Case report

Gastric Xanthelasma: Case report and Literature Review

Abstract

Gastric xanthelasma (GX) are benign clusters of lipid-laden macrophages present in lamina propria. Though the pathogenesis of GX is not known, it is associated with dyslipidemia, Helicobacter pylori infection related chronic gastritis, hyperplastic gastric polyps, intestinal metaplasia, diabetes mellitus and synchronous or metachronous gastric cancer. We present a case of a 44-year-old female who presented GX without concomitant Helicobacter pylori infection. A review of literature describing common clinico-pathologic differentials of GX is also presented.

Introduction

Xanthelasmas are non-malignant plaque like lesions commonly seen in the dermis or hypodermis and are composed of lipid laden (foamy) histiocytes. [1,2] Xanthelasmas are rare in the gastrointestinal tract (GIT), comprising about 0.23% to 7% of all cases. The usual locations in the GIT are stomach (76%), esophagus (12%) and duodenum (12%). In the stomach, antrum and prepyloric regions are the commonest sites; though the location in the fundus and corpus has also been described. Frequently, gastric xanthelasmas (GX) are detected as incidental findings in ~~on~~ esophagogastroduodenoscopy (EGD). The GXs are associated with dyslipidemia, *Helicobacter pylori* infection, hyperplastic gastric polyps, intestinal metaplasia and diabetes mellitus. [3]

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Identification and diagnosis of supposedly benign GX are ~~is~~ important as high frequency of gastric cancer precursor lesions and early gastric cancer have been reported in its association. [4] We report a case of a 44-year-old ~~44 year old~~ female who presented with a combination of GX, gastric erosions and anemia. We also review the literature for common clinical and pathological differentials of GX.

Case report

A 44-year-old non-diabetic, normotensive female presented with symptoms of upper abdominal discomfort, bloating and fatigue ~~since~~ for 6 months. There was no history of nausea, vomiting, weight loss, alteration in bowel habits, melena, hematochezia, hematemesis or heavy menstrual bleed. She was pale on physical examination and did not have cutaneous xanthelasmas. The labs revealed iron deficiency anemia (hemoglobin 8 g/dL, transferrin saturation 6%, serum ferritin 11 ng/mL) Serum anti-tissue transglutaminase, IgA, vitamin B12 and serum folate levels were normal. Fecal occult blood testing was negative on three different occasions. Serum lipid profile (total serum cholesterol and triglycerides) was normal. She was referred for EGD and colonoscopy for evaluation of anemia. EGD showed multiple sub-centimetric well demarcated nodular plaques in the corpus and fundus of the stomach. Antrum and duodenum were normal. (Figure 1) The rapid urease test performed on the gastric biopsy was negative. Colonoscopic examination was unremarkable.

A Histological examination from the gastric nodule biopsy revealed epithelial erosions and chronic inflammatory infiltrates with clusters of oval shaped cells with abundant foamy cytoplasm present within the lamina propria. (Figure 2). These cells stained positive for CD-68 and negative for cytokeratin (CK) AE1/AE3 on immunohistochemistry (IHC). (Figure 2) Ziehl-

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Neelsen (ZN) and Periodic Acid-Schiff (PAS) stains were negative. There was no evidence of intestinal metaplasia, dysplasia or malignancy in the examined sections. Stain for *Helicobacter pylori* was negative. Duodenal biopsy showed a normal villous pattern.

The anemia was attributed to nutritional deficiencies and resolved after six months of oral iron supplementation. Her clinical symptoms of abdominal discomfort and bloating resolved with Rabeprazole ~~20mg /day~~ 20 mg/day.

Discussion

GXs are yellow-red plaque like lipid-filled histiocytic lesions usually found in the gastric antrum along the lesser curvature. These are detected incidentally on EGD done for evaluation of other gastrointestinal symptoms. Patients with GX, commonly males in the 5th and 6th decade of life, report vague symptoms of dyspepsia, nausea and vomiting, though the causal association has not been established. The GX can occur in isolation without cutaneous xanthelasmas, even without dyslipidemia.

Endoscopically, GX appear as single or multiple, sub-centimetric yellow-red mucosal patches or plaques.[5] Biopsy of the lesion for histopathology and IHC is important to differentiate it from other conditions with similar clinical and/or endoscopic characteristics such hyperplastic polyps, carcinoid tumors, signet cell adenocarcinoma, xanthogranuloma, Russell body gastritis and pseudoxanthoma elasticum. Table 1 summarizes the key differences between the differential diagnoses of GX.

The etiology of GX is unclear. *Helicobacter pylori* infection has been implicated in the development of GX. The Majority of the patients with GX have *Helicobacter pylori* on the

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surface of epithelial cells. [6] *Helicobacter pylori* associated chronic gastritis and gastric atrophy are also risk factors for gastric cancer, explaining the association of GX with synchronous or metachronous gastric cancer. [7,8] Our case is unique as GX was present without any evidence of Helicobacter pylori infection.

A high incidence of early gastric cancer has been documented in patients with GX as compared to those without. [1,2] Presence of concomitant diabetes mellitus, advanced age and chronic atrophic gastritis are the risk factors for the development of gastric cancer in patients with GX. [9] Anemia, as seen in our patient, and also reported previously, is unlikely to be due to GX. However in presence of combination of anemia and GX, early gastric cancer should be excluded. A cohort study reported that GX may be an early predictive marker for subsequent development of gastric cancer. [9] Therefore, follow up with periodic EGD may be considered in at risk patients, though evidence for this recommendation is weak.

The natural course of GX is not known at present. Since GX are usually asymptomatic and an incidental finding, no treatment is required. Whether treatment of Helicobacter pylori infection treats GX is not known. However, the use of endoscopic mucosal resection (in the presence of associated polyps), argon plasma coagulation and heat probe therapy for treatment of the gastric lesions has been reported. [10]

Conclusions

In summary, GX are rare and inherently non-neoplastic lesions, but with an association with gastric cancer. Demonstration of foamy histiocytes on histology characterize the GX. The clinical significance of GX is poorly understood. However, because of its association with gastric cancer, it is important to have a high index of suspicion to recognize these lesions. More

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information on the natural course and correlations between GX, clinical symptoms and outcomes is needed.

References

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Table 1. Differential Diagnosis of Gastric Xanthelasma

	Risk factors	Clinical features	Endoscopic features	Histopathological examination	Immunohistochemistry	Remarks
Hyperplastic polyps	Helicobacter pylori infection, autoimmune metaplastic atrophic gastritis, increaseing age, females, long term use of proton pump inhibitors	Dyspepsia, heartburn, rarely may cause gastrointestinal bleed or gastric outlet obstruction.	Small, flat or sessile dome-shaped lesions with smooth surface and lobular structure	Foveolar hyperplasia, Infiltration of lamina propria with inflammatory cells	Mutated p53 gene, high proliferation index (Ki-67) seen in those with foveolar hyperplasia.	-
Carcinoid tumors	Chronic atrophic gastritis, pernicious anemia, hypergastrinemia, Zollinger Ellison	Nausea, vomiting, abdominal discomfort, dyspepsia, early satiety, gastrointestinal bleeding	Multiple small subcentimetric to large polypoid lesions or nodules found in the gastric body	Abundant eosinophilic cytoplasm, polygonal shaped tumor cells with round to oval nuclei and	Chromogranin A, Neuron specific enolase, Synaptophysin, pancytokeratin	Can present as carcinoid syndrome-with symptoms of flushing, diarrhea, right sided heart

	Syndrome, Multiple Endocrine Neoplasia		and fundus with normal appearing overlying mucosa.	salt pepper chromatin	positivity	failure. Increased maignancy and metastasis risk in solitary carcinoids as compared to multiple carcinoids due to hypergastrinemia.
Russell body gastritis	Helicobacter pylori, Human immunodeficiency virus, Epstein Barr virus, Candida esophagitis, Ethanol use	Nausea, dyspepsia, and epigastric pain	Hyperemic/ whitish, edematous, and nodular erosions in the antrum	Presence of plasma cells with eosinophilic cytoplasmic inclusions of immunoglobulin in the gastric lamina propria.	Positive for CD138, CD79a and they show polytypic expression of kappa and lambda light chains (Fig. 2). The Russell bodies were negative for pan-cytokeratin	Rarely associated with concurrent gastric cancer
Signet cell adenocarcinoma	Germline mutation in E cadherin (CDH1 gene)	Decreased appetite, weight loss, bloating	Ulcerated mass lesion in the stomach, commonly in the	Poorly cohesive malignant tumor cells with prominent	Cytokeratin (CK) and PAS positive cells	Signet ring cell early gastric cancer has better survival

	Family history of gastric cancer Chronic atrophic gastritis, *Helicobacter pylori* infection		antrum	mucin in the cytoplasm and eccentric crescent shaped nuclei, Periodic acid Sciff stain positive		then non signet ring cell adenocarcinoma. Poor prognosis in advanced disease.
Pseudoxanthoma elasticum	Autosomal recessive genetic disease with mutations in ABCC6 gene	Small yellow papules on the nape and sides of the neck and in flexural areas Increased risk for GI bleeding due to the poor vascular integrity	Linear or nodular yellowish raised submucosal lesions	Accumulation of pleomorphic elastotic material that reveals progressive mineralization	-	No specific treatment, Experimental therapies include anti-VEGF, inorganic phosphate, phosphate binders Genetic testing and counselling
Xanthogranuloma	Immunological disorders, defects in lipid transport (lymphatic	Pain abdomen, bloating	Multiple golden yellow or bright yellow nodules	Foamy histiocytes mixed with acute and chronic inflammatory cells	Positive for CD 68 Negative for AE1/3, S100 and CAM5.2	Colon, uterus and Pancreas may also have xanthogranuloma,

	obstruction)					Can masquerade gastric cancer

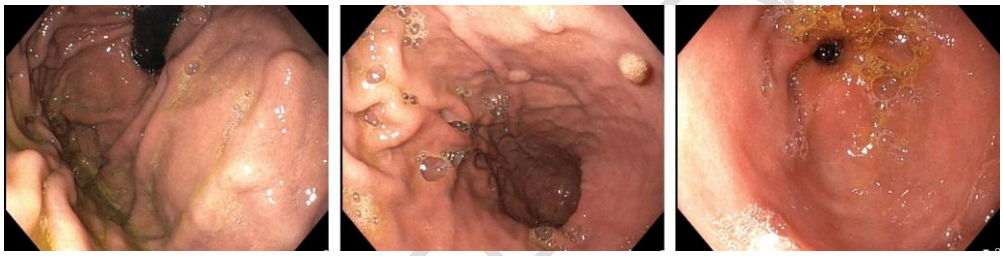

Figure 1. Esophagogastroduodenoscopy showing yellowish white nodular lesions in the gastric corpus and fundus. Antrum is normal.

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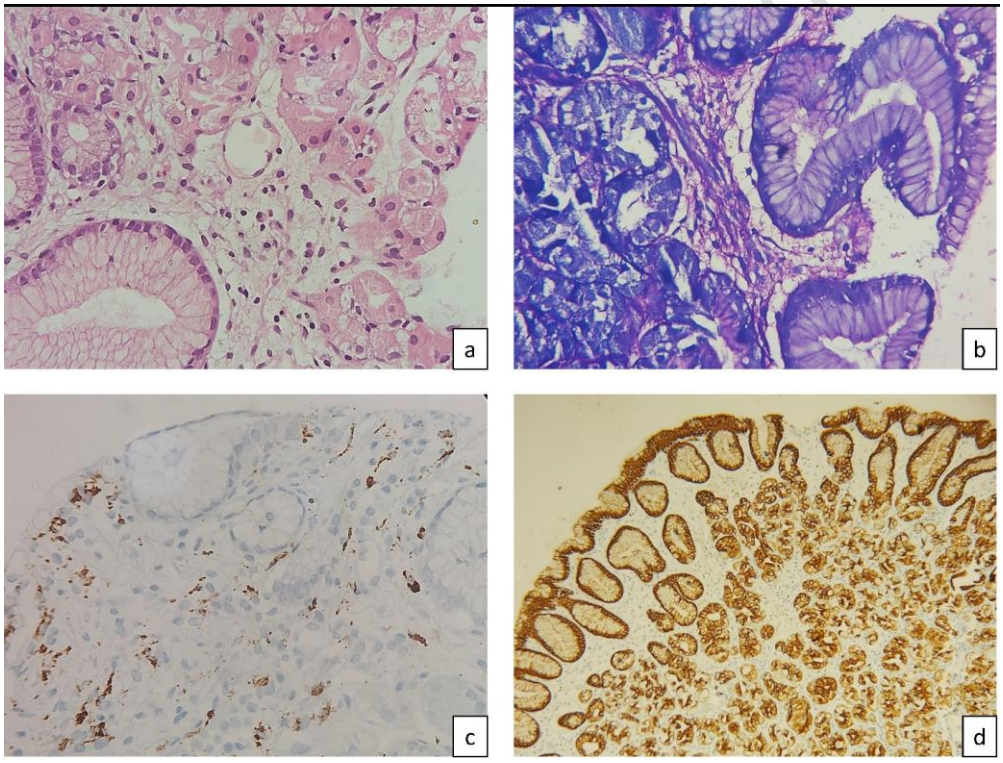

Figure 2. a) Hematoxylin and Eosin stain showing presence of foamy histiocytes in the lamina propria. b) Giemsa stain negative for Helicobacter pylori c) Immunohistochemistry shows CD 68

positive histiocytes in the lamina propria and d) cytokeratin (AE1/3) negative histiocytes and cytokeratin (AE1/3) positive epithelium.