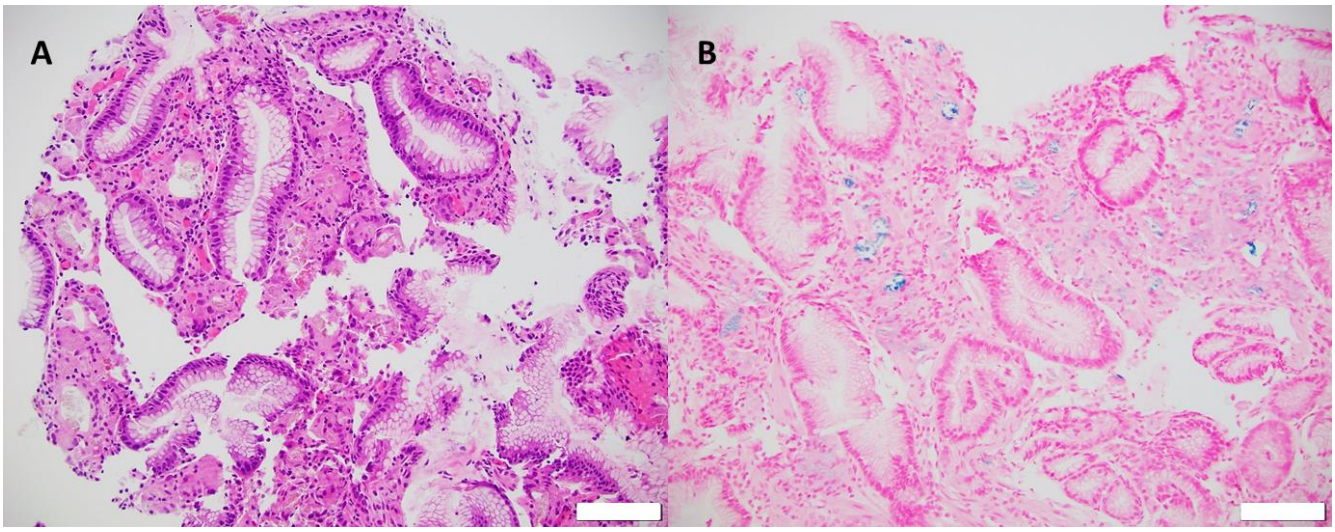
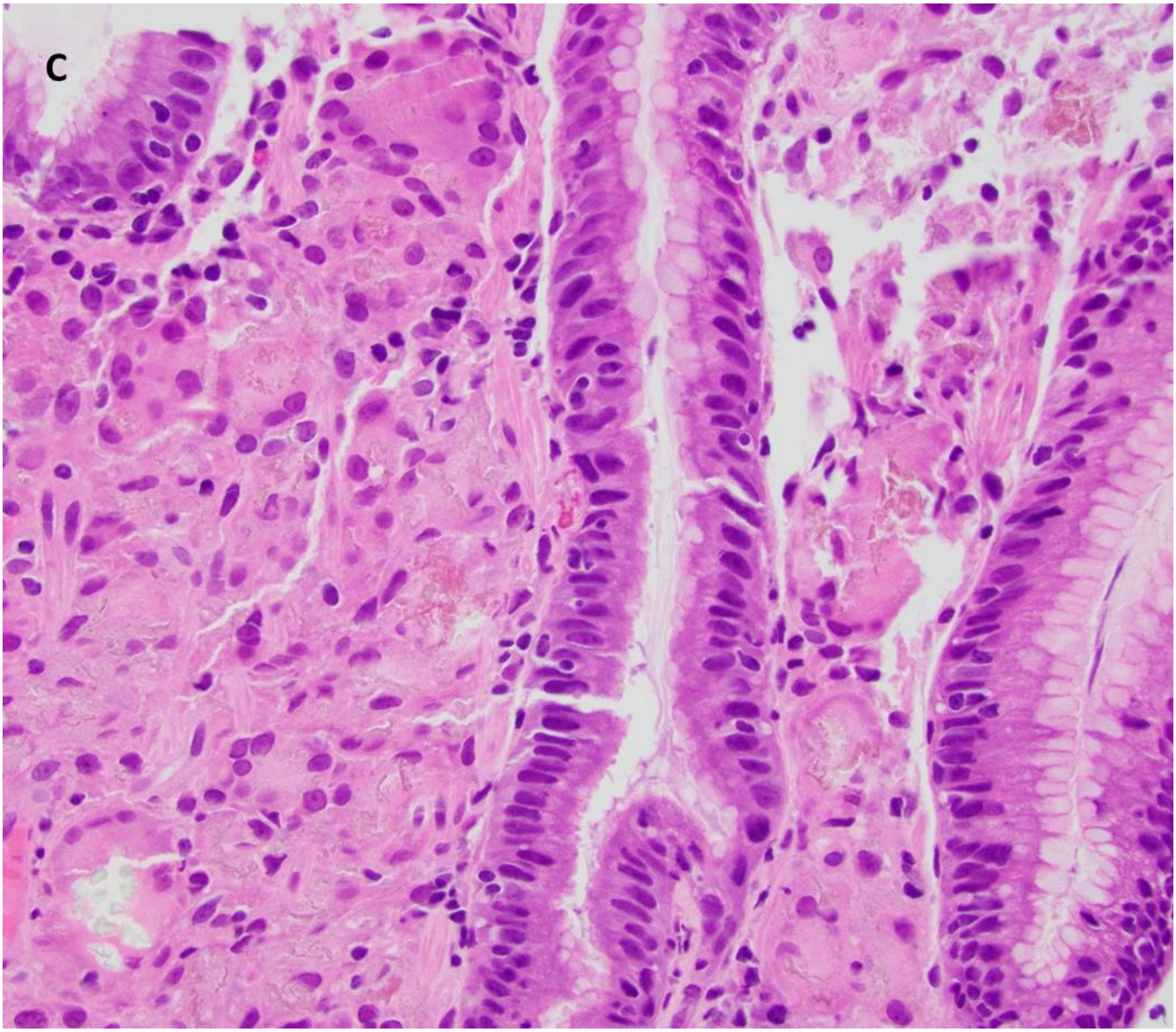
A 36 year old male with end-stage renal disease secondary to type-1 diabetes mellitus, on chronic hemodialysis, complained of nausea and vomiting at a pre-kidney and pancreas transplant clinical appointment. The patient was referred for upper GI endoscopy. Upon endoscopic evaluation, prominent folds with small erosions were seen in the prepyloric region of the stomach. Cold forceps biopsies were taken for histologic evaluation to rule out H. pylori infection. Representative H&E and iron stain images are below for review. H. pylori and von Kossa stains were negative.

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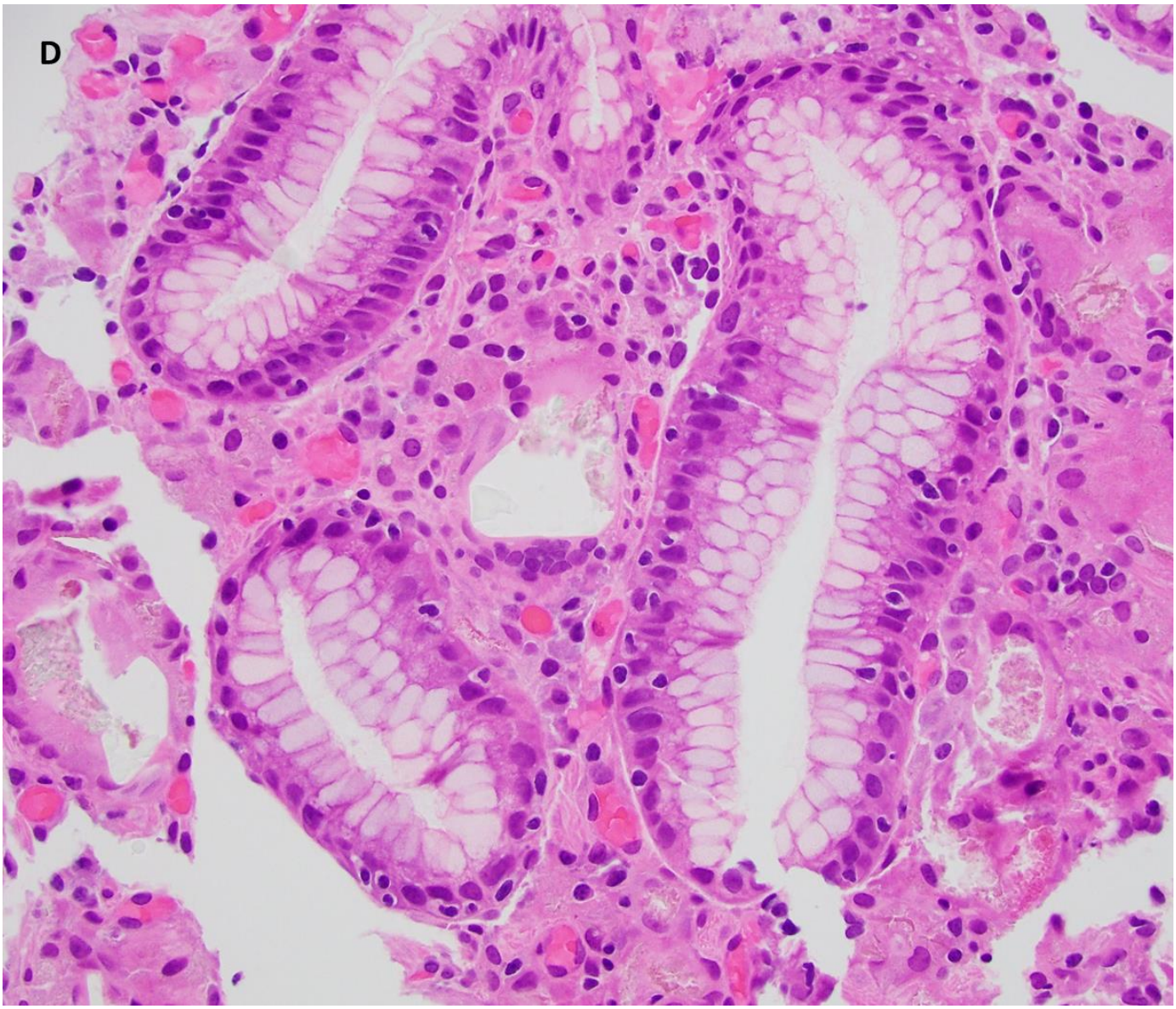

A) H&E 20x, B) Iron stain 20x, C) H&E 40x, D) H&E 40x

What is the diagnosis?

a. Iron therapy related gastric injury
b. Langerhans cell histiocytosis
c. Mycobacterium avium complex infection
d. Lanthanum deposition
e. Pseudomelanosis of the stomach
f. Gastric calcinosis

ANSWER AND DISCUSSION ON NEXT PAGE

Answer and discussion:

Lanthanum deposition (choice D) is the correct answer. Lanthanum carbonate is used as an alternative to calcium-based phosphate binders to manage hyperphosphatemia in patients with chronic renal diseases on dialysis, preventing the development of secondary hyperthyroidism in these patients. Lanthanum carbonate deposition in the gastrointestinal tract is uncommon, but has been described most frequently in stomach, followed by the duodenum and colon. The significance of the deposits is unknown. Adverse gastrointestinal effects including dysphagia, nausea, vomiting and reflux have been reported in patients taking lanthanum. Endoscopically, lanthanum carbonate deposition appears as polypoid mucosa, ulcerations, or erosions. On histologic examination, biopsies may show prominent histiocytosis and multinucleated giant cells that expand the lamina propria and surround deposits of refractile, granular foreign material. This material may appear amphiphilic, eosinophilic, colorless or purple/brown and may also be seen phagocytosed within histiocytes. The material has been demonstrated to be lanthanum phosphate via scanning electron microscopy and energy dispersive x-ray analysis. The background gastric mucosa will often show changes consistent with chemical-type injury. Von Kossa stains will be negative for calcium, and iron stains will often show focal positivity in larger granular deposits; PAS-D stains may also show faint staining of the granular material. Given that lanthanum deposition within the gastroduodenal mucosa is encountered infrequently, the histiocytic expansion of the lamina propria and/or pigment deposition can be mistaken for other processes.

Iron therapy related gastric injury, or iron pill gastritis, is the most common of the diagnoses listed and is seen in approximately 0.9% of all upper-GI mucosal biopsies. It is more commonly encountered in the stomach than the esophagus. About half of patients with iron pill gastritis may also have a concurrent infectious or mechanical injury leading to a background of chronic or active gastritis, or chemical-type injury, similar to the background seen in lanthanum deposition. Endoscopic examination shows mucosal erosions in the stomach, with ulceration in severe cases. These erosions are thought to be caused by the oxidation of inorganic iron coating the epithelial surface, catalyzing the formation of reactive oxygen metabolites. Histologically, there are varying amounts of crystalized, yellow-to-brown, extracellular hemosiderin deposits on the surface epithelium and within the lamina propria, with eroded or intact epithelium displaying, sometimes marked, reactive changes. Prussian blue strongly stains these iron deposits. This strong staining for iron, the uniform yellow-to-brown appearance of the depositions, as well as the clinical history of oral iron supplementation will help make this diagnostic distinction.

Langerhans cell histiocytosis (LCH) is an abnormal histiocytic proliferation that is more common in children than in adults; however, rare cases of adult gastric Langerhans cell histiocytosis have been reported. Adults with LCH are usually asymptomatic, and endoscopic exam may show a polypoid or elevated mucosal lesion. Histologically, the lamina propria and/or submucosa are markedly expanded by histiocytic cells that are associated with other inflammatory cells including eosinophils (often very prominent), neutrophils, plasma cells, and lymphocytes. Langerhans cells will have positive immunohistochemical staining for CD1a, Langerin (CD207), S100, CD68, HLA-DR, and vimentin. The prominent histiocytes seen within the lamina propria of patients with lanthanum deposition are non-Langerhans; S100 and CD1a staining will be negative, ruling out this diagnosis. Additionally, deposition of pigmented material is not seen in LCH.

Mycobacterium avium complex (MAC) infection of the stomach occurs mostly in immunocompromised patients, particularly in patients with acquired immunodeficiency syndrome (AIDS) with CD4 cell counts less than 100/ul who are at risk for disseminated GI tract MAC infections. These patients may present with abdominal pain, fever, weight loss and diarrhea. Endoscopically, the mucosa can appear normal,

coarsely granular, or show white plaques/nodules. Histologically, the lamina propria will be expanded by a marked foamy histiocytic infiltrate. However, unlike cases of *Mycobacterium tuberculosis*, well-formed granulomas are not generally seen. Acid-fast histochemical stains will highlight numerous organisms within the foamy macrophages. This clinical history, positive AFB stain, along with the lack of foreign material deposition will readily allow the distinction between MAC infection and lanthanum deposition.

Pseudomelanosis is the accumulation of pigmented macrophages in the lamina propria of the small bowel or, less commonly, the stomach. These patients tend to be older adults with a history of end stage renal disease, hypertension, diabetes mellitus, cardiovascular disease or iron deficiency anemia, and some cases have been attributed to medications such as diuretics, beta-blockers, and iron supplements. Unlike melanosis coli, pseudomelanosis is not associated with laxative use. Endoscopically, pseudomelanosis in the stomach appears as black, speckled mucosa. This pigment has been found to be composed of varying amounts of iron, calcium and sulfur. Histologic examination will show granular black pigment and pigmented macrophages within the lamina propria. The pigment is variably positive by iron stain or Masson-Fontana trichrome stain. Unlike the variably pigmented and refractile lanthanum depositions, pseudomelanosis is generally found to be uniformly black-brown, and can give the appearance of melanin. Additionally, multinucleated giant cells are not a histologic feature of pseudomelanosis.

Gastric mucosal calcinosis (GMC) is a disorder of calcium-phosphate metabolism that is seen most frequently in the setting of renal failure. In the most common clinical scenario, referred to as metastatic calcification, hypercalcemia and/or hyperphosphatemia leads to the deposition of calcium salts in otherwise normal tissue. Metastatic calcification preferentially occurs in gastric, kidney, heart, and lung tissue, possibly due to their relative intracellular alkalinity. Cardiac and pulmonary calcifications are associated with significant morbidity; however, the natural history of gastric calcinosis is not entirely clear. Dystrophic calcification also occurs in the stomach due to deposition of calcium salts secondary to inflammation (particularly seen with atrophic gastritis), infection or neoplasia. Additionally, medications such as isotretinoin, sucralfate, aluminum-containing antacids and citrate-containing blood products have been associated with GMC. Patients are generally asymptomatic and endoscopic examination is generally normal or remarkable for small round, flat nodules/plaques. Histologic examination reveals blueish purple material within the superficial lamina propria. These deposits may be rimmed by histiocytes; however, the background mucosa and epithelium are generally otherwise normal. These deposits have been shown by x-ray microanalysis to be comprised of aluminum, phosphorus, calcium and chlorine and will be highlighted by a von Kossa stain. This positive von Kossa staining, seen in the setting of an otherwise unremarkable mucosal biopsy, will favor the diagnosis of GMC.

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