Autoimmune Gastropathy in Type 1 Diabetic Patients With Parietal Cell Antibodies

Histological and clinical findings

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OBJECTIVE — Approximately 15–20% of type 1 diabetic patients exhibit parietal cell antibodies (PCAs) targeting gastric H^+/K^+ATPase. We examined whether iron deficiency anemia, pernicious anemia, and autoimmune gastritis, which may predispose to gastric tumors, were more frequent in PCA^+ than in PCA^- patients.

RESEARCH DESIGN AND METHODS — Gastric biopsies from 88 consecutively recruited type 1 diabetic patients (51 men and 37 women, 47 PCA^+ and 41 PCA^-, aged 42 ± 13 years) were evaluated using the updated Sydney system. Immunostaining was done for parietal cells, B- and T-cells, enterochromaffin-like (ECL) cells, and *Helicobacter pylori* (*HP*). PCAs were assayed by indirect immunofluorescence, H^+/K^+ATPase antibodies by enzyme immunoassay, and *HP* by serology, urea breath test, and histology. Pentagastrin tests were performed in 42 subjects.

RESULTS — Autoimmune gastritis (AG) was present in 57% of PCA^+ and 10% of PCA^- cases (OR 12.5, $P < 0.0001$). PCA positivity ($\beta = 1.44$; $P = 0.04$) and hypergastrinemia ($\beta = 0.01$; $P = 0.026$), but not *HP*, age, diabetes duration, sex, and HLA-DQ type were risk factors for AG. Iron deficiency anemia (OR 3.9, $P = 0.015$), pernicious anemia (OR = 4.6, $P = 0.022$), and hypochlorhydria (OR = 20.0, $P = 0.0002$) were more frequent in AG^+ individuals. *HP* infection was present in 47 patients but did not influence corpus histology or gastrinemia. (Pre)malignant lesions were found in 26% of PCA^+ subjects: ECL cell hyperplasia in 7 AG^+ patients, comprising 1 with a gastric carcinoid tumor, and corpus intestinal metaplasia in 11 AG^+ patients, including 1 with linitis plastica.

CONCLUSIONS — PCA^+ type 1 diabetic patients should be screened for autoimmune gastritis, iron deficiency, and pernicious anemia. Particularly hypergastrinemic PCA^+ patients with autoimmune gastritis are at increased risk for (pre)malignant gastric lesions.

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Type 1 diabetes results from autoimmune destruction of insulin-secreting β-cells (1). Moreover, 15–20% of patients exhibit parietal cell antibodies (PCAs) (2–4), particularly subjects with GAD-65 antibodies and HLA-DQA1*0501-B1*0301 haplotype (5). PCAs are two to three times more frequent in these patients than in control subjects (2–4). PCAs target gastric H^+/K^+ATPase (6,7) and denote autoimmune gastritis (8–10). Chronic autoaggression to the proton pump may result in hypo/achlorhydria, hypergastrinemia, and iron deficiency anemia (11–14). PCAs may also inhibit intrinsic factor secretion, leading to pernicious anemia, which is 10 times more common in type 1 diabetic than in nondiabetic subjects (15,16). Pernicious anemia and autoimmune gastritis may predispose to gastric tumors (17–22), although this has not been consistently observed (23). Gastric adenocarcinomas develop in 1–10% of subjects with autoimmune gastritis through intestinal meta/dysplasia (17–19). Carcinoid tumors develop in 4–7% of these subjects on a background of enterochromaffin-like (ECL) cell hyperplasia induced by sustained pronounced hypergastrinemia (20,21). Recently, *Helicobacter pylori* (*HP*) has been suggested to induce autoimmune gastritis (24–26).

Determining risk factors for and early diagnosis of autoimmune gastropathy is important for the prevention/treatment of iron deficiency anemia, pernicious anemia, and (pre)malignant gastric lesions (intestinal meta/dysplasia and ECL hyper/dysplasia). To our knowledge, we are the first to study the prevalence of autoimmune gastropathy in relation to PCAs, *HP*, gastrinemia, HLA-DQ type, age, sex, and diabetes duration. We evaluated a combination of histological parameters using the updated Sydney system (27) and criteria for preatrophic autoimmune gastritis (28), with specific attention for parietal cell mass (29,30), *HP*, mucosal B- and T-cells (9), ECL cells (20), and intestinal metaplasia (27).

RESEARCH DESIGN AND METHODS

We studied 88 type 1 diabetic patients (51 men and 37 women), comprising 47 PCA^+ and 41 PCA^- subjects matched for

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Abbreviations: AG, autoimmune gastritis; AIF, antibodies to intrinsic factor; ECL, enterochromaffin-like; GADA, GAD antibody; *HP*, *Helicobacter pylori*; PCA, parietal cell antibody.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

age, sex, duration of diabetes, and metabolic control. They were consecutively recruited according to PCA status irrespective of symptoms from 399 patients (75 PCA^+ and 324 PCA^-) attending the outpatient Antwerp University diabetes clinic. All together, 63% (47 of 75) of all PCA^+ patients and 37% (41 of 110) of all eligible, matched PCA^- patients agreed to undergo gastroscopy. Every patient fulfilled the criteria of type 1 diabetes (31). No patient used antibiotics, anti-inflammatories, prokinetics, or proton pump inhibitors or had Crohn's disease, colitis ulcerosa, celiac disease, systemic lupus erythematosus, or rheumatoid arthritis. The study was approved by the local ethics committee. Each subject gave informed consent, in accordance with the Helsinki Declaration.

Methods

Islet cell antibodies (ICAs, normal level <12 Juvenile Diabetes Foundation units) were determined by indirect immunofluorescence on cryosections of human donor pancreas, GAD-65 antibodies (GADAs) (normal level <2.6% tracer bound), and tyrosine phosphatase (IA2 antigen, normal level <0.5% tracer bound) by liquid-phase radiobinding assay using Centricon-purified recombinant human ^{35}S-GAD65 and the ^{35}S-labeled intracellular domain of IA2 as tracer (32), respectively. PCAs were detected using indirect immunofluorescence on rat gastric mucosa (Medical Diagnostics California, Carlsbad, CA) (normal level <1/20 dilution) (3). This assay correlated well with the enzyme immunoassay for H^+/K^+ATPase antibodies (Varelisa, Pharmacia and Upjohn, Freiburg, Germany) (normal level <10 units/ml) ($n = 175$, $r = 0.85$, $P < 0.0001$). Antibodies to intrinsic factor (AIF) were measured by radiobinding assay (Diagnostic Products, Los Angeles, CA) (normal level <1.1). Iron deficiency anemia was defined as microcytic hypochromic anemia with a transferrin saturation ≤20% or a decreased iron (male < 8.95, female < 7.16 μmol/l) or ferritin level (male < 20, female < 12 μg/l) (13). Pernicious anemia was defined as macrocytic anemia, subnormal vitamin B12 levels, with positive AIF and/or PCA. Serum gastrin was measured by radioimmunoassay technique (Euro-Diagnostics, Malmö, Sweden) (normal level <110 ng/l), vitamin B12 (normal level 120–715 pmol/l), and erythrocyte folate levels (normal level 270-1950 nmol/l) using Simultrac-SNB RIA kit (ICN, Orangeburg, NY). HLA-DQ typing was performed as previously described (33).

Serum was assayed for *HP* IgG antibodies by enzyme-linked immunosorbent assay (Roche Diagnostics, Brussels, Belgium). ^{13}C Urea breath tests were performed as previously described (34). Antrum, corpus, and fundus biopsies were examined for *HP* colonization using modified Giemsa and/or immunostaining (35). *HP* infection was diagnosed if any test was positive. The period between urea breath test and gastroscopy was maximally 14 days.

Gastric acid secretion studies were performed in 42 patients (15 PCA^+ and 27 PCA^-) after a 12-h overnight fast using pentagastrin-stimulated acid output (6 μg/kg s.c. Pentagastrin Injection BP; Cambridge Laboratories, Newcastle upon Tyne, U.K.) (35). Hypochlorhydria was defined as a maximal acid output <15 mmol H^+/h.

Gastroscopy and histology

At upper gastrointestinal endoscopy (Olympus Videoscope GIF/Q140; Olympus, Melville, NY), at least two biopsies from fundus, corpus, antrum, and descending duodenum were taken and evaluated by two investigators, unaware of the patient's clinical and laboratory data to minimize interobserver variation. The visual analog scale of the updated Sydney system was used to evaluate inflammation (chronic infiltrate), activity (acute infiltrate), atrophy (glandular loss), intestinal metaplasia, and *HP* colonization, graded as follows: 0 = absent, 1 = mild, 2 = moderate, and 3 = severe (27). Furthermore, the distribution of lymphocytic infiltration (1 = diffuse, 2 = focal, and 3 = diffuse and focal), degree of lymphocytic destruction of oxyntic glands, and status of oxyntic glands (1 = partial atrophy and 2 = partial atrophy with preserved islets of oxyntic mucosa) (28), and the presence of ECL cells were evaluated (20). Preatrophic autoimmune gastritis includes diffuse lymphocytic infiltration of the lamina propria, focal lymphocyte-mediated destruction of oxyntic glands, and parietal cell pseudohypertrophy (28). Parietal cells were quantified as the percentage of total cells per gland, counted on four sections (fundus/corpus) stained by hematoxylin and eosin, modified Giemsa, and immunohistochemistry. Twenty glands per biopsy were evaluated (magnification ×390). Twelve sections were counted from each patient, enabling intraobserver variation to be determined. The result per patient represents the mean of these values, and the result of different groups (PCA^+ and PCA^-) represents an average of these means.

Immunostaining was performed for *HP* (polyclonal rabbit *HP* IgG antibodies, dilution 1/200; Dako, Glostrup, Denmark) (35), B-cells (CD20) (L26, M0755, 1/80; Dako), T-cells (CD45RO) (UCHL1, M0742, 1/80; Dako), chromogranin A (DAK-A3, M0869, 1/200; Dako), and H^+/K^+ATPase. Antigen retrieval by microwave pretreatment using an EDTA buffer (pH 9) was applied for immunostaining of *HP* and B- and T-cells. Incubation steps for H^+/K^+ATPase immunostaining were as follows: monoclonal mouse H^+/K^+ATPase (β-subunit) antibody (IgG1) (Clone 2,611, MA3-923, 1/4,000; Affinity Bioreagents, Golden, CO); biotinylated goat anti-mouse immunoglobulin (E0433, 1/400; Dako), streptavidine-biotinylated horseradish peroxidase (K0377, 100 μl/coupe, 20′; Dako), and 3,3′-diaminobenzidine tetrahydrochloride (HK 153–5K; BioGene, San Ramon, CA). MA3-923 binds to an epitope within amino acids 1–13 or 15–28 located on the cytoplasmic side of the β-subunit of H^+/K^+ATPase and inhibits its enzymatic activity (36).

Statistical analysis

Results were analyzed using SPSS (SPSS, Chicago, IL). Distributions of continuous data were tested for normality by Kolmogorov-Smirnov test. The unpaired *t* test, Mann-Whitney-*U* test, or ANOVA was used to determine differences between groups. Bonferroni adjustments for multiple comparisons were made. Pearson's or Spearman's rank correlation test was used. Differences in distributions of categorical data were evaluated by χ^2 or Fisher's exact test. Stepwise forward logistic regression analysis was done to assess the strength and independency of associations. A two-tailed $P < 0.05$ was considered significant.

RESULTS — We biopsied 47 PCA^+ and 41 matched PCA^- type 1 diabetic patients with a mean age of 42 ± 13 years, a disease duration of 20 ± 11 years, and an HbA_{1c} level of 7.8 ± 1.1%. ICAs were

Table 1—*Clinical and histological features in PCA$^+$ versus PCA$^-$ type 1 diabetic patients*

	PCA$^+$	PCA$^-$	*P*
n (M/F)	47 (26/21)	41 (25/16)	NS
Age (years)	41 ± 13	43 ± 13	NS
Duration of diabetes (years)	19 ± 12	22 ± 10	NS
GADA$^+$	37 (79)	23 (56)	0.038
H^+/K^+ ATPase (units/ml)	234.7 ± 325.3	7.9 ± 10.5	0.007
HP$^+$	24 (51)	23 (56)	NS
Iron deficiency anemia	15 (32)	5 (12)	0.04
Pernicious anemia	11 (23)	1 (2)	0.005
Gastrin (ng/l)	265 ± 292	127 ± 69	0.027
Hypergastrinemia (gastrin > 110 ng/l)	22 (47)	9 (22)	0.025
Hypochlorhydria (*n* tested 42)	11/15	5/27	0.0008
Maximal acid output (mmol H^+/h)	7.8 ± 7.0	16.9 ± 10.4	0.004
Autoimmune atrophic gastritis	27 (57)	4 (10)	<0.0001
HP-associated gastritis	10 (21)	17 (41)	NS
Parietal cell mass (%)	20 ± 10	29 ± 6	<0.0001
Corpus atrophy	1 (0–3)	0 (0–2)	0.02
Corpus *HP*	1 (0–3)	0 (0–2)	NS
Corpus inflammation	1 (0–2)	1 (0–2)	NS
Corpus metaplasia	0 (0–3)	0 (0–2)	NS
Corpus intestinal metaplasia	11 (23)	1 (2)	0.004
Distribution of lymphocytic infiltration	2 (0–3)	2 (0–3)	0.038
Degree of lymphocytic infiltration	2 (0–4)	2 (0–3)	NS
Lymphocytic destruction of glands	0 (0–3)	0 (0–1)	NS (0.06)
State of the oxyntic glands	0 (0–2)	0 (0–1)	0.014
State of the intact parietal cells	0 (0–1)	0 (0–0)	NS
ECL cell$^+$	7 (15)	0 (0)	0.013
B-cells (counts/mm^2)	1,461 ± 516	698 ± 379	0.031
T-cells (counts/mm^2)	645 ± 266	278 ± 147	0.032

Data are means ± SD, median (range), or *n* (%).

positive in 34%, IA2As in 40%, and GADAs in 68%. This group comprised 18 PCA$^-$ *HP*$^-$, 23 PCA$^+$ *HP*$^-$, 23 PCA$^-$ *HP*$^+$, and 24 PCA$^+$ *HP*$^+$ subjects. Intra- and interobserver variations in evaluating histological sections were minimal: 2.4 and 5.1%, respectively.

PCA status

PCAs were equally common in male and female subjects, and in particular GADA$^+$ patients were prone to exhibit PCAs (OR 2.9 [1.1–7.4], $P = 0.038$). Iron deficiency anemia (3.4 [1.1–10.3], $P = 0.04$) and pernicious anemia (12.2 [1.5–99.5], $P = 0.005$) were more frequent in PCA$^+$ than in PCA$^-$ subjects (Table 1). Women were more prone to have iron deficiency anemia than men (4.6 [1.5–13.5], $P = 0.005$). In the group of 399 patients, from which these 88 were recruited, iron-deficiency anemia (21 vs. 9%, $P = 0.0035$) and pernicious anemia (15 vs. 0.3%, $P < 0.0001$) were more prevalent in PCA$^+$ than in PCA$^-$ patients. Gastrin levels were higher ($P = 0.027$) and hypergastrinemia was more common in PCA$^+$ patients (3.1 [1.2–8.0], $P = 0.025$), but vitamin B12 and folate levels were similar. Basal ($P = 0.012$), maximal ($P = 0.004$), and peak acid output ($P = 0.011$) were lower and hypochlorhydria was more frequent (12.1 [2.7–54.3], $P = 0.0008$) in PCA$^+$ subjects. Maximal (1.7 ± 2.9 vs. 14.4 ± 10.1 mmol H^+/h, $P = 0.048$) and peak acid output (2.2 ± 3.8 vs. 21.2 ± 13.7 mmol H^+/h, $P = 0.03$) were lower in those with than without pernicious anemia.

Autoimmune atrophic gastritis was present in 57% of PCA$^+$ and 10% of PCA$^-$ subjects (OR 12.5 [3.8–40.7], $P < 0.0001$). Corpus atrophy was more severe ($P = 0.02$) and there were less parietal cells ($P < 0.0001$) in those with PCA. Interestingly, the percentage of parietal cells in glands correlated inversely with PCA titer ($r = -0.45$, $P = 0.004$) and H^+/K^+ATPase antibody level ($r = -0.51$, $P = 0.001$). Signs of preatrophic autoimmune gastritis were more frequent in PCA$^+$ patients, as documented by a more pronounced lymphocytic infiltration in corpus mucosa and partial atrophy of oxyntic glands. Concentrations of B-cells and T-cells were greater in those with PCA, with B-cells predominating. Corpus intestinal meta/dysplasia and ECL cell hyper/dysplasia were more common in PCA$^+$ patients.

HP status

HP infection was diagnosed in 47 patients with a similar prevalence in PCA$^+$ and PCA$^-$ patients (Table 1). Two-way ANOVA with PCA and *HP* status as fixed factors showed that *HP* infection did not influence iron, gastrin, and H^+/K^+ ATPase antibody levels, parietal cell mass, corpus or antrum atrophy and metaplasia, and ECL cell hyperplasia. Parameters of preatrophic autoimmune gastritis were also similar in *HP*$^+$ and *HP*$^-$ patients. Antral inflammation ($P = 0.005$) was more pronounced in *HP*-infected subjects.

Autoimmune gastritis findings

Stratifying patients according to the presence of AG showed no differences in sex, age, duration of diabetes, HLA-DQ type, or thyroid peroxidase antibody positivity (aTPO) between these two groups (Table 2). However, H^+/K^+ATPase antibody ($P = 0.001$) and gastrin levels ($P = 0.001$) were higher in AG$^+$ patients. Concentrations of gastrin correlated positively with H^+/K^+ATPase antibody levels ($r = 0.73$; $P < 0.0001$) and inversely with the percentage of parietal cells per gland ($r = -0.43$, $P = 0.002$). Logistic regression showed that PCA status ($\beta = 1.44$; $P = 0.04$) and gastrin levels ($\beta = 0.01$; $P = 0.026$), but not *HP*, age, diabetes duration, sex, or HLA-DQ type, were independent risk factors for autoimmune gastritis. Iron deficiency anemia (OR 3.9 [1.4–10.9], $P = 0.015$), pernicious anemia (4.6 [1.3–16.9], $P = 0.022$), and hypochlorhydria (OR 20.0, $P = 0.0002$) were more frequent in the AG$^+$ group.

There were less parietal cells ($P < 0.0001$) and corpus inflammation ($P = 0.021$) was more severe in patients with autoimmune gastritis. Concentrations of B-cells ($P = 0.03$) were higher in those with autoimmune gastritis. Antral morphology was similar between the two groups. Corpus intestinal metaplasia was present in 11 AG$^+$ patients, including one PCA$^+$ patient with linitis plastica, com-

Table 2—*Comparison of clinical and histological features in type 1 diabetic patients with and without autoimmune gastritis*

	Autoimmune gastritis	No autoimmune gastritis	*P*
n (M/F)	31 (16/15)	57 (34/23)	NS
Age (years)	44 ± 12	41 ± 13	NS
Duration of diabetes (years)	20 ± 12	20 ± 11	NS
aTPO$^+$	10 (32)	16 (28)	NS
PCA$^+$	27 (87)	20 (35)	<0.0001
H^+/K^+ ATPase (units/ml)	154.6 ± 121.0	21.5 ± 36.2	0.001
HP$^+$	13 (42)	34 (60)	NS
Gastrin (ng/l)	333 ± 335	131 ± 88	0.001
Vitamin B12 (pmol/l)	319 ± 229	376 ± 182	NS
Red blood cell folic acid (nmol/l)	923 ± 417	1008 ± 369	NS
Iron deficiency anemia	12 (39)	8 (14)	0.015
Pernicious anemia	8 (26)	4 (7)	0.022
Hypochlorhydria (*n* tested 42)	10/12	6/30	0.0002
Maximal acid output (mmol H^+/h)	4.1 ± 3.6	14.3 ± 10.2	0.001
Parietal cell mass (%)	15 ± 8	29 ± 4	<0.0001
Corpus atrophy	1 (0–3)	0 (0–1)	<0.0001
Corpus *HP*	0 (0–1)	0 (0–3)	0.018
Corpus inflammation	1 (1–2)	1 (0–2)	0.021
Corpus metaplasia	0 (0–3)	0 (0–1)	0.013
Corpus metaplasia	11 (35)	1 (2)	<0.0001
ECL cell$^+$	7 (23)	0 (0)	0.0004
B-cell (counts/mm^2)	1,595 ± 525	834 ± 418	0.03
T-cell (counts/mm^2)	639 ± 259	395 ± 202	NS

Data are means ± SD, median (range), or *n* (%).

pared with one AG$^-$ subject (OR 30.8 [3.7–254.1], $P < 0.0001$). ECL cell hyperplasia was found in seven PCA$^+$ patients with autoimmune gastritis, of whom one showed a carcinoid tumor, but in no PCA$^-$ subjects. Six of seven patients with ECL hyperplasia presented with hypergastrinemia (13.4 [1.5–117.6], $P = 0.007$). A combination of corpus intestinal metaplasia and ECL cell hyperplasia was present in six PCA$^+$ patients with autoimmune gastritis. Thus, (pre)malignant lesions were found in 12 of 47 (26%) PCA$^+$ and 39% of PCA$^+$ type 1 diabetic patients with autoimmune gastritis.

CONCLUSIONS — Type 1 diabetic, particularly GADA$^+$ (5), patients have a high prevalence of PCA. PCA positivity and hypergastrinemia were risk factors for autoimmune gastritis. PCA$^+$ subjects are prone to develop iron deficiency anemia, pernicious anemia, autoimmune gastritis, intestinal metaplasia, and ECL hyperplasia.

PCAs, gastric acid production, and anemia

PCAs target gastric H^+/K^+ATPase. We and others (6,35) have showed that acid output was lower in PCA$^+$ patients and that fasting pH correlated with iron levels, supporting evidence that hypochlorhydria may impair iron absorption and cause iron deficiency anemia (11). Gastrin levels were higher in our PCA$^+$ patients and correlated with H^+/K^+ATPase antibody levels and inversely with the percentage of parietal cells. Others (12,37,38) noted that gastrin levels correlated with peak acid output and corpus atrophy.

Pernicious anemia, present in 2.6–4% of type 1 diabetic subjects (3,16), was 10 times more common in our PCA$^+$ than PCA$^-$ patients. PCA and AIF may impair vitamin B12 absorption and cause pernicious anemia, which appears in later stages of autoimmune gastritis (39). Pernicious anemia affects both sexes equally (3,15,16).

Histological findings and pathogenetic considerations

PCA$^+$ subjects had a higher prevalence of autoimmune gastritis with (2,3,9) or without (28) total atrophy, higher mucosal B- and T-cell concentrations with B-cells predominating (9,40), and less parietal cells in oxyntic glands (20 vs. 29%) than PCA$^-$ patients. In normal stomachs parietal cells occupy 28–34% of oxyntic glands (30).

We confirmed a correlation between PCA titer and the severity of corpus atrophy (38). This suggests that humoral mechanisms involving cytotoxic autoantibodies play a role in mediating mucosal damage in autoimmune gastritis (9,41). PCA can lyse parietal cells in vitro (41), but it is unlikely that they are pathogenic in vivo, because gastric H^+/K^+ATPase is not accessible to circulating autoantibodies (10). However, PCA in gastric secretions might have direct access to the apical surface of parietal cells (6). Recently, CD4$^+$ T-cells recognizing H^+/K^+ATPase were suggested to mediate autoimmune gastritis (10). Burman et al. (42) observed that T-cells predominated in autoimmune gastritis. Moreover, not every patient with autoimmune gastritis has PCA. Possible explanations for seronegative cases are exhaustion of the autoimmune response as the parietal cell autoantigens are depleted (43), an immunological reaction restricted to a cellular response, unrecognized autoantibodies, and the development of autoimmune gastritis before the development of PCAs (9).

At least four biopsies were studied to document autoimmune gastritis, thereby reducing sampling error. Autoimmune gastritis (57%) and (pre)malignant gastric lesions (26%) were frequent in our PCA$^+$ subjects. Results are based on a representative number of PCA$^+$ and matched PCA$^-$ patients. Not all eligible patients agreed to undergo gastroscopy, and this might, however, have introduced some bias. We estimate that at least one-third of all PCA$^+$ type 1 diabetic patients have autoimmune gastritis. Its prevalence in the total diabetic population would be 5–10%. Nearly 40% of our PCA$^+$ patients with autoimmune gastritis exhibited (pre)malignant gastric lesions; 11 patients had intestinal metaplasia, comprising 1 with an adenocarcinoma, and 7 showed ECL cell hyperplasia, including 1 subject with a gastric carcinoid tumor. The prevalence of gastric carcinoid tumors, developing on a background of ECL cell hyperplasia induced by chronic hypergastrinemia, ranges from 4–7% in patients with autoimmune gastritis/pernicious anemia and is 13 times more prevalent than in control subjects (17,19,20). Autoimmune gastritis with

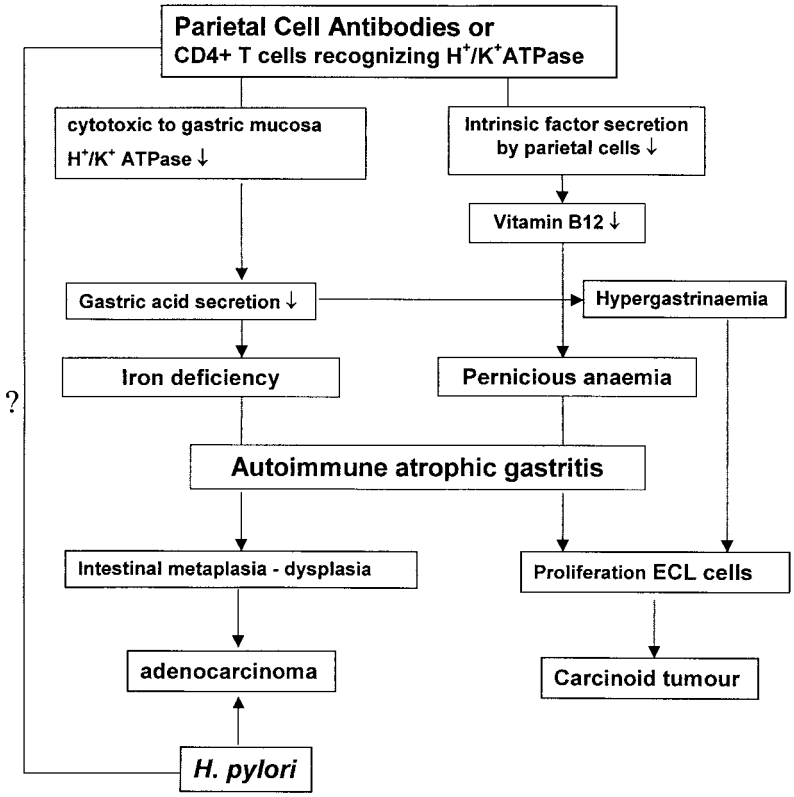

Figure 1—*Schematic presentation of manifestations of autoimmune gastropathy. Pathogenetic considerations and a possible role of PCA are discussed in the* CONCLUSIONS *section.*

hypo/achlorhydria may not only result in hypergastrinemia but also in overgrowth of bacteria producing mutagenic *N*-nitroso compounds, which can lead to intestinal metaplasia-dysplasia, precancerous conditions (44). Patients with atrophic gastritis/pernicious anemia have a three- to fivefold increased gastric cancer risk, ranging from 1 to 9% (17,18), although this has not been shown in all studies (23).

HP infection

Longitudinal studies suggest that *HP* may induce early stages of autoimmune gastritis by stimulating granulocytes to produce autodestructive oxygen radicals, which are mutagenic and ultimately lead to corpus atrophy (45) and *HP* self-destruction due to intestinal metaplasia or achlorhydria (46). Models for the pathogenesis of *HP*-associated autoimmunity are molecular mimicry and/or T-helper 1–induced expression of HLA class II and costimulatory molecules on gastric epithelial cells (24–26). However, we and others (35,46,47) have found no or a negative relation between *HP* infection and autoimmune gastritis. Nevertheless, eradicating *HP* and doing a rebiopsy 6 months later to note its effect on histology is recommended.

Management proposal

Manifestations of autoimmune gastropathy (Fig. 1) are sufficiently prevalent, and the benefits of early diagnosis and treatment (supplementation of iron or vitamin B12 or removal of [pre]malignant gastric lesions) are such that all type 1 diabetic patients should be screened. It seems prudent to test PCA status at onset of diabetes and then yearly for 3 years, then at 5 years and 5-yearly thereafter, or at any time if there are clinical indications, because the test may later become positive (43). At yearly intervals gastrin, iron, vitamin B12 levels, and a complete blood count should be performed. We also suggest performing at least once endoscopy with biopsy in PCA^+ patients, particularly in those with high gastrin levels. Patients with mild to moderate mucosal dysplasia should be followed endoscopically every 5 years (17). Polyps should be removed, and adenocarcinoma should be excised. Gastric carcinoid tumors are rare and have a far better outcome than carcinoma. Endoscopic surveillance at 5-year intervals has been proposed for ECL hyperplasia (19). For gastric carcinoid tumors associated with autoimmune gastritis, <1 cm and/or fewer than three, expectant therapy or endoscopic removal of accessible tumors is proposed (48). Alternative options include antrectomy (49) and treatment by octreotide (50).

Conclusions

PCA^+ type 1 diabetic patients are at increased risk for iron deficiency anemia, pernicious anemia, hypochlorhydria, autoimmune gastritis, and (pre)malignant gastric lesions. Therefore, all PCA^+ patients should be thoroughly examined, particularly those with hypergastrinemia, and gastroscopy with biopsies should be performed.

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