Metaplastic (chronic) atrophic gastritis

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Literature review current through: **Sep 2023.**
This topic last updated: **Sep 09, 2022.**

INTRODUCTION

Gastritis usually has an infectious or autoimmune etiology. This topic review discusses the two types of metaplastic (chronic) atrophic gastritis [1,2]. Other forms of gastritis and gastropathy are presented separately. (See "Gastritis: Etiology and diagnosis" and "Acute and chronic gastritis due to Helicobacter pylori" and "Acute hemorrhagic erosive gastropathy and reactive gastropathy" and "Granulomatous gastritis" and "Approach to the patient with large gastric folds".)

DEFINITION

The term metaplastic (chronic) atrophic gastritis, also referred to as gastric atrophy, is used to describe a form of chronic gastritis that, in addition to inflammation, is associated with mucosal thinning, loss of specialized cells in gastric glands, and changes in epithelial cell types (ie, metaplasia).

SUBTYPES

Metaplastic (chronic) atrophic gastritis includes two main subtypes, autoimmune and environmental metaplastic atrophic gastritis (AMAG and EMAG). Although the AMAG and EMAG may be pathogenetically and clinically distinct, they often share histologic features and may

overlap clinically. (See 'Autoimmune metaplastic atrophic gastritis' below and 'Environmental metaplastic atrophic gastritis' below.)

Autoimmune metaplastic atrophic gastritis — AMAG is a form of metaplastic (chronic) atrophic gastritis that results in the replacement of the normal oxyntic mucosa in the gastric corpus by atrophic and metaplastic mucosa, leading to a corpus predominant atrophic gastritis, reduced or absent acid and pepsin production, and loss of intrinsic factor, which may progress to a severe form of vitamin B12-deficiency anemia known as pernicious anemia (PA).

Epidemiology — AMAG and PA have prevalences of 2 percent and 0.15 to 1 percent, respectively [3]. The prevalence of AMAG increases with age and is higher in women as compared with men. In the United States, AMAG has a similar prevalence among White, Hispanic, and African American populations, and occurs over a wide age range [4]. There is an association of AMAG with other autoimmune diseases [5,6]. Up to one-third of patients with autoimmune thyroid disease and 6 to 10 percent of patients with type 1 diabetes mellitus (DM) have concurrent AMAG [7].

Etiopathogenesis — AMAG is associated with a T-cell mediated destruction of the oxyntic mucosa and production of autoantibodies directed against parietal cell antigens and intrinsic factor. In a mouse model of autoimmune gastritis, antibodies were directed against the hydrogen-potassium ATPase enzyme in parietal cells [8]. The chronic inflammation, glandular atrophy, and epithelial metaplasia of AMAG are closely paralleled by elevated serum antibodies to parietal cell antigens and to intrinsic factor, reflecting its autoimmune origin. Serum pepsinogen I levels, produced in the oxyntic mucosa, decrease also, as does gastric pepsinogen secretion. (See 'Laboratory features' below and 'Laboratory testing' below.)

Both genetic and environmental factors may play a role in the pathogenesis of AMAG. Autoimmune gastritis susceptibility genes (*Gasa 1, 2, 3,* and *4*) have been discovered on chromosomes 4 and 6 and the H2 gene complex in murine models. Some of these genes are located on the same locus as mouse DM susceptibility genes, which may account for the strong association between AMAG and type 1 DM in humans [9]. Asymptomatic relatives of patients with AMAG are sometimes found to have established AMAG and even PA [5].

There is evidence that *H. pylori* might serve as a trigger of AMAG and PA and that *H. pylori* infection at a younger age triggers the development of autoimmune gastritis, which progresses clinically over time from iron deficiency anemia (perhaps due to iron malabsorption because of hypochlorhydria/achlorhydria) to cobalamin deficiency with macrocytosis [10]. *H. pylori* infection has also been associated with iron deficiency anemia in patients without evidence of gastrointestinal blood loss or metaplastic atrophic gastritis by mechanisms that are unclear. The

association between AMAG and *H. pylori* infection in many patients has led to speculation that *H. pylori* may, in some cases, induce AMAG via antigenic mimicry or cross-reactivity. However, this hypothesis is controversial and the subject of active research [11]. Patients with AMAG are less likely to be infected by *H. pylori* than age-matched controls [12]. Two possible explanations are that the metaplastic intestinal epithelium becomes unsuitable (lacks host receptors) for *H. pylori* colonization, and that the associated hypochlorhydria encourages overgrowth of the stomach by other bacterial species [13].

Despite their inverse relationship, chronic *H. pylori* gastritis and AMAG share some clinical and pathologic features. Both can be associated with an atrophic form of body gastritis and hypochlorhydria. In addition, some patients with *H. pylori* infection have circulating parietal cell autoantibodies [14]. Serologic testing for past *H. pylori* infection may be helpful in such patients. (See "Indications and diagnostic tests for Helicobacter pylori infection in adults", section on 'Serology'.)

Clinical features — Patients with AMAG may be asymptomatic, but many of them have dyspepsia with postprandial distress [15]. Patients with AMAG may be symptomatic from vitamin B12 malabsorption and PA [2,5,15]. The presence of symptoms attributable to anemia depends on the rate that deficiency has developed, the severity of the deficiency, the hemoglobin level, and the person's overall health. Patients with B12 deficiency usually have vague or nonspecific symptoms (eg, fatigue, irritability, cognitive decline), which are likely to be due (at least in part) to anemia. B12 deficiency can cause glossitis (including pain, swelling, tenderness, and loss of papillae of the tongue). B12 deficiency can also cause subtle neurologic, cognitive, or psychiatric changes. The most common neurologic manifestation is symmetric paresthesias or numbness and gait problems. (See "Clinical manifestations and diagnosis of vitamin B12 and folate deficiency".)

Laboratory features — Patients with AMAG may present with the following laboratory abnormalities [4]:

- **Elevated fasting serum gastrin** – Hypergastrinemia in AMAG results from uninhibited gastrin secretion as a consequence of parietal cell atrophy and hypochlorhydria/achlorhydria.
- **Decreased serum pepsinogen I/II ratio** – Atrophy of zymogenic chief cells in the oxyntic mucosa results in a reduction in serum pepsinogen I but not serum pepsinogen II levels [1].
- **Iron deficiency anemia** – Iron deficiency anemia may be the most common hematologic presentation of AMAG and can precede the onset of PA by several years [11,16]. Gastric

acid normally enhances iron solubility and intestinal iron absorption by converting the ferric form of iron into the more absorbable ferrous form. Gastric acid also facilitates peptic digestion of dietary proteins bound to iron. Hypochlorhydria/achlorhydria and reduced peptic activity in AMAG decreases bioavailable iron, leading to iron malabsorption and deficiency.

- **Low serum vitamin B12 level** – Low gastric acid and peptic activity reduce liberation of B12 bound to dietary proteins. Also, antibodies to intrinsic factor impair vitamin B12 absorption. Manifestations of vitamin B12 deficiency include anemia with macrocytosis (high mean corpuscular volume), elevated methylmalonic acid, pancytopenia, and hypersegmented neutrophils. (See "Treatment of vitamin B12 and folate deficiencies".)

Individuals with AMAG may also have laboratory findings of other concurrent autoimmune disorders (eg, thyroid disease, type 1 diabetes mellitus) [4-6,15,17,18]. (See 'Epidemiology' above and "Disorders that cause hypothyroidism", section on 'Chronic autoimmune (Hashimoto's) thyroiditis' and "Clinical presentation, diagnosis, and initial evaluation of diabetes mellitus in adults", section on 'A1C'.)

Cancer risk — Patients with AMAG are at increased risk for the development of gastric neuroendocrine tumors and adenocarcinomas.

Gastric neuroendocrine (carcinoid) tumors — Limited data on the long-term incidence of gastric neuroendocrine tumors in patients with metaplastic (chronic) atrophic gastritis suggest an annual incidence of 0.68 percent per person-years [19]. Neuroendocrine tumors arise from transformation of enterochromaffin-like (ECL) cells (which are responsible for histamine secretion) within the oxyntic mucosa due to chronic stimulation by high circulating levels of gastrin. The hypochlorhydria or achlorhydria associated with AMAG induces hyperplasia of the antral/pyloric G cells (the cell type responsible for producing gastrin) and hypergastrinemia. Gastrin exerts a trophic effect on endocrine cells (eg, ECL cells) within the metaplastic and atrophic body mucosa, which increase in number and may give rise to hyperplastic nodules both within and around the glands [20,21]. The relationship between gastrin-induced ECL cell hyperplasia and neuroendocrine tumor formation is supported by the observation that antrectomy, with resultant loss of G cell mass and normalization of plasma gastrin concentrations, can lead to reversal of endocrine hyperplasia and reduced carcinoid tumor size [22,23]. (See "Clinical characteristics of well-differentiated neuroendocrine (carcinoid) tumors arising in the gastrointestinal and genitourinary tracts".)

Neuroendocrine tumors in AMAG patients usually appear grossly as multiple small (<1 cm) mucosal nodules or polyps. However, most nodular and polypoid lesions encountered in the

gastric body and antrum in patients with AMAG are retained islands of uninvolved mucosa (pseudopolyps) or benign epithelial hyperplastic lesions, making biopsy of visible nodules imperative [24,25]. (See 'Endoscopy and biopsy' below.)

Gastric adenocarcinomas — Gastric adenocarcinoma develops in patients with AMAG via intervening steps of intestinal metaplasia (IM) and dysplasia [1,26,27]. There is evidence that pseudopyloric metaplasia is a precursor for IM [28,29]. Estimates of the magnitude of the risk vary widely in the published literature [30-36]. A meta-analysis of 27 studies that included a total of 22417 patients showed that the calculated pooled gastric cancer incidence rate was 0.27 percent per person-year and the overall gastric cancer relative risk in PA was 6.8 (95% CI 2.6 to 18.1) [36]. However, patients included in these studies may have had low vitamin B12 serum levels due to conditions other than autoimmune gastritis. A subsequent retrospective study of 150 patients diagnosed with AMAG on endoscopic gastric biopsy, found a high prevalence (5.3 percent) and incidence (14.2 cases per 1000 person-years) of gastric adenocarcinoma, far exceeding that of the general population (0.073 cases per 1000 person-years) [37].

Environmental metaplastic atrophic gastritis

Epidemiology and risk factors — Environmental metaplastic atrophic gastritis (EMAG) is thought to be due to the adverse effects of environmental factors, such as *H. pylori* infection and perhaps dietary constituents, on the gastric mucosa. However, few studies have attempted to identify risk factors for EMAG as confirmed by biopsy. Instead, in such epidemiologic studies, individuals with EMAG are usually identified indirectly by screening with serum pepsinogen concentrations. A shortcoming of this approach is that *H. pylori* infection, which is often common in the populations under study, increases serum pepsinogen levels [38,39]. As a result, the prevalence of EMAG is most likely to have been underestimated using serum pepsinogen screening [40]. However, the correlation between a low serum pepsinogen I level and histologic demonstration of EMAG is well-documented, and pepsinogen determination is the best available tool for population studies of this disorder [1,41,42]. (See "Gastritis: Etiology and diagnosis", section on 'Additional tests in selected patients'.)

EMAG and intestinal-type gastric cancer are closely associated pathologically, clinically, and epidemiologically. Thus, similar contributing factors are proposed for the two conditions.

Helicobacter pylori — *H. pylori* plays a pivotal role in the development of EMAG and gastric adenocarcinoma. Histopathologic studies indicate that chronic *H. pylori* infection progresses over decades through stages of chronic superficial gastritis, gastric atrophy, IM, dysplasia, and cancer [1,27,43]. The mechanisms whereby some patients with *H. pylori* infection develop IM and carcinoma, while others do not, are multifactorial and likely involve an interplay

of bacterial virulence factors and host susceptibility factors. (See "Association between Helicobacter pylori infection and gastrointestinal malignancy".)

Dietary and other risk factors — Numerous studies have investigated possible dietary causes of EMAG (ie, high salt intake), with inconclusive or inconsistent results [44]. Other possible risk factors include cigarette smoking, alcohol consumption, and chronic bile reflux [1].

Clinical and laboratory features — Patients with EMAG may be asymptomatic, but many of them have dyspepsia. In contrast to AMAG, fasting serum gastrin levels are not markedly elevated in EMAG. Parietal cell and intrinsic factor autoantibodies and PA are absent. (See 'Laboratory testing' below.)

Cancer risk — Patients with EMAG are at a 10- to 15-fold increased risk for gastric cancer, particularly the intestinal type [1,27]. It is hypothesized that increased macrophage-derived inflammatory drivers present in EMAG may be responsible for the progression from metaplasia to carcinoma in this population [28]. (See 'Cancer risk' above and 'Histologic features of AMAG and EMAG' below.)

DIAGNOSIS

The diagnosis of metaplastic (chronic) atrophic gastritis is based on the histologic evaluation of gastric biopsies which demonstrate atrophy of the gastric mucosa with the loss of glandular cells and their replacement by metaplastic epithelium.

Endoscopy and biopsy — The endoscopic appearance of chronic atrophic gastritis is normal during the early disease stages. Only in cases with extensive atrophy are the rugal folds flattened and the submucosal vessels visible. Mucosa may appear pseudopolypoid as polypoid areas represent islands of preserved oxyntic mucosa adjacent to areas of atrophy. Chromoendoscopy may be superior to white-light endoscopy [45].

Biopsy is the most reliable method to diagnose metaplastic atrophic gastritis and diagnose *H. pylori*. Assessment of the severity of gastric atrophy and determining the subtype of chronic atrophic gastritis requires gastric biopsy mapping with an adequate number of biopsies from specific sites. We perform gastric biopsy mapping on the index (initial) endoscopy in patients at increased risk of gastric cancer or in whom metaplastic atrophic gastritis is suspected (eg, pernicious anemia [PA], multiple pseudopolypoid lesions).

Biopsy mapping protocol — Biopsies of at least two topographic sites (ie, from both the antrum and the corpus, at the lesser and greater curvature of each). The incisura angularis is

especially affected by metaplasia and atrophy and should be included in the biopsy protocol (figure 1) [46]. Additional biopsies of suspicious-looking lesions should also be taken. Biopsies should include adjacent flat (nonpolypoid) antral and body mucosa. In autoimmune metaplastic atrophic gastritis (AMAG), polypoid areas may represent islands of preserved oxyntic mucosa and atrophy will be missed unless the flat area near the polyp is also sampled [11]. (See "Gastric intestinal metaplasia", section on 'Upper endoscopy with biopsy'.)

Biopsies of the antrum and body should be clearly labelled in separate vials. Biopsies of the incisura are typically included with the antral biopsies. Severe metaplastic (chronic) atrophic gastritis can deprive pathologists of the histologic clues needed to identify the origin of the biopsy. Thus, it is essential that biopsy specimens be taken from areas that endoscopists believe are unequivocally within the body/fundus or antrum, and indicate their origin clearly and place them in separate containers.

Immunostaining for endocrine cells (eg, G cells and enterochromaffin-like [ECL] cells) is also helpful for confirming that pseudopyloric metaplasia has replaced oxyntic mucosa. G cells are sparse or absent in pseudopyloric glands; in comparison, they are plentiful in biopsy specimens from the true antrum in AMAG and environmental metaplastic atrophic gastritis (EMAG), except when there is marked antral intestinal metaplasia and atrophy. The presence of ECL cell hyperplasia in patients with AMAG can help confirm that a biopsy specimen is from the body or fundus.

Histopathologic features of metaplastic (chronic) atrophic gastritis — Two main types of metaplasia are seen in chronic atrophic gastritis: pseudopyloric metaplasia and intestinal metaplasia (IM). Metaplasia, especially of the intestinal type, is virtually a universal feature of chronic atrophic gastritis and is often the most dependable defining morphologic feature. IM is a precursor lesion to dysplasia and gastric cancer.

Other types of metaplasia may be seen in chronic atrophic gastritis, including pancreatic (acinar), ciliated cell, and squamous. These are rare and of uncertain clinical significance.

Pseudopyloric metaplasia — Pseudopyloric metaplasia or spasmolytic polypeptide-expressing metaplasia refers to the replacement of parietal and chief cells in the oxyntic mucosa by epithelial mucus-secreting cells of the type normally found in the antral (ie, pyloric) mucosa [11]. These epithelial cells appear to arise from chief cells surviving in damaged oxyntic glands, rather than from stem cells [47]. The pseudopyloric glands have the coiled architecture seen in normal antrum, but are smaller, less numerous, contain less mucin, and do not have antral-type endocrine cells, especially G cells. There is evidence that pseudopyloric metaplasia is a precursor for IM [29].

Intestinal metaplasia — IM is defined by the replacement of the surface, foveolar, and glandular epithelium in the oxyntic or antral mucosa (or both) by intestinal epithelium, which is easily recognized by the presence of goblet cells [1,48,49]. IM can be further divided into three subtypes. The different subtypes of IM can be distinguished, in part, by the mucins produced by the goblet cells:

- Type I, or complete IM, is most obvious and shows fully formed small intestinal epithelium, including eosinophilic absorptive enterocytes with a defined brush border, goblet cells, and Paneth cells. The goblet cells contain predominately sialomucins.
- Type II, or incomplete IM, resembles colonic epithelium, with no defined brush border, and consists of goblet cells containing multiple irregular mucin droplets of varying sizes interspersed among gastric-type mucin cells (picture 1). The goblet cells in type II IM (as in type I) contain predominately sialomucins.
- Type III is also incomplete, and the interspersed goblet cells resemble colonic epithelium and contain predominately sulfomucins rather than sialomucins.

Type III metaplasia has been linked with gastric cancer of the intestinal type in some studies but not others [48,49]. Thus, the clinical utility of subtyping of intestinal metaplasia is unclear, but advocated by some experts [1,50]. The risk of gastric cancer appears to be greatest in patients with extensive IM involving the lesser curvature from the cardia to the pylorus or the entire stomach compared with patients with more focal or antral-predominant IM [51]. (See "Gastric intestinal metaplasia", section on 'Risk factors'.)

Histologic staging of severity — Histopathological staging of atrophic gastritis can be used to identify patients with advanced atrophic gastritis and aid in prediction of cancer risks [52-54]. High stage disease (Operative Link on Gastritis Assessment [OLGA] III/IV) is associated with a high risk of gastric cancer (table 1) [55]. Operative Link on Gastric Intestinal Metaplasia Assessment (OLGIM), another proposed staging system, shows less interobserver variability and is prognostically useful (table 2) [4,52,53]. However, OLGIM may be less sensitive than OLGA in identifying high-risk gastritis, and some experts recommend using a combination of OLGA and OLGIM for staging of chronic gastritis [56].

Determining the subtype

Histologic features of AMAG and EMAG

- **Autoimmune metaplastic atrophic gastritis** – In patients with AMAG, the metaplasia, glandular atrophy, and inflammation are confined to the gastric body and fundus. In the

early stages, referred to as active autoimmune gastritis, the oxyntic mucosa is infiltrated and destroyed by lymphocytes and plasma cells. The uneven destruction of specialized cells (ie, parietal and chief cells) within the oxyntic glands, with preserved islands of relatively normal oxyntic mucosa, leads to pseudopolyposis [57,58].

Histologic features of early/evolving AMAG seen on oxyntic mucosal biopsies include at least two of the following [59]:

- Deep/full-thickness chronic inflammation
- Oxyntic gland destruction
- Prominent eosinophils
- Intestinal/pseudopyloric/pancreatic metaplasia
- Parietal cell pseudohypertrophy

It has been suggested that autoantibodies against the hydrogen-potassium ATPase inhibit acid secretion and cause parietal cell pseudohypertrophy because of enlargement of canaliculi [8]. This is analogous to the morphologic effect of proton pump inhibitors (which block the hydrogen-potassium ATPase) on parietal cells [60].

In more advanced or end-stage AMAG, gross examination of the stomach by endoscopy or contrast radiography may demonstrate absent or inconspicuous rugae in the gastric body and fundus [61]. In addition, the submucosal blood vessels may be endoscopically visible through the thin, atrophic, overlying mucosa. Atrophy and metaplasia are usually absent in the antrum in AMAG.

In end-stage AMAG, metaplastic glands completely or almost completely replace oxyntic glands. In extreme cases, the mucosa becomes villiform, closely resembling normal small intestine. The epithelial cells may also appear megaloblastic in patients who have coexisting untreated PA with vitamin B12 deficiency. Nodular or linear ECL cell hyperplasia may be evident.

The proportions of pseudopyloric metaplasia versus IM within the body and fundus vary widely among patients with AMAG, and either form can predominate. This variability must be taken into account when obtaining and interpreting gastric biopsy specimens. Correct anatomic localization of the biopsy to the fundus/body or antrum requires that the endoscopist provide accurate information about the biopsy sites. (See 'Endoscopy and biopsy' above.)

Metaplasia is usually absent or only slight in the antrum in patients with AMAG, but changes consistent with reactive gastropathy are often present for unclear reasons.

- **Environmental metaplastic atrophic gastritis** – The principal pathologic features in EMAG are multiple, focally distributed areas of atrophy, metaplasia, and inflammation. As a rule, these changes are most heavily concentrated in the antrum, but the location may vary depending upon the stage of the disease. Changes may be more evident along the lesser curvature at the junction of the body and antrum (ie, the transitional zone) in patients with mild or early disease. In severe or advanced disease, metaplastic epithelium can almost completely replace the normal antral mucosa.

  The progression from early to advanced stages of EMAG is often reflected by proximal migration of the transitional zone, which can be demonstrated by endoscopic biopsy and in resection specimens [62]. Oxyntic mucosa (ie, mucosa of the body and fundus) adjacent to the transitional zone is progressively replaced by intestinal and pseudopyloric metaplastic mucosa. In addition, the intact oxyntic mucosa may be thinned and have a reduced number of parietal cells. These changes need to be considered when trying to make a pathologic distinction between EMAG and AMAG on gastric biopsy specimens. A white villiform pattern may be visible endoscopically, particularly using advanced imaging modalities such as narrow-band imaging [63].

  Gastric biopsy specimens may show IM in a single or a few nests of glands. We suggest a diagnosis of EMAG should **not** be made from biopsy specimens unless at least 20 percent of the available antral or transitional mucosa is replaced by metaplastic glands, or there is unequivocal glandular atrophy. If metaplasia involves less than 20 percent of the mucosa, the extent and severity should be quantitated in the pathology report. Providers should recognize, however, that the presence of intestinal metaplasia on gastric histology implies the diagnosis of atrophic gastritis because intestinal metaplasia is the result of underlying atrophic mucosa [64].

Laboratory testing — Serologic testing for both anti-intrinsic factor and antiparietal cell antibodies and fasting gastrin levels are recommended as an adjunct to the histologic diagnosis of AMAG. Antibodies to intrinsic factor are highly specific for AMAG but lack sensitivity [59]. Antibodies against parietal cells have lower specificity but are approximately 80 percent sensitive. A combination of the two tests, in conjunction with an elevated fasting serum gastrin level, can support the diagnosis of AMAG in patients with of early/evolving histologic features.

Low serum pepsinogen I levels or/and a low pepsinogen I/II ratio is a non-invasive test for detecting patients with advanced stages of metaplastic (chronic) atrophic gastritis (EMAG and AMAG) [45]. (See 'Patients with advanced atrophic gastritis' below.)

MANAGEMENT

Endoscopic surveillance in selected patients — Endoscopic surveillance in patients with metaplastic (chronic) atrophic gastritis is controversial and has not been uniformly recommended [45,65].

Patients with advanced atrophic gastritis — Recommendations for endoscopic surveillance in patients with metaplastic (chronic) atrophic gastritis are based on the severity of atrophy, extent of intestinal metaplasia, and risk factors for gastric cancer (eg, family history of gastric cancer).

- In patients with advanced stages of atrophic gastritis (severe atrophic changes **or** intestinal metaplasia in both antrum and corpus, Operative Link on Gastritis Assessment/Operative Link on Gastric Intestinal Metaplasia Assessment III/IV) without a family history of gastric cancer, we suggest endoscopic surveillance every three years.

- Patients with advanced stages of atrophic gastritis and with a family history of gastric cancer may benefit from a more intensive follow-up (eg, every one to two years after diagnosis).

For patients with mild to moderate atrophy restricted to the antrum, surveillance is not recommended as evidence to support it are lacking [45]. Low pepsinogen I serum levels or/and a low pepsinogen I/II ratio, particularly when associated with *H. pylori*-negative serological status, may identify patients at higher risk of gastric cancer to whom endoscopy should be offered, however the frequency of such testing is uncertain [45].

Our recommendations are consistent with 2019 European Society of Gastrointestinal Endoscopy (ESGE) guidelines on the management of epithelial precancerous conditions and lesions in the stomach [45]. The American Society for Gastrointestinal Endoscopy (ASGE) 2015 guidelines do not recommend surveillance in all patients with gastric intestinal metaplasia, but state that patients with gastric intestinal metaplasia who are at increased risk of gastric cancer due to ethnic background or family history may benefit from screening [65].

Patients with pernicious anemia/autoimmune metaplastic atrophic gastritis — In patients with pernicious anemia, an upper endoscopy should be performed to identify prevalent lesions (carcinoid tumors and gastric cancer) at the time of diagnosis and to stage the severity of autoimmune metaplastic atrophic gastritis (AMAG). (See 'Biopsy mapping protocol' above and 'Histologic staging of severity' above.)

While the 2015 ASGE guidelines do not recommend routine endoscopic surveillance after an initial endoscopic evaluation, we suggest endoscopic follow-up every three to five years in patients with AMAG [45,66]. However, the effectiveness of endoscopy in improving outcomes for patients with pernicious anemia is unclear. Our recommendations are consistent with 2019 ESGE guidelines [45].

Eradication of H. pylori — There is no specific treatment for metaplastic (chronic) atrophic gastritis. The offending agent (eg, *H. pylori*), if identified, should be eliminated as early as possible. Eradication of *H. pylori* may lead to partial regression of atrophic gastritis. Whether eradication of *H. pylori* can affect the natural history of gastric IM and its associated cancer risk is uncertain. *H. pylori* eradication before the development of extensive gastric IM may be effective in reducing gastric cancer incidence, but there may be a point of no return during the sequence of *H. pylori*-induced carcinogenesis, coinciding with the presence of extensive metaplastic (chronic) atrophic gastritis [67-70]. (See "Association between Helicobacter pylori infection and gastrointestinal malignancy" and "Gastric intestinal metaplasia", section on 'General measures in all patients'.)

Additional testing — In addition to the evaluation for *H. pylori*, patients with atrophic gastritis should be screened for other treatable conditions, such as B12 and iron deficiency [64].

SUMMARY AND RECOMMENDATIONS

- The term metaplastic (chronic) atrophic gastritis, also referred to as gastric atrophy, is used to describe a form of chronic gastritis that, in addition to inflammation, is associated with mucosal thinning, loss of specialized cells in gastric glands, and changes in epithelial cell types (ie, metaplasia). Metaplastic (chronic) atrophic gastritis includes two main subtypes: autoimmune and environmental metaplastic atrophic gastritis (AMAG and EMAG). Although the AMAG and EMAG may be pathogenetically and clinically distinct, they often share histologic features and may overlap clinically. (See 'Definition' above and 'Subtypes' above.)

- AMAG is a form of metaplastic (chronic) atrophic gastritis that results in the replacement of the normal oxyntic mucosa in the gastric corpus by atrophic and metaplastic mucosa, leading to a corpus predominant atrophic gastritis, reduced or absent acid and pepsin production and loss of intrinsic factor which may progress to a severe form of vitamin B12-deficiency anemia known as pernicious anemia (PA). Laboratory abnormalities that are associated with AMAG include hypergastrinemia, iron deficiency anemia, antibodies to parietal cells and intrinsic factor, and vitamin B12 deficiency. Patients with AMAG have an

increased risk for gastric neuroendocrine tumors and gastric adenocarcinoma. (See 'Autoimmune metaplastic atrophic gastritis' above.)

- EMAG is thought to be due to the adverse effects of environmental factors, such as *H. pylori* infection and perhaps dietary constituents, on the gastric mucosa. Patients with EMAG may be asymptomatic, but many of them have dyspepsia. In contrast to AMAG, fasting serum gastrin levels are not markedly elevated in EMAG, and autoantibodies to parietal cell and intrinsic factor and PA are absent. (See 'Environmental metaplastic atrophic gastritis' above.)

- The diagnosis of metaplastic (chronic) atrophic gastritis is based on the histologic evaluation of gastric biopsies which demonstrate atrophy of the gastric mucosa with the loss of glandular cells and their replacement by metaplastic epithelium. Assessment of the severity of gastric atrophy and determining the subtype of chronic atrophic gastritis requires gastric biopsy mapping with an adequate number of biopsies from specific sites (figure 1). (See 'Diagnosis' above.)

- AMAG is confined to the gastric body and fundus. Mucosal changes in patients with EMAG affect both the body/fundus and the antrum in a multifocal distribution, but with heaviest involvement of the antrum. Serologic testing for both anti-intrinsic factor and antiparietal cell antibodies and fasting gastrin levels should be performed as an adjunct to the histologic diagnosis of AMAG. (See 'Determining the subtype' above.)

- There is no specific treatment for metaplastic (chronic) atrophic gastritis. The offending agent (eg, *H. pylori*), if identified, should be eliminated as early as possible. (See 'Eradication of H. pylori' above.)

- The risk of gastric cancer in patients with metaplastic (chronic) atrophic gastritis is uncertain and probably does not warrant routine surveillance in patients with mild to moderate atrophy restricted to the antrum. Exceptions include patients with advanced stages of atrophic gastritis (Operative Link on Gastritis Assessment /Operative Link on Gastric Intestinal Metaplasia Assessment III/IV) and those with PA. (See 'Endoscopic surveillance in selected patients' above.)

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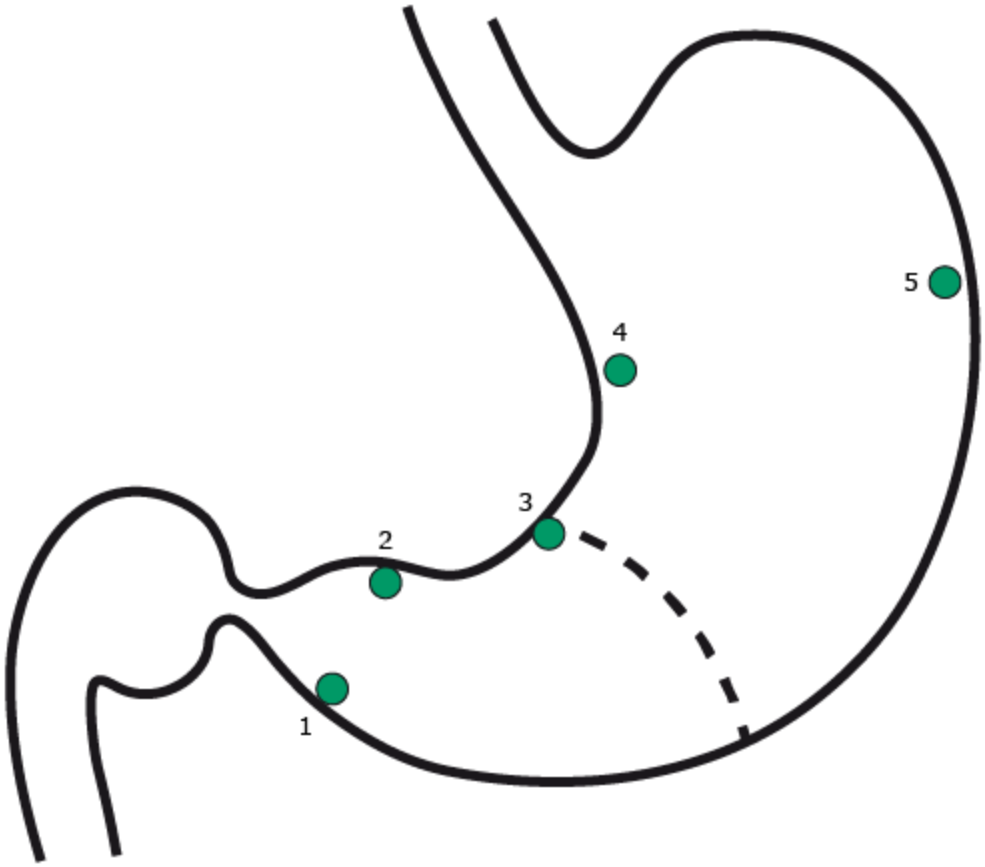
Topic 30 Version 23.0

GRAPHICS

Gastric biopsy mapping protocol



Gastric biopsies should be obtained from the following sites:

(1) Antrum, greater curvature, within 3 to 5 cm of pylorus

(2) Antrum, lesser curvature, within 3 to 5 cm of pylorus

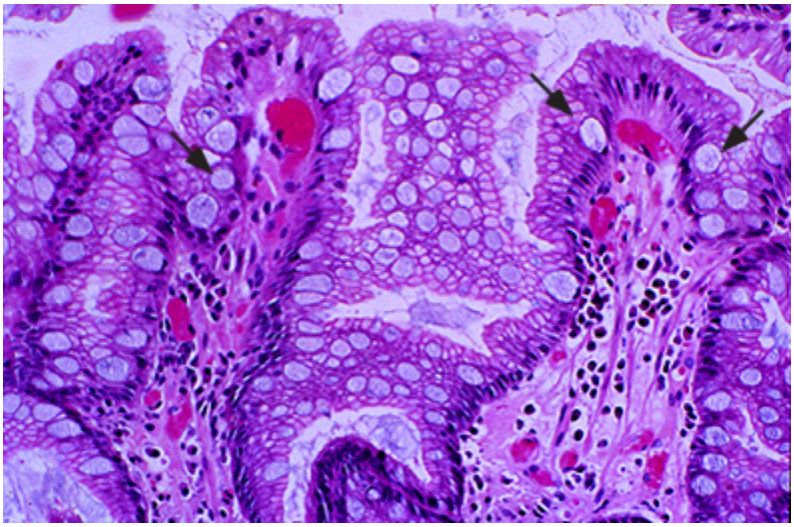
(3) Incisura angularis

(4) Corpus, lesser curvature

(5) Corpus, greater curvature

Graphic 90132 Version 2.0

Incomplete intestinal metaplasia

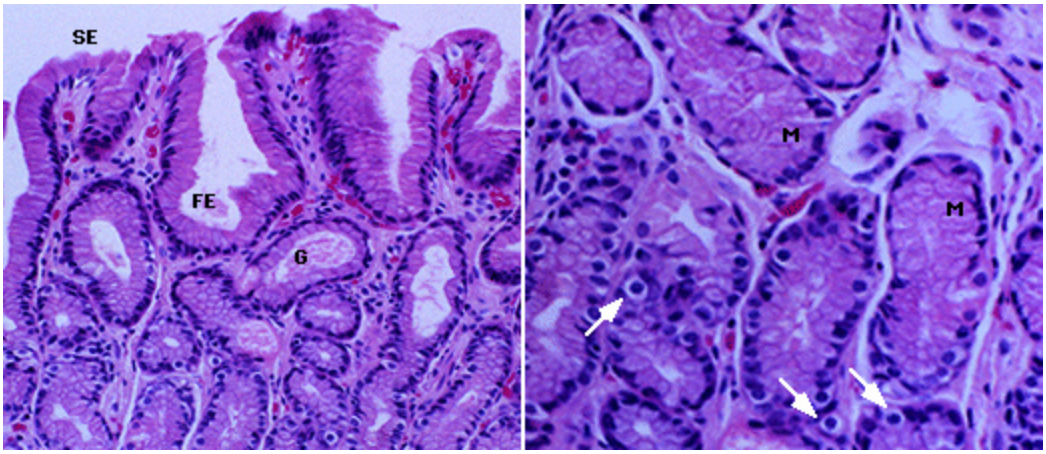


High power view (H&E stain) of chronic atrophic gastritis with incomplete intestinal metaplasia showing metaplastic goblet cells in the surface and foveolar epithelium (arrows).

Courtesy of Robert Odze, MD.

Graphic 64199 Version 3.0

Normal gastric antrum



Left panel: Normal surface (SE) and foveolar epithelium (FE) and glands (G). Right panel: Higher power view of the glands shows mucous cells (M) and gastrin-secreting endocrine cells (arrows).

Courtesy of Robert Odze, MD

Graphic 79895 Version 1.0

OLGA staging system for identifying patients with metaplastic (chronic) atrophic gastritis who are at high risk for evolution to gastric cancer

Stage 0	Scores of 0 (no atrophy) in corpus and antrum
Stage I	Score of 1 (mild atrophy) in corpus with score of 0 or 1 in antrum, **or** score of 0 in corpus and score of 1 in antrum
Stage II	Score of 2 (moderate atrophy) or 3 (severe atrophy) in corpus with score of 0 in antrum, **or** score of 2 in corpus with score of 1 in antrum, **or** score of 0 or 1 in corpus with score of 2 in antrum
Stage III	Score of 3 in corpus with score of 1 in antrum, **or** score of 2 in corpus and 2 in antrum, **or** score of 0 or 1 in corpus with score of 3 in antrum
Stage IV	Scores of 3 in corpus and antrum, **or** score of 3 in corpus and 2 in antrum or score of 2 in corpus and 3 in antrum

OLGA: Operative Link for Gastritis Assessment.

Original table modified for this publication. From: Rugge M, Correa P, DiMario F, et al. OLGA staging for gastritis: A tutorial. Dig Liver Dis 2008; 40:650. Table used with the permission of Elsevier Inc. All rights reserved.

Graphic 121370 Version 2.0

OLGIM staging system for identifying patients with metaplastic (chronic) atrophic gastritis who are at high risk for evolution to gastric cancer

Stage 0	Scores of 0 (no IM) in corpus and antrum
Stage I	Score of 1 (mild IM) in corpus with score of 0 or 1 in antrum, **or** score of 0 in corpus and score of 1 in antrum
Stage II	Score of 2 (moderate IM) or 3 (severe IM) in corpus with score of 0 in antrum; score of 2 in corpus with score of 1 in antrum; **or** score of 0 or 1 in corpus with score of 2 in antrum
Stage III	Score of 3 (severe IM) in corpus with score of 1 or 2 in antrum, **or** score of 0 or 1 in corpus with score of 3 in antrum
Stage IV	Scores of 3 in corpus and antrum, **or** score of 3 in corpus and 2 in antrum or score of 2 in corpus and 3 in antrum

IM: intestinal metaplasia.

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Graphic 116254 Version 1.0

Contributor Disclosures

Pamela J Jensen, MD No relevant financial relationship(s) with ineligible companies to disclose. **Mark Feldman, MD, MACP, AGAF, FACG** No relevant financial relationship(s) with ineligible companies to disclose. **J Thomas Lamont, MD** Equity Ownership/Stock Options: Allurion [Weight loss]. Consultant/Advisory Boards: Teledoc [Gastrointestinal diseases]. All of the relevant financial relationships listed have been mitigated. **Shilpa Grover, MD, MPH, AGAF** No relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

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