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Case Report

An Unusual Association of Folic Acid Deficiency with Gastric Neuroendocrine Tumor Type I

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ABSTRACT

The association of gastric neuroendocrine tumour type I with macrocytic anaemia due to vitamin B12 deficiency is commonly encountered. For the subsequent treatment guidance, the etiological cause of macrocytic anaemia must always be precisely established. We presented the case of a 63-year-old patient admitted for marked physical asthenia, palpitations, abdominal pain, flatulence, paresthesia in the upper and lower limbs and concentration difficulties. Clinical examination revealed pale, dry skin, Hunter's glossitis, and tachycardic heart sounds. Bloodwork showed pancytopenia with macrocytic normochromic anaemia, vitamin B12 within normal limits, but with low folic acid levels. The reticulocyte crisis was documented on day 3 after initiating folic acid treatment. Exploration by upper digestive endoscopy and colonoscopy described multiple polypoid tumours in the greater curvature of the stomach. The histopathological and immunohistochemical examination lead to the diagnosis of gastric neuroendocrine tumours (NET) type G1. To our knowledge, there are no reports in the literature about an association of this type of tumour with folate deficiency-induced anaemia.

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Introduction

Gastric neuroendocrine tumours (G-NET) type 1 are often accidentally diagnosed after a biopsy of gastric polyps. They are found during endoscopy performed to explore macrocytic anaemia due to vitamin B12 deficiency or pernicious anaemia, which is currently associated with G-NET type 1. This type which characterizes our patient is found in 70-80% of cases in women aged 50-60.[1] It arises on the background of chronic atrophic gastritis (CAD), the parietal cells being unable to secrete gastric acid. CAD represents the common cause for both folate deficiency and G-NET type 1. It is an inflammatory condition in which the gastric glandular structures are replaced by glandular structures inappropriate for the location or by connective tissue. The most frequent etiologies of CAD described in the literature are chronic infection with Helicobacter pylori and autoimmune gastritis.[2]

We presented a unique combination of G-NET type 1 with macrocytic anaemia due to folic acid deficiency, with vitamin B12 values within normal limits, in the case of a 63-year-old patient who was admitted for palpitations, marked physical asthenia, abdominal pain, paresthesia in the upper and lower limbs and concentration difficulties. Histopathological examination of samples taken from upper digestive endoscopy revealed G-NET type 1. Contrary to our expectations, it was determined that the symptoms of macrocytic anaemia were not due to vitamin B12 deficiency but to folic acid deficiency.

Case Report

A 63-year-old woman was admitted to the emergency department for palpitations, marked physical asthenia, retrosternal chest pain relieved by rest, lasting about 3-4 minutes, dyspnea, productive mucopurulent cough, abdominal pain in the hypogastrium, loss of appetite, headache and vertigo, concentration difficulties, paresthesia in the fingers of the upper and lower limbs, constipation, flatulence, symptoms that have worsened in the week before hospital admission. The patient's medical history revealed smoking (0.3 pack year) and chronic alcoholism (75 g pure alcohol/day). She had no regular treatment at home. The patient declared she knew about her anaemia and sinus tachycardia for about 40 years but showed no medical records. The RT-PCR test excluded SARS-COV2 infection upon admission.

Clinical examination revealed an underweight patient (a body mass index of 16.94 kg/m^2) with pale and dry skin, Hunter glossitis, total edentation, tachycardic heart sounds 106 beats/min, a blood pressure of 99/57 mmHg, rhonchi at the right basal hemithorax, SpO_2 98% in room air, tenderness on palpation in the hypogastrium. Bloodwork showed leukopenia (GA: 2020/mm^3), macrocytic normochromic anemia (hemoglobin 5.3 g/dL), FEV 143.5/fL, folic acid 1.7 ng/mL (reference range 3.1-20.5 ng/mL), vitamin B12 221 pg/mL (reference range 187-883 pg/mL), thrombocytopenia (53,000/mm^3), nonspecific inflammatory syndrome (CRP 3.5 mg/dL, ferritin 92 ng/mL), hypoproteinemia (total proteins 5 g/dL) with hypoalbuminemia (albumin 3.06 g/dL) in context of poor diet due to total edentation, protein electrophoresis within normal limits, elevated NT-proBNP (1,246 pg/mL), cholestasis syndrome (GGT 345 U/L, total bilirubin 1.68 mg/dL, direct bilirubin 1.20 mg/dL), hyperuricemia (uric acid 6.3 mg/dL), pathological urinalysis test, but with negative urine culture, and negative

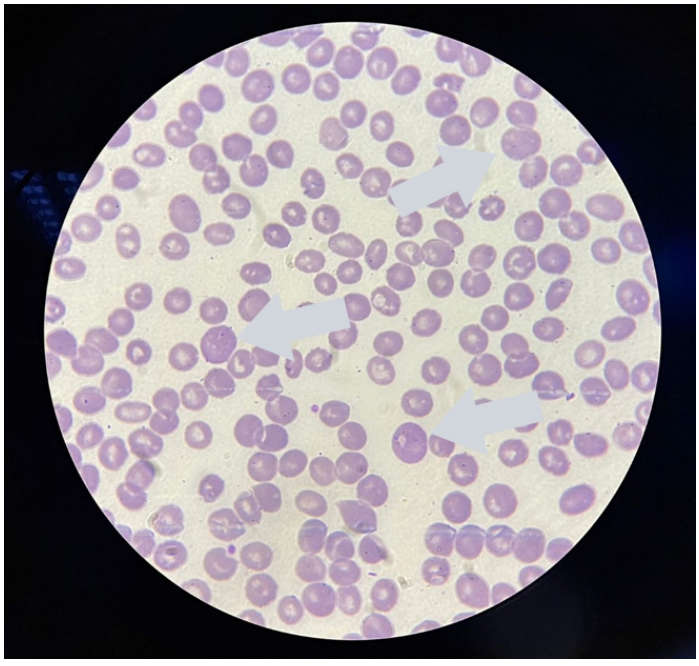

Figure 1. Peripheral blood smear: microscopic aspect in HE stain x100 immersion objective (with a drop of cedar oil) – anisocytosis: normo- and macrocytes (arrows).

blood culture. A peripheral blood smear showed anisocytosis with macrocytosis (place for *Figure 1*). The thyroid function and markers for viral hepatitis, CEA and CA 19-9 were within normal limits. Microbiological examination and sputum culture revealed infection with beta-lactamase-producing *Neisseria meningitides* and *Streptococcus pneumonia*. Antibiotic treatment was initiated with amoxicillin and clavulanic acid 1.2 g every 8 hours, combined with gentamicin 160 mg every 24 hours for seven days, with favourable evolution of respiratory symptoms.

ECG upon admission showed sinus tachycardia, with repolarization changes (negative T waves in V2-V5, DII, and flattened T waves in V6, DIII, aVF, aVL). Cardiac enzymes were normal, thus ruling out an acute event. The echocardiographic examination described normal-sized heart cavities without kinetic alterations, thrombus, or pericardial fluid.

Thus, we interpreted the anaemia as due to folic acid deficiency. Because of its severity, we did not repeatedly delay the treatment to measure vitamin B12 levels. The diagnosis was further supported by the reticulocyte crisis documented 3 days after the initiation of folic acid treatment with a dose of 15 mg per day (reticulocytes increased from baseline 40,000/mm^3 to 250,000/mm^3).

The abdominal ultrasound examination revealed an enlarged, hyperreflective liver (right hepatic lobe 162 mm and left hepatic lobe 57 mm) with a fine granular surface, without macro nodules; vascular dilatations on the topography of the round ligament up to 6 mm; rectum with thickened walls, rectilinear, layered, apparently regular, about 13 mm thick; portal vein with normal diameter; spleen with bipolar diameter 113 mm, homogenous structure; perihepatic fluid - 15 mm thick, perisplenic - 14 mm, fluid in hypogastrium containing fibrin septa, vesicouterine fluid - 30

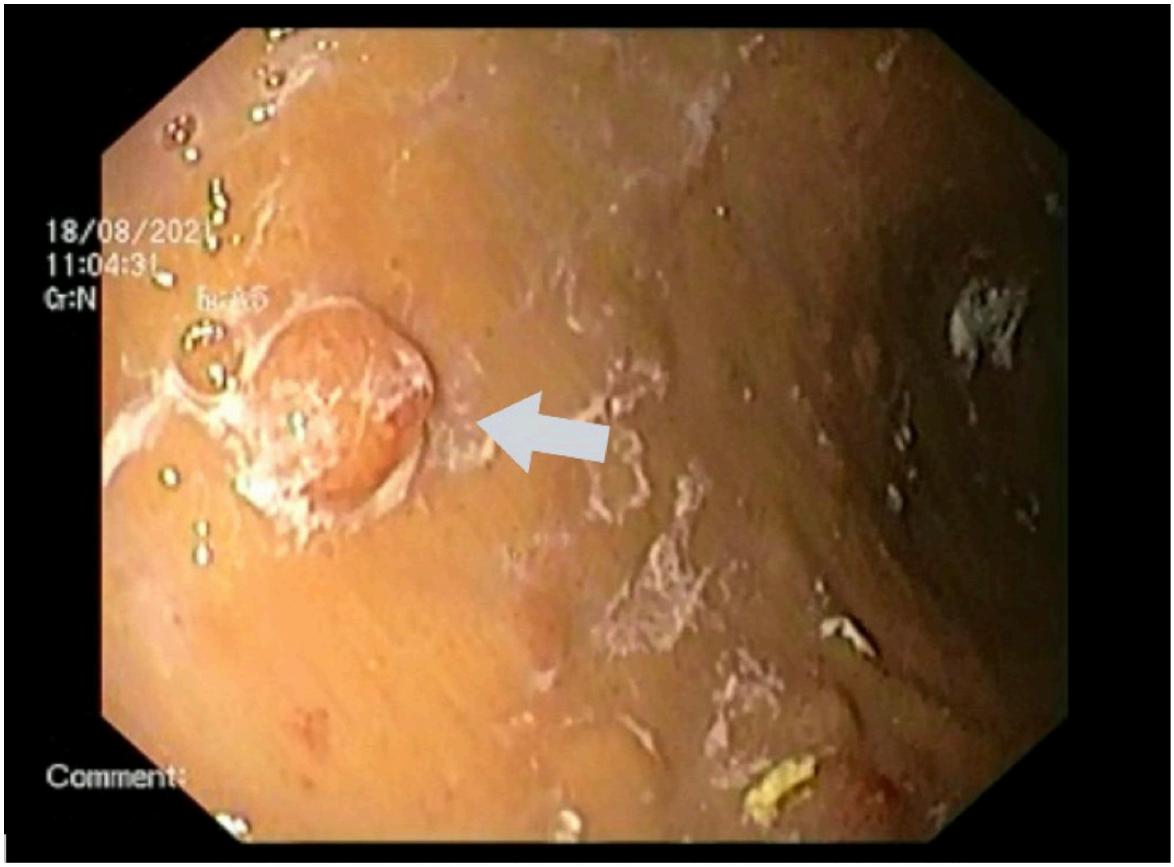

Figure 2. Upper digestive endoscopy: atrophic gastritis, sessile polyp (arrow).

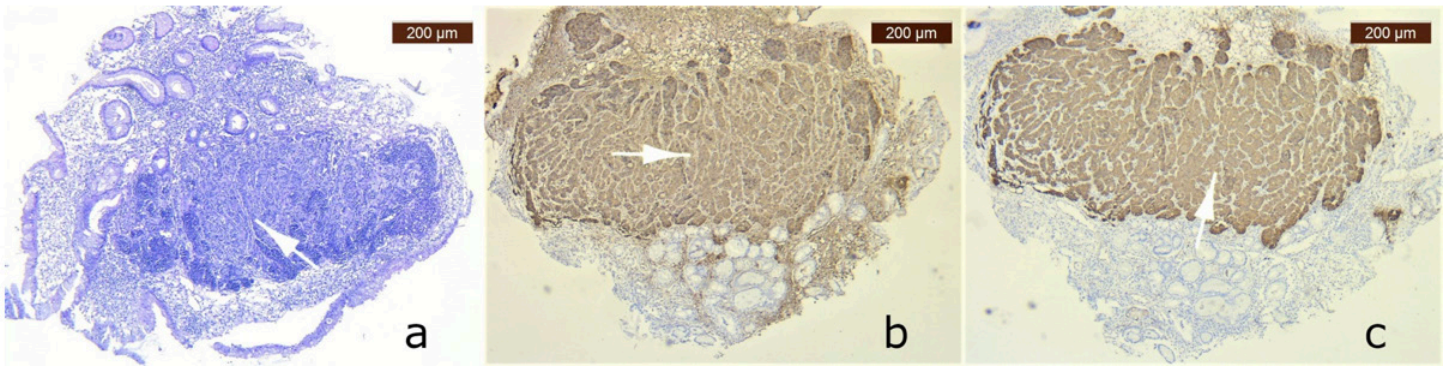

Figure 3. Polyp biopsy: histological aspect in: HE stain x50 - Tumor isle (arrow) with round and prismatic cells, hyperchromic nuclei and pale eosinophilic cytoplasma (a); immunohistochemical tests for Chromogranin A x50 (b) and Synaptophysin x50 (c).

mm, fluid in the pouch of Douglas - 20 mm, right pleural fluid - 39 mm. The upper digestive endoscopy revealed a small sliding hiatal hernia, Schatzki ring, atrophic gastritis, friable gastric mucosa, bleeding easily when touched; 4 sessile polyps (Paris Is) on the great curvature of the stomach, which were biopsied (place for *Figure 2*). Exploration of the large bowel by colonoscopy did not show any abnormalities.

The biopsy showed the absence of mitoses and the Ki-67 index <1%. Alcian blue stain showed goblet cells and sustained complete type intestinal metaplasia. Immunohistochemical tests for chromogranin A and synaptophysin showed diffuse positivity in the majority of the tumour cells and the neuroendocrine cells from the adjacent mucosa, highlighting neuroendocrine cells' hyperplasia foci. It concluded that the morphological and immunohistochemical aspects correspond to a multifocal gastric neuroendocrine tumour type 1 (G1) with neuroendocrine cell hyperplasia (place for *Figure 3* and *Figure 4*).

The paraclinical examination showed normal ESR, gamma globulins and transaminase levels, no signs of hepatocellular insufficiency (normal coagulation profile), except a low albumin level and total proteins, interpreted as secondary to the patient's dental problems, and elevated levels of total and direct bilirubin. There were no signs of portal hypertension (absent oesophagal varices in upper digestive endoscopy, normal diameter of inferior vena cava, portal vein and spleen at abdominal ultrasound), which, combined with the paraclinical profile, reduced the probability of a diagnosis of hepatic cirrhosis. However, we do not exclude chronic alcoholic liver disease. Upon discharge, the patient was scheduled for an endocrinology consultation and was recommended specific blood tests to rule out celiac disease to expand the investigation and start the specialized treatment, but the patient didn't comply.

Discussion

G-NETs originate in stomach enterochromaffin-like (ECL) cells, which regulate gastric acid production. They represent less than 1% of stomach neoplasms but still constitute ¼ of all gastro-pancreatic neuroendocrine tumours and 10-30% of all NETs, with an incidence of 0.002-0.1 per 100,000 population per year.[1] Most G-NETs are accidentally diagnosed by anatomopathological examination of polyps identified during upper digestive endoscopy. These represent 0.6-2% of the identified and biopsied gastric polyps.[1]

According to the gastro-pancreatic NET classification systems proposed by ENETS, NANETS and WHO 2019, they are histologically divided into low (G1), intermediate (G2) and high (G3) grades. This classification is based on the rate of cell proliferation (mitosis rate, Ki-67 index) as followed: G1 – <2 mitoses/2 mm^2, Ki-67 index <3%; G2 – 2-20 mitoses/2 mm^2, Ki-67 index 3-20%; G3 – >20 mitoses/2 mm^2, Ki-67 index >20%.[3] G-NETs are also subclassified into type

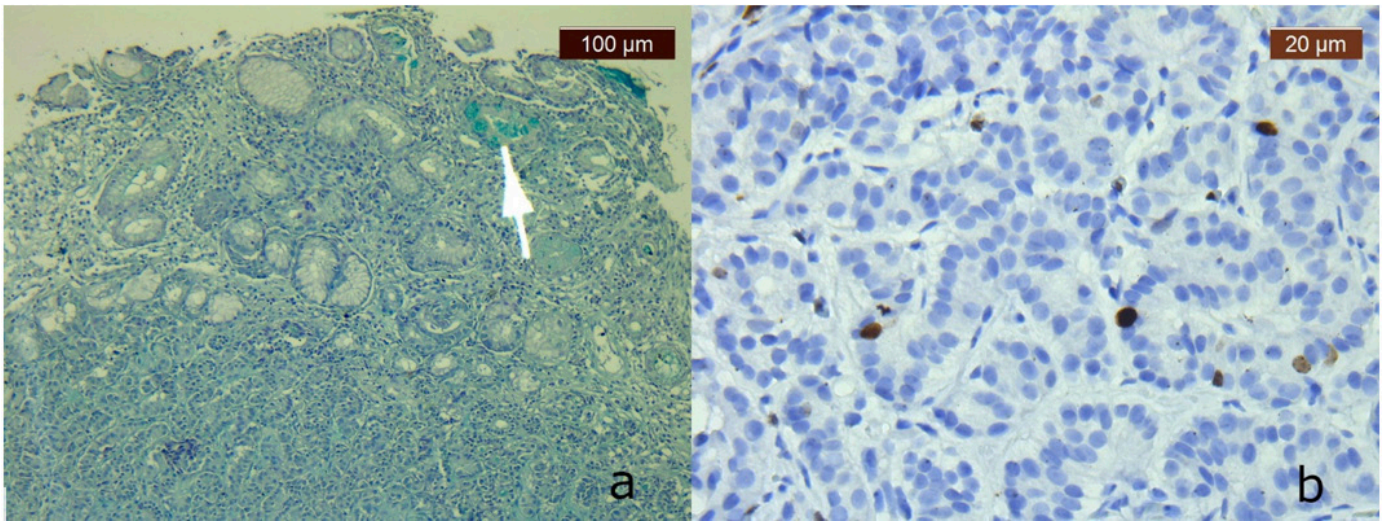

Figure 4. Polyp biopsy: histological aspect in: Alcian blue stain x 100 –goblet cells stained in light blue (arrow (a); Ki-67 immunostaining x400 –positive in less than 1% of the tumor cells in the most active area (b).

1 (occurs on the background of atrophic gastritis type A, is the most common), type 2 (occurs on the background of Zollinger-Ellison syndrome or in MEN I) and type 3 (sporadic).[1]

Type 1, described in the case of our patient, is represented by non-secreting tumours, most commonly asymptomatic, but which can ulcerate and thus lead to bleeding and secondary anaemia.[5] This type arises on the background of chronic atrophic gastritis, leading to hyperplasia of gastric antral G cells and consecutive hypergastrinemia. Gastrin binds to the colecystokinin2 (CCK-2) receptor on the ECL cells, determining hyperplasia and subsequently the development of G-NET type 1.[2,4] Also, the destruction of parietal cells in the long-term evolution of atrophic gastritis can lead to decreased intrinsic factor secretion and, consequently, decreased absorption of vitamin B12. Thus, vitamin B12 deficiency and macrocytic hyperchromic anaemia are frequently associated with autoimmune gastritis and hypergastrinemia, but only 5% of people with chronic atrophic gastritis develop G-NET.[1,6]

In our case, it was impossible to determine serum intrinsic factor and gastrin levels to characterize the detected macrocytic anaemia completely. The symptoms presented upon admission and the anaemic syndrome detected place the patient in the clinical-paraclinical description typical to G-NET type 1. One of the particularities of this case was the low values of folic acid and normal values of vitamin B12 level. Folate absorption is mainly influenced when transported across the intestinal wall. This process is pH dependent and is optimal at low pH. In the case of achlorhydria, found in CAD, the gastric pH is elevated above the level necessary for folate to be absorbed, thus leading to folate deficiency and macrocytic anaemia.[7]

The diagnosis of folate deficiency anaemia was based in our case on the clinical symptoms and signs, the low acid folic levels and the reticulocytes crisis documented after three days from folic acid administration. Optimally, the differential diagnosis between folate and vitamin B12 deficiency is based on serum homocysteine, methylmalonic acid, intrinsic factor and anti-parietal cell antibodies levels, but we could not perform these tests in our hospital due to technical difficulties during the patient's hospitalization.

As stated earlier, CAD represents the common cause of folate deficiency and G-NET type 1. On the other hand, we cannot exclude the coincidental association between macrocytic anaemia due to folate deficiency and G-NET type 1 described in our case. Our patient presented a history

of chronic alcoholism and was underweight, suggesting poor folate intake. Both conditions can cause folate deficiency. G-NET type 1 is found most commonly in the gastric fundus, having a polypoid appearance in 78% of cases and a small size (5-8 mm).[8] The peculiarity of the presented case is the location of the neuroendocrine tumour on the great curvature of the stomach.

As stated in the 2021 NCCN guidelines, the optimal strategy for G-NET type 1 is endoscopic resection in prominent tumours. However, it does not provide a limit value for the tumour size that defines the notion of "prominent" and according to which the decision of resection should be taken.[9] According to the NCCN guidelines from 2015, our patient falls into the category of "multiple tumours under 2 cm", with the recommendation to monitor the evolution or to resect the tumour and the adjacent mucosa. The guideline recommends clinical-paraclinical and endoscopic re-evaluations every 6-12 months in the first three years, then annually (if no changes are observed), and imaging when the clinical examination indicates it. In the event of new lesions or an increase in the size of existing tumours, an antrectomy is recommended to remove the source of gastrin secretion.[10] The ENETS 2016 guidelines recommend using conservative treatment strategies in the case of small G-NETs type 1, as the risk of metastasis of this type is small and directly related to the tumour size (the cut-off value being 10 mm). Thus, the recommendation of endoscopic mucosal resection or dissection of the submucosa is made in the case of 10 mm or greater tumours.[11]

Regarding folic acid deficiency anaemia, the recommended dose for treatment is 5 mg per day of folic acid for four months. The patient also needs further investigation to rule out possible celiac disease.[12] The best serological screening tools for this diagnosis are the determination of IgA anti-tissue transglutaminase and IgA anti-endomysial.[13] As we could not perform during hospitalization due to technical problems, we recommended the patient undergo them upon discharge. However, the patient didn't experience typical symptoms of Celiac disease. The patient did not comply with the recommendations and failed to return for a scheduled checkup one month after discharge.

Type 1 G-NET has a very good prognosis and a 5-year survival rate of 95%.[14] Due to the low potential of metastasis, this type is considered benign, with only three deaths due to evolution to secondary lesions in 724 cases evaluated.[15] However, we must not ignore the potential of this type of tumour to progress to a malignant lesion. For instance, in 2012, Spampatti and co-workers described a case of G-NET type 1 with an unusually aggressive evolution, resulting in death, in the case of a 60-year-old patient with type 2 diabetes and pernicious anaemia.[15] The reason for G-NET type 1 recurrence, with a median recurrence of 24 months and a 3% rate of transformation into poorly differentiated G3 neuroendocrine carcinoma, is the persistence of gastric hypersecretion at the antral level.[1]

Concluisons

When evaluating a case of chronic megaloblastic anaemia, we should not forget this rare association with G-NETs. They can perpetuate the anaemia through ulceration and bleeding. There is also the risk, even in sporadic cases, for them to evolve into a malignant lesion, thus changing the patient's prognosis. The most commonly known is the association of gastric neuroendocrine tumour type I with macrocytic anaemia due to vitamin B12 deficiency. To our knowledge, there are no reports in the literature about an association of this type of tumour with folate deficiency-induced anaemia. Therefore we consider the publication of this case to help our colleagues.

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Conflict of Interests

The authors declare that they have no conflict of interest.

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Informed Consent

Written consent was obtained from the patient.

Authors' Contribution

Literature Review, Critical Review, Manuscript preparing held by all authors.

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