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ORIGINAL ARTICLE

Association of autoimmune thyroid diseases, chronic atrophic gastritis and gastric carcinoid: experience from a single institution

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Abstract
Purpose Autoimmune polyendocrine syndromes (APS) type III are characterized by the association of autoimmune thyroid disease (ATD) with other autoimmune diseases such as diabetes, alopecia, pernicious anemia, vitiligo and chronic atrophic gastritis. A strong association between ATD and atrophic gastritis (AG) has been demonstrated. Moreover 10 % of patients affected by AG have a predisposition to develop gastric carcinoid and adenocarcinoma as a result of chronic hypergastrinemia caused by achlorhydria and subsequent ELC cells neoplastic transformation.
Methods The aim of the study is to evaluate, in a consecutive series of patients followed for ATD in our outpatients clinic, the prevalence of AG. In the period 2004–2014, 242 patients with ATD underwent a screening performing APCA, Vitamin B12, ferritin, iron, and hemoglobin and red cells count measurements with subsequent gastroscopy in case of APCA positivity.
Results We found 57/242 (23.5 %) patients with APCA positivity. Of these patients 33/57 (57.8 %), 31 F and 2 M, were affected by Graves disease; 24/57 (42.1 %) 21 F and 3 M by Hashimoto thyroiditis; 10/57 (17.5 %) presented with anemia, 14/57 (24.5 %) with vitamin B12 deficiency, 9/57 (15.7 %) with iron deficiency. In 2/57 a gastric carcinoid was found.
Conclusions Our data confirm the high association rate of AG in ATD which frequently is not an isolated disease but configure the picture of APS type III and need to be followed accordingly. An early diagnosis may be useful for diagnosis of gastric carcinoids and to explain and treat a gastric related L-thyroxine malabsorption and presence of chronic unexplained anemia.

Keywords Autoimmune disease · Thyroid disease · Autoimmune gastritis · Carcinoid · Graves' disease

Introduction

Chronic atrophic gastritis (AG) and pernicious anemia are common autoimmune disorders, being present in up to 2 % of the general population [1]. In patients with diabetes mellitus type 1 (DM1) or autoimmune thyroid disease (ATD), the prevalence is 3- to 5-fold increased [1, 2]. AG is characterized by atrophy of the corpus and fundus and presence of circulating autoantibodies to the parietal cell (APCA) and to their secretory product, intrinsic factor (AIF). Chronic auto-aggression to the gastric proton pump, H/K ATPase, may result in decreased gastric acid secretion, hypergastrinemia, and iron deficiency anemia [3, 4]. In a later stage of the disease, pernicious anemia may result from vitamin B12 deficiency. In patients with ATD, the presence of autoimmune gastrointestinal diseases can be suspected in cases of chronic unexplained refractory anemia [5].

AG can cause levothyroxine malabsorption as a major clinical feature [6, 7]. Moreover in up to 10 % of patients, autoimmune gastritis may predispose to gastric carcinoid tumors or adenocarcinomas [8]. AG is often part of the autoimmune polyendocrine syndromes (APS) type III characterized by: ATD (100 %), DM1 (8 %), alopecia (2 %) and Vitiligo (7 %). APCA can be found in 22 % of patients with Graves' disease (GD) and 32–40 % of those with

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Hashimoto thyroiditis (HT), while AG is present in 18 % of patients with GD and 30 % of patients affected by HT and pernicious anemia is present in 2 % of patients with GD and 4–12 % of those with HT [9, 10].

While in patients with APS type I an autoimmune regulator (AIRE) gene responsible of the disease has been identified, in patients with APS type III, though specific HLA haplotypes (B8 and DR3) are frequently observed, the inheritance is polygenic and complex. The incomplete concordance in monozygotic twins suggests that environmental factors are important in its pathogenesis [11]. To date, no genetic tests may identify patients with APS III, but susceptibility genes are known which increase the risk for developing autoimmune disorders, although they must not be causative. Actual diagnosis of APS III involves serological measurement of organ-specific autoantibodies and subsequent functional testing. Management of patients with APS III, including their family relatives, is best performed in centres with special expertise in autoimmunity [12].

The aim of this study is to evaluate, in a retrospective cohort of patients followed for ATD in our outpatients clinic, the prevalence of gastric autoimmune diseases.

Materials and methods

In the period 2004–2014, a retrospective cohort of 242 patients affected by ATD referred to our outpatient clinic and underwent a screening for gastric autoimmune diseases performing anti-parietal cells antibodies (APCA), vitamin B 12, ferritin, iron, hemoglobin and red blood cells count measurements with subsequent gastroscopy in case of APCA positivity. None of the patients underwent therapy with corticosteroids or other immunosuppressive drugs during the previous 6 months before APCA dosage was performed.

Laboratory tests

At the time of admission standard routine tests included: complete blood cells count, complete thyroid function assessment, TSI (thyroid stimulating immunoglobulin), Tg-Ab, TPO-Ab, APCA, vitamin B12, ferritin and iron blood levels. Patients with APCA positivity were subsequently addressed to endoscopy for confirmation of AG.

Diagnosis of anemia, defined as anaemia not related to evident or occult bleeding and/or to erythropoietic disorder, was based on the presence of hemoglobin level <12 and 13 mg/dl for female and male patients, respectively.

APCA were evaluated on serum using a solid-phase immunosorbent assay commercial kit (Elisa Kit, Euroimmun AG Seekamp 31, 23560, Lübeck, Germany).

Endoscopic assessment of autoimmune gastritis

The diagnosis of AG was based on the combined presence of APCA positivity and histological confirmation of atrophic body gastritis. Therefore, at time of our data revision 31/57 (54.4 %) patients with APCA positivity underwent gastroscopy with biopsies taken from the antrum and the mid-body. Atrophic gastritis was defined as focal or complete replacement of oxyntic glands by metaplastic pyloric or intestinal glands, according to the updated Sydney System [13].

Statistical analysis

Numbers and percentages are provided for qualitative data. Percentages were compared using χ^2 test, and the *t* test was used for continuous variables. All tests were 2-sided, and a *p* value 0.05 was considered statistically significant.

Statistical analyses were performed with SPSS software, version 13.0 for Windows (SPSS Inc, Chicago, IL, USA).

Results

Prevalence of APCA+ patients

A total of 242 patients, 207 (85.5 %) female and 35 (14.4 %) male, mean age 41.3 years (range 12–78) underwent a screening for gastric autoimmune diseases. 94/242 (38.8 %) were affected by GD and 148/242 (61.2 %) by HT.

We found 57/242 (23.5 %) patients with ATD with APCA positivity: 52 female and 5 male, F:M = 10.4:1.0, mean age 47.6 years (range 24–67). Of these patients 33/57 (57.9 %), 31 female and 2 male, were affected by GD (with concomitant thyroid cancer in two patients); 24/57 (42.1 %) 21 female and 3 male, by HT (with concomitant thyroid cancer in two patients, Table 1). The prevalence of APCA positivity in patients with GD vs HT was respectively 35.2 and 16.3 % ($p = 0.002$), (Table 2). 31/57 patients with APCA positivity and ATD (18 GD and 13 HT) underwent gastroscopy. Of these patients 22 (71.0 %) presented AG at histopathological examination, 12/18 (66.6 %) with GD and 10/13 (76.9 %) with HT. Among these 22 patients with confirmed diagnosis of AG at gastroscopy 9 (41.0 %), 5/18

Table 1 Prevalence of APCA+ in patients with autoimmune thyroid diseases

Patients	Screening population	APCA positivity (%)
Number	242	57 (23.5)
Female	207	52 (25.1)
Male	35	5 (14.3)

(27.7 %) with GD and 4/13 (30.7 %) with HT, presented Helicobacter pylori positivity.

Comorbidity in APCA+ patients (Fig. 1)

We found 10/57 (17.5 %) patients with anemia, 14/57 (24.5 %) with vitamin B12 deficiency, 9/57 (15.7 %) with iron deficiency. In 2/57 patients (3.5 %), all females, aged 41 and 67 years, a gastric carcinoid type 1 (GC type 1) was found. These patients presented with diarrhea, flushing and dyspepsia and high levels of gastrin and Chromogranin A (Cg A). Symptoms disappeared after endoscopic excision of the tumor in both patients (Fig. 2).

Discussion

AG is an autoimmune disorder, that affects the parietal cell-containing gastric corpus and fundus with sparing of the antrum [14]; mononuclear cells infiltration in the submucosa, with extension into the lamina propria between the gastric glands, parietal cells (which contain proton pump and produce intrinsic factor) and principal cells (containing digestive enzymes), frequently produces degenerative changes and parietal cells loss. Mucosa changes cause a progressive reduction of gastric acid secretion, until achlorhydria and replacement of parietal cells with mucus-containing cells resembling those of the small bowel mucosa (intestinal metaplasia). Determining immunological and genetic risk factors and early diagnosis of autoimmune gastritis are important to prevent and/or treat iron deficiency anemia, pernicious anemia, and pre-malignant gastric lesions. APCA and AIF are positive, respectively, in 60–85 % and 30–50 % of patients affected by AG. Autoimmune gastritis is often associated with other autoimmune diseases configuring the picture of an autoimmune polyendocrine syndromes type III (APS III), which frequently includes type 1 diabetes [15] and autoimmune thyroid disease (Hashimoto's thyroiditis and Graves' disease) [1, 16, 17].

In our series we found 57/242 (23.5 %) patients with ATD and APCA positivity, similarly to Pacini et al. findings (29.7 %) [18]. In previously published series APCA can be found in 22 % of patients with GD and 32–40 % of those with HT [9, 19], while in our series we found an higher frequency of APCA positivity in GD patients vs HT patients, and this may be related to genetic or environmental influences in our population but further studies are needed to demonstrate this hypothesis.

Table 2 Prevalence of APCA+ in 242 patients affected by HT and GD

No. of patients	APCA negative (%)	APCA positive (%)	*p**
GD 94	61 (64.9)	33 (35.1)**	0.002
HT 148	124 (83.8)	24 (16.2)**	0.001

HT Hashimoto thyroiditis, *GD* Graves' disease

* Chi-square test

** 2 patients affected by thyroid carcinoma

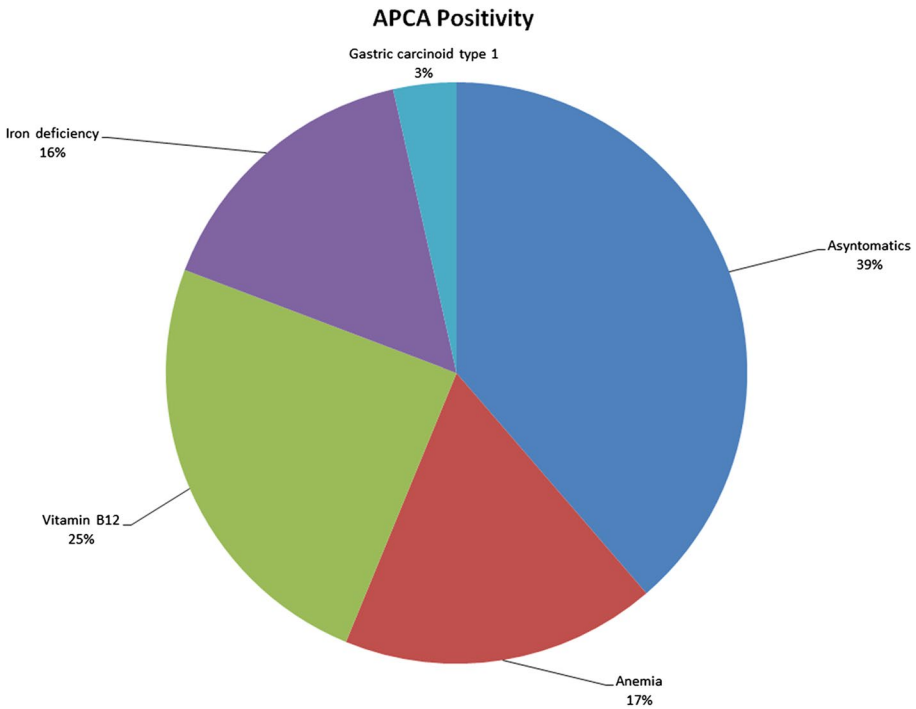

Fig. 1 Prevalence of associated diseases in 57 patients with ATD and APCA positivity

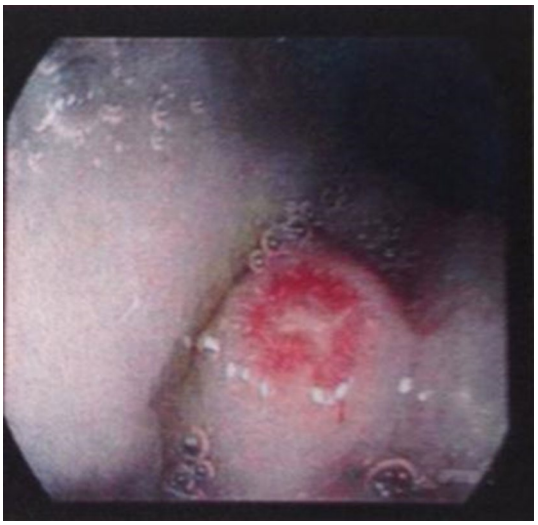

Fig. 2 Endoscopic image of GT type 1 in a patient with PAS type III

In our series the mean age of patients with AG was lower (47 years) than usual because many of the patients with ATD that underwent the screening for gastric autoimmunity were young. So we can assume that AG may be underestimated in the youth population because autoimmunity screening is not performed routinely.

Due to their pathogenetic role, APCA such as many serum autoantibodies can be detected a long time before the clinical onset and during the course of organ-specific autoimmune diseases. For these reasons, autoantibodies can be used as predictive markers of an on-going disease (in healthy subjects) and of disease activity and severity (in ill patients). These autoantibodies can be used for screening purposes in open populations or high-risk groups because can have a predictive role in organ-specific autoimmune. It was established that 36 % of patients with APCA positivity will develop AG within 5 years [20]. In our series among 31/57 patients APCA positive who underwent gastroscopy 22 (71.0 %) presented AG: 12/18 (66.6 %) with GD and 10/13 (76.9 %) with HT.

Typical features of AG are: megaloblastic anemia, vitamin B12 deficiency, achlorhydria, iron deficiency anemia, hypergastrinemia, and predisposition to GC type 1. The clinical picture is often characterized by gastrointestinal symptoms such as glossitis, tongue hypotrophy, aphthosis, angular cheilitis, diarrhea, malabsorption; symptoms and signs of anemia such as fatigue, palpitations, pallor of skin and mucous membranes; less frequently by neurological events such as different degree od demyelinating neuropathy (mostly in the legs), until pareto-spastic gait, positive Babinski and Romberg signs. In out-patients clinic a common clinical sign that may do suspect for AG is a high dose intake of levo-thyroxine to achieve euthyroidism.

Literature data report that in APCA positive patients 10–15 % presented with megaloblastic anemia/vitamin B12 deficiency and 20–40 % with iron deficiency likewise in our series (Table 2).

Supplemental vitamin B12 therapy is the treatment of choice in patients affected by megaloblastic anemia and vitamin B12 deficiency, it is possible to choose between parenteral and oral replacement therapy with vitamin B12.

Indeed, according to the American Thyroid Association (ATA) Guidelines for the treatment of hypothyroidism, gastrointestinal conditions should be considered when a patient's levothyroxine dose is much higher than expected; in these patients an evaluation for gastrointestinal disorders such as Helicobacter pylori related gastritis, atrophic gastritis, or celiac disease should be considered. Furthermore, if such disorders are detected and effectively treated, re-evaluation of thyroid function and levothyroxine dosage is recommended [21].

In up to 10 % of patients affected by AG there is a predisposition to the formation of gastric carcinoid tumors and adenocarcinomas [8]. In particular, GC type 1, evolving from ECL cell hyper/dysplasia induced by hypergastrinemia, may develop in 4–9 % of patients with autoimmune gastritis/pernicious anemia [22–24]. For this reason, although there are controversial indications in literature, patients with positive APCA and/or AG need a proper follow-up. To this end it is important to perform: yearly a gastrin, Cg A, iron, vitamin B12 and complete blood count dosage; an endoscopic surveillance (gastroscopy and gastric mucosa biopsies) at least once and every 5 years in patients with mucosa dysplasia or moderate ECL cells hyperplasia (especially if high gastrin levels are associated) [15].

GC type 1 are reported, on the basis of a prospective study, to represent up to 23 % of all digestive neuroendocrine neoplasms [25]. They may be divided into three types: types 1 and 2 are ECLomas, due to chronic hypergastrinemia, while type 3 carcinoids are rare and sporadic, as they are not a consequence of any gastric background pathology. GC type 1 arise in achlorhydria secondary to (autoimmune) atrophic fundic gastritis, while type 2 develop in response to hypergastrinemia resulting from neoplastic secretion from gastrinomas (Zollinger–Ellison Syndrome), mostly in patients presenting with multiple endocrine neoplasia type 1 (MEN 1) [26, 27]. GC type 1 represent 75–80 % of all and they usually are non-functioning tumors, typically found during upper gastro-intestinal endoscopy performed for dyspepsia or for macrocytic or iron deficiency anemia [3]. This condition is associated to slow gastric emptying (explaining dyspepsia) and progressive reduction of acid output, thus impairing iron and vitamin B12 absorption [3]. GC type 1 present frequently as polyps in the gastric fundus, but can be also detected

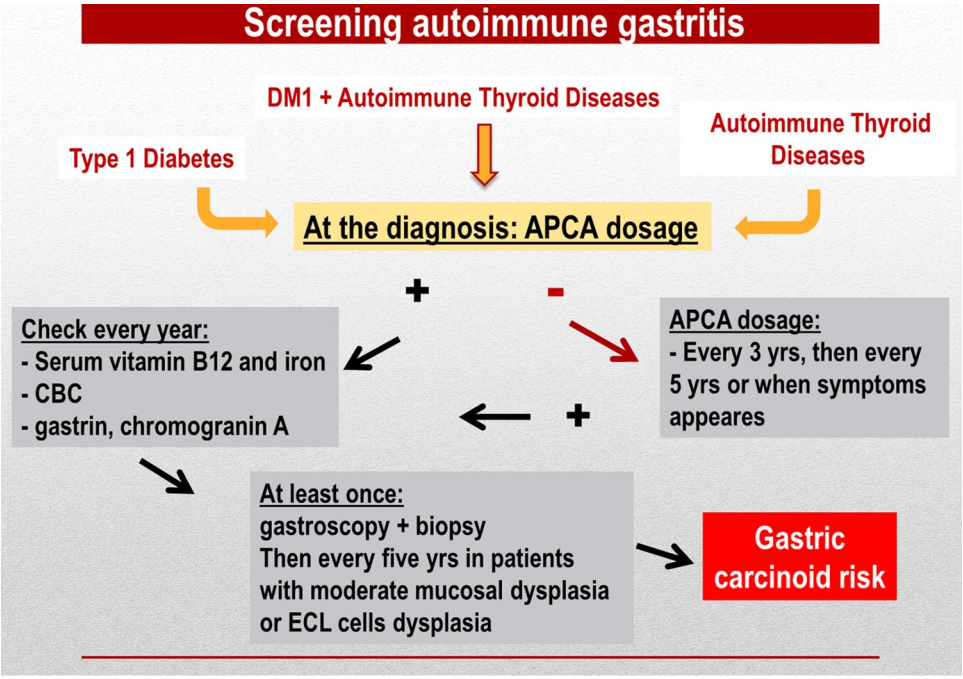

Fig. 3 Screening proposal in patients with ATD

only at biopsies (microcarcinoids 22.2 %); they occur more frequently in women and 70–80 % of tumors are classically diagnosed in the 5th and 7th decades, although with the more extensive use of endoscopy the age limit may be younger particularly in those patients with multiple autoimmune diseases; lesions are multiple in about 65 % of cases, with a median diameter of 5 mm [27, 28]. GC type 1 are usually benign (NET G1) and well differentiated so they have almost universally good prognosis with rare tumor-related death at follow-up, however rare cases of metastatic spread and bad prognosis have been described in the literature. Even if GC type 1 are often asymptomatic, the most frequently reported symptoms include abdominal pain, flushing, diarrhea (as we found in our patients) and also anemia-related symptoms and extremely rarely a carcinoid syndrome [29]. Serum Cg A blood level can indicate the presence of an increased ECL cell mass more accurately than morphological methods [30]. The guidelines ENets for follow-up of GC type 1 in patients with chronic atrophic gastritis propose clinical and laboratory monitoring in parallel with endoscopic procedures (EGD+ gastric mapping) that is at diagnosis and periodically every 1–2 years, by measuring serum iron and vitamin B12. An early diagnosis may be useful for diagnosis of GTC1 and to explain and treat a gastric related L-thyroxine malabsorption as well as the presence of a chronic unexplained anemia.

The therapy of choice is the endoscopic lesion resections. Surgery should be limited to the cases of invasion beyond submucosa, metastases and poorly differentiated lesions. Gastrin suppression by surgical (i.e. antrectomy) or medical (i.e. somatostatin analogs) is debatable [27]. Nevertheless today there are no defined guidelines for the screening and follow-up of autoimmune atrophic gastritis in patients with APS III.

Our data confirm the high association rate of AG in ATD which frequently are not isolated diseases but configure the picture of APS type III and need to be followed accordingly. The limit of our study is that so far not all the patients with APCA positivity underwent gastroscopy, but our partial data indicating AG in 22/31 (71.0 %) patients confirm the high prevalence of the disease in these patients.

In conclusion, we propose, accordingly to literature indications, in patients affected by ATD or DM 1 or both diseases, to perform an APCA serum dosage at the diagnosis. APCA positive patients should undergo a periodic determination of gastrin, serum iron, vitamin B12, blood count, Cg A and at least once endoscopy with biopsies of the gastric mucosa and then every 5 years in patients with moderate mucosal dysplasia or ECL cell hyperplasia (especially those with high levels of gastrin); negative patients should perform an APCA serum dosage every year for 3 years and then every 5 years or when the symptoms appear (Fig. 3).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures involving human participants were in accordance with the ethical standards of institutional research committee and with Helsinki declaration as revised in 2013. This is a retrospective study that did not involved animal participants.

Informed consent Informed consent of the present retrospective study was waived.

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