Atrophic Body Gastritis in Patients With Autoimmune Thyroid Disease

An Underdiagnosed Association

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Background: Atrophic body gastritis (ABG) has never been histologically characterized in patients with autoimmune thyroid disease (AITD), and its prevalence may be substantially different from that previously assessed based on only indirect evidence.

Objective: To detect and characterize the presence of ABG in patients with AITD.

Methods: Sixty-two patients with AITD (5 men and 57 women), aged between 21 and 74 years, have been screened for the presence of ABG by assaying serum gastrin levels. Patients with hypergastrinemia underwent gastroscopy followed by the histological examination of multiple biopsy specimens. The diagnosis of ABG was based on hypergastrinemia and pentagastrin-resistant achlorhydria, confirmed by histological examination.

Results: Twenty-two (35%) of 62 patients had hypergastrinemia (mean ± SEM gastrin level, 1070 ± 288 pmol/L). The diagnosis of ABG has been histologically confirmed in all 22 patients, and the score of atrophy was moderate to severe. In group A (patients aged 20-40 years; n = 21), 6 patients (29%) had ABG, compared with 11 patients (37%) in group B (patients aged 41-60 years; n = 30) and 5 patients (45%) in group C (patients aged 61-80 years; n = 11). Antiparietal cell antibodies were detected in only 68% (15/22) of patients with ABG. Anemia was observed in 82% (18/22) of patients with AITD and ABG but only in 22% (9/40) of patients without ABG (P < .0001).

Conclusions: In the patients with AITD studied, about one third had ABG, which was diagnosed also in young patients; the measurement of gastrin levels represented the most reliable tool in the diagnosis of ABG; and the presence of anemia, even microcytic, was suggestive of undiagnosed ABG.

Arch Intern Med. 1999;159:1726-1730
PATIENTS AND METHODS

For 13 months, 1035 outpatients were sequentially examined by the same physician (M.C.) in our tertiary outpatient Center for Thyroid Disease, University of Rome “La Sapienza,” Rome, Italy. Autoimmune thyroid disease was diagnosed in 62 patients (6.0%) (5 men and 57 women) aged 21 to 74 years (mean ± SD, 47.5 ± 14.0 years), who, besides other criteria, displayed pathological levels of antiperoxidase antibodies (>200 U/L; median, 1380 U/L; range, 269-6500 U/L) at the time of diagnosis and in at least 2 measurements during a 12-month period. This cohort represented the study population. At presentation, 26 patients were clinically euthyroid, 26 had overt or subclinical hypothyroidism, and 10 had hyperthyroidism. Patients were divided according to age as follows: group A, 20 to 40 years (n = 21); group B, 41 to 60 years (n = 30); and group C, 61 to 80 years (n = 11). Chronic autoimmune thyroiditis was diagnosed in 52 patients, 47 with goiter (Hashimoto thyroiditis) and 5 without goiter (atrophic thyroiditis). Graves disease was diagnosed in 10 patients. Serum gastrin levels and the presence of APCab and Helicobacter pylori IgG antibodies, as well as that of anemia, were evaluated in all patients. Patients with increased fasting gastrin levels, which represent a regular feature of gastric atrophy,19,20 underwent further functional and morphologic characterization of the fundic mucosa of the stomach by gastric secretory tests, gastroscopy, and histological evaluation of multiple biopsy specimens, which were obtained during the gastroscopic examination. However, a higher gastrin level cutoff (>210 pmol/L; 2.5 times the cutoff of the method) was used in this study, as a small increase of the gastrin levels, due to H pylori infection and not related to gastric atrophy, has been reported.21 This clear-cut criterion has been used to avoid gastroscopic examinations, which, in patients without definite clinical and/or biochemical evidence of gastric atrophy, would not have been strictly necessary. However, patients without hypergastrinemia (gastrin level >210 pmol/L) but showing the presence of APCab also underwent gastroscopy and histological evaluation of multiple biopsy specimens to compare the reliability of this diagnostic parameter as a marker of ABG.3,8,12

Informed consent was obtained from each patient before any invasive procedure, and the protocol was consistent with the Declaration of Helsinki.

DIAGNOSIS OF AITD

Diagnostic procedures included routine clinical examinations, serum free triiodothyronine and free thyroxine and basal thyrotropin measurements, antiperoxidase antibody detection, and ultrasonography. Where appropriate, patients underwent radioiodine uptake and scintigraphic mapping, ultrasonography-assisted fine needle aspiration biopsy, and a thyrotropin-releasing hormone test for serial thyrotropin measurements and detection of anti–thyrotropin receptor antibodies in serum. The antiperoxidase and anti–thyrotropin receptor antibodies were measured by a radioligand assay (intra-assay variation, 3.6%; interassay variation, 4.6%) (Radin Techland, Liege, Belgium) and a radioreceptor assay (Ares-Serono, Milan, Italy), respectively. Free triiodothyronine and free thyroxine levels were assayed by radioimmunometric assay (Radin Techland).

DIAGNOSIS OF ABG

The diagnosis of ABG was based on hypergastrinemia and pentagastrin-resistant achlorhydria, confirmed by

Continued on next page
The reliability of the biological parameters used as diagnostic criteria of ABG in patients with AITD is shown in Figure 2. In the study population, the presence of APCAb was detected in 25 (40%) of the 62 patients (median, 500 U/mL; range, 130-1000 U/mL); however, APCAb were present only in 15 (68%) of 22 patients with the AITD plus ABG association. Gastroscopy was also performed in the remaining 10 APCAb-positive patients, as their presence was considered a marker of ABG. None of these patients showed histological evidence of this disease. Thus, 7 false-negative results and 10 false-positive results were due to that marker in the diagnosis of ABG. The presence of PA was diagnosed in 10 (16%) of 62 patients with AITD, all of whom had ABG. Specificity was thus 100%, but sensitivity as a marker of ABG was low (35%) of ABG in patients with AITD. Such a prevalence is consistent with previous reports.4,26 However, it was not possible to evaluate the sensitivity of gastrin levels as a marker, since, for the reasons previously described, not all the patients studied underwent gastroscopy. However, the gastrin levels were normal in the 10 APCAb-positive patients with no evidence of ABG. Overall, only 7 of 22 patients with ABG presented simultaneously with hypergastrinemia, APCAb, and PA.

DIAGNOSIS OF ANEMIA

The diagnosis of microcytic anemia was based on the simultaneous presence of decreased hemoglobin level (<120 g/L for women and <136 g/L for men) and mean corpuscular volume (<80 fl), which were associated with reduced levels of serum iron (<11 pmol/L [<61 µg/dL]) and ferritin (<30 µg/L). All patients with microcytic anemia were assessed for other causes of iron deficiency, and obvious causes of blood loss (eg, overt gastrointestinal tract bleeding or excessive menstrual blood loss) were carefully checked. Furthermore, all patients were examined for occult causes of lower gastrointestinal tract bleeding; the fecal occult blood test was performed in patients 40 years and younger; and a double-contrast barium enema was given or a colonoscopy was performed, where appropriate, in those older than 40 years.

The diagnosis of macrocytic anemia was based on decreased hemoglobin levels and a mean corpuscular volume greater than 100 fl. The diagnosis of PA was based on the following criteria: the presence of macrocytic anemia, the presence of anti–intrinsic factor antibodies, pentagastrin-resistant achlorhydria, and response to cyanocobalamin therapy, as described.4,23

STATISTICAL ANALYSIS

Data are expressed as the mean ± SEM or median, where appropriate. Subgroup percentages were compared using the Fisher exact test. Software (INSTAT Graphpad [1990-92], San Diego, Calif) for DOS was used in the statistical analysis.

Comment

Atrophic body gastritis is an asymptomatic disease, and its prevalence has never been assessed in an unselected population.9,12 Nevertheless, it is important to make an early diagnosis because patients with ABG have a 3 times greater risk for developing gastric cancer,12,13 and ABG is responsible for unexplained iron-deficient anemia.9,14 The results of the present study reveal a high prevalence (35%) of ABG in patients with AITD. Such a prevalence is substantially higher than that previously reported based on indirect evidence (ie, the presence of APCAb and/or PA).4,26 In fact, a 12.3% prevalence of PA has been reported in patients with primary hypothyroidism26; the same researchers,26 however, reported that, when achlorhydria was used as a marker, the prevalence rose to 32%, a finding comparable with that recorded in the present study. The results of the present study revealed the presence of ABG in 6 of 21 young patients (<40 years) with AITD. Two (9.5%) of these patients also had PA. These findings are in contrast with those in the historical ar-
article by Irvine,4 who reported no ABG or PA in a large cohort of patients with AITD who were younger than 40. This discrepancy could be due to the use, at that time, of less reliable markers for an early diagnosis. In fact, the detection of APCAb and the presence of PA, used at that time as markers,3,4,6,8 showed, in the present study, an inadequate overall accuracy in the diagnosis of this disease. The reliability of measuring fasting gastrin levels to screen patients at risk for ABG is well established12,15; indeed, the most frequent cause of marked hypergastrinemia has been shown to be represented by ABG,24 although an appropriate cutoff level should be used to avoid the bias due to H pylori infection.21 The present study showed that the measurement of gastrin levels is also an important tool in the diagnostic work-up of ABG in patients with AITD, and represents a better diagnostic marker than those previously advocated.3,4,6,8,15

The presence of anemia has been described in patients with impaired thyroid homeostasis, 27 mainly referred to as PA.7,8,26 The results of this study confirm the higher prevalence of anemia in patients with AITD compared with that reported in referral patients.29 However, a marked difference has been found between patients with and those without ABG (82% vs 22%, P < .001), which was only partly due to the prevalence of PA. This fact indicates that, particularly in young patients with AITD, even the presence of unexplained microcytic anemia should be considered as highly suggestive of the presence of undiagnosed ABG. This assumption is in keeping with the finding that hypochlorhydria may lead to iron deficiency and anemia.28 In this respect, all patients with AITD should be routinely monitored at follow-up for the presence of anemia, which may represent the only clinical sign of undiagnosed ABG.14

The pathogenetic event responsible for the clinical relationship between AITD and ABG remains to be elucidated. The close association with various autoimmune diseases and the presence in familial clusters of AITD and

| Table 1. Functional and Morphologic Factors of Autoimmune Thyroid Disease in 22 Patients With Atrophic Body Gastritis

<table>
<thead>
<tr>
<th>Factors</th>
<th>Values*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional</td>
<td>Values</td>
</tr>
<tr>
<td>Fasting gastrin levels, pmol/L</td>
<td>1070 ± 288</td>
</tr>
<tr>
<td>Basal acid output, mEq/h</td>
<td>0.04 ± 0.03</td>
</tr>
<tr>
<td>Peak acid output, mEq/h</td>
<td>1.3 ± 0.7</td>
</tr>
<tr>
<td>Morphologic†</td>
<td>Values</td>
</tr>
<tr>
<td>Chronic inflammation</td>
<td>1.37 ± 0.11</td>
</tr>
<tr>
<td>Atrophy</td>
<td>2.42 ± 0.18</td>
</tr>
<tr>
<td>Intestinal metaplasia</td>
<td>1.15 ± 0.23</td>
</tr>
</tbody>
</table>

*All values are given as mean ± SEM.
†Values are given as updated Sydney scores. 1 indicates mild; 2, moderate; and 3, severe.

| Table 2. Presence of Atrophic Body Gastritis (ABG) in Patients With Autoimmune Thyroid Disease (AITD) in Relation to Clinical Diagnosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%) of Patients</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hashimoto thyroiditis</td>
<td>47 (76)</td>
<td>. .</td>
</tr>
<tr>
<td>Atrophic thyroiditis</td>
<td>5 (8)</td>
<td>.77 .54</td>
</tr>
<tr>
<td>Graves disease</td>
<td>10 (16)</td>
<td>&gt;.99 &gt;.99</td>
</tr>
</tbody>
</table>

*Values derived using the total sample as a reference.
†Values derived using patients with AITD, but without ABG, as a reference.

| Table 3. Prevalence of Anemia in Patients With Autoimmune Thyroid Disease (AITD) With or Without Atrophic Body Gastritis (ABG)

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%) of Patients</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>27/62 (43)</td>
<td>. .</td>
</tr>
<tr>
<td>Patients with AITD and without ABG</td>
<td>9/40 (22)</td>
<td>.04 . .</td>
</tr>
<tr>
<td>Patients with AITD and ABG</td>
<td>18/22 (82)</td>
<td>.002 &lt;.0001</td>
</tr>
</tbody>
</table>

*Ellipses indicate data are not applicable.
†Values derived using the total sample as a reference group.
‡Values derived using patients with AITD, but without ABG, as a reference group.

Figure 1. Prevalence of chronic atrophic body gastritis (ABG) in patients with autoimmune thyroid disease (AITD).

Figure 2. Reliability of different markers used in the diagnosis of atrophic body gastritis (ABG) in patients with autoimmune thyroid disease (AITD). APCAb indicates antiparietal cell antibodies.

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ABG suggest an immunological cross-reaction.\textsuperscript{1,2,4,7} In this respect, Elisei et al.\textsuperscript{30} by comparing the sequence of the gastric parietal cell antigen with that of thyroid peroxidase, found a homologous 11-residue peptide in both proteins; on these grounds, these researchers suggested the existence of an epitope common to thyroid peroxidase and the gastric parietal cell antigen, which had previously been identified as the hydrogen-potassium adenosine triphosphatase, the acid-producing structure of the stomach.\textsuperscript{31} However, the role of antiperoxidase antibodies in the pathogenesis of AITD is, as yet, unclear.\textsuperscript{16} Moreover, the role of cross-reactive antibodies in the pathogenesis of coexisting thyroid and gastric autoimmune diseases has been excluded,\textsuperscript{32} and the pathogenesis of ABG is not exclusively of autoimmune origin.\textsuperscript{33} Thus, the correlation between AITD and ABG is clinically evident but as yet pathogenetically undefined.

In conclusion, data emerging from the present investigation indicate that about one third of patients with AITD have histologically and functionally proved ABG; ABG can be present even in young (<=40 years) patients; the presence of ABG is not related to the clinical status of the AITD; the measurement of plasma gastrin levels represents the most reliable tool in the diagnosis of ABG in patients with AITD; and in patients with AITD, the presence of unexplained anemia, not necessarily PA, is highly suggestive of the presence of undiagnosed ABG.

Accepted for publication December 21, 1998.

This study was supported by grant 05/15/0110 from the Ministero Universit\`a e Ricerca Scientifica e Tecnologica (1995-1996); and the Institute of Experimental Medicine of the National Research Council, Rome, Italy.

We thank Jens H. Rehfeld, PhD, for providing antibody 4562.

Preliminary results of this study were presented at the 11th International Thyroid Congress, Toronto, Ontario, September 16, 1995.

We thank Marian Shields, MD, for help with the linguistic style in the preparation of the manuscript.

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REFERENCES