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Factors associated with elevated serum chromogranin A levels in patients with autoimmune gastritis

STOMACH

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ABSTRACT

Background/Aims: Chromogranin A is an important tool in the diagnosis of neuroendocrine tumors. Autoimmune gastritis is an autoimmune disorder marked by hypergastrinemia, which stimulates enterochromaffin-like cell proliferation. Chromogranin A is also elevated in autoimmune gastritis patients with a different level of increase in each patient. The goal of this study is to explore constituents that influence serum chromogranin A levels in autoimmune gastritis patients.

Materials and Methods: One hundred and eighty-eight autoimmune gastritis patients and 20 patients with type I gastric carcinoid tumors were analyzed retrospectively and compared to 110 functional dyspepsia patients in terms of factors that might affect serum chromogranin A levels.

Results: The mean serum chromogranin A level was 171.17±67.3 ng/mL in autoimmune gastritis patients (n=62) without enterochromaffin-like cell hyperplasia, and 303.3±102.82 ng/mL in patients (n=126) with enterochromaffin-like cell hyperplasia ($p<0.001$). The presence of corpus atrophy (p=0.026, OR: 5.03, CI 95%: 1.21–20.88, β=1.61) and presence of enterochromaffin-like cell hyperplasia (p=0.017, OR: 6.59, CI 95%: 1.4–31.08, β=1.88) were found as risk factors associated with serum chromogranin A level.

Conclusion: Factors influencing raised serum chromogranin A levels in autoimmune gastritis were the presence of ECL cell hyperplasia and serum gastrin levels. Serum chromogranin A levels maybe helpful in distinguishing autoimmune gastritis patients and gastric carcinoid type I from the control group, but not useful in the differentiation of individuals with autoimmune gastritis from patients with gastric carcinoids.

Keywords: Enterochromaffin-like cell hyperplasia, hypergastrinemia, gastric carcinoid

Original Article

INTRODUCTION

Autoimmune gastritis (AIG) is an organ-specific and autoimmune inflammatory disorder branded by the absence of gastric parietal cell mass and autoantibody development against some molecules containing H^+/K^+-ATPase and intrinsic factors. The reduction and/or absence of gastric parietal cell mass causes replacement of the parietal cell mass by atrophic mucosa. Vitamin B_{12} metabolism is impaired and iron deficiency anemia can also occur in the final stages of this disease (1). Autoimmune gastritis is also a risk factor for gastric neuroendocrine tumors (carcinoids) and gastric cancer development (2). Gastric cancer incidence ranges from 1 to 3% for gastric carcinoma and from 2 to 12.5% for carcinoid tumors in patients with AIG with or without pernicious anemia (3-6). Gastric carcinoid tumors that occur in patients with AIG are labeled as type I gastric carcinoids. Type I gastric carcinoids are usually discovered parenthetically during gastroscopies carried out due to other reasons such as iron deficiency or dyspeptic complaints. In these patients, the overall survival ratios are somewhat better in which the disease-specific survival rate reaches 100% (7). Type I gastric carcinoid tumors are known as benign lesions and have an indolent course; however, up to 5% of patients with type I gastric carcinoids may cause metastases (8). Chromogranin A (CgA) is a glycoprotein that is found in neuroendocrine cells and it is an important tool in the determination of neuroendocrine tumors (9). There is a positive association between serum CgA levels and the

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size of enterochromaffin-like (ECL) cell masses in patients with AIG, gastrinoma, and it is also found to be high in patients who take long-term proton pump inhibitors (10-12). Serum CgA levels reflect the degree of proliferative changes in gastric ECL cells and ECL cell mass is an important determinant for CgA elevation in hypergastrinemic states (5,11,13). Therefore, our observations during our previous studies including AIG patients showed that these patients exhibit varying degrees of elevated serum CgA levels; and this finding has led us to investigate the pattern of serum CgA levels further to identify the factors that might affect serum levels of CgA in patients with AIG.

MATERIALS AND METHODS

In this study, we investigated patients with AIG and gastric carcinoid tumor type I during a 5-year time period. The diagnosis of AIG was established on gastric histopathological findings. In addition, serum gastrin levels and antiparietal cell antibodies were also investigated in each patient (14). Histologically, a chronic inflammatory infiltrate is associated with the depletion of oxyntic glands, parietal cells, and zymogenic cells in AIG, which affects gastric fundal and corporal mucosa (15). We investigated demographic characteristics of each patient, biochemical data, *Helicobacter pylori* infection, and histopathological properties of gastric biopsy specimens. This information was retrieved retrospectively from hospital medical records. Serum CgA levels were measured by using commercially available kits (CGA-ELISA CT; CIS bio international, Gifsur-Yvette Cedex, France). Although the optimum cut-off value for discriminating normal subjects from the ones diagnosed with neuroendocrine tumors was reported to be 94 ng/mL by the manufacturer, we also included 110 functional dyspepsia patients with CgA results as a control group in order to determine a cut-off value for the patients studied. This method was preferred because determining proper cut-off point specific to the patients studied in this study was thought to be more convenient rather than manufacturer recommended cut-off points. Conditions that might affect CgA levels such as hypertension, coronary artery disease, cardiac insufficiency, hepatic and renal failure, malignancies (breast, pancreas, hepatocellular, colon, ovarian, prostate, or neuroendocrine tumors) hyperparathyroidism, hyperthyroidism, irritable bowel syndrome, autoimmune and systemic inflammatory diseases, and proton pump inhibitors and H_2 receptor antagonist drug use were excluded from the study (16). Firstly, histological examinations of the biopsy specimens were evaluated in terms of ECL cells and were graded as described by Solcia et al. (17). In brief, endocrine hyperplasic changes have been classified as follows: 0 for the absence of hyperplasia, 1 for diffuse hyperplasia, 2 for linear hyperplasia, and 3 for micronodular hyperplasia. Secondly, histological examinations were performed according to the Sydney Classification and chronic inflammation (lymphocyte and plasma cell infiltration of the lamina propria), neutrophil activity, atrophy, *Helicobacter pylori* density, and intestinal metaplasia degrees were scored in a semi-quantitative scale as follows: 0 for none, 1 for mild, 2 for moderate, and 3 for marked (18). Factors such as age, sex, ECL cell hyperplasia, *Helicobacter pylori*, and histopathological changes of the gastric mucosa were analyzed whether any effect existed on serum CgA level. This study was approved by local the institutional review board (Decision date: May 25 2015, no: 09-384-15).

Statistical Analysis

Statistical analysis was performed using SPSS 16.0 (SPSS Inc.; Chicago, IL, USA) for Windows. According to the normality of data determined by the Shapiro–Wilk test, parametric or non-parametric tests were preferred. If the distribution was not normal, values were expressed as median (range), and nominal variables were expressed as *n* and (%). The Student's t-test was used for the comparison of significance of the differences in mean values between groups, and the Mann–Whitney U-test was used for the significance of the differences in median values. Nominal variables were evaluated by Pearson's chi-square χ-test or Fisher's exact test. The relationship between two continuous variables was evaluated by Pearson's correlation test. Spearman's correlation test was used if the distribution was normal. The significance of differences of mean values between groups was determined by the ANOVA test, and the significance of difference of median values was analyzed by using the Kruskal–Wallis test. The optimal cut-off values for serum CgA levels were determined by receiver-operating characteristic (ROC) curve analysis. A p value less than 0.05 was considered significant.

RESULTS

Patients

The characteristics of patient groups are shown in Table 1. The study population consisted of 188 patients with AIG (mean age: 57.25±12.28 years; 120 female, 68 male), 20 patients with AIG related gastric carcinoid tumor type I (mean age: 55.45±13.04 years; 14 female, 6 male) and 110 patients as a functional dyspepsia group (mean age: 54.63±14.87 years; 73 female, 37 male). There were no significant differences between groups by means of age and sex (p=0.240, p=0.810). Serum Anti Hp IgG was positive in 88 (46.8%) patients with AIG, in 12 (60%) patients with carcinoid tumor type I, and in 20 (18.2%) patients with functional dyspepsia. Serum APCA was positive in 165 (87.8%) patients with AIG, in 14 (70%) patients with carcinoid tumor type I, and in 8 (7.3%) patients with functional dyspepsia.

Serum chromogranin A (CgA) level

The mean serum CgA level was 259.74±71.99 ng/mL in patients with AIG and 277.05±109.15 ng/mL in patients with gastric carcinoid tumor type I (p=1.00). The mean CgA level was found to be 76.53±35.67 ng/mL in the functional dyspepsia group and the mean CgA levels of patients with AIG and gastric carcinoid type I were significantly greater than that of the functional dyspepsia group (p<0.001). The mean serum CgA level was 171.17±67.3 ng/mL in AIG patients (n=62) without ECL cell hyperplasia, and 303.3±102.82 ng/mL in pa-

Table 1. Baseline demographic characteristics of the four group

	AIG (n=188)	Carcinoid Tumor (n=20)	Control (n=110)	p
Age (Mean±SD)	57.25±12.28	55.45±13.04	54.63±14.87	0.240
Sex (Female/Male)	120/68 (63.8/36.2%)	14/6 (70/30%)	73/37 (66.4/33.6%)	0.810
Chromogranin A	259.74±111.99	277.05±159.15	76.53±45.67	<0.001
Gastrin	575.97±283.46	715.12±521.56	86.51±52.67	<0.001
Anti Hp IgG (-/+)	100/88 (53.2/46.8%)	8/12 (40/60%)	90/20 (81.8/18.2%)	<0.001
APCA (-/+)	23/165 (12.2/87.8%)	6/14 (30/70%)	102/8 (92.7/7.3%)	<0.001
ECL hyperplasia (-/+)	62/126 (32.9/67.1 %)			
Atrophy (+1/+2/+3)	16/94/78 (8.5/50/41.5%)		18/65/27 (16.4/59.1/24.5%)	
Inflammation (0/+1/+2/+3)	12/27/130/19 (6.4/14.4/69.1/10.1%)		8/19/72/11 (7.3/17.3/65.4/10%)	
Activity (0/+1/+2/+3)	128/36/22/2 (68.1/19.1/11.7/1.1%)		60/25/23/2 (54.6/22.7/20.9/1.8%)	

AIG: autoimmune gastritis; SD: standard deviation; Hp: helicobacter pylori; IgG: immunoglobulin G; APCA: anti-parietal cell antibody; ECL: enterochromaffin-like cell

tients (n=126) with ECL cell hyperplasia (p<0.001). A subgroup analysis of patients with ECL cell hyperplasia was performed; and in patients (n=13) showing diffuse ECL cell hyperplasia, the mean CgA level was 342.33±97.47 ng/mL. This value was 258.35±81.06 ng/mL in patients (n=21) showing linear ECL cell hyperplasia and 292.74±100.6 ng/mL in patients (n=79) with micronodular hyperplasia (p=1.00) (Figure 1). According to the histological examination results, while the mean CgA level was 126.31±49.64 ng/mL in patients showing 1(+) atrophy, this value was 238.19±102.28 ng/mL and 313.08±100.97 ng/mL in patients with 2(+) and 3(+) atrophy, respectively (p<0.001; r=0.51) (Figure 2). As for the lymphocyte infiltration of gastric mucosa, the mean CgA level was 75.5±28.02 ng/mL in patients without lymphocyte infiltration, and the mean CgA levels were 149.3±47.5 ng/mL, 284.62±71.6 ng/mL, and 599.2±101.3 ng/mL in patients with 1(+), 2(+), and 3(+) lymphocyte infiltration, respectively (p<0.001). According to the results of gastric mucosa neutrophil activity, the mean CgA level was 263.2±115.8 ng/mL in patients without neutrophil activity, and the median CgA levels were 230.29±93.5 ng/mL, 282.59±115.67 ng/mL, and 317±63.63 ng/mL in patients with 1(+), 2(+), and 3(+) neutrophil activity, respectively (p=0.266). There was also a positive association within serum CgA and serum gastrin level in patients with AIG (r=0.47).

Regression analysis in AIG

First, we carried out regression analysis to elucidate the factors associated with an elevation of the serum CgA level. This analysis showed that the serum CgA level was associated with ECL hyperplasia, positivity of Anti Hp IgG, and corpus atrophy in the univariate and multivariate analysis (Table 2).

Discriminant analysis in AIG vs. control group

In this study, the ROC curve analysis revealed that the cut-off value for the serum CgA level was 128 ng/mL for AIG patients in order to discriminate from the control group with a sensitivity and specificity of 89.9% and 90%, respectively (AUROC: 95.5, PPV: 93.8, 95%, CI: 90.3–96.2; NPV: 83.9, 95%, CI: 79.1–87.7) (Figure 3). For gastric carcinoid type I patients, the ROC curve analysis showed that the optimum cut-off value for the serum CgA level was 150 ng/mL in order to discriminate carcinoid patients from the control group with a sensitivity and specificity of 75% and 92.7%, respectively (AUROC: 89.1, PPV: 65.2, 95%, CI: 56.3–73.2; NPV: 95.3, 95%, CI: 89.7–98) (Figure 4). However, serum CgA level alone was not sufficient to distinguish patients with AIG from patients with gastric carcinoid type I (p=0.870).

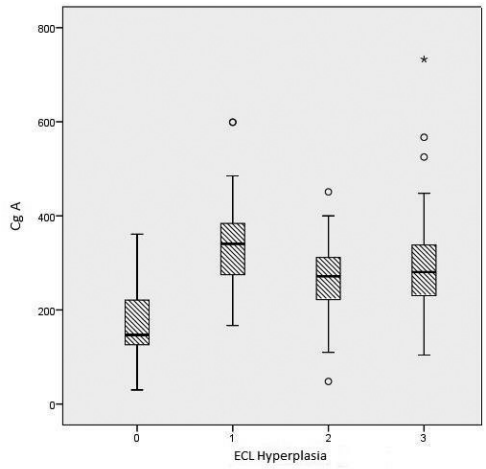

Figure 1. Subgroup analysis of patients with ECL cell hyperplasia. In patients (n=13) showing diffuse ECL cell hyperplasia, the mean CgA level was 342.33±97.47 μg/L, 258.35±81.06 μg/L in patients (n=21) showing linear ECL cell hyperplasia, and 292.74±100.6 μg/L in patients (n=79) with micronodular hyperplasia (p=1.00) (Cg A: chromogranin A, ECL: enterochromaffin-like cell, 0=no hyperplasia, 1=diffuse hyperplasia, 2=linear hyperplasia, 3=micronodular hyperplasia).

DISCUSSION

This study investigated the factors affecting serum CgA levels in patients with AIG. This study showed, the presence of ECL cell hyperplasia (p=0.017), degree of atrophy (p=0.026), degree of neutrophil activity (p<0.001), and degree of lympho-

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Table 2. Univariate and multivariate analysis of CgA in patients with autoimmune gastritis

	Univariate Analysis			Multivariate Analysis		
Factors	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Atrophy	7.69	4.9–12.04	<0.001	23.75	8.71–46.19	<0.001
ECL Hyperplasia	10.98	1.44–17.85	<0.001	83.75	11.45–184.2	<0.001
Anti-Hp IgG	1.19	1.08–1.21	<0.001	1.82	1.11–7.12	<0.001
Gastrin (pg/mL)	1.988	1.985–1.991	<0.001			
Inflammation	1.602	1.243–1.847	0.029			
Age	0.935	0.916–0.955	<0.001			
Sex	1.273	0.768–2.110	0.350			

OR: odds ratio; CI: confidence interval; ECL: enterochromaffin-like cell; Hp: helicobacter pylori; IgG: immunoglobulin G; CgA: chromogranin A

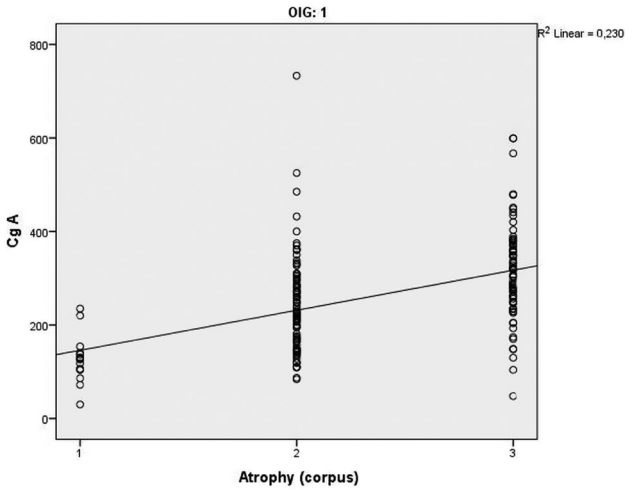

Figure 2. Scatter diagram showing the correlation between CgA and degree of atrophy of the corpus mucosa. As the degree of atrophy increases, the CgA level increases as well. (p<0.001, r=0.854).

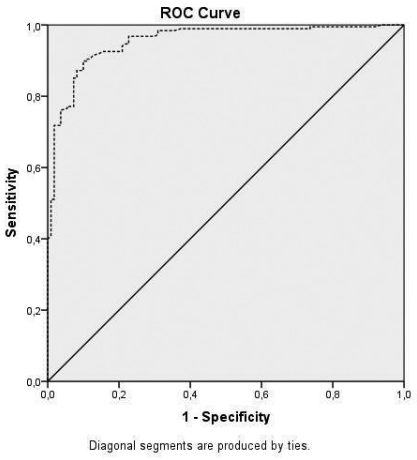

Figure 3. ROC curve analysis suggested that the optimum cut-off value for the serum Cg A level was 128 μg/L for AIG patients in order to discriminate from the control group with a sensitivity and specificity of 89.9% and 90%, respectively.

cyte infiltration (p<0.001) were found as factors that affected the serum CgA level. However, independent determinants of elevated serum CgA levels were the presence of ECL cell hyperplasia (p=0.017, OR: 6.59, CI 95%: 1.4–31.08, β=1.88) and presence of corpus atrophy (p=0.026, OR: 5.03, CI 95%: 1.21–20.88, β=1.61). The optimum serum CgA cut-off value was 128 ng/mL for AIG in order to discriminate AIG from the control group with a specificity of 0.90 and 0.89, and specificity of 0.92 and 0.75. The optimum serum CgA cut-off value was 150 ng/mL for gastric carcinoid type I patients. However, the ROC curves analysis was not successful for determining a suitable cut-off value for the differential diagnosis between AIG and patients with gastric carcinoid type I. Although CgA is used for neuroendocrine tumors, CgA elevation is seen in individuals with carcinoid tumors, in chronic atrophic gastritis (19), and due to patients using proton-pump inhibitors (PPIs) for a long period of time (5), which causes ECL cell hyperplasia. Vannella et al. (20) followed-up 367 chronic atrophic gastritis patients regularly with gastroscopy. They reported that an increase in gastrin and CgA levels were both associated with the presence of type I gastric carcinoid in the univariate analysis. Although CgA is an important and sensitive biomarker in neuroendocrine tumors (21), it may also reach high values in patients with atrophic gastritis. Syversen et al. (22) investigated the clinical significance of

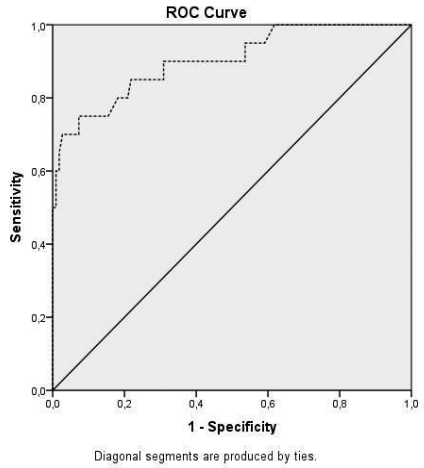

Figure 4. ROC curve analysis suggested that the optimum cut-off value for the serum CgA level was 150 μg/L in order to discriminate gastric carcinoid type I patients from the control group with a sensitivity and specificity of 75% and 92.7%, respectively.

elevated serum CgA levels in 153 patients and reported that serum CgA is an important marker for neuroendocrine neoplasia. Gastric adenocarcinoma also caused elevated levels of CgA, and this finding is a reflection of the neuroendocrine differentiation in the tumor. They concluded that CgA is a useful marker in the supervising of enterochromaffin-like (ECL) hyperplasia due to therapy with PPIs or atrophic gastritis. In this study, they found the highest serum CgA levels in patients with carcinoids; however, in the current study, the highest serum CgA level was 733 ng/mL and the minimum value was 25 ng/mL. This great discrepancy between patients in the same group has led us to investigate the parameters to see if there would be some factors other than the presence of a neuroendocrine tumor. None of our patients were using PPIs or acid secretion inhibitors. Peracchi et al. (23) examined the clinical significance of CgA levels in atrophic body gastritis patients in order to identify gastric carcinoid tumors. They measured CgA levels in 45 healthy subjects, 9 patients with type-1 gastric carcinoids, and 43 patients with atrophic body gastritis (21 patients without and 22 patients with ECL cell hyperplasia/dysplasia). They found the highest CgA values in subjects with carcinoid tumors and with ECL cell hyperplasia/dysplasia, but there were no significant differences in the CgA levels between the different subgroups of atrophic body gastritis patients sorted according to the ECL cell status. In our study, the median serum CgA level was found higher in patients with ECL cell hyperplasia compared to patients without ECL cell hyperplasia; however, there were no significant differences between the various subgroups of AIG patients by means of ECL cell status. However, possible sources of serum CgA elevation was also investigated in patients with gastrinoma and in patients that had undergone long-term acid suppression therapy; and it was found that serum CgA values reflected the degree of gastric ECL cell proliferation (13,5). There was also a positive correlation between serum gastrin and CgA levels in our study: it was observed that as the gastrin level increases, CgA level also increases. The possible explanation for this finding can be the effect of gastrin on gastric ECL cells because it is stated that ECL cell mass is a major determinant of CgA elevation in hypergastrinemic conditions (19). It has been reported that CgA is widely expressed in neuroendocrine cells (9) and in AIG patients, the serum CgA level is affected by gastrin secretion from antral gastrin-releasing cells (23). This finding may help explain why some patients without ECL cell hyperplasia have increased serum CgA levels. We also investigated the relationship between the CgA level and the following: degree of atrophy, neutrophil activity, inflammation, and intestinal metaplasia. While there was a positive correlation between the degree of atrophy, inflammation, and CgA level, no correlation was found between neutrophil activity, intestinal metaplasia of the corpus mucosa, and CgA level. It has been reported that there is a correlation between ECL cell hyperplasia and gastritis grade (24); however, these studies do not include the updated Sydney system for their evaluation methods of gastritis. It is possible to make a supposition that atrophy, activity, and inflammation of the corpus mucosa increase the serum CgA levels via the increase in serum gastrin levels and ECL cell hyperplasia.

In conclusion, serum CgA levels may be helpful for the differentiation of patients with AIG and gastric carcinoid type I from the control group, but it is not useful in the discrimination of patients with AIG from patients with gastric carcinoid tumors. Major determinants of elevated serum CgA level in AIG patients were: the presence of corpus atrophy, positivity of Anti Hp IgG, and the presence of ECL cell hyperplasia. While evaluating CgA results in the clinical setting in patients with AIG, factors that might affect CgA levels should be taken into account.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ankara University School of Medicine (Date: 25 May 2015, Approval Number: 09-384-15).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Ç.K.; Design - I.S.; Supervision - I.S.; Materials - Ç.K.; Data Collection and/or Processing - Ç.K., F.K.; Analysis and/or Interpretation - Ç.K., I.S.; Literature Review - Ç.K.; Writer -I.S.; Critical Review - I.S.

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REFERENCES

1. Neumann WL, Coss E, Rugge M, Genta RM. Autoimmune atrophic gastritis--pathogenesis, pathology and management. Nat Rev Gastroenterol Hepatol 2013; 10: 529-41. [CrossRef]
2. Bordi C, D'Adda T, Azzoni C, Pilato FP, Caruana P. Hypergastrinemia and gastric enterochromaffin- like cells. Am J Surg Pathol 1995; 19(Suppl 1): S8-19.
3. Borch K, Renvall H, Liedberg G. Gastric endocrine cell hyperplasia and carcinoid tumors in pernicious anemia. Gastroenterology 1985; 88: 638-48. [CrossRef]
4. Sjoblom SM, Sipponen P, Miettinen M, Karonen SL, Jrvinen HJ. Gastroscopic screening for gastric carcinoids and carcinoma in pernicious anemia. Endoscopy 1988; 20: 52-6. [CrossRef]
5. Stockbrugger RW, Menon GG, Beilby JO, Mason RR, Cotton PB. Gastroscopic screening in 80 patients with pernicious anaemia. Gut 1983; 24: 1141-7. [CrossRef]
6. Annibale B, Azzoni C, Corleto VD, et al. Atrophic body gastritis patients with enterochromaffin-like cell dysplasia are at increased risk for the development of type I gastric carcinoid. Eur J Gastroenterol Hepatol 2001; 13: 1449-56. [CrossRef]
7. Delle Fave G1, Kwekkeboom DJ, Van Cutsem E, et al; Barcelona Consensus Conference participants. ENETS Consensus guidelines for the management of patients with gastroduodenal neoplasms. Neuroendocrinology 2012; 95: 74-87. [CrossRef]
8. Gough DB, Thompson GB, Crotty TB, et al. Diverse clinical and pathologic features of gastric carcinoid and the relevance of hypergastrinemia. World J Surg 1994; 18: 473-9. [CrossRef]

9. Deftos LJ. Chromogranin A: its role in endocrine function and as an endocrine and neuroendocrine tumor marker. Endocr Rev 1991; 12: 181-7. **[CrossRef]**
10. Nobels FR, Kwekkeboom DJ, Bouillon R, Lamberts SW. Chromogranin A: its clinical value as marker of neuroendocrine tumors. Eur J Clin Invest 1998; 28: 431-40. **[CrossRef]**
11. Bashir S, Gibril F, Ojeaburu JV, et al. Prospective study of the ability of histamine, serotonin or serum chromogranin A levels to identify gastric carcinoids in patients with gastrinomas. Aliment Pharmacol Ther 2002; 16: 1367-82. **[CrossRef]**
12. Sanduleanu S, De Bruine A, Stridsberg M, et al. Serum chromogranin A as a screening test for gastric enterochromaffin- like cell hyperplasia during acid - suppressive therapy. Eur J Clin Invest 2001; 31: 802-11. **[CrossRef]**
13. Stabile BE, Howard TJ, Passarro E Jr, O'Connor DT. Source of plasma chromogranin A elevation in gastrinoma patients. Arch Surg 1990; 125: 451-3. **[CrossRef]**
14. Vargas JA, Alvarez-Mon M, Manzano L, et al. Functional defect of T cells in autoimmune gastritis. Gut 1995; 36: 171-5. **[CrossRef]**
15. De Block CE, De Leeuw IH, Van Gaal LF. Autoimmune gastritis in type 1 diabetes: A clinically oriented review. J Clin Endocrinol Metab 2008; 93: 363-71. **[CrossRef]**
16. Lawrence B, Gustafsson BI, Kidd M, Pavel M, Svejda B, Modlin IM. The clinical relevance of chromogranin A as a biomarker for gastroenteropancreatic neuroendocrine tumors. Endocrinol Metab Clin North Am 2011; 40: 111-34. **[CrossRef]**
17. Solcia E, Fiocca R, Villani L, Luinetti O, Capella C. Hyperplastic, dysplastic, and neoplastic enterochromaffin-like-cell proliferations of the gastric mucosa. Classification and histogenesis. Am J Surg Pathol 1995; 19(Suppl 1): S1-7.
18. Dixon MF, Genta RM, Yardley JH, Correa P. Classification and grading of gastritis. The updated Sydney system. International workshop on the histopathology of gastritis, Houston 1994. Am J Surg Pathol 1996; 20: 1161-81. **[CrossRef]**
19. Kleveland O, Syversen U, Slørdahl K, Waldum HL. Hypergastrinemia as a cause of chromogranin a increase in blood in patients suspected to have neuroendocrine tumor. Digestion 2001; 64: 71-4.**[CrossRef]**
20. Vannella L, Sbrozzi-Vanni A, Lahner E, et al. Development of type I gastric carcinoid in patients with chronic atrophic gastritis. Aliment Pharmacol Ther 2011; 33: 1361-9. **[CrossRef]**
21. Modlin IM, Gustafsson BI, Moss SF, Pavel M, Tsolakis AV, Kidd M. Chromogranin A – biological function and clinical utility in neuro endo- crine tumor disease. Ann Surg Oncol 2010; 17: 2427-43. **[CrossRef]**
22. Syversen U, Ramstad H, Gamme K, Qvigstad G, Falkmer S, Waldum HL. Clinical significance of elevated serum Cg A levels. Scand J Gastroenterol 2004; 39: 969-73. **[CrossRef]**
23. Peracchi M, Gebbia C, Basilisco G, et al. Plasma chromogranin A in patients with autoimmune chronic atrophic gastritis, enterochromaffin-like cell lesions and gastric carcinoids. Eur J Endocrinol 2005; 152: 443-8. **[CrossRef]**
24. Lamberts R, Creutzfeldt W, Strüber HG, Brunner G, Solcia E. Long-term omeprazole therapy in peptic ulcer disease: gastrin, endocrine cell growth, and gastritis. Gastroenterology 1993; 104: 1356-70. **[CrossRef]**