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Effective endoscopic management of gastric neoplastic complications in patients with autoimmune gastritis: results of a monocentric study of 88 patients

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Abstract

Background We evaluated the efficacy of endoscopic treatment (ET) for gastric neoplastic complications of autoimmune gastritis (AIG). We also assessed the safety of ET and the risk factors for the occurrence of neuroendocrine tumors (NETs) and gastric adenocarcinoma (GA).

Methods This was a retrospective, single-center, observational study. All patients diagnosed with AIG between 1987 and 2019 and had at least 1 upper endoscopy available were included.

Results The study population comprised 88 patients (68.2% female). The median follow up was 5 years (range 1-28). A total of 132 NETs were diagnosed in 39/88 patients (44.3%) (median age 50.0 years, range 27.0-85.0 years). The mean lesion size was 7.1 mm (range 1-30); there were 80 G1 NETs and 52 G2 NETs. Among the 132 lesions, 86.3% (114/132) were endoscopically resected, mostly by endoscopic mucosal resection (105/114, 92.1%), without complications. Only 1 patient underwent surgery. Twelve patients (13.6%) (7 females; median age, 76.0 years; range, 53.0-90.0 years) presented with GA. Of these, 66.7% (8/12) needed surgery, while 4 patients underwent exclusive endoscopic resection. Only 2 patients presented with NETs and GA (2.8%). Patients who presented with NETs were significantly younger at AIG diagnosis than patients with GA: 52.0 (18.0-85.0) vs. 67.0 (44.0-81.0) years (P=0.008). Patients who presented with GA were significantly older than those who presented with NETs: 76.0 (53.0-90.0) vs. 50.0 (27.0-85.0) years (P<0.001).

Conclusion ET of NETs for AIG is effective and safe. GA is rarer, occurs in significantly older patients, and usually requires surgery.

Keywords Autoimmune gastritis, gastric adenocarcinoma, neuroendocrine tumors, endoscopic treatment

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Introduction

Autoimmune gastritis (AIG) affects 2-5% of the elderly population [1]. This chronic inflammatory condition results in atrophic and metaplastic mucosa, leading to oxyntic mucosa-predominant atrophic gastritis, reduced or absent acid production, and the loss of intrinsic factor. This may in turn progress to a severe form of vitamin B12 deficiency anemia known as pernicious anemia. Despite advances in the understanding of AIG pathogenesis and molecular biology, the diagnosis of AIG is still challenging for clinicians, and AIG remains underdiagnosed [2]. Gastric adenocarcinoma (GA) and neuroendocrine tumors (NETs) are the most dreaded long-standing complications of AIG [3]. The incidence of GA in patients with AIG is controversial [4-6]. Many studies have

reported a higher risk of GA in patients with AIG. A Swedish study followed 21,265 patients with AIG for an average of 7.1 years. These patients had a significantly elevated risk for gastric cancer distal to the cardia (standardized incidence ratio [SIR] 2.4, 95% confidence interval [CI] 2.1-2.7), which increased with the follow-up duration [7]. A recent meta-analysis of 27 studies and 22,417 patients revealed that the calculated pooled gastric cancer incidence rate was 0.27% per person-year, and the overall relative risk of gastric cancer in AIG was 6.8 (95%CI 2.6-18.1) [8]. However, Rugge *et al* recently suggested that the excess of GA risk reported in patients with AIG could plausibly result from unrecognized previous/current *Helicobacter pylori* (*H. pylori*) comorbidity [9]. The most conspicuous excess risk was for NETs (SIR 26.4, 95%CI 14.8-43.5) [5]. Type 1 gastric NETs may arise in 0.4-7.0% of AIG patients screened by endoscopy [10].

Considering the heterogeneity of the described cohorts and the absence of larger randomized controlled trials with longer follow-up periods, the European Society of Gastrointestinal Endoscopy recommends follow-up endoscopy at 3- to 5-year intervals in patients with AIG [11]. Endoscopy is useful for diagnosing AIG, and detecting and potentially resecting neoplastic gastric lesions. Resection of type 1 G1/G2 NETs [1-2 cm] is the standard approach with good results [12,13]. However, there are no randomized data comparing an aggressive endoscopic approach (resecting all visible tumors) to more selective endoscopic therapy (resecting only larger lesions). Although some studies have reported greater rates of R0 resection with endoscopic submucosal dissection (ESD) and multiband mucosectomy than with endoscopic mucosal resection (EMR), the resection technique that should be used to remove NETs is still controversial [14-17].

With respect to GA, the indications for endoscopic resection (ER) are well defined. ER has been shown to be equal to surgical resection in terms of long-term outcomes when the lesion is resected *en bloc*, and when certain conditions are followed [18]. However, few studies have focused on the results of endoscopic treatment for gastric NETs and GA, specifically in patients with AIG.

The main objective of this study was to evaluate the efficacy of endoscopic management of gastric neoplastic lesions (NETs and GA) in patients with AIG. The secondary objectives were to assess the safety of endoscopic treatment and to evaluate the risk factors for the occurrence of NETs and GA in patients with AIG.

Patients and methods

Study design and data collection

This was a retrospective single-center observational study from an anticancer institute that is a tertiary referral center for endoscopy. All patients were identified via the full-text software ConSoRe™ [19] by searching for the keywords "autoimmune gastritis" or "Biermer's disease" from 1987 to 2019. ConSoRe™ is a new generation of Big Data health software developed by Unicancer, one of Europe's largest cancer research organizations. ConSoRe™ employs artificial intelligence based on machine learning and natural language processing. Some of the patients were being followed-up for AIG at our institute; the remainder were referred from other centers for resection of gastric lesions that developed in patients they were following for AIG, or that were discovered concurrently with the diagnosis of AIG.

Inclusion criteria and exclusion criteria

Patients with a confirmed diagnosis of AIG on the basis of typical histological features and at least 1 upper endoscopy result available were included. Patients for whom no endoscopic data were available, or who were being followed for familial adenomatous polyposis, were excluded.

Relevant data were extracted, including patient demographics (sex, date of birth, comorbidity), associated autoimmune disease and associated cancer, age at diagnosis of AIG, biological results (vitamin B12, iron deficiency, parietal cell antibodies and intrinsic factor antibodies, chromogranin A and gastrin values [upper limit of normal value 108 ng/mL and ULNV 126 pg/mL, respectively], the date and results of the first upper endoscopy, histological results of gastric biopsy, *H. pylori* infection found on biopsy, duration of endoscopic follow up (years), and occurrence of hyperplastic polyps (HPs). Data on NETs and GA, including date of occurrence, lesion size, number of lesions, type of treatment (surgery, endoscopic treatment), endoscopic treatment (modality of resection: ESD, EMR, polypectomy [hot, cold forceps], hybrid resection with EMR and ESD), surgery type and associated treatment (chemotherapy, radiochemotherapy), complication rates, and histological data (for NETs according to the 2019 World Health Organization [WHO] classification of tumors of the digestive system [20], and for GA following pathological TNM staging and eCurasystem), were also collected.

Definitions and follow up

The diagnosis of AIG was made by a senior gastroenterologist on the basis of gastric biopsy: diffuse atrophic gastritis oxyntic mucosa with variable proportions of intestinal metaplasia, pseudopyloric metaplasia and hyperplasia of the endocrine-like cells. The antrum is either normal or shows reactive gastropathy or gastrin-cell hyperplasia. It is associated with consistent clinical, biological (vitamin B12 deficiency) and serological (parietal cell antibodies and intrinsic factor antibodies) features. The follow up was evaluated from the time of the first upper endoscopy to the time of the last upper endoscopy.

Synchronous NETs were defined when multiple NETs were found during upper endoscopy, and metachronous NETs were defined as the appearance of new NETs during follow up after complete endoscopic resection of former NETs.

Surgical or endoscopic resection was considered R0 if both the vertical and horizontal margins were negative; if 1 of the margins was positive, resection was considered R1.

Endoscopic procedures

All procedures were performed under sedation with propofol or under general anesthesia. Endoscopic mucosal resection was performed after injecting a saline solution mixed with indigo carmine using the COOK MEDICAL™ snare. ESD was performed with the Dual knife™ or ITknife nano™ (OLYMPUS™, Tokyo, Japan). The procedures were performed on outpatients or patients with short hospitalizations.

Statistical analysis

The data were collected via Microsoft Excel software. Descriptive statistics are expressed as means with extremes. For quantitative data, the medians and means were calculated. For qualitative data, the percentages and frequencies were calculated. The statistical tests were carried out using SAS Enterprise Guide v7.15 software. The factors studied as part of the univariate analysis were age at diagnosis of GA, NET and AIG; sex; pulmonary comorbidity; alcohol intake; cardiovascular comorbidity; surgical history; diabetes; neurological comorbidity; associated autoimmune disease; positivity for parietal cell antibodies and intrinsic factor, and *H. pylori* infection. Multivariate logistic regression was used to evaluate the impact of the following parameters on the occurrence of GA and NETs: sex; age at diagnosis of GA, NET and AIG; pulmonary comorbidity; alcohol intake; diabetes; and cardiovascular comorbidity. Factors included in the univariate and multivariate models were derived from publications on a related topic. Associated odds ratios (ORs) were estimated with Wald's bilateral CIs and tests for significance.

Ethical considerations

The study was approved by the clinical research and innovation department of the Paoli-Calmettes Institute (IRB: ENDOBIERMER-IPC 2021-036, approval in 2021).

Results

Patient characteristics

Overall, 574 medical files from the Paoli-Calmette Institute from 1987 to 2019 were extracted using the ConSoRe™ software via the keywords "AIG" and "Biermer's disease". We excluded 115 patients whose AIG was mentioned only in their case history without endoscopic data, 322 patients who did not have AIG, 48 patients whose AIG was excluded because we had only histologic samples recorded for pathology expertise in our center without endoscopic data, and 1 patient whose AIG was excluded because he had familial adenomatous polyposis.

Eighty-eight patients were ultimately included. A total of 68.2% of the patients were female (60/88), and 34% of the patients (30/88) had associated autoimmune diseases. A total of 27.2% of the patients had associated cancer (24/88). The characteristics of our patients are shown in Table 1.

AIG

The median age at diagnosis was 57.5 years (range 18.0-85.0). The median follow up was 5 years (range 1-28). Seventy-nine patients (89.7%) had at least 1 follow-up endoscopy. The clinical clusters, biological data at diagnosis and follow-up data are presented in Table 2.

NETs

In total, 132 NETs were found in 39/88 patients (44.3%). The median age at diagnosis was 50.0 years (range 27.0-85.0). The mean size of the lesions was 7.1 mm (range 2-30). A total of 86.3% of the lesions were resected (114/132); 105 lesions were resected by EMR (92.1%), 2 by ESD (1.75%), 1 with hot forceps (0.87%) and 5 with cold forceps (5.2%). Forty NETs were classified as R1 in the histological report (40/114; 35%). No adverse events occurred after the ER of NETs (no delayed bleeding or perforation). Fifteen NETs were only biopsied and monitored, either because the NETs were discovered fortuitously on systematic gastric biopsies with no significant visible lesions, or because their size was inferior at 1 cm (11.3%). A total of 60.6% of the lesions were Grade 1 (80/132) and 39.3% were Grade 2 (52/132), according to the WHO classification. No Grade 3 tumors were found. The median Ki-67 index of the Grade 2 NETs was 4.7 (3-12.2). A total of 72.4% of the patients had multiple NETs. Three patients presented with 14, 38 and 25 NETs, respectively, which were completely resected in 4, 6 and 5 sessions (Fig. 1). 48.7% of the patients had multiple NETs (synchronous or metachronous). Metachronous NETs appeared during follow up in 46.1% (18/39) of the patients who had already presented with a NET, all of whom were treated endoscopically. No recurrence occurred after resection. Only 1 patient underwent surgery because of NETs. This patient was a 35-year-old female who underwent EMR for 2 well-differentiated G1 NETs (Ki-67=1%) in 2013 (T2). In 2016, 6 more EMRs for G2 NETs (Ki-67=3%) were performed. In 2019, she underwent EMR for a G2 NET, with a Ki-67 index of 8.74%. After discussion in a multidisciplinary meeting and considering the numerous recurrences and the increase in the Ki-67 index, a total gastrectomy was performed with lymph node dissection: 3 G1-G2 NETs measuring 2, 4 and 5.5 mm with Ki-67 values of 6.6%, 12.2% and 5.2%, respectively, were recorded on the resected specimen, and no lymph nodes were invaded. Six patients had gastrin-cell hyperplasia found on gastric biopsy (6/75). No NET-related deaths were reported in

Table 1 Patients

Patients	N=88	%
Female	60	68.2
Comorbidity		
Cardiovascular	46	52.3
Pulmonary	8	9.1
Diabetes	14	15.9
Smoking	16	18.2
Alcohol consumption	4	4.5
Associated autoimmune disease	30	34.0
Autoimmune thyroiditis	22	
Rheumatoid arthritis	1	
Bullous pemphigoid	1	
Myasthenia	2	
Antiphospholipid syndrome	1	
Autoimmune pancreatitis	1	
Vitiligo	3	
Psoriasis	1	
Coeliac disease	1	
Diabetes	1	
Juvenile arthritis	1	
Systemic lupus erythematosus	1	
Raynaud's syndrome	1	
Addison's disease	1	
Scleroderma	1	
Autoimmune hemolytic anemia	1	
Associated cancer except gastric cancer	24	27.2
Hemopathy	5	
Prostate	3	
Lung	1	
Bladder	1	
Esophagus	1	
Colon	1	
Ovary	1	
Breast	2	
Head and neck	1	
Malt lymphoma	2	
Neuroendocrine pancreatic tumor	1	
Meningioma	1	
Thyroid carcinoma	2	
Lung carcinoid tumor	1	
Neuroendocrine gut tumor	1	

Table 2 Autoimmune gastritis

Autoimmune gastritis	N = 88	%
Age at diagnosis	N=70/88	79.5
Median	57.5	
Mean	55.3 (18-85)	
Clinical clusters at diagnosis	N=39/88	44.3
Incidental finding	8	
Anemia	11	
Vitamin B12 deficiency	4	
Neurological symptoms	1	
Asthenia	1	
Weight loss	1	
Diarrhea	2	
Associated autoimmune disease	2	
Epigastralgia	9	
Biological results	N=35/88	39.7
Vitamin B12 deficiency	16	
Iron deficiency	7	
High gastrin rate	22	
Mean rate pg/mL (min–max) ULNV <126 pg/mL	N=16/22	
	1403.3 (118-3517)	
Positive intrinsic factor antibodies	11	
Positive parietal cell antibodies	11	
Chromogranin A rate ng/mL ULNV <108 ng/mL	N=11/88	
Mean (min-max)	315.5 (100-962)	
H. pylori infection found on biopsy	N=5/73	6.8
Occurrence of hyperplasic polyp	N=7/88	7.9
Duration of endoscopic follow up (years)	N=78/88	88.6
No follow-up endoscopy	9	
Indeterminate	1	
Median (min-max)	5 (1-28)	

ULNV, upper limit of normal value

our study, and no patients developed metastasis from a gastric NET; the disease-specific survival for NETs was 100%. The characteristics of the NETs can be found in Table 3.

GA and adenoma

Twelve patients (13.6%) (7 females, median age 76.0 years (range 53.0-90.0) presented with GA, and 1 patient had an adenoma (1.1%). The management of these patients is presented in Fig. 2 and the histological results in Table 4.

Among the 88 patients, 12 developed a GA. Among these 12 patients, the exact dates of diagnoses for AIG and GA were known for 10/12 patients. In 6 of these 10, the diagnosis of GA was concomitant with the diagnosis of AIG: i.e., GA was not previously known in 6/10 patients (60%). Only 1 patient who presented with GA had a confirmed *H. pylori* infection on biopsy.

Eight patients underwent ER, and no delayed complications occurred (Fig. 3). One patient presented with procedural bleeding that was treated endoscopically. 4 patients had exclusive ER. Two patients presented with recurrence and 1 patient presented with a metachronous lesion. One patient with a resected specimen classified as pT1b sm1 R0 with submucosal involvement of 800 microns developed gastric linitis 4 years later. As he was 94 years old with altered status, he was managed with only palliative care. One patient had a 10 mm T1a m1 resection with recurrence 2 years later; the 2 lesions

Table 3 Neuroendocrine tumors

Neuroendocrine tumors		%
Number of patients	N=39/88	44.3
Number of lesions	N=132	
Age at diagnosis		
Median (year)	60 (35-91)	
Size	N=106/132	
Mean (min-max)	7.11 (1-30)	
Median	5.75	
G1	80	60.6
G2	52	39.3
G3	0	0
Ki-67	N=116/132	
Mean (min-max)	2.89 (1-12.2)	
Multiple	19/39	48.7
Treatment		
Endoscopy	114	86.3
Surgery	3	2.2
Biopsy and watch	15	11.3
Endoscopic treatment	N=114/132	
ESD	2	1.75
EMR	105	92.1
Hot forceps	1	0.87
Cold forceps	6	5.2
Complications	0	0
R1	40	35
Occurrence of new lesions	18	46.1

ESD, endoscopic submucosal dissection; EMR, endoscopic mucosal resection

that were resected by ESD were classified as pT1b R1 and pT2 R1. Because the patient refused surgery, the scar was resected, and no residual lesion was observed in the final report. No relapse was recorded after a 2-year follow up. One patient had a 40 mm pT1a m1 lesion resected by a hybrid technique (ESD and EMR), and 2 resections were then performed via EMR for a low-grade tubulovillous adenoma. Four patients needed additional surgery: 2 patients with depth invasion >PT1b 500 microns, 1 patient with pT1a invasion because of positive vertical and horizontal margins, and 1 patient with pT1a m^3 invasion because of a positive horizontal margin. Eight patients underwent surgery: 6 underwent total gastrectomy, 1 partial gastrectomy and 1 superior polar esophagogastrectomy. Three patients received perioperative chemotherapy, and 1 received preoperative radiochemotherapy. None of these patients presented with recurrence after surgery or died of GA.

Only 2 patients presented with a NET and a GA (2.8%). One patient presented with a mixed neuroendocrine nonneuroendocrine neoplasm associated with multiple G1 NETs, and he underwent total gastrectomy. One patient

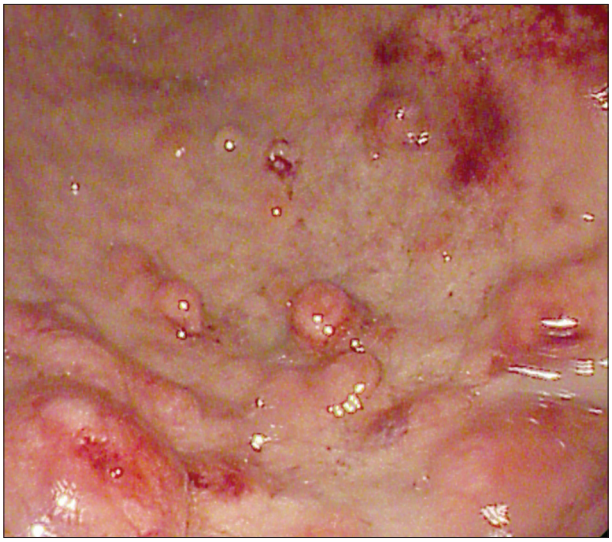

Figure 1 Multiple neuroendocrine tumors, G1

presented with a 30 mm G1 NET in 2008 resected by EMR, and in 2015, he presented with an 8 mm GA classified as pT1a m3 R0 and resected by EMR.

HPs

Seven patients had histologically confirmed HPs, and 5 underwent resection (3 EMR and 2 ESD). For 71% of the patients (5/7), the HPs were multiple, metachronous or synchronous. According to current recommendations, these polyps were resected for histological diagnosis and no dysplasia was found. Notably, even the 2 patients who underwent complete ER by ESD of the HP presented multiple cases of HP recurrence.

Evaluation of the risk factors for NET and GA occurrence

According to the univariate analysis, the patients who presented with GA were significantly older [76.0 (53.0-90.0) years] than those who presented with NETs [50.0 (27.0-85.0) years] (P<0.001). Only 1 patient presented with GA before the age of 65 years. The patients who presented with NETs were significantly younger at the time of AIG diagnosis than were those who presented with GA [52.0 (18.0-85.0)] vs. [67.0 (44.0-81.0)] (P=0.0087), and significantly more men than women presented with NETs (P=0.0482). There was also a significant association between pulmonary comorbidities and GA. The 4 patients had asthma and obstructive sleep apnea, chronic obstructive pulmonary disease and smoking, asthma, and bronchiectasis. *H. pylori* status was not a significant risk factor for GA.

According to the multivariate analysis, the only significant risk factor for GA was patient age (P=0.0326). The significant risk factors for NETs were male sex (P=0.0323) and patient age at the time of AIG diagnosis (P=0.0247). The results of the univariate analysis are presented in Table 5, and the results of the multivariate analysis are presented in Table 6.

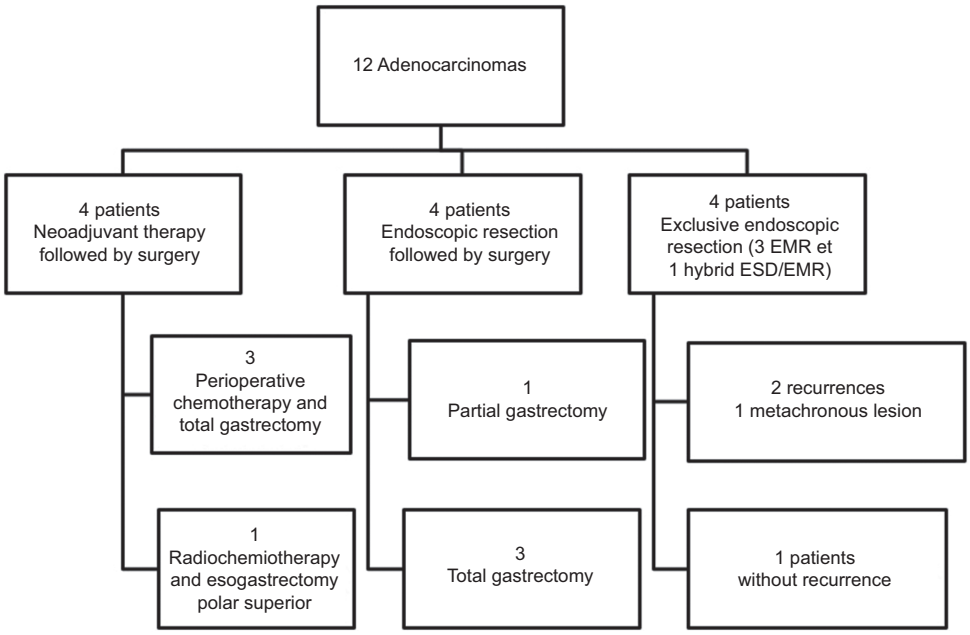

Figure 2 Flowchart of adenocarcinomas

Discussion

To our knowledge, this retrospective study analyzing the endoscopic management of 132 NETs and 12 GAs occurring in 88 patients followed for AIG represents one of the largest series with a significant follow up in a western country [21].

The main results confirm that endoscopic treatment of NETs is effective and safe. Almost all patients with NETs were managed endoscopically, without surgery or complications, even those who presented with many NETs (the lesions were endoscopically resected in multiple sessions) or G2 NETs. The number of G2 NETs was particularly high in our study (39.3%), possibly because of selection bias, given that we are tertiary referral centers for ER. However, Vanoli *et al* reported that G2 NETs were not associated with tumor behavior in type I NETs [22]. In our study, 92.1% of NETs were resected by EMR, and only 1.75% were resected by ESD, with a significant percentage of positive margins. Several studies have demonstrated superior complete resection rates of gastric NETs using ESD, compared with those achieved with EMR [14,15]. Hopper *et al* reported that complete *en bloc* ER of multiple G1 NETs can be safely and easily performed via a multiband mucosectomy technique [16].

First, our study was a retrospective analysis over several decades, and advanced techniques such as ESD were not as developed as those currently available. However, according to the results of our study, EMR appears to be effective. This may be because the median size of the lesion is small (7.1 mm) and because gastric NETs are slow-growing tumors, which could explain why lesions treated by EMR did not relapse during patient follow up. Noh *et al* reported a better complete resection rate for ESD than EMR for NETs, even for small lesions less than 1 cm; however, the disease-free survival rate did not differ significantly between the groups [17]. Despite

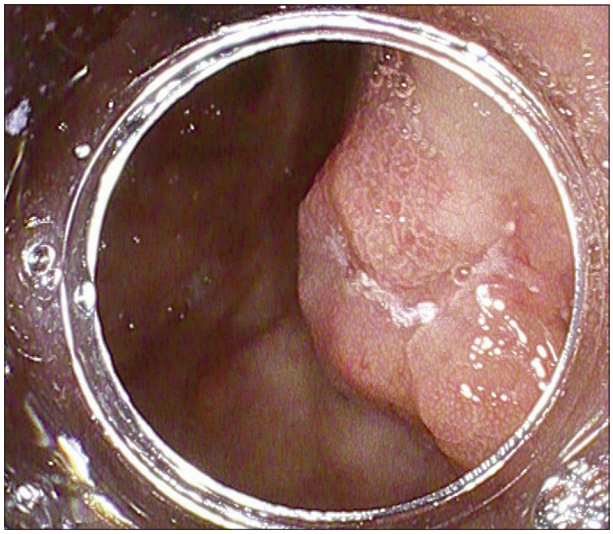

Figure 3 Adenocarcinoma pT1b

the recommendation of the European Neuroendocrine Tumor Society to remove NETs between 1 and 2 cm, in all published studies reporting ER of type 1 NETs, lesions of ≤1 cm are resected. This may be because size evaluation is not easy, complete ER is safe and allows complete removal of the lesion with a complete pathological examination, and follow up is easier, especially in the case of multiple NETs.

In our study, a GA was found in only 12 patients (13.6%). This finding corroborates published data that the occurrence of GA in AIG patients is not frequent [4-7]. However, despite therapeutic progress, the prognosis of GA remains unfavorable. Therefore, detection at an early stage for GA occurring in patients followed for AIG is crucial. In our study, we observed that, for 60% of our patients, the diagnosis of AIG

Table 4 Histology of gastric adenocarcinoma

Patient	Treatment	Method	size (mm)	Histology after endoscopic resection	ESGE classification	eCura	Histology after surgery	Recurrence
Patient 1	Endoscopic treatment	EMR	15	pT1b sm1 800 micron R0	High risk resection	C-2		Yes
Patient 2	Endoscopic treatment	EMR	8	pT1a m3 R0	Very low risk resection	A		No
Patient 3	Endoscopic treatment	EMR/ESD	40	pTisR0	Very low risk resection	A		No
Patient 4	Endoscopic treatment	EMR	10	pT1a R0	Very low risk resection	A		Yes
Patient 5	Endoscopic treatment and surgery	ESD/Partial gastrectomy		pT1a positive vertical and horizontal margin	High risk resection	C-2	pT1aN0 R0	No
Patient 6	Endoscopic treatment and surgery	EMR/ESD/Total gastrectomy	15	pT2 positive vertical margin	High risk resection	C-2	pT0N0	No
Patient 7	Endoscopic treatment and surgery	EMR/Total gastrectomy	25	MINEN pT1b sm3	High risk resection	C-2	MINEN pT1b N0RO, multiple G1 NETs	No
Patient 8	Endoscopic treatment and surgery	EMR/ESD/Total gastrectomy	30	pT1a m3 positive horizontal margin	Local risk resection	C-1	pT0N0	No
Patient 9	Perioperative chemotherapy and surgery	Total gastrectomy	40				pT3N1R0	No
Patient 10	Perioperative chemotherapy and surgery	Total gastrectomy extending to the tail of the pancreas and to the colon	40				pT3N0R0	No
Patient 11	Perioperative chemotherapy and surgery	Total gastrectomy	70				pT3N1R0	No
Patient 12	Radiochemotherapy and surgery	Esophagogastrectomy polar superior (Lewis Santy procedure)	55				PT3N0R0	No

ESGE, European Society of Gastrointestinal Endoscopy; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection

was concomitant with the diagnosis of GA. Unfortunately, these patients did not benefit from screening. Lenti *et al* reported that AIG is burdened by substantial diagnostic delay, especially in female patients, which is due to a lack of awareness, particularly among gastroenterologists [23]. These findings suggest that there should be better sensitization of gastroenterologists to the diagnosis of AIG. Moreover, in our study, only 5 patients met the criteria for ER of superficial adenocarcinoma, as defined by the Japanese and European guidelines [18,24]. A total of 66.7% of the patients who were diagnosed with GA needed surgery (8/12), and 50% needed neoadjuvant therapy (4/8). These data corroborate the fact that, in the French population, fewer than 5% of superficial cancers are resected endoscopically [25]. Despite high-resolution endoscopic technologies, the proportion of gastric cancers diagnosed at the superficial stage has not increased over time.

Table 5 Results of univariate analysis of risk factors for NET and GA occurrence

Factors	N	All (n=88)	GA and not NET (n=10)	GA and NET (n=2)	Not GA and not NET (n=39)	Not GA and NET (n=37)	P-value
Female	N (%)	60 (68.2)	7 (70.0)		31 (79.5)	22 (59.5)	0.0482
Male	N (%)	28 (31.8)	3 (30.0)	2 (100.0)	8 (20.5)	15 (40.5)	
Age at diagnosis	N	49	10	2		37	<0.001
	Mean (SD)	58.2 (15.8)	74.3 (9.8)	67.0 (8.5)		53.4 (14.4)	
	Median [Min–Max]	59.0 [27.0-90.0]	76.0 [53.0-90.0]	67.0 [61.0-73.0]		50.0 [27.0-85.0]	
Positive *H. pylori* status	N (%)	5 (5.7)	1 (10.0)		2 (5.1)	2 (5.4)	0.9198
Age at AIG diagnosis	N	70	9	1	30	30	0.0087
	Mean (SD)	55.3 (16.1)	68.0 (11.5)	73.0 (.)	56.4 (14.8)	49.9 (16.4)	
	Median [Min–Max]	57.5 [18.0-85.0]	67.0 [44.0-81.0]	73.0 [73.0-73.0]	58.5 [23.0-84.0]	52.0 [18.0-85.0]	
Smoking	N (%)	16 (18.2)		1 (50.0)	8 (20.5)	7 (18.9)	0.2910
Alcohol consumption	N (%)	4 (4.5)		1 (50.0)	1 (2.6)	2 (5.4)	0.0153
Pulmonary comorbidity	N (%)	8 (9.4)	2 (20.0)	2 (100.0)	2 (5.4)	2 (5.6)	<0.001
Cardiovascular comorbidity	N (%)	46 (54.1)	7 (70.0)	1 (50.0)	23 (62.2)	15 (41.7)	0.2365
Surgery	N (%)	46 (54.1)	5 (50.0)	1 (50.0)	25 (65.8)	15 (42.9)	0.2665
Diabetes	N (%)	14 (16.5)			6 (16.2)	8 (22.2)	0.3570
Neurological comorbidity	N (%)	7 (8.1)	1 (10.0)		4 (10.5)	2 (5.6)	0.8412
Associated autoimmune disease	n (%)	31 (36.0)	6 (60.0)		12 (31.6)	13 (36.1)	0.2674
Positive parietal cell antibodies	n (%)	13 (50.0)			11 (64.7)	2 (25.0)	0.1070
Intrinsic factor antibodies	n (%)	12 (46.2)	2 (100.0)		7 (43.8)	3 (37.5)	0.2710

NET, neuroendocrine tumor; GA, gastric adenocarcinoma; H. pylori, Helicobacter pylori; SD, standard deviation; AIG, autoimmune gastritis

Notably, GA occurred at a median age of 76.0 years in our study, which indicates that there should be an extended follow up for patients who remain fit for treatment. These data agree with the median age at diagnosis for patients with gastric cancer worldwide, which is 70 years [26]. Furthermore, a cohort of 4517 patients with AIG who were followed for 20 years revealed that the risk of stomach cancer was highest in the first year after the diagnosis of AIG (SIR 7.4, 95%CI 5.3-10.1), but an elevated risk persisted throughout the follow-up period [27]. In a recently published study, Rugge *et al* suggested that the high risk of gastric cancer reported for patients with AIG could plausibly be caused by unrecognized previous/current *H. pylori* comorbidity [4]. Two hundred eleven naïve *H. pylori*-negative patients (tested by serology, histology, and molecular biology) with AIG (F: M=3.15:1; P<0.001) were prospectively followed up with paired biopsies (T1 vs. T2; mean follow-up years: 7.5±4.4; median: 7), and no excess risk of gastric or other malignancies was found. However, in the Rugge *et al* study, the median age at the first endoscopy was only 56 years, and that at the second endoscopy was 64 years. First, we were unable to obtain *H. pylori* biopsy results for all the patients who presented with GA. Second, it is possible to have an infection with a negative gastric biopsy. Therefore, it could be interesting to recommend *H. pylori* serology in patients with AIG whose gastric biopsies are negative for *H. pylori* to identify patients at increased risk.

In our study, only 2 patients presented with an association between a GA and a NET (2.8%). NETs appeared in younger

Table 6 Results of multivariate analysis of risk factors for NET and GA occurrence

Multivariate analysis NET positive GA negative						
Total Nb. Obs	Total events	Variable	Obs (%)	Event (%)	Odds Ratio [95%CI]	P-value
68	31	Male	21 (30.88%)	12 (57.14%)		
		Female	47 (69.12%)	18 (38.30%)	0.23 [0.06-0.88]	0.0323
		Age at diagnosis			0.96 [0.92-0.99]	0.0247
		Pulmonary comorbidity	6 (8.82%)	1 (16.67%)	0.14 [0.01-1.61]	0.1149
		Alcohol consumption	3 (4.41%)	2 (66.67%)	1.24 [0.08-20.03]	0.8805
		Diabetes	13 (19.12%)	7 (53.85%)	1.55 [0.39-6.20]	0.5324
		Cardiovascular comorbidity	37 (54.41%)	14 (37.84%)	0.55 [0.16-1.90]	0.3468
		H. pylori status positive	5 (7.35%)	2 (40.00%)	0.48 [0.06-4.04]	0.5003
Multivariate analysis GA positive and NET negative						
Total Nb. Obs	Total Nb. Events	Variable	Obs (%)	Event (%)	Odds Ratio [95%CI]	P-value
68	9	Male	21 (30.88%)	3 (14.29%)		
		Female	47 (69.12%)	6 (12.77%)	1.53 [0.24-9.83]	0.6551
		Age			1.08 [1.01-1.16]	0.0326
		Pulmonary comorbidity	6 (8.82%)	2 (33.33%)	6.57 [0.55-78.69]	0.1373
		Alcohol consumption	3 (4.41%)	0 (0.00%)	0.00 [0.00-0.00]	0.9829
		Diabetes	13 (19.12%)	0 (0.00%)	0.00 [0.00-1.36]	0.9657
		Cardiovascular comorbidity	37 (54.41%)	6 (16.22%)	1.04 [0.16-6.89]	0.9669
		H. pylori status positive	5 (7.35%)	1 (20.00%)	4.35 [0.29-66.08]	0.2892

NET, neuroendocrine tumor; GA, gastric adenocarcinoma; CI, confidence interval; H. pylori, Helicobacter pylori

subjects than in the GA group (50.0 [27.0-85.0] vs. 76.0 [53.0-90.0], P<0.001), and the patients who presented with NETs were younger at the time of AIG diagnosis (52.0 [18.0-85.0] vs. 67.0 [44.0-81.0], P=0.0087). Sjöblom *et al* reported that patients who had NETs had a long duration of AIG and a young age of onset [28]. Vanoli *et al* reported that both enterochromaffin-like cell dysplasia and severe hyperplasia indicate a higher risk of NET development in AIG with hypergastrinemia/G-cell hyperplasia [22]. In patients with AIG, NETs appear earlier than GA. The occurrence of GA represents the final outcome of the inflammation–atrophy–metaplasia–dysplasia–carcinoma sequence, known as the Correa cascade, which occurs later during AIG [29]. The finding that patients with NETs are younger than those with GA could indicate that the latter develop from the former. Moreover, the relationship between NETs and GA should be examined via immunohistochemistry with appropriate antibodies to mark ECL cells, since carcinomas in patients with AIG can be neuroendocrine carcinomas [30,31]. We found that significantly more men than women had gastric NETs in our study; however, these data have not been confirmed in the literature. Notably, Lahner *et al* studied sex differences in autoimmune atrophic gastritis and reported that gastric neoplastic lesions were similarly distributed among female and male patients [32]. In our series, 7.9% of the patients had a HP, 5/7 were resected and no dysplasia was found. This finding is in accordance with data from the literature indicating that HPs are associated with AIG [33]. Some recent studies have suggested the presence of dysplastic elements in up to 19% of HPs, including some cases of focal carcinoma. The risk of patients with HP developing cancer increases with the polyp size, suggesting that endoscopic removal of gastric polyps >0.5 cm in size should be recommended to eliminate sampling error [34].

In our series, 7.9% of the patients underwent ER of an HP. This finding is in accordance with data from the literature indicating that HPs are frequent in patients with AIG [33]. Some recent studies have suggested the presence of dysplastic elements in up to 19% of HPs, including some cases of focal carcinoma, leading some authors to recommend endoscopic removal of gastric polyps >2.5 cm in size; however, no dysplasia was found in the HPs resected in our series [34].

The major limitation of our study was the retrospective nature of the analysis, with some missing data, due in part to the patients being referred for gastric polyp resection in our tertiary center by a referring gastroenterologist who did not provide all the biological data. There was also selection bias, because the study was conducted at an anticancer institute that is a tertiary referral center for endoscopy.

In conclusion, this study confirms that endoscopic treatment of type 1 NETs is preferable to surgery, in view of the good prognosis of these tumors and because it is safe, even in patients

with multiple NETs or G2 NETs. With respect to GA, surgery is presently the most common treatment. This study highlights the need for better sensitization of gastroenterologists to the diagnosis of AIG and better training to detect precancerous lesions. The factors that influence the development of NETs or GA in patients with AIG remain to be elucidated.

Summary Box

What is already known:

- Gastric adenocarcinoma (GA) and neuroendocrine tumors (NETs) can occur in autoimmune gastritis
- Patients with type 1 NETs have a good prognosis
- Hyperplastic polyps are common in patients with autoimmune gastritis

What the new findings are:

- This study confirms that endoscopic treatment of type 1 NETs is preferable to surgery, in view of the good prognosis of these tumors and because it is safe, even in patients with multiple lesions or G2 NETs
- The patients who presented with NETs were significantly younger at the time of AIG diagnosis than were those who presented with GA, 52.0 (18.0-85.0) vs. 67.0 (44.0-81.0) years (P=0.0087), whereas the patients who presented with GA were significantly older, 76.0 (53.0-90.0) years, than those who presented with NETs, 50.0 (27.0-85.0) years (P<0.001)
- With respect to GA, surgery is presently the most common treatment

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