GASTRIC CARCINOID TYPE 1 IN A PATIENT WITH AUTOIMMUNE POLYGLANDULAR SYNDROME: ADDITIONAL ENDOCRINOLOGICAL EVALUATION REQUIRED

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SUMMARY – Autoimmune polyglandular syndrome by definition consists of two or more endocrinological insufficiencies or two organ specific autoimmune diseases. There are no stringent criteria for endocrinological evaluation of patients with one endocrine insufficiency. However, detailed endocrinological evaluation should be undertaken in patients with two autoimmune diseases. Additionally, follow up thereafter should be a must in these patients in order to avoid the possibility of not diagnosing subsequent autoimmune diseases that can occur. The aim of this case report is to point to the necessity of endocrinological screening to be made in patients presenting with gastric carcinoid type 1. We report on a 62-year-old woman who was diagnosed with primary hypothyroidism in 1993. In 2011, she was re-admitted to the hospital due to increasing fatigue. Macrocytic anemia, low vitamin B12 levels and positive parietal antibodies confirmed pernicious anemia. Furthermore, she underwent gastroscopy, which revealed two polyps in the corpus of the stomach and one in the fornix. Endoscopic mucosal resection was performed and histopathologic analysis confirmed three G1 gastric carcinoids (Ki67 2%). Additional endocrinological evaluation disclosed positive glutamic acid decarboxylase antibodies, but normal fasting and postprandial glucose and HbA1c. In 2013, she was diagnosed with glucose intolerance and subsequently with latent autoimmune diabetes of adulthood. Plasma glucose and HbA1c normalized after dietary intervention. Due to the increase of serum chromogranin A, prophylactic antrectomy was performed in 2014. The patient is still followed-up and has normal chromogranin A, gastrin and HbA1c levels.

Key words: *Stomach neoplasms; Carcinoid tumor; Polyendocrinopathies, autoimmune; Anemia, pernicious; Glucose intolerance; Diagnosis, differential; Case reports*

Introduction

Polyglandular autoimmune syndrome (PAS) is an accumulation of multiple endocrine gland insufficiencies or other organ specific autoimmune diseases[1]. There are two major types of PAS. Type I is a monogenetic autoimmune disease which becomes fully manifested by the age of 20[2]. Type II is a polygenetic disorder that

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consists of two or more endocrine or other autoimmune organ specific diseases[3]. A novel classification suggests additional division to PAS type II, III and IV[1]. According to the new classification, PAS type II consists of Addison's disease, diabetes mellitus type 1 and autoimmune thyroid disease. PAS type III excludes the presence of Addison's disease and is further divided into category IIIA (autoimmune thyroiditis with immune-mediated diabetes), IIIB (autoimmune thyroiditis with pernicious anemia) and IIIC (autoimmune thyroiditis with vitiligo and/or alopecia and/or other organ specific disease). Organ specific diseases include celiac disease, hypogonadism and myasthenia gravis, while organ non-specific diseases include sarcoidosis, Sjögren's syndrome and rheumatoid arthritis[1]. PAS type IV consists of two organ specific diseases and/or organ non-specific diseases[1]. A great deal of controversy exists about the novel classification and it has not been fully established[4]. There are no stringent criteria for endocrinological evaluation of patients with one endocrine insufficiency. However, detailed endocrinological evaluation should be undertaken in patients with two autoimmune diseases[3]. Additionally, follow up thereafter should be a must in these patients in order to avoid the possibility of not diagnosing subsequent autoimmune diseases that can occur[3].

Autoimmune gastritis, eventually leading to pernicious anemia, is an organ specific autoimmune disease characterized by pathological lesions affecting the fundus and body of the stomach, which are typified by gastric mucosal atrophy, selective loss of parietal cells from the gastric mucosa, submucosal lymphocytic infiltration, as well as circulating gastric parietal cell autoantibodies[5]. Subsequently, pernicious anemia, which is considered to be the most common cause of vitamin B12 deficiency, may develop. Moreover, gastric parietal cell antibodies induce apoptosis in parietal cells, which leads to achlorhydria and compensatory increase in serum gastrin levels. Chronic hypergastrinemia stimulates enterochromaffin-like cells, which eventually leads to enterochromaffin-like cell hyperplasia and gastric carcinoid type 1. However, the prevalence of gastric carcinoid in patients with pernicious anemia is less than 1%[6].

We report on a 62-year-old woman with a history of hypothyroidism who presented with pernicious anemia and gastric carcinoid type 1. Screening for other components of PAS II revealed high antibody titers to decarboxylic glutaminic acid. The patient was diagnosed with glucose intolerance two years later.

Case Report

A 62-year-old female patient with a medical history of autoimmune thyroid disease accompanied with hypothyroidism was admitted in 2011 due to increasing fatigue and newly diagnosed macrocytic anemia. The patient had been diagnosed with primary hypothyroidism in 1993 and had been well substituted with levothyroxine ever since. Physical examination was unremarkable. Laboratory examinations revealed hemoglobin level of 130 g/L and mean cell volume of 120 fl. Further testing showed decreased vitamin B12

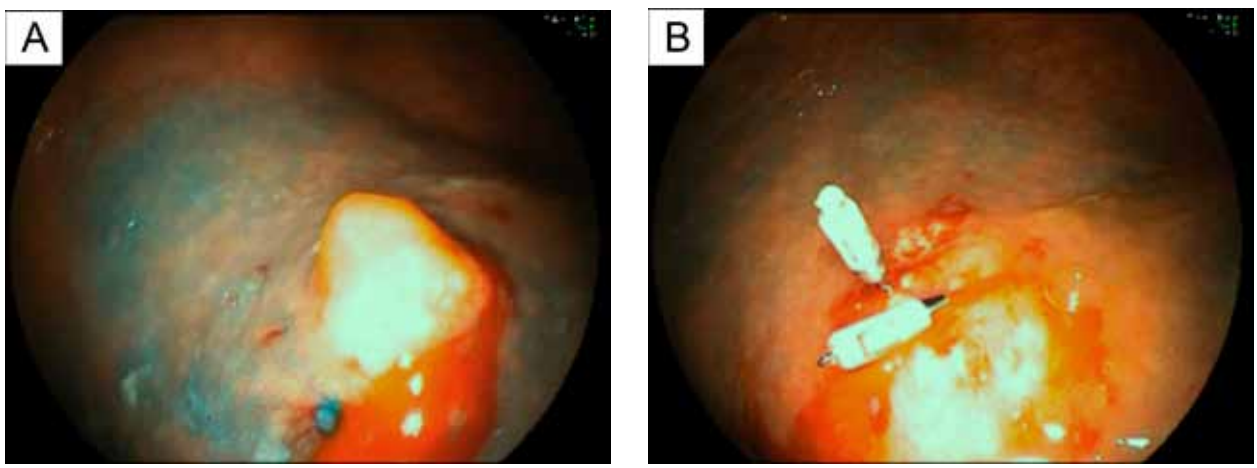

Fig. 1. A 13 mm large carcinoid in the fornix of the stomach (A); endoscopic mucosal resection of the tumor (B).

level of 78 ng/L (normal range: 211-911) along with positive parietal cell antibodies. Electrolytes and the rest of the complete blood count (CBC) panel were within the normal reference values.

Upper gastrointestinal (GI) endoscopy revealed three polyps within the gastric wall. Two small polyps were located in the corpus of the stomach and one approximately 10 mm large polyp was found in the fornix of the stomach (Fig. 1A). Since the patient had pernicious anemia, we presumed the polyps to be carcinoid tumors. Hence, we performed endoscopic ultrasound in order to assess invasion into the gastric wall. All three polyps seemed to be limited to the submucosa, and therefore endoscopic mucosal resection was performed (Fig. 1B). Histopathologic examination confirmed two 6 mm large G1 carcinoids (Ki67 2%) (Fig. 2A-D) in the corpus and one 13 mm large G1 carcinoid in the fornix of the stomach (Ki67 2%). There were signs of muscularis propria invasion by the largest polyp, and margins of the resected polyp were negative. In order to assess the presence of locoregional and distant metastases, we performed 99Technetium scintigraphy, which revealed two focal lesions in the mediastinum. However, multislice computed tomography showed normal findings.

Detailed endocrinological evaluation demonstrated a gastrin level of 22000 pg/mL (normal range: 13-115), chromogranin A 88 mcg/L (normal <100) , ACTH 8.98 pmol/L (normal <13.3), morning cortisol 607 nmol/L (normal range: 171-536), 17-hour cortisol 155 nmol/L (normal range: 64-327), T3 1.54 nmol/L (normal range: 1.1-3.1), T4 92.1 nmol/L (normal

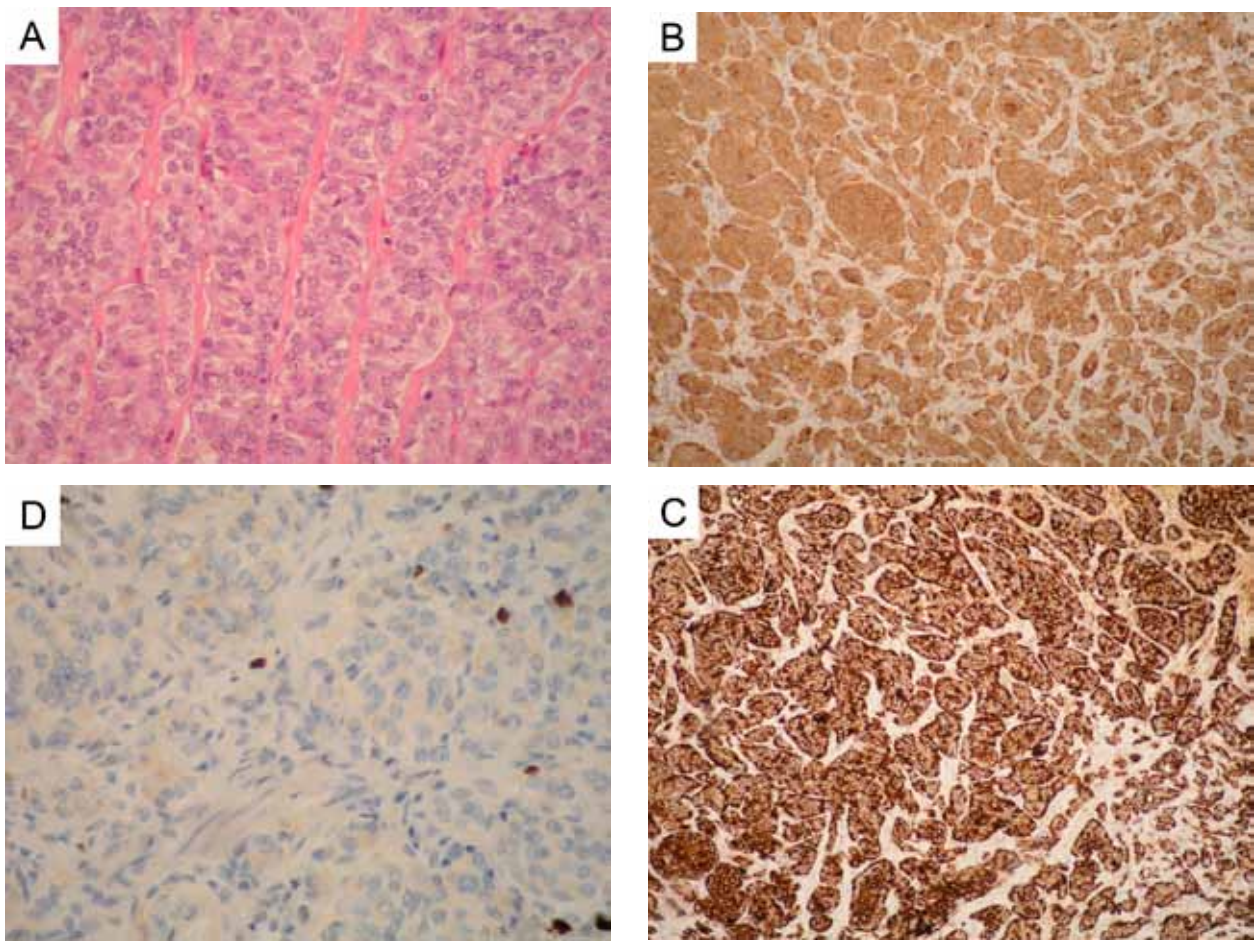

Fig. 2. Round nests of tumor cells with uniform nuclei surrounded with fibrovascular stroma, hematoxylin-eosin ×400 (A); positive synaptophysin (B) and chromogranin (C) expression, ×100; positive Ki67 expression in approximately 2% of tumor cells, ×400 (D).

range: 60-165), TSH 1.19 mIU/L (normal range: 0.4-4.0), antiTPO >600.0 mIU/L (normal range: <50), LH 26.0 IU/L (normal range: 7.7-58.5), and FSH 39.5 IU/L (normal range: 25.8-134.8).

Since our patient had two autoimmune diseases, we measured other organ specific antibodies available in our hospital. Antibodies to glutamic acid decarboxylase (GADA) were increased to 87.5 U/mL (normal <1.0). However, her HbA1c was within the normal limits (5.4%, normal range <6%), as well as fasting and postprandial glucose.

Vitamin B12 in a dose of 1000 mcg intramuscularly was administered regularly, and thereafter her CBC panel was within the normal ranges. Blood glucose and HbA1c were also regularly checked since the patient had positive GAD antibodies. In 2013, we found fasting glucose of 5.9 mmol/L, postprandial glucose of 8 mmol/L and HbA1c of 6.1%. This indicated glucose intolerance and prediabetes. Dietary measures were prescribed, after which fasting and postprandial glucose and HbA1c normalized.

During three-year follow up, upper GI endoscopy showed no signs of residual tumor mass or recurrence. However, chromogranin A levels increased to 145 mcg/L three years after polypectomy. Multislice computed tomography, magnetic resonance imaging and 99Technetium-sestimibe scintigraphy showed normal findings. However, we decided to perform antrectomy in order to reduce the risk of local recurrence and distant metastasis. Serum gastrin decreased to 54 pg/mL and chromogranin A decreased to 5 mcg/L.

Discussion

This is the first case of a patient with gastric carcinoid type I in whom screening for other components of PAS disclosed positive GADA antibodies and an early stage of latent autoimmune diabetes of adulthood (LADA).

Latent autoimmune diabetes of adulthood describes patients with a type 2 diabetic phenotype combined with islet antibodies and slowly progressive β-cell failure[7]. LADA patients are not insulin dependent during the first few years after the diagnosis of diabetes. However, β-cell function gets impaired over the period of six years, which leads to insulin dependency in most LADA patients[7]. High titers of islet antibodies correlate positively with β-cell failure[8]. In a study by Borg *et al*., 67% of patients with GADA levels above 41.4 U/mL developed insulin dependent diabetes mellitus over the period of 5 years[9]. Our patient had a GADA level of 87.5 U/mL at the time of screening, and was diagnosed with prediabetes two years later. Based on a high titer of GADA, it is most likely that the patient will develop insulin dependent diabetes mellitus despite dietary and lifestyle changes. Therefore, measurement of GADA is of great value for early diagnosis and treatment of LADA. However, screening for LADA should not have been made in our patient based on the new classification of PAS. Older classification of PAS recognizes only type I and type II. Type II is defined by the presence of two organ specific or non-organ specific autoimmune diseases[3]. The new classification of PAS defines type II as the coexistence of autoimmune thyroid disease and type 1 diabetes mellitus or Addison's disease[1]. Older type II PAS is then subdivided into type III and IV [1]. Type III is associated with thyroid autoimmunity and other autoimmune diseases, excluding Addison's and type 1 diabetes. Subclassification of type III includes 3A (autoimmune thyroiditis combined with immune mediated diabetes mellitus), 3B (autoimmune thyroiditis with pernicious anemia) and 3C (autoimmune thyroiditis with vitiligo or alopecia)[1]. Type IV is defined as two or more other organ specific autoimmune diseases[1]. We find the older classification to be more appropriate. The diagnosis of PAS type IIIB could be made in our patient in 2011. Since type IIIB does not involve other organ specific diseases, we did not have to screen the patient for other autoimmune diseases. We suggest that PAS type II is a spectrum of several autoimmune diseases and that the combination of all diseases is possible. Clear and more straightforward guidelines need to be proposed to avoid any sort of misguidance and to give a pinpoint diagnosis. To diagnose type 2 PAS, patients must present minimally with two endocrine insufficiencies or two organ specific autoimmune diseases. The time frame of other insufficiencies presenting is impossible to predict, but with screening antibodies better prediction can be foreseen[10]. Therefore, we propose that antibodies be measured in patients with two or more autoimmune diseases. There are no strict guidelines for screening in patients with one endocrine insufficiency. We tend to agree with Dittmar *et al*. who propose screening at

three-year intervals for patients with one endocrine insufficiency[3]. We believe that it will suffice to measure TSH, anti-TPO, morning cortisol and ACTH, CBC, HbA1c and testosterone in men.

Gastric carcinoid type I is the most common type which accounts for approximately 70%-80% of all gastric carcinoids[11]. Type II is associated with the concomitant presence of gastrinoma and is encountered in 5% of patients. Type III carcinoids are defined as sporadic and are not related to hypergastrinemia[11]. Type I carcinoids are mostly non-functional, low grade tumors with low malignant potential[12]. Therefore, endoscopic polypectomy by snare or endoscopic mucosal resection (EMR) is most appropriate treatment for type I carcinoids[13]. In case of polyps >1 cm, endoscopic ultrasound should be performed to assess wall and lymph nodal invasion before polypectomy. Surgery should be performed in case of involvement beyond the submucosa, or positive margins after EMR[13]. Type I carcinoids are often multiple and local recurrence is common, since hypergastrinemia associated with autoimmune gastritis is persistent[14]. In case of local recurrence or metastasis, antrectomy should be performed in order to reduce serum gastrin levels[13]. We initially performed EMR for all carcinoids in our patient. Although local recurrence did not occur, a constant rise in serum chromogranin A levels was observed. Due to the increase in serum chromogranin A levels, we decided to perform antrectomy in our patient. The procedure was uneventful and both serum chromogranin A and gastrin normalized only three months after the surgery.

In conclusion, suspicion of gastric carcinoid must be raised in all patients with pernicious anemia and atrophic gastritis. Additionally, screening for other endocrinological deficiencies and autoimmune diseases should be performed in all patients with gastric carcinoid type I. Positive organ specific antibodies can facilitate an early diagnosis and treatment.

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Sažetak

KARCINOID ŽELUCA TIPA 1 U BOLESNIKA S AUTOIMUNIM POLIGLANDULARNIM SINDROMOM ZAHTIJEVA DODATNE ENDOKRINOLOŠKE PRETRAGE

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Autoimuni poliglandularni sindrom čine dvije ili više endokrinih insuficijencija ili najmanje dvije za organ specifične autoimmune bolesti. Ne postoje jasne smjernice za endokrinološko testiranje i praćenje bolesnika s jednom endokrinom insuficijencijom. Bolesnici s dvije endokrine insuficijencije ili za organ specifične autoimmune bolesti trebaju detaljnu endokrinološku obradu kako bi se isključila mogućnost postojanja treće autoimmune bolesti. Cilj ovoga prikaza slučaja jest naglasiti nužnost dodatne endokrinološke obrade u bolesnika s karcinoidom želuca tipa 1. Prikazujemo slučaj bolesnice kojoj je godine 1993. otkrivena primarna hipotireoza. Godine 2011. bolesnica je hospitalizirana zbog izražene opće slabosti i malaksalosti. Makrocitna anemija, nizak vitamin B12 i pozitivna protutijela na parijetalne stanice potvrdili su dijagnozu perniciozne anemije. Gornjom endoskopijom probavnog trakta otkrivena su dva polipa u korpusu i jedan u forniksu želuca. Nakon endoskopskog ultrazvuka učinjena je endoskopska mukozektomija svih triju polipa. Patohistološka analiza potvrdila je karcinoide gradusa 2 (Ki67 2%). Dodatnim endokrinološkim testiranjem otkrivena su povišena protutijela na dekarboksilazu glutamata uz uredne vrijednosti glukoze u plazmi i HbA1c. Godine 2013. otkrivena je intolerancija glukoze te je postavljena dijagnoza latentnog autoimunog dijabetesa odrasle dobi. Glukoza u plazmi se normalizirala nakon higijensko-dijetetskih mjera. Zbog porasta kromogranina A u serumu učinjena je antrektomija godine 2014. Bolesnica sad ima uredan kromogranin A, gastrin i HbA1c.

Ključne riječi: *Želučani tumori; Karcinoidni tumor; Poliendokrinopatije, autoimune; Anemija, perniciozna; Glukoza, intolerancija; Prikazi slučaja*