain D. Gastric siderosis: patterns and significance. Am J Surg Pathol. 2006;30(4):514–20. https://doi.org/10.1097/00000478–200604000–00013.
258. Antunes AG, Cadilla J, Guerreiro H. Gastric siderosis as a cause of dyspepsia. BMJ Case Rep. 2016;2016 https://doi.org/10.1136/bcr-2016–216862.