CLINICAL STUDY

Chronic autoimmune atrophic gastritis associated with primary hyperparathyroidism: a transversal prospective study

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Abstract

Design: The coexistence of chronic autoimmune atrophic gastritis (CAAG) and primary hyperparathyroidism (PHPT) has been described previously, even if its extent and underlying mechanisms remain poorly understood. We therefore prospectively evaluated this association in two series of patients, one with CAAG and the other with sporadic PHPT.

Methods: From January 2005 to March 2012, 107 histologically confirmed CAAG patients and 149 PHPT patients were consecutively enrolled. Routine laboratory assays included serum calcium, parathyroid hormone (PTH), plasma gastrin and chromogranin A (CgA). In CAAG patients with high PTH levels, ionized calcium and 25(OH)-vitamin D were evaluated. All CAAG and hypergastrinemic PHPT patients received an upper gastrointestinal endoscopy. Exclusion criteria were familial PHPT, MEN1 syndrome, treatment with proton pump inhibitor drugs, Helicobacter pylori infection and renal failure.

Results: Of the 107 CAAG patients, nine (8.4%) had PHPT and 13 (12.1%) had secondary hyperparathyroidism stemming from vitamin D deficiency. Among the 149 PHPT patients, 11 (7.4%) had CAAG. Gastrin and CgA levels were similar in the CAAG patients with vs those without hyperparathyroidism (either primary or secondary), and calcium and PTH levels were similar in the PHPT patients with vs those without CAAG.

Conclusions: This study confirms a non-casual association between PHPT and CAAG. The prevalence of PHPT in CAAG patients is threefold that of the general population (8.4 vs 1–3%), and the prevalence of CAAG in PHPT patients is fourfold that of the general population (7.4 vs 2%). The mechanisms underlying this association remain unknown, but a potential role for autoimmunity is suggested.


Introduction

Chronic autoimmune atrophic gastritis (CAAG), or type A gastritis, is an organ-specific autoimmune disorder characterized by the atrophy of the gastric gland mucosa in the fundus and the body, which contains acid-secreting parietal cells. CAAG is the leading cause of pernicious anaemia, and out of the patients with pernicious anaemia, ~90% have antibodies against the parietal cells and 70% against intrinsic factor (1). Hypochlorhydria, determined by the progressive destruction of acid-secreting parietal cells and leading to hypergastrinemia, is observed in the majority of these patients. Gastrin has a trophic effect on the enterochromaffin-like (ECL) cells of the gastric mucosa. Hypergastrinemia therefore results in the ECL cell hyperplasia (which varies from simple, linear to micronodular) to the development of dysplasia and gastric carcinoid type 1 (GC1) (2).

CAAG is clinically heterogeneous and has an asymptomatic course or presents with dyspepsia, mild micro- or normocytic anaemia and pernicious anaemia. This condition is a risk factor for gastric adenocarcinoma and GC1. CAAG occurs in ~2% of the general population, with a higher prevalence in elderly females, particularly those older than 60 years (3). It accounts for ~10% of chronic gastritis cases; the remaining 90% are due to chronic Helicobacter pylori infection that is characterized by chronic gastritis that occurs primarily in the gastric antrum (chronic atrophic gastritis type B) and sometimes affects the entire gastric mucosa (pangastritis).

A significant association between CAAG and other autoimmune diseases has already been described: more than 50% of CAAG patients have circulating anti-thyroidperoxidase antibodies. Moreover, because patients with type 1 diabetes mellitus have a three-
fivelfold increased risk of developing CAAG, some studies have suggested screening by an upper endoscopy with biopsies (4), CAAG has been described in the context of polyglandular autoimmune (PGA) syndromes. In PGA type 1 syndrome, which is characterized by hypoparathyroidism, Addison’s disease, diabetes mellitus and mucocutaneous candidiasis, pernicious anaemia occurs in 13% of patients, whereas in PGA type 3 syndrome, which is characterized by diabetes mellitus and autoimmune thyroid diseases, CAAG occurs in ~15% of the cases. Patients with CAAG may also develop other autoimmune manifestations, such as vitiligo, alopecia, celiac disease, myasthenia gravis and autoimmune chronic hepatitis (1, 5).

Primary hyperparathyroidism (PHPT) is a common endocrine disorder with a prevalence of three per thousand in the general population, a male:female ratio of 1:3.3 (6) and a prevalence of 2.5–3% in women aged over 65 years (7). The increased parathyroid hormone (PTH) levels may be the result of parathyroid adenoma (80–85% of cases), hyperplasia (15%) or carcinoma (1–3%). Hypercalcæmia, osteoporosis and nephro lithiasis represent the primary clinical manifestations of PHPT.

Data indicating a possible association between PHPT and CAAG are scarce. Since the 1970s, sporadic cases of the coexistence of pernicious anaemia and PHPT have been reported (8, 9, 10), and three studies (11, 12, 13) have documented the presence of an increased prevalence of CAAG/pernicious anaemia in patients with PHPT (1.8–13.5 vs 0.3–2% in the general population (1, 3)). In 2005, Peracchi et al. (14) reported an increased prevalence of PHPT in patients with CAAG (5.7% compared with a prevalence of 1–3% in the general population (15, 16)). Recently, Thomas et al. (17) did not confirm this association but rather demonstrated an increased incidence of PHPT (15.4%) in patients with GC1, a condition that actually occurs in patients with CAAG. The association of PHPT with GC1 has been observed sporadically in other studies, and the mechanisms involved remain unknown (18, 19, 20, 21, 22, 23).

This prospective study was aimed at evaluating whether there is significant association between CAAG and PHPT. Patients were enrolled and divided into two groups, one with PHPT and the other with CAAG, regardless of the presence of GC1.

**Materials and methods**

From January 2005 to March 2012 at the Gastroenterology Unit II and Endocrinology Unit, Fondazione IRCCS Ca’ Granda, Ospedale Maggiore Policlinico (Milan, Italy), a total of 256 patients were prospectively and consecutively enrolled and divided into two series of patients: one suffering from CAAG and the other from PHPT (Fig. 1). Moreover, an internal healthy control group of 95 subjects, matched by age and gender with the patient groups, was included to properly evaluate the main laboratory data.

**Patients with CAAG**

This group included 107 patients with histologically confirmed CAAG, 86 females and 21 males, aged 21–88 years, with a median age of 57.4 years. According to the Sydney classification (24), 42 patients had mild chronic gastritis, 40 had moderate and 25 had severe cases. The status of the ECL cells was classified according to Solcia et al. (2): 32 patients had no cell hyperplasia, while simple, linear and micronodular hyperplasia was found in 14, 5 and 32 of them respectively. Twenty-four patients had GC1: in 10 patients, GC1 was single and in 14 multiple, all of variable size (diameter 0.2–3 cm). The associated reported autoimmune diseases were primary hypothyroidism in 22 patients, vitiligo in six, celiac disease in three, type 1 diabetes mellitus in three, Graves’ disease in two, early menopause with anti-ovarian-positive antibodies in two, lichen planus in two, PGA type 1, myasthenia gravis and scleroderma in one patient each; multiple sclerosis was reported in one case. Anti-parietal cell antibodies were present in 78 patients (73%).

Criteria for exclusion were presence of \( H. pylori \) infection (according to histology and/or positive \( H. pylori \) IgG titre), ongoing treatment with proton pump inhibitor (PPI) drugs and with medication that can interfere with calcium metabolism or with PTH secretion, such as thiazides and lithium, renal failure, severe hepatic failure and concomitant malignancy.

**Patients with sporadic PHPT**

This group included 149 consecutive patients with PHPT (119 females and 30 males, aged 35–87 years,

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**Image**: Figure 1 The study design illustrates the patient distribution in the study and the results (number of patients is indicated in parentheses). CAAG, chronic autoimmune atrophic gastritis; PTH, parathyroid hormone; PHPT, primary hyperparathyroidism.
median age 61.5 years). The diagnosis was based on internationally accepted criteria (25). Ninety-eight patients were operated on: in 89 patients (90.8%), PHPT resulted from a sporadic PTH-secreting solitary adenoma of the parathyroid chief cells; the remaining nine patients (9.2%) had parathyroid hyperplasia. None of the patients had parathyroid carcinoma. The histological diagnosis of adenoma was based on the finding of an encapsulated lesion with a definite rim of normal or atrophic gland outside the capsule and according to the surgeon’s examination of other normal glands. Diagnosis of parathyroid hyperplasia instead was made in the presence of diffusely enlarged gland(s) without normal parathyroid tissue at the periphery. The main laboratory data of the patients are provided in Table 1.

From a clinical perspective, 57 patients (50.3%) had a history of nephrolithiasis, whereas none had a history of osteitis fibrosa cystica. The bone mineral density (BMD) was markedly reduced at both the lumbar spine and the proximal femur (median Z-scores: −0.73 (range, −5.00 to +4.63) and −0.62 (−4.00 to +5.28) respectively). The associated autoimmune diseases observed in PHPT patients were type 1 diabetes mellitus in two patients, primary hypothyroidism in two, and vitiligo, celiac disease, Graves’ disease and dermatitis herpetiformis in one patient each. Patients with the presence of familial PHPT, MEN1 syndrome, familial hypocalciuric hypercalcaemia (FHH), ongoing PPI regimen, treatment with thiazides and lithium and renal failure were excluded.

All patients underwent routine laboratory testing. All CAAG and the subset of hypergastrinaemic PHPT patients also underwent an upper gastrointestinal endoscopy procedure. All the subjects gave written informed consent to participate in the study, which was approved by the Local Ethics Committee.

Laboratory investigations

The levels of total and ionized calcium, albumin, phosphate, intact PTH, 25(OH)-vitamin D, creatinine, gastrin and chromogranin A (CgA) were measured in venous samples obtained after an overnight fast; anticoagulant-free tubes were used for the serum samples and tubes containing EDTA (1 mg/ml blood) or heparin were used for the plasma ones. Within 30 min of the collection, the anticoagulant tubes were centrifuged at 4°C for 10 min at 1800 g and then the plasma was collected, separated into aliquots of ~500–1000 µl/tube and stored at −30°C until the assays were run. Urinary calcium and the clearance of creatinine and calcium were measured using 24-h urine collections. In patients with CAAG and in those with PHPT and high gastrin levels, the presence of antibodies against gastric parietal cells was investigated.

Serum calcium, albumin, creatinine and urinary calcium and creatinine were measured by standard colorimetric techniques. Total calcium was corrected for serum albumin (total calcium_{adj}) according to the formula: (total calcium (mg/dl) + (4.4 − albumin (mg/dl)) × 0.8). Plasma ionized calcium was measured using a potentiometric method (Radiometer ABL System 625, Copenhagen, Denmark) on heparinized blood samples within 30 min of blood collection. Serum intact PTH was measured by chemiluminescence (Elecsys Intact PTH assay, F Hoffmann-La Roche, Basel, Switzerland), with a sensitivity of 6.0 ng/ml. 25(OH)-vitamin D was measured using a chemiluminescent, with a direct and competitive quantitative method (DiaSorin, Saluggia, Italy), and a sensitivity of 10 nmol/l. Plasma gastrin levels were measured using a RIA Kit (DiaSorin, Stillwater, MN, USA), with a sensitivity of 6 ng/l. CgA levels were measured as described previously (14) using a commercially available ELISA Kit (Dako A/S, Glostrup, Denmark), with a sensitivity of 2.1 µl.

Upper gastrointestinal endoscopy

All CAAG and hypergastrinaemic PHPT patients underwent upper gastrointestinal endoscopy, which was performed using standard endoscopes (Olympus, Tokyo, Japan). At least six gastric biopsies were obtained in all cases: four from the gastric body and the fundus and two from the antrum with additional sampling of all

### Table 1 The demographic and laboratory characteristics are presented for the patients with CAAG and sporadic PHPTa.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controlsb</th>
<th>CAAG (107)</th>
<th>PHPT (149)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>20/75</td>
<td>21/86</td>
<td>30/119</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.0 (25–85)</td>
<td>57.4 (21–88)</td>
<td>61.5 (35–87)</td>
<td>NS</td>
</tr>
<tr>
<td>Gastrin (ng/l)</td>
<td>20–110</td>
<td>732 (141–1840)</td>
<td>52.0 (24–1605)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chromogranin A (µ/l)</td>
<td>4–26</td>
<td>39 (10.7–527)</td>
<td>17.0 (6–61)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PTH (ng/l)</td>
<td>24–65</td>
<td>57.5 (25.5–250)</td>
<td>149 (55–628)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total calcium_{adj} (mmol/l)</td>
<td>2.12–2.57</td>
<td>2.40 (2.17–3.12)</td>
<td>2.79 (2.37–3.92)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>25(OH)-vitamin D (nmol/l)</td>
<td>45–200</td>
<td>49 (10–117)</td>
<td>55 (25–132)</td>
<td>NS</td>
</tr>
</tbody>
</table>

CAAG, chronic autoimmune atrophic gastritis; PHPT, primary hyperparathyroidism.
aThe data are expressed as median and range.
bData from internal healthy control group.

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the potential lesions. The biopsies were fixed in Bouin’s fluid for 4–5 h at 18 °C and then rinsed in 70 ethanol/30 water (v/v), dehydrated and fixed in paraffin. All the biopsies were processed as described (2). The degree of gastritis was classified according to the Sydney classification system (24), and the status of the ECL cells was classified according to Solcia et al. (2).

Bone mineral density

BMD was measured by dual-energy X-ray absorptiometry (DXA; Hologic, Waltham, MA, USA) of the spine (LS; DXA L2–L4, in vivo precision 1.0%) and the femoral neck (in vivo precision, 2.3%) in all the PHPT patients. Individual BMD values were expressed as Z-score (age- and sex-matched comparison in S.D. units).

Statistical analysis

Results are given as median and range. In most groups, there was not a normal distribution of the data (Kolmogorov–Smirnov test). Differences between groups were identified with the Mann–Whitney U test and relationships between the variables were determined by Spearman’s coefficient. A P value of <0.05 was considered statistically significant. To evaluate whether the number of groups was adequate, a post hoc power analysis was performed, assuming an equal effect size in the sample and in the general population. Analyses were performed using GraphPad Prism version 5.00 and GraphPad State Mat version 2, for Windows (GraphPad Software, San Diego, CA, USA).

Results

The demographic and biochemical characteristics of the CAAG and PHPT patients are presented in Table 1.

Patients with CAAG

All the CAAG patients had elevated gastrin levels (median, 732 ng/l (range 141–1840)), which in 74% of the cases was associated with increased levels of circulating CgA (39 μl (10.7–527)). The highest levels of both gastrin (1314 ng/l (394–1840)) and CgA (76 μl (35–527)) occurred in the patients with GC1. In the patients without GC1, the median gastrin and CgA levels were 638 ng/l (141–1695) and 32.5 μl (10.7–349) respectively (P=0.02 for both).

Nine out of the 107 patients (8.4%), all females, aged 35–84 years, median 60 years, were diagnosed with PHPT on the basis of hypercalcaemia with elevated PTH levels (Table 2). Total serum calcium levels in all the PHPT patients. Individual BMD values were expressed as Z-score (age- and sex-matched comparison in S.D. units).

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Results

The demographic and biochemical characteristics of the CAAG and PHPT patients are presented in Table 1.
Table 3 The demographic and laboratory characteristics are presented for patients with both CAAG and PHPT in the two study populationsa.

<table>
<thead>
<tr>
<th></th>
<th>PHPT from CAAG series</th>
<th>CAAG from PHPT series</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Gender (F/M)</td>
<td>9/1</td>
<td>10/1</td>
</tr>
<tr>
<td>PTH (ng/l)</td>
<td>121 (77.6–250)</td>
<td>128 (66–325)</td>
</tr>
<tr>
<td>Total calcium\textsubscript{ab} adj (mmol/l)</td>
<td>2.82 (2.45–3.12)</td>
<td>2.94 (2.5–3.37)</td>
</tr>
<tr>
<td>Gastrin (ng/l)</td>
<td>618 (232–1816)</td>
<td>437 (159–1605)</td>
</tr>
</tbody>
</table>

CAAG, chronic autoimmune atrophic gastritis; PHPT, primary hyperparathyroidism.

*aThe data are represented as median and range.

years, had concomitant histologically confirmed CAAG. Eight of the PHPT patients had an adenoma, two had four-gland hyperplasia at the time of surgery and one patient is currently receiving follow-up care. None of these patients had GC1. In this subgroup of patients, the circulating gastrin and CgA levels did not differ significantly from those of the 107 CAAG patients (median gastrin levels, 437 ng/l (159–1605) vs 732 ng/l (141–1840) and median CgA levels, 38 μ/l (10–61) vs 39 μ/l (10.7–572)). In these patients, no relationship between the gastrin levels and the concentration of serum PTH, calcium\textsubscript{ab} adj and ionized calcium was observed. In the remaining patients without CAAG, gastrin levels were within the normal range. Among the PHPT patients, there was no significant difference in the concentration of PTH (128 ng/l (66–325) vs 149 ng/l (55–628)) and total serum calcium\textsubscript{ab} adj (2.94 mmol/l (2.50–3.37) vs 2.79 mmol/l (2.37–3.92)), between the patients with vs those without CAAG.

The demographic and biochemical characteristics of the patients with both CAAG and PHPT within the two patient series are presented in Table 3. Based on our sample size of 107 patients with CAAG and 149 with PHPT, considering the 2% prevalence of both CAAG and PHPT in the general population, as previously reported (3, 15, 16), and as we observed a PHPT prevalence of 8.4% in CAAG patients and a CAAG prevalence of 7.4% in PHPT patients, this study reached a statistical power of 92 and 93% respectively, for PHPT and CAAG groups.

Discussion

A non-casual association between CAAG and PHPT has clearly been demonstrated by the present transversal prospective study. Indeed, there was an increased prevalence of PHPT in patients with CAAG (8.4 vs 1–3% in the general population (15, 16)) and an increased prevalence of CAAG in patients with PHPT (7.4 vs 2% in the general population (3)). Previously, sporadic cases of CAAG and PHPT coexistence had been reported (8, 9, 10), and an increased prevalence of CAAG in patients with PHPT has been described in three studies (11, 12, 13), and only one study reported an increased prevalence of PHPT in patients with CAAG (14). In detail, in a retrospective study of 441 patients operated for PHPT, Selking et al. (11) found a 1.8% prevalence of pernicious anaemia, which usually occurs in CAAG, compared with a prevalence of 0.3% in the general population. Primrose et al. (12) described the coexistence of hypergastrinemia and achlorhydria, which is suggestive of a diagnosis of CAAG, in 5.2% of 32 patients with PHPT, and Corleto et al. (13) demonstrated the presence of CAAG in 7/52 (13.5%) patients with PHPT. On the other hand, Peracchi et al. (14) documented the presence of PHPT in 3/52 patients with CAAG (5.8%), whereas Thomas et al. (17) did not find PHPT cases in a series of 30 CAAG patients without GC but reported a PHPT prevalence of 15.4% in 26 patients with GC1, suggesting a possible association between GC1 and PHPT rather than between CAAG and PHPT. The coexistence of PHPT and GC1 has been described as a sporadic association in several studies (18, 19, 20, 21, 22, 23), but the mechanisms (responsible) for this association are still unknown. Fujimori et al. (26) and Bjorklund et al. (27) identified a mutation in exon 3 of the CTNNB1 gene, encoding β-catenin accumulation, both in parathyroid tumours and in carcinoids, but this mutation has not been confirmed in later studies (28, 29). An alteration in P21 and P27 has also been suggested (30, 31), though their role in ECL and parathyroid oncogenesis remains to be elucidated (17). Overall, further studies are needed to evaluate the possibility of a direct association between GC1 and PHPT. However, it is important to remember that the onset of GC1 is strictly related to the presence of CAAG. In our study, no GC1 were observed in any of the 20 patients with coexistent CAAG and PHPT, although 24 GC1 (22.4%) were identified in the group of 107 patients with CAAG.

The event sequence leading to the association between CAAG and PHPT remains to be elucidated, even if it is possible to hypothesize a common pathogenic mechanism for these diseases. There is no evidence that hypergastrinemia could influence PTH secretion in humans (11, 17, 23), whereas hypercalcaemia and/or elevated PTH levels may stimulate gastrin secretion (32, 33, 34, 35). In our study, gastrin and CgA concentrations did not significantly differ in CAAG patients according to the presence or absence of PHPT. Conversely, no significant differences were found in the concentration of total serum calcium, ionized calcium and PTH between the PHPT patients with and those without CAAG. Furthermore, in patients with both CAAG and PHPT, there was a correlation between gastrin and PTH levels, regardless of the origin population. CAAG is an autoimmune disease that is associated with other autoimmune diseases and type 1 and type 3 PGA syndromes (5). The pathogenesis of sporadic PHPT remains undetermined. According to some studies, a subset of PHPT cases could result from autoimmune pathogenic causes (36, 37).
hypothesis was first suggested by the observation of a higher PHPT incidence in females, with a male:female ratio of 1:2.4 (15, 16). Several autoimmune diseases, such as Graves’ disease, Hashimoto’s thyroiditis, Sjögren’s syndrome, rheumatoid arthritis, systemic lupus erythematosus, type 1 diabetes mellitus and celiac disease, may occur in patients with PHPT and a single case of PHPT was described in association with type 1 PGA syndrome (38). Furthermore, the presence of anti-parathyroid cell antibodies has been observed in PHPT patients (36, 37). Recently, Charrèt et al. (37) reported the presence of anti-calcium sensing receptor (CaSR) autoantibodies in 5/75 PHPT patients (6.6%), a prevalence that is similar to the prevalence of PHPT in the CAAG patients (i.e. 8.4%) and of CAAG in the PHPT patients (i.e. 7.4%) observed in our study. Therefore, although the pathogenic mechanisms underlying the association between CAAG and PHPT remain to be established, several lines of evidence suggest a possible role for autoimmunity. Theoretically, an autoimmune origin of PHPT could facilitate the development of multiple parathyroid hyperplasia, a finding that usually occurs in 10–15% of the patients (25). In this study, we found four-gland hyperplasia in 3/7 (42.9%) CAAG patients with PHPT and available histology and in 2/10 (20%) PHPT patients with CAAG. Parathyroid hyperplasia also occurred in 5/27 (18.5%) patients with antiparathyroid cell autoantibodies (36) and in 1/5 (20%) PHPT patients with circulating anti-CaSR autoantibodies (37). These data clearly indicate that autoimmunity could account for both parathyroid hyperplasia and solitary adenoma. As far as our study is concerned, the small number of cases precludes a proper conclusion on the importance of the histological differences in the two patient groups.

In the CAAG patients, we observed a high prevalence of secondary hyperparathyroidism due to vitamin D deficiency, which was present in 13 patients (12.1 vs 7% in general population (39)). In patients with CAAG, the regulation of calcium and/or vitamin D metabolism may be impaired, potentially because of the malabsorption of calcium and/or vitamin D in the intestine, which accounts for the frequent occurrence of osteoporosis in patients with autoimmune atrophic gastritis or gastric achlorhydria (40, 41). On the other hand, vitamin D plays an important role in regulating the immune system by inhibiting adaptive immunity (42, 43, 44). A chronic vitamin D deficiency could therefore promote the occurrence of other autoimmune diseases, including CAAG (45).

In conclusion, we have clearly documented that high levels of gastrin and PTH can coexist outside the MEN1 setting. Our findings have demonstrated a significant association between CAAG and PHPT, indicating that it would be prudent to screen CAAG patients for PHPT and vice versa. Although the pathogenic mechanisms underlying this association remain to be fully elucidated, a possible role for autoimmunity may be suggested, and it could be interesting to evaluate the anti-parathyroid cell and anti-CaSR autoantibodies in patients with both CAAG and PHPT.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Atrophic gastritis and hyperparathyroidism

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