Autoimmune Gastritis in Type 1 Diabetes: A Clinically Oriented Review

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Autoimmune Gastritis in Type 1 Diabetes: A Clinically Oriented Review

Christophe E. M. De Block, Ivo H. De Leeuw, and Luc F. Van Gaal

Department of Diabetology-Endocrinology, Antwerp University Hospital and University of Antwerp, B-2650 Edegem, Belgium

Context: Autoimmune gastritis and pernicious anemia are common autoimmune disorders, being present in up to 2% of the general population. In patients with type 1 diabetes or autoimmune thyroid disease, the prevalence is 3- to 5-fold increased. This review addresses the epidemiology, pathogenesis, diagnosis, clinical consequences, and management of autoimmune gastritis in type 1 diabetic patients.

Synthesis: Autoimmune gastritis is characterized by: 1) atrophy of the corpus and fundus; 2) autoantibodies to the parietal cell and to intrinsic factor; 3) achlorhydria; 4) iron deficiency anemia; 5) hypergastrinemia; 6) pernicious anemia may result from vitamin B12 deficiency; and 7) in up to 10% of patients, autoimmune gastritis may predispose to gastric carcinoid tumors or adenocarcinomas. This provides a strong rationale for screening, early diagnosis, and treatment. The management of patients with autoimmune gastritis implies yearly determination of gastrin, iron, vitamin B12 levels, and a complete blood count. Iron or vitamin B12 should be supplemented in patients with iron deficiency or pernicious anemia. Whether regular gastroscopic surveillance, including biopsies, is needed in patients with autoimmune gastritis/pernicious anemia is controversial. The gastric carcinoids that occur in these patients generally do not pose a great threat to life, whereas the danger of developing carcinoma is controversial. Nevertheless, awaiting a consensus statement, we suggest performing gastroscopy and biopsy at least once in patients with autoantibodies to the parietal cell, iron-, or vitamin B12-deficiency anemia, or high gastrin levels.

Conclusion: The high prevalence of autoimmune gastritis in type 1 diabetic patients and its possible adverse impact on the health of the patient provide a strong rationale for screening, early diagnosis, periodic surveillance by gastroscopy, and treatment. (J Clin Endocrinol Metab 93: 363–371, 2008)
Definition and Diagnosis of Autoimmune Gastritis

Autoimmune gastritis affects the parietal cell-containing gastric corpus and fundus with sparing of the antrum (8, 18). PCA, targeted against gastric H⁺/K⁺ ATPase, are detected in 60–85% and intrinsic factor antibodies in 30–50% of patients with autoimmune gastritis (5, 19).

Besides pernicious anemia, iron deficiency anemia is frequently observed (9, 10). Furthermore, autoimmune gastritis is characterized by hypo- or achlorhydria, high serum gastrin, and low pepsinogen I concentrations (20, 21). Chronic hypergastrinemia causes the ECL cells in the oxyntic mucosa to undergo hyperplasia (22), which may progress toward dysplasia and gastric carcinoid tumors (11, 21) (Fig. 1).

PCA are detected by immunofluorescence staining of the cytoplasm of gastric parietal cells (23). However, Karlsson et al. (24) showed that the ELISA to detect gastric H⁺/K⁺ ATPase antibodies is 10-fold more sensitive than the indirect immunofluorescence technique and has a high specificity. Current ELISAs have a sensitivity and specificity of respectively 85–93% and 80–85%. PCA are detected 60–90% of patients with autoimmune gastritis and/or pernicious anemia (1, 8, 23).

The recognition of antibodies to intrinsic factor derives from the work of Taylor et al. (25) and Schwartz (15). Two types of autoantibodies bind to intrinsic factor (AIF). Type I AIF block the binding of vitamin B12 to intrinsic factor, thereby preventing the transport of vitamin B12 from the stomach to its absorption site in the terminal ileum. Type I AIF are demonstrable in 70% of patients with pernicious anemia (24). Type II autoantibodies do not interfere with vitamin B12 transport. They can be found in 30–40% of patients with pernicious anemia.

The destruction of H⁺/K⁺ ATPase-containing parietal cells results in hypo- or achlorhydria. This can be measured using 24-h gastric pH-metry or after stimulation with pentagastrin. Hypochlorhydria is defined as a maximal acid output less than 15 mmol H⁺/h after injection of pentagastrin. A progressive decrease in acid secretion in the case of autoimmune gastritis with a decreased parietal cell mass has been found (21, 26, 27). Total achlorhydria is diagnostic of pernicious anemia. Achlorhydria interrupts the negative feedback of somatostatin on antral gastrin-producing cells causing hypergastrinemia (28). Fasting serum gastrin levels correlate negatively with peak acid output, and positively with the degree of corpus atrophy (21, 29) and with PCA levels (21). Low serum pepsinogen I levels, resulting from destruction of chief cells or zymogenic cells, are also characteristic of autoimmune gastritis (20, 30, 31).

Endoscopy and Pathology

On endoscopy, the affected corpus and fundus mucosa appears shiny and red because of the visibility of submucosal blood vessels. The stomach wall thins, and the rugal folds flatten or disappear. In biopsy specimens, lymphocytic infiltrates are present in the submucosa and lamina propria (19, 21). In the next stage, there is a marked reduction in the number of oxyntic glands, parietal and zymogenic cells, followed by replacement of normal glands by glandular structures lined with mucus-containing cells resembling those of the small bowel mucosa (intestinal metaplasia) (Fig. 1). A proliferation of ECL cells in the oxyntic mucosa (22), due to sustained hypergastrinemia, can be seen, which may progress in a small proportion of patients toward gastric carcinoid tumors (11, 32–34).

Epidemiology

In the general population, there is an age-related increase in the prevalence of PCA, from 2.5% in the third decade to 12% in the eighth decade (1, 2). The prevalence is even higher in subjects affected by another autoimmune disorder. In type 1 diabetes, PCA are found in 10–15% of children and 15–25% of adults (4, 5, 35–37) (Fig. 2). The respective prevalences of autoimmune gastritis and pernicious anemia in the general population are 2 and 0.15–1% (2, 3, 38, 39), compared with respectively 5–10% and 2.6–4% in type 1 diabetes (5, 21, 38, 40, 41).

Iron deficiency anemia is present in 20–40% of patients with autoimmune gastritis (10, 42), whereas pernicious anemia can be diagnosed in up to 15–25% of patients (43). The progression of autoimmune gastritis to pernicious anemia is likely to span 20–30 yr (44).

Finally, gastric carcinoid tumors are observed in 4–9% of patients with autoimmune gastritis/pernicious anemia, which is 13 times more frequent than in controls (11, 32–34, 45). Patients with autoimmune gastritis/pernicious anemia also have a 3- to

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**TABLE 1. Characteristics of autoimmune gastritis**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrophic fundus and corpus, antrum spared</td>
<td>PCA and AIF</td>
</tr>
<tr>
<td>Hypo/achlorhydria</td>
<td>Hypergastrinemia</td>
</tr>
<tr>
<td>Low serum pepsinogen I concentrations</td>
<td>Vitamin B12 deficient megaloblastic (pernicious) anemia</td>
</tr>
<tr>
<td>Iron deficiency anemia</td>
<td>Increased chromogranin A levels: ECL cell hyperplasia and gastric carcinoids</td>
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<tr>
<td>Association with endocrine organ-specific autoimmune disease</td>
<td>Type 1 diabetes mellitus</td>
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<tr>
<td>Type 1 diabetes mellitus</td>
<td>Hashimoto’s thyroiditis, Graves’ disease</td>
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<tr>
<td>Addison’s disease</td>
<td>Autoimmune polyglandular syndrome types II and III</td>
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6-fold increased gastric cancer risk, ranging from 0.9–9% (11, 32, 34, 46–48).

Pathogenesis

The target autoantigens in autoimmune gastritis are the 100-kd catalytic α-subunit and the 60- to 90-kd glycoprotein β-subunit of the gastric H⁺/K⁺ ATPase (49, 50). Autoantibodies to the PCA and to their secretory product, intrinsic factor, are present in the serum and in gastric juice. The titer of PCA correlates with the severity of corpus atrophy and is inversely proportional to the concentration of parietal cells (21, 29). CD4+ T cells recognizing parietal cell H⁺/K⁺ ATPase mediate autoimmune gastritis. During normal cell turnover, parietal cells release H⁺/K⁺ ATPase, which may result in its selective uptake and processing by antigen-presenting cells (51). Alternatively, Helicobacter pylori infection may play an initiating role in the pathogenesis of autoimmune gastritis and pernicious anemia (52–55) by inducing autoreactive T cells through gastric H⁺/K⁺ ATPase-H. pylori molecular mimicry at the T-cell level (53, 54), epitope spreading, and bystander activation. B cells produce autoantibodies to gastric H⁺/K⁺ ATPase and to their secretory product, intrinsic factor with help from activated CD4+ T cells (50). Finally, parietal cell loss from the gastric mucosa may result from CD4+ T cells initiated perforin-mediated cytotoxicity or Fas-FasL apoptosis (55).

Regardless of whether PCA are pathogenic or not, their presence provides a convenient diagnostic probe for autoimmune atrophic gastritis. A precise understanding of the pathogenesis of autoimmunity may lead to rational therapeutic strategies directed toward restoration of tolerance or impeding the progres-
sion of autoimmunity. Whether *H. pylori* could trigger autoimmune gastritis or not remains controversial. However, should this be the case, *H. pylori* eradication could prevent autoimmune gastric disease. Currently, it is recommended that *H. pylori* infection should be tested and treated in patients with gastric atrophy, intestinal metaplasia/dysplasia, and hypo- or achlorhydria.

**Predisposing Factors**

Accurate prediction of autoimmune diseases (autoimmune gastritis) using antibodies (PCA and AIF), and demographic (age, gender) and genetic [human leukocyte antigen (HLA) class II, cytotoxic T lymphocyte-associated protein 4, others] risk factors might help to prevent these diseases. Primary prevention includes avoiding those environmental factors (*H. pylori*) that might trigger the disease. Secondary prevention consists of modulating the destructive process (CD4⁺ T cells mediating oxyntic gland atrophy) before the onset of clinical symptoms [iron deficiency, pernicious anemia, and (pre)malignant gastric lesions]. However, at present, there is no consensus on whom to screen or at what frequency.

**Demographic factors**

Advancing age is a risk factor that has been associated with PCA positivity. In the general population, PCA positivity increases from 2.5% in the third decade to 12% in the eighth decade (1, 2). In type 1 diabetic patients, PCA are present in 10–15% of children and 15–25% of adults (41). Some authors (4, 35) report a female preponderance for PCA positivity, although this has not been consistently observed (37, 41).

**Endocrine and immunological factors**

Autoimmune gastritis is frequently accompanied by other autoimmune diseases, including type 1 diabetes (5) and autoimmune thyroid disease (Hashimoto’s thyroiditis and Graves’ disease) (6, 38, 56). Autoimmune gastritis is also part of the autoimmune polyglandular syndrome type 3 (57). Pernicious anemia occurs in up to 4% of type 1 diabetic patients (5, 40), 2–12% of patients with autoimmune thyroid disease (6, 58), 6% of those with Addison’s disease, 9% of those with primary hyperparathyroidism, and 3–8% of those with vitiligo (1) (Fig. 3).

In patients with type 1 diabetes, immunological risk factors that have been associated with PCA positivity include persistent islet cell antibody positivity (35, 36), glutamic acid decarboxylase-65 antibody positivity (41, 59), and thyroid peroxidase autoantibody positivity (41, 59). The association with glutamic acid decarboxylase-65 antibodies might be explained by the fact that glutamate decarboxylase-65 is not only present in the pancreas and brain but can also be found in the thyroid gland and stomach. PCA are more frequent in type 1 diabetic patients than in their first-degree relatives, even after HLA matching, suggesting that the diabetic condition itself plays an important role (60).

PCA can be found in 22% of patients with Graves’ disease and 32–40% of those with autoimmune hypothyroidism (61–64). Pernicious anemia is present in 2% of patients with Graves’ disease and 4–12% of those with Hashimoto’s thyroiditis (6, 61, 62). Moreover, up to 50% of patients with autoimmune gastritis/pernicious anemia show thyroid peroxidase autoantibodies (21, 62). These results support the recommendation of screening patients with autoimmune thyroid disease for autoimmune gastritis. The close association between autoimmune thyroid disease and autoimmune gastritis suggests an immunological cross-reaction. In this respect, one group found a homologous 11-residue peptide in thyroid peroxidase and the gastric parietal cell antigen, the H⁺/K⁺ ATPase (65).

**Immunogenetic factors**

A genetic predisposition to autoimmune gastritis/pernicious anemia has been suggested by its familial occurrence, and the presence of PCA and autoimmune gastritis in 20–30% of relatives of patients with pernicious anemia (1, 5, 58).

HLA haplotypes can partly determine the tissue to which an autoimmune process develops. However, the evidence of a link between pernicious anemia and particular HLA haplo/genotypes is weak. Associations of pernicious anemia with HLA DR4, with DR2 (66, 67) and DR5 haplotypes (5), have been reported. In type 1 diabetic patients, a weak association between PCA pos-
vitamin B12 for 1 wk, followed by monthly injections of 100 
μg/d for 1 month, and then 1000 μg/wk for 1 month, and then 
by monthly im injection of 1000 μg is proposed (19, 88).

Environmental factors

_H. pylori_ might be implicated in the induction of autoimmune gastritis (52, 53, 55). This hypothesis is supported by studies reporting a high prevalence of _H. pylori_ seropositivity and a low prevalence of positive _H. pylori_ staining in subjects with atrophic corpus gastritis (69–72). Furthermore, the finding of gastric autoantibodies in 20–50% of _H. pylori_-infected patients and reports of a positive correlation between gastric autoantibodies and antibodies to _H. pylori_ in patients with autoimmune gastritis/pernicious anemia (71, 73–76) suggest that chronic _H. pylori_ infection is linked with gastric autoimmunity. However, a correlation between _H. pylori_ and PCA has not been reported in all studies (39, 77, 78). Moreover, others found no or a negative link between _H. pylori_ and atrophic corpus gastritis (79). On the other hand, _H. pylori_ eradication in patients who have antigastric antibodies leads to the loss of those antibodies in some subjects (80). These data add new information to the possible reversibility of gastric mucosa atrophy.

Clinical Presentation

Iron deficiency anemia

Approximately 20–30% of patients with iron deficiency anemia with no evidence of gastrointestinal blood loss may have autoimmune gastritis (9, 42, 81). Iron deficiency anemia may develop in advance of pernicious anemia, or both conditions may coexist (82, 83).

Examination of the peripheral blood shows a hypochromic, microcytic anemia, decreased serum iron levels (male < 50 μg/dl and female < 40 μg/dl), a transferrin saturation less than or equal to 20%, and a decreased ferritin concentration (male < 20 μg/liter and female < 12 μg/liter). However, these parameters are influenced by gender, acute phase responses, acute liver injury, or malnutrition (84). A Perls staining of a bone marrow smear showing absence of iron that is stored as hemosiderin in the reticuloendothelial cells of the bone marrow is definitive proof of iron deficiency, but invasive. The soluble transferrin receptor has been proposed as the best noninvasive and sensitive marker of functional iron status because of its small day-to-day variation, and independence of inflammation, liver parenchymal, and hormonal status (10, 85).

Symptoms and signs of iron deficiency include pallor, fatigue, reduced exercise or work performance, and palpitations, reduced learning ability, defects in immunity, and even an increased frequency of premature births (84). Early detection and treatment of iron deficiency and the conditions that are at its origin could significantly reduce morbidity. Treatment consists of oral supplementation of 600 mg FeSO₄. Alternatively, iron can be infused iv (84).

The iron status of an individual depends on the amount of dietary iron, its bioavailability, and the extent of iron losses (84). Although no absorption of iron occurs in the stomach, the gastric hydrochloric acid plays a significant role. Hydrochloric acid not only helps to remove protein-bound iron by protein denaturation but also helps in the reduction of ferric iron (Fe³⁺) to the ferrous state (Fe²⁺), necessary to improve absorption (86). Decreased gastric acidity, due to chronic autoaggression to parietal H⁺/K⁺ ATPase in autoimmune gastritis (27), may reduce the availability of iron for absorption and lead to iron deficiency anemia (9, 10).

Pernicious anemia

Pernicious anemia can be considered an end stage of autoimmune gastritis (44). Approximately 10–15% of PCA-positive patients and up to 25% of those with autoimmune gastritis present with pernicious anemia (1, 5).

Two mechanisms are responsible for vitamin B12 malabsorption in patients with pernicious anemia. First, the progressive loss of parietal cells leads to failure of intrinsic factor production and a reduction in vitamin B12 absorption. Second, intrinsic factor autoantibodies prevent the formation of the vitamin B12-intrinsic factor complex (19).

Examination of the peripheral blood reveals macrocytosis and anemia, a low serum vitamin B12 concentration, and normal folate concentration. A Schilling test, which measures vitamin B12 absorption in the presence and absence of intrinsic factor, is used to establish pernicious anemia as the cause of vitamin B12 deficiency (19).

The usual presentation of vitamin B12 deficiency is with symptoms of anemia. Gastrointestinal manifestations include a smooth and beefy red tongue (atrophic glossitis), and a predisposition to gastric tumors (see *Gastric carcinoid tumors* and *Gastric cancer*). Neurological complications include peripheral neuropathy manifested by paraesthesia and numbness usually of the legs, and cerebral manifestations such as confusion, impaired memory, and even frank psychosis (megalooblastic madness) (19, 87).

Early detection and treatment of vitamin B12 deficiency and the underlying conditions could significantly reduce morbidity. The classical treatment is by daily im injections with 100 μg vitamin B12 for 1 wk, followed by monthly injections of 100 μg vitamin B12. In severe cases, parenteral administration of 1000 μg/d for 1 wk, followed by 1000 μg/wk for 1 month, and then by monthly im injection of 1000 μg is proposed (19, 88).
Gastric carcinoid tumors

Gastric carcinoid tumors, evolving from ECL cell hyper/dysplasia induced by hypergastrinemia, may develop in 4–9% of patients with autoimmune gastritis/pernicious anemia (11, 32–34, 89). Up to 85% of gastric carcinoid tumors are associated with autoimmune gastritis/pernicious anemia (90–92). In type 1 diabetes, ECL cell proliferative changes occur in approximately 9% of PCA-positive patients and in up to 30% of those with autoimmune gastritis (93). This provides a strong rationale for screening, early diagnosis, and treatment.

The tumors are usually incidentally identified during diagnostic endoscopic evaluation for anemia. The most frequently reported symptoms include abdominal pain, flushing and diarrhea, anemia-related symptoms, and extremely rarely a carcinoid syndrome (92). Gastricopy with histological examination [immunostaining for chromogranin A (CgA) and/or neuron-specific enolase] is the most powerful diagnostic tool. However, a gastroscopy can be considered unpleasant, and is hampered by the fact that such lesions are usually not endoscopically detectable, or unevenly distributed, and may be overlooked (91, 94). Moreover, part of an increased ECL cell density in atrophic mucosa may not be true hyperplasia but rather an expression of a selective glandular atrophy sparing the ECL cells. Thus, morphology is subject to sampling error and may over- or underestimate ECL cell mass. Serum CgA measurements may indicate the presence of an increased ECL cell mass more accurately than morphological methods (95). CgA can be released into the circulation from ECL cells of the stomach (65). Its levels correlate strongly with ECL cell density in the corpus and fundus mucosa and with gastrin levels (33, 93, 95, 96). CgA has a specificity of 85–90% and a sensitivity of 70–80% in diagnosing neuroendocrine tumors. A recent study showed a sensitivity of 100% and specificity of 59% for CgA to detect ECL cell hyper/dysplasia (93). Therefore, we recommend, besides performing a gastroscopy with biopsy, measuring CgA in PCA-positive patients, particularly those with hypergastrinemia, who are at risk for developing autoimmune gastritis and, possibly, carcinoid tumors.

Gastric carcinoid tumors are relatively benign lesions, metastasizing in less than 10% of cases, and death rarely results from these tumors (92).

An algorithm for the appropriate management of patients with gastric carcinoid tumors has been proposed by Gilligan et al. (97). For autoimmune gastritis- associated carcinoid tumors less than 1 cm and/or fewer than three to five in number, expectant therapy or endoscopic removal of accessible tumors, followed by endoscopic surveillance are appropriate (11, 34, 91, 94, 97). For lesions more than 1 cm in size and/or more than five in number, antrectomy has been proposed (91, 98). Either antrectomy or endoscopic polypectomy should be followed by endoscopic surveillance at 6-month intervals, and any recurrence should be treated with surgical excision. Ferraro et al. (99) showed in a limited group of eight patients with hypergastrinemic atrophic gastritis that once a day administration of octreotide is safe and effective in reducing hypergastrinemia and associated ECL changes. In a small number of patients, a spontaneous regression has been reported (100).

Gastric cancer

A three to six times higher gastric cancer risk in patients with autoimmune gastritis/pernicious anemia has been observed in some (11, 32, 34, 46–48) but not all (101, 102) studies. The prevalence of gastric carcinoma in patients with pernicious anemia is 1–3%, and 2% of patients with gastric carcinoma have pernicious anemia (103).

Achlorhydria, overgrowth of bacteria promoting the formation of N-nitroso compounds, and a high dietary salt consumption might promote the formation of a gastric carcinoma (104, 105).

Regular endoscopic surveillance is warranted in patients with pernicious anemia (32–34). Patients with mild/moderate mucosal dysplasia should be followed endoscopically every 5 yr (32). Polyps should be removed, and adenocarcinoma should be excised. Complete surgical eradication of a gastric tumor, with resection of adjacent lymph nodes, is the only chance for a cure (106).

Management Proposal

Early detection of PCA, autoimmune gastritis, and associated pathology (Fig. 1) is important in preventing iron deficiency anemia, which may influence work capacity and cardiopulmonary status, and pernicious anemia, which can cause neurological complications and (pre)malignant gastric lesions. For type 1 diabetic patients, it seems prudent to test PCA status at the onset of diabetes and then yearly for 3 yr, then five yearly thereafter, or at any other time if there are clinical indications because the test may later become positive. Particularly those patients with positive glutamate decarboxylase-65 antibodies and thyroid peroxidase antibodies should be screened.

Treating patients with PCA and/or autoimmune gastritis implies a proper follow-up. At yearly intervals, gastrin, iron, vitamin B12 levels, and a complete blood count should be performed. Iron or vitamin B12 supplements should be given to patients with iron deficiency or pernicious anemia. It is controversial whether patients with autoimmune gastritis/pernicious anemia should be placed under a surveillance program with regular gastroscopies, including multiple gastric biopsies. The gastric carcinoids that occur in these patients generally do not pose a great threat to life, whereas the danger of developing carcinoma is controversial. Nevertheless, awaiting a consensus statement, we suggest performing gastroscopy and biopsy at least once in patients with PCA positivity, anemia, or high gastrin levels. Patients with mild to moderate mucosal dysplasia should be followed endoscopically every 5 yr (32). Polyps should be removed, and adenocarcinoma should be excised. Gastric carcinoid tumors are rare and have a far better outcome than carcinoma (92). Endoscopic surveillance at 5-yr intervals has been proposed for ECL cell hyperplasia (11), especially for those patients with high gastrin (>300 ng/liter) and CgA (>120 ng/ml) levels (93). For gastric carcinoid tumors associated with autoimmune gastritis, smaller than 1 cm and/or fewer than three, expectant therapy or endoscopic removal of accessible tumors is proposed (97).
Conclusions
Autoimmune gastritis and pernicious anemia are among the most common autoimmune diseases with respective prevalences of 2 and 0.15–1% in the general population, increasing with age. Moreover, in patients with autoimmune thyroid disease or type 1 diabetes, the prevalence is 3- to 5-fold increased.

In the clinical setting, PCA are a good marker of autoimmune gastropathy, such as iron deficiency anemia, pernicious anemia, and autoimmune gastritis. The well-known complications of these three disorders can influence the prognosis of the patient. Treating patients with PCA and/or autoimmune gastritis implies a proper follow-up. At yearly intervals, gastrin, iron, vitamin B12 levels, and a complete blood count should be performed. Moreover, both autoimmune gastritis and pernicious anemia predispose to gastric carcinoid tumors, which manifest themselves only late in the disease process. The possible adverse impact on the health of the patient provides a strong rationale for screening, periodic surveillance by gastroscopy with biopsy, early diagnosis, prevention, and/or treatment.

Understanding the current advances in autoimmune gastritis is key to the development of novel therapeutic strategies directed toward restoration of tolerance or toward impeding the progression of autoimmunity, and for making rational choices in the management of autoimmune gastropathy.

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Address all correspondence and requests for reprints to: Christophe De Block, M.D., Ph.D., Department of Diabetology-Endocrinology, Antwerp University Hospital and University of Antwerp, Wilrijkstraat 10, B-2650 Edegem, Belgium. E-mail: christophe.de.block@uza.be.

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