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The various faces of autoimmune endocrinopathies: Non-tumoral hypergastrinemia in a patient with lymphocytic colitis and chronic autoimmune gastritis

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Abstract

Serum gastrin levels exceeding 1000 pg/ml (normal, <100) usually raise the suspicion for a neuroendocrine tumor (NET) that secretes gastrin. Rarely, such elevated gastrin levels are seen in patients with pernicious anemia which most commonly is associated with autoimmune gastritis (AG). AG can occur concomitantly with other autoimmune disorders including lymphocytic colitis (LC). Gastrin stimulates enterochromaffin-like cells which increase histamine secretion. Histamine excess can cause diarrhea as can bacterial overgrowth or LC. We present a 57-year-old woman with diarrhea, sporadic epigastric pain, and bloating. She also had a history of interstitial cystitis and took pentosan polysulfate and cetirizine. She had no history of ulcers, renal impairment or carcinoid syndrome. Fasting serum gastrin was 1846 pg/ml. Esophagoduodenal gastroscopy and biopsies revealed chronic gastritis and a pH of 7 with low stomach acid. Serum gastrin and plasma chromogranin A were suggestive of a gastrinoma or NET. Pernicious anemia was unlikely. Imaging studies did not reveal any tumor. Random colonic biopsy was compatible with LC, possibly explaining her diarrhea, although we also considered excessive histamine from elevated gastrin, bacterial overgrowth, and pentosan polysulfate which can cause diarrhea and be misleading in this setting, pointing to the diagnosis of gastrinoma. At 4 year follow-up in 2012, fasting serum gastrin was 1097 pg/ml and the patient asymptomatic taking only cetirizine for nasal allergies. This case illustrates that diarrhea may be associated with very high serum gastrin levels in the setting of chronic gastritis, LC, and interstitial cystitis (pentosan use), without clear evidence for a gastrinoma or NET. If no history of ulcers or liver metastases is present in such cases, watchful observation rather than an extensive/invasive and costly search for a NET may be

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Conflict of interest statement

Prof. Christian A. Koch has served as consultant for Novo Nordisk, as principal investigator of the SEISMIC study and the TR321 trial and has nothing relevant to disclose other than that this case has been presented as a poster at the 14th European Congress of Endocrinology in Florence, Italy, published as an abstract in *Endocrine Abstracts* 2012, Vol.29, P797.

justified. Considering the various forms of polyglandular syndrome, this may represent a variant and we here provide an algorithm for working up such patients, while also reviewing literature on the intertwined relationship between the immune and endocrine systems.

Keywords

Gastrin; Gastrinoma; Neuroendocrine tumor; Colitis; Gastritis; Polyglandular syndrome

Introduction

Serum gastrin (G) levels >1000 pg/ml usually raise the suspicion for a neuroendocrine tumor (NET) secreting gastrin. On the other hand, two thirds of patients with gastrinoma have fasting serum gastrin levels <10 fold normal (Berna et al., 2006; O'Toole et al., 2009). Rarely, such elevated gastrin levels are seen in patients with pernicious anemia (PA) which most commonly is associated with autoimmune gastritis (AG) (Koch, 2009; Korman et al., 1970; Lewin et al., 1976). AG can occur concomitantly with lymphocytic colitis (LC) (Bohr, 1998; Bohr et al., 1996a; Cindoruk et al., 2002; Koskela et al., 2011; Leung et al., 2009; Pardi et al., 2002a; Remaine, 2000; Rostami et al., 2000; Triantafillidis et al., 2003). In the setting of polyglandular syndromes, other autoimmune diseases including type 1(A) diabetes mellitus, Graves' disease, Hashimoto's thyroiditis, Addison's disease, hypoparathyroidism, lymphocytic hypophysitis, premature ovarian failure, hypogonadism, autoimmune hepatitis, alopecia areata, vitiligo, Sjogren's syndrome, multiple sclerosis, celiac disease, and Crohn's disease may be present or evolving (Betterle et al., 2002; Brown, 2009; Dittmar and Kahaly, 2010; Kahaly, 2009; Koch et al., 2000; Manetti et al., 2007; Melcescu et al., 2010; Michels and Gottlieb, 2010; Mitchell and Pearce, 2012; Triantafillidis et al., 2003; Vrijman et al., 2012). Gastrin stimulates enterochromaffin-like cells which increase histamine secretion. Histamine excess can cause diarrhea as can bacterial overgrowth or LC. Histamine 1-receptor antagonists such as cetirizine, clemastine, hydroxyzine, and others do not inhibit stimulation of gastric acid production in the secretory canaliculi (Nilsson et al., 1993).

Lymphocytic colitis (LC), first described by Lazenby et al. (1989), belongs together with collagenous colitis (CC) to the group of microscopic colitis (MC). New clinical entities resembling MC are: multinucleated giant cell colitis, Brainard colitis or Clear Cell Colitis (CCC). Adults typically present with LC or CC, while children with CCC (a form of microscopic colitis characterized by the presence of various large mononuclear clear cells in lamina propria) (Bryant et al., 1996). Microscopic colitis (MC) represents 4% to 13% of cases in a population cohort with non-bloody diarrhea of unknown origin (Agnarsdottir et al., 2002; Bohr et al., 1995, 1996b; Fernandez-Banares et al., 1999; Olesen et al., 2004; Pardi et al., 2002b).

Based on different studies, the prevalence of collagenous colitis and lymphocytic colitis is 10 to 15.7 per 100,000 and 14.4 per 100,000, respectively (Bohr, 1998; Bohr et al., 1995; Fernandez-Banares et al., 1999; Pardi et al., 2002b).

Although there are a multitude of factors which might contribute to the development of these diseases, autoimmunity seems to play an essential part in patients with MC. Known

accompanying autoimmune diseases with MC are described in Table 1 (Bohr et al., 1996a; Bohr, 1998; Cindoruk et al., 2002; Pardi et al., 2002a, 2002b; Remaine, 2000; Rostami et al., 2000).

Laboratory tests commonly seen in MC include: mild anemia, elevated erythrocyte sedimentation rate, positive auto-antibodies including rheumatoid factor, antinuclear antibody/ANA (30%–50%), P-ANCA (10%–14%), anti-mitochondrial antibody, hypokalemia, hypoalbuminemia, abnormalities in serum levels of IgG, IgM, C3 or C4 complement. The microscopic pathology exam in LC and CC typically shows: intraepithelial lymphocytosis with greater than 20 lymphocytes per 100 epithelial cells (pathognomonic for LC), epithelial cell damage (cell flattening, subepithelial blebs, and denuded epithelium), crypts typically have normal architecture but minimal crypt distortion may be present sometimes. A histopathological distinction between LC and CC is represented by the thickening of the subepithelial collagen band ($>7\text{--}80\text{ }\mu\text{m}$) in CC (Baert et al., 1999; Mullhaupt et al., 1998; Pardi et al., 2002b). The pathogenic mechanisms involved in these conditions (inflammatory process, collagen deposition) result in a decrease in colonic water absorption from a normal amount of 159 ml/h to the abnormal amount of 26 ml/h, reduced active and passive NaCl absorption, reduced exchange of Cl/HCO_3 and of electrolytes (BoLinn et al., 1985; Giardello et al., 1987). The inflammatory infiltrate of the colonic mucosa is therefore associated with a reduction in colonic fluid absorption, which probably contributes to the development of diarrhea. Stool weight correlates with the intensity of lamina propria cellularity (Lee et al., 1992). Colonoscopy with multiple biopsies (including the right and transverse colon) is necessary for correctly diagnosing MC (Rostami et al., 2000). To avoid misdiagnosing patients with irritable bowel syndrome, it is essential to perform a colonic biopsy when LC or CC is suspected. LC seems to have a milder presentation and a better prognosis.

Case study

A 57-year-old white female presented in 2008 with chronic diarrhea (3–4 stools a day), sporadic epigastric pain, weight loss, and bloating for the last 2 years. She had no renal stones, galactorrhea, hypoglycemic attacks, dizziness, confusion, headache or any visual changes. Her past medical history included a cholecystectomy, partial hysterectomy, and interstitial cystitis. Current medications included pentosan polysulfate (for interstitial cystitis) and the antihistamine cetirizine (for nasal allergies, over the counter per patient report).

Family history was negative for renal stones, stomach ulcers, pituitary or pancreatic or multiple endocrine neoplasia type 1/MEN1 tumors but positive (both parents) for colorectal cancer, colonic polyps, type 2 diabetes, gallstones and irritable bowel syndrome. The patient did not smoke or drink any alcohol and was physically active on a daily basis. Known allergies included trimethoprim/sulfamethoxazole, codeine, nitrofurantoin, and ammoniated mercury. Physical examination was unremarkable without skin tags or features of MEN1. After initial laboratory screening by gastroenterologists revealed an elevated serum gastrin level of 1848 pg/ml (normal, <100), she was referred to the Endocrinology service which confirmed the elevated gastrin levels on several occasions.

Specific laboratory investigations for neuroendocrine and celiac disease are shown in Table 2.

Additional biochemical markers tested were: parathormone of 34 pg/ml (normal) with a serum calcium of 9.5 mg/dl (normal), insulin-like growth factor-1/IGF-1 of 244 ng/ml (at the upper limit of normal), and prolactin of 7 ng/ml (normal). Normal serum levels of vitamin B12 (748 pg/ml, normal: 240–900), methylmalonic acid (0.13 mcmol/l), homocysteine (8.7 mcmol/l, normal: 5–15), hemoglobin (15.2 g/dl) and MCV (90.5) ruled out a possible pernicious anemia which can be present in 10% of cases of autoimmune gastritis.

A celiac serology panel was negative (anti-gliadin IgG, anti-gliadin IgA, antiendomysial IgA and anti-human tissue transglutaminase IgA). Serum levels of gastrin and plasma chromogranin A were suggestive of a gastrinoma or NET (see Table 2). A pH of 7 (normal, 1.5) with low stomach acid was determined. Electrolyte values were normal with a potassium of 3.6 mmol/l. Serum glucose was 89 mg/dl, creatinine and blood urea nitrogen/BUN were within normal range.

An esophagogastroduodenal (EGD) exam revealed mild erythema in the pre-pyloric region and antrum compatible with patchy mild autoimmune gastritis. Biopsies of the antrum and body of the stomach and CLO (campylobacter like organism) urease test did not identify *Helicobacter pylori* or intestinal metaplasia.

Colonoscopy exam showed grade I hemorrhoids, no obstructive colonic tumor, and rectal proctitis. Cold forceps biopsies were performed to assess for microscopic colitis at the ascending colon, proximal transverse, descending or sigmoid colon and rectum.

General microscopic description: the patient's random colon biopsies demonstrated a diffuse increase in lamina propria chronic inflammatory cells with no glandular architectural distortion. There was patchy surface epithelial damage with mucin loss and increased intraepithelial lymphocytes. Numerous intraepithelial lymphocytes were seen infiltrating the crypts. The intraepithelial lymphocytes mark as T lymphocytes on immunoperoxidase staining for CD3. No subepithelial collagen deposition was present. The report concluded that these changes were compatible with lymphocytic colitis (see Fig. 1A, B, C).

To rule out a possible neuroendocrine pancreatic tumor or other NET/carcinoid tumor, we performed a magnetic resonance imaging MRI exam of the abdomen. A pancreatic protocol MRI with arterial, venous, and delayed phase imaging did not reveal a pancreatic lesion. Computed tomography CT abdomen/pelvis with oral/IV contrast was nondiagnostic for any pathological findings in pancreas, adrenal glands, kidney and bowel. Nomasses, adenopathy or abnormal fluid collections have been identified and no other localized inflammatory changes.

The patient was not willing to stop pentosan administered for her cystitis but started prednisone 20 mg daily for several weeks without much relief of her diarrhea. She then took a proton pump inhibitor and rifaximin for 10 days which decreased bloating and diarrhea. We searched for possible interactions of pentosan with gastrin levels and diarrhea. Side effects from pentosan include abdominal pain and diarrhea (very rare).

Serum gastrin levels decreased but remained elevated (686 pg/ml and 796 pg/ml, Table 2) on prednisone 20 mg daily and a proton pump inhibitor plus the second generation antihistamine drug cetirizine 10 mg daily. Cystoscopy with urinary bladder biopsy revealed urothelial mucosa with changes consistent with moderate to severe interstitial cystitis and no granulomas, viral, parasitic dysplasia or malignancy. In 2012 at 4 year follow-up, surveillance colonoscopy only showed grade 1 internal hemorrhoids, while the patient was asymptomatic and taking only cetirizine over the counter for nasal allergies, a multivitamin, and 1 g of calcium carbonate daily. Fasting serum gastrin was 1097 pg/ml (Mayo Clinic Laboratories, Rochester, MN). She was explained the possible need of an EGD to screen for the presence of a rare gastric carcinoid tumor in the setting of chronic hypergastrinemia but she refused any further testing as she felt well.

Discussion

We present for the first time a case of an association of hypergastrinemia, autoimmune atrophic gastritis, and LC, which might represent another variant of polyglandular syndrome, an autoimmune endocrinopathy. It illustrates that diarrhea may be associated with very high fasting serum gastrin levels in the setting of chronic gastritis (possible bacterial overgrowth), LC, and interstitial cystitis (pentosan use), without clear evidence for a gastrinoma or NET. If no history of ulcers or liver metastases is present in such cases, watchful observation rather than an extensive/ invasive and costly search for a NET may be justified. Non-tumoral hormone (over)secretion has also been observed with many other conditions or medications (Boden and Owen, 1977; Charmandari et al., 2008; Maladaki et al., 2012; Nicola et al., 2011; Wallace et al., 2010).

Our case, a 57 year-old woman presented with symptoms of a protracted course of secretory diarrhea, weight loss, intermittent epigastric pains and bloating for approximately 2 years and apparently in remission at 4 year follow-up. Due to the patient's history and symptoms, we had to structure an investigational panel which covered neuroendocrine tumors (gastrinoma, VIPoma, carcinoids), chronic gastrointestinal conditions and autoimmune disorders.

Laboratory tests showed an initial gastrin level of 1848 pg/ml (March 2008) with fluctuating levels of 686 pg/ml in April and 796 pg/ml in June 2008. Because of low basic acid output, we did not perform a secretin test.

We attempted to rule out possible gastroenteropancreatic/GEP tumors such as gastrinoma, vasoactive intestinal peptide/VIPoma, as well as pernicious anemia, autoimmune gastritis, drugs or a MEN 1 syndrome (Thakker et al., 2012).

Normal levels of PTH, calcium, IGF-1 and prolactin and no other localized cranial signs (double vision, headache) and symptoms helped ruling out a possible MEN 1 association. The abdominal MRI and CT exams with contrast were noncontributory for GEP tumors.

Vasoactive intestinal peptide (25.7 pg/ml) and calcitonin normal values supported further the nontumoral differential diagnosis. Persistently high levels of gastrin accompanying LC might be caused by an association with another autoimmune disorder (autoimmune

gastritis). The patient's watery diarrhea and weight loss might have pointed to a possible gastrinoma. However, we determined a pH of 7 with hypochlorhydria which oriented us to a different explanation for high gastrin levels: autoimmune gastritis (Fig. 2). Hypochlorhydria leads to G-cell hyperplasia and could explain elevated serum gastrin levels (rarely >1000 pg/ml) in the context of an autoimmune gastritis (Korman et al., 1970; Lewin et al., 1976). Antiparietal antibody and antiintrinsic factor antibodies which may be present in this form of gastritis were not determined. Their presence in the future could represent the onset of a vitamin B12 deficiency which the patient did not have (yet).

Elevated gastrin levels can lead to enterochromaffin-like cell hyperplasia, which occasionally undergoes transformation to a carcinoid tumor (Burkitt et al., 2009; Lendel et al., 2007; Murugesan et al., 2009). The concomitantly to gastrin elevated plasma chromogranin A level of 262 ng/ml in our patient may be explained by enterochromaffin-like cell hyperplasia. Intragastric pH, chromogranin A and gastrin levels may be altered in patients taking proton pump inhibitors or histamine type 2-receptor antagonists (Dhillon et al., 2006; Koop et al., 1996; Murugesan et al., 2009; Pregun et al., 2011). Long term treatment with these compounds may elevate these tests and at least 5 days of discontinuation is recommended before testing for fasting serum gastrin (Pregun et al., 2011). Our patient did not take an H2- but rather an H1-receptor antagonist, cetirizine. The rise of serum gastrin in patients on H2-receptor antagonists can occasionally promote development of gastric carcinoids associated with type A gastritis. These NETs usually are benign and indolent as opposed to sporadic gastrin-secreting NET which can be life-threatening (Hosokawa et al., 2005; Rindi et al., 1993).

The longstanding course of gastrointestinal symptoms in our patient suggested a differential diagnosis between celiac and inflammatory bowel disease. Celiac disease occurs in up to 40% of cases with MC (Table 1) but in our case a celiac serology panel was negative. No dietary element was suggestive for this condition. Surprisingly, colonoscopy showed no colonic tumor or changes suggestive of Crohn's disease or ulcerative colitis, both conditions known to occur in polyglandular syndrome (Betterle et al., 2002; Kahaly, 2009).

To investigate for other causes of non-bloody diarrhea (such as LC) in 2008 at presentation with hypergastrinemia, cold forceps biopsies were performed at the ascending colon, proximal transverse, descending or sigmoid colon and rectum. Microscopic exams of random colonic/rectum biopsies were compatible with lymphocytic colitis. The patient's LC may have explained her (past) diarrhea, although we also considered excessive histamine from elevated gastrin, bacterial overgrowth, and Pentosan polysulfate (used to treat her interstitial cystitis) which can cause diarrhea and be misleading in this setting, pointing to the diagnosis of gastrinoma. Interestingly, Wilcox and Mattia (2002) described a patient with histological findings of CC and later LC in reaction to the use of lansoprazole. This finding may alert physicians to include the interference of drugs (PPIs) in the differential diagnosis of MC. The concomitant occurrence of lymphocytic and collagenous colitis with celiac disease (which involves the small intestine and has the same histopathological changes as MC) may represent a more generalized disease of the gut, involving both the large and the small intestines (Padmanabhan et al., 2003). We consider hypochlorhydria and autoimmune gastritis as the main causes of high serum gastrin levels that were observed in our patient.

Therapeutic trials with oral budesonide (3/day), prednisone 20 mg daily, balsalazide, and colestevam have improved the overall clinical status of such patients. We did not repeat the colonoscopy with biopsies to check for histological remission but colonoscopy in 2012 only showed hemorrhoids in a now asymptomatic patient. The pathogenesis of MC and its associations with autoimmune disorders are still under investigation. In our patient, we can speculate about a similar immunologic mechanism as an explanation of this concomitant occurrence of LC and autoimmune gastritis with non-tumoral hypergastrinemia.

Immunologic research and new tools for classifying and monitoring autoimmune diseases have progressed and will further broaden our understanding of complex disorders including those affecting the endocrine system (Cruse and Lewis, 2012; Maecker et al., 2012; Mitchell and Pearce, 2012). Despite all highly sophisticated contemporary technology in this regard including discovery tools (i.e. proteomics assays: FACS, CyTOF, protein arrays; and genomics assays: SNPs and gene expression, high-throughput sequencing of B-cell and T-cell receptors) and computational tools (i.e. cellular data: CytoBank, automatic cell-population gating for high-dimensional flow cytometry; gene expression, B-cell and T-cell data, and the integration of data), the translation into new diagnostic and prognostic methods with improved classification of disease categories for better therapeutic targets, still depends on a thorough understanding of the mechanisms of action in one individual patient. In that regard, it is also important to look into a respective patient's family and environmental factors that might influence disease development and progression (Ahmad et al., 2007; Brauer et al., 2004; Majumdar et al., 2010; Newman et al., 2009).

Regulatory T cells appear to play an important role in homeostasis of the immune responses and to prevent autoimmunity (Suggs et al., 2011). The neuroendocrine system is in close interplay with immune systems and hormonal imbalances such as deficiency of testosterone, growth hormone, vitamin D, and others in endocrine hypertension, are frequently seen in contemporary societies, with an ever growing number of obese individuals (Chrousos, 2009; Koch and Chrousos, 2013; Koch et al., 1999; Melcescu et al., 2012; Ullah et al., 2010, 2011). Toll-like receptors (TLR) represent a link between the immune, hormonal, and metabolic systems (Kanczkowski et al., 2008). TLR4 expression has been shown to be decreased in patients with acquired immune deficiency syndrome (AIDS) and in those with adrenocortical tumors (Kanczkowski et al., 2010; Miller Sanders et al., 2010). On the other hand, TLR4 showed full (100%) expression in patients infected with the human immunodeficiency virus (without AIDS) and could be raised by native low-density lipoprotein and oxidized lipoprotein in primary cultures of human umbilical vein endothelial cells (Catar et al., 2007; Sanders et al., 2008). In patients infected with HIV, one should consider several endocrine aspects (Koch and Pacak, 2001; Ungnapatanin et al., 2012). Another example demonstrating that endocrine organs are under the control of the immune system and vice versa represents research on dendritic cells which are important in initiating the body's immune response and have been used for anticancer vaccination (Jacobs et al., 2010; Morrison et al., 2003; Papewalis et al., 2008; Wang et al., 2011).

Interestingly, the mere measurement of autoantibodies may not be clinically meaningful in many individuals without knowing the direct impact on the respective tissue (for instance, the thyroid gland in individuals with positive antithyroid peroxidase antibodies), although

there are more and more data on risk of disease development. In that regard, a recent meta-analysis found the presence of maternal thyroid autoantibodies being strongly associated with miscarriage and preterm delivery with attenuation of that risk by administering levothyroxine which implies that some of these women were hypothyroid which likely could have been simply assessed by measuring thyroid stimulating hormone (TSH) (Thangaratinam et al., 2011). Positive stimulating/agonistic TSH-receptor antibodies are one of the risk factors for developing worsening thyroid eye disease and a drug-like TSH-receptor antagonist inhibits thyrotropin receptor-mediated stimulation of cAMP production in Graves' orbital fibroblasts (Neumann et al., 2012). In analogy, agonistic autoantibodies directed at G protein-coupled receptors such as the TSH-receptor may cause many other (endocrine) disorders including cerebrovascular impairment, stroke, and dementia, as recently shown in a rat model with antibodies against the $\alpha 1$ -adrenergic receptor (Karczewski et al., 2012). For patients with type 1 (autoimmune) diabetes, a recent proof-of-concept, randomized, controlled clinical trial showed stimulation of the host innate immune response by Bacillus-Calmette-Guerin (BCG) treatment or Epstein Barr virus infection which transiently modified the autoimmunity in these patients (Faustman et al., 2012). BCG has also been used in patients with multiple sclerosis, Parkinson's disease, interstitial cystitis, and in bladder, lung, colorectal, and skin (melanoma) cancer. Often, immune-mediated disorders such as type 1 diabetes show genetic heterogeneity. To better understand mechanisms of disease and gain insights into self-tolerance, it likely still is most fruitful to start with monogenic disorders in which there is a single gene defect such as the polyglandular syndrome type 1 caused by mutations in the autoimmune regulator (AIRE) gene (Betterle et al., 2002; Fierabracci et al., 2012; Kahaly, 2009; Koch et al., 2002). In addition to the more common polyglandular syndrome type 2 (Schmidt or Smith syndrome), there is discussion about other types and variants of polyglandular syndromes under which perhaps our patient presented here may fit. For patients presenting with hypergastrinemia and autoimmune gastritis we propose the work-up shown in Fig. 2.

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Fig. 1.

A. Lymphocytic colitis. Low power view (10×) of the normal colonic architecture with intraepithelial lymphocytes infiltrating the crypts and surface epithelium. The lamina propria is expanded by lymphocytes and plasma cells. B. Lymphocytic colitis. High power view (40×) of intraepithelial lymphocytes infiltrating a crypt. C. Lymphocytic colitis. The intraepithelial lymphocytes marked as T lymphocytes on immunoperoxidase staining for CD3.

Fig. 2.

Diagnostic algorithm for hypergastrinemia. GAD, glutamic acid decarboxylase; IA2, protein tyrosine phosphatase; 17-OH and 21-OH, 17- and 21-alpha hydroxylase (steroidogenic P450 enzymes); scc, side chain cleavage enzyme (steroidogenic P450 enzyme); Tg, thyroglobulin; TPO, thyroid peroxidase; AMA, anti-mitochondrial antibody; ASMA, anti-smooth muscle antibody; ANA, antinuclear antibody; ALKM-1, anti-liver-kidney microsome-1 antibodies; ALC-1, anti-liver cytosol antibody-1; anti-SLA/LP, anti-soluble liver/liver pancreas antigen; anti-ASGPR, anti-asialoglycoprotein receptor (modified by Murugesan et al., 2009).

Table 1

Autoimmune disorders accompanying MC.

Common autoimmune diseases	Rare autoimmune diseases
Celiac disease (6–40%)	CREST syndrome
Thyroid disorders (up to 20%)	Sjögren's syndrome
Diabetes mellitus (10%)	Wegener's granulomatosis
	Dermatomyositis
	Systemic lupus erythematosus
	Autoimmune gastritis

Table 2

Main biochemical analyses of our case.

Celiac serology	Fasting gastrin	Chromogranin A	VIP	Calcitonin
Anti-gliadin IgG; IgA	1848 (3/08)	262	25.7	<5
Anti-endomysial IgA;	686 (4/08)			
Anti-tissue	796 (6/08)			
Transglutaminase IgA	1097 (7/12)			
All negative	N<100 pg/ml	N<225 pg/ml	(N<50 pg/ml)	(N<5 pg/ml)