EJCRIM
European Journal
of Case Reports
in Internal Medicine

THE INVESTIGATION OF B12 DEFICIENCY LEADING TO THE SERENDIPITOUS DIAGNOSIS OF GASTRIC CARCINOID TUMOUR

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Received: 30/05/2024
Accepted: 10/06/2024
Published: 29/07/2024

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: A signed written informed consent was obtained from the patient prior to writing the manuscript giving permission to publish the clinical history.

How to cite this article: Karam K, Saleh S, Chebbo H, Jalloul S, Fiani E. The investigation of B12 deficiency leading to the serendipitous diagnosis of gastric carcinoid tumour. Titolo articolo. *EJCRIM* 2024;**11**:doi:10.12890/2024_004673

ABSTRACT

Gastric carcinoid is a rare type of gastric malignancy accounting for around 7% of all gastrointestinal neuroendocrine tumours (NETs). While most gastric NETs (gNETs) are readily visible through direct visualisation by upper endoscopy, around 25% of gastric carcinoids are invisible because they are located in the submucosal gastric regions of the body and fundus. gNETs located in the intra-mucosal areas can be identified by gastric mapping; this can be done by taking random gastric biopsies from the antrum, body and fundus.

We report a case of a well-differentiated gastric NET type 1 with atrophic gastritis diagnosed on upper endoscopy and pathological immunohistochemistry staining.

KEYWORDS

Gastric NET, atrophic gastritis, pernicious anaemia

LEARNING POINTS

- The case highlights that not all gNETs are visible under direct endoscopic visualisation.
- It is essential to understand the different types of gNETs.
- Understand that both type and size of gNETs impact therapeutic implications and prognosis.

INTRODUCTION

Neuroendocrine tumours (NETs) arise from cells of the endocrine and nervous system and most commonly originate from the gastrointestinal (GI) tract[1]. Tumours arising from the gastric mucosa are known as gastric NETs (gNETs) or gastric carcinoids and they represent around 1% of all NETs, and around 1.8% of gastric cancers[2]. They are classified into four subgroups with types 1, 2 and 4 being more inert while type 3 is more biologically aggressive. Another type of gNET has been recently described as arising in the setting of chronic proton pump inhibitor (PPI) use; tumours arising in the setting of chronic PPI use appear to behave in a less malignant

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fashion than true-sporadic tumours[3]. The incidence of gNETs is 4.85 per 100,000 patients[4]. The incidence of gastric carcinoids has been soaring due to increased numbers of patients undergoing diagnostic endoscopy, and the use of acid suppressive therapy such as PPIs[5]. For instance, PPI therapy induces secondary hypergastrinemia through enterochromaffin-like (ECL) cells hyperplasia, dysplasia and ultimately neoplasia[6]. We describe a case of a 74-year-old female patient with low vitamin B12 who underwent oesophagogastroduodenoscopy (EGD) and was found to have gastric NET type 1 in the context of autoimmune atrophic gastritis.

CASE DESCRIPTION

A 74-year-old female patient with no known past medical history sought medical attention due to the incidental finding of a low vitamin B12 of 90 pg/ml (normal values are 160 to 950 pg/ml) on a routine blood test, that was not reversed by cobalamin intake. The patient denied any history of gastrectomy or bariatric surgery, or ileal resection or bypass. Serology for celiac disease was negative and a previous colonoscopy with ileal biopsies revealed no inflammatory bowel disease, specifically Crohn's disease. A negative carbohydrate breath test excluded small intestinal bacterial overgrowth. The patient was not on a vegan or strictly vegetarian diet. Also, she was not taking any agents that block or impair absorption or metabolism of vitamin B12, such as metformin, PPI (e.g. omeprazole) or H_2 receptor antagonist (e.g. cimetidine). She was referred to a gastroenterology specialist for concern of a gastrointestinal condition that should be addressed. She underwent a diagnostic EGD to rule out the presence of atrophic gastritis that could be mediated by autoantibodies against intrinsic factor or gastric parietal cells (i.e. pernicious anaemia). An EGD revealed flattened gastric folds and atrophic changes with non-specific nodular mucosa *(Fig. 1 and 2)*. Gastric mapping was carried out by taking random gastric biopsies from the antrum, body and fundus. Biopsies disclosed a morphology consistent with a neuroendocrine tumour in the setting of autoimmune gastritis. The Ki-67 index was less than 2%, suggestive of a well-differentiated gastric NET type 1. An immunohistochemistry staining was positive for chromogranin A (CgA) and synaptophysin, and negative for cytokeratin 7 and 20, corroborating a diagnosis of carcinoid tumour.

DISCUSSION

Low vitamin B12 stems from multiple aetiologies: gastric, small bowel disease, pancreatic, diet and agents that impair absorption of vitamin B12. Gastric causes include autoantibodies against intrinsic factor or gastric parietal cells (i.e. pernicious anaemia), a history of gastrectomy and bariatric surgery. Small bowel disease aetiology embodies malabsorption syndrome, a history of ileal resection or bypass, inflammatory bowel disease such as Crohn's disease, celiac disease and small intestinal bacterial overgrowth.

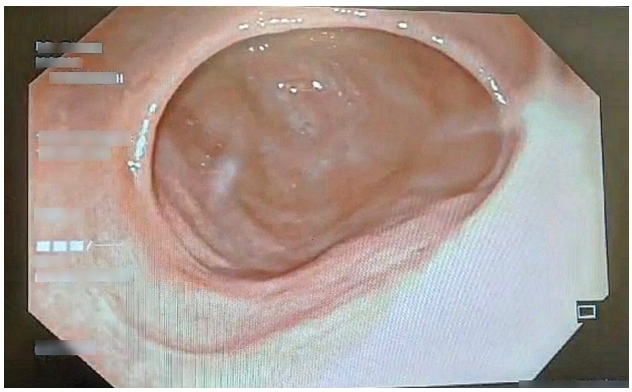

Figure 1. A frontal view of the antrum and body revealing flattened gastric folds and pale mucosa consistent with chronic atrophic gastritis.

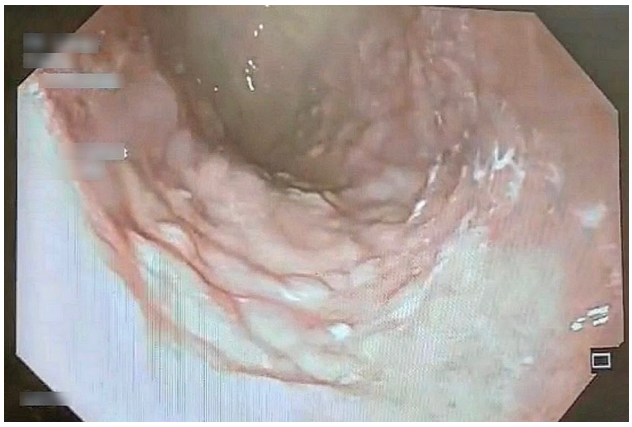

Figure 2. A retroflexed view showing flattened gastric folds and atrophic changes interspersed with non-specific nodular mucosa in gastric corpus and fundus.

Pancreatic insufficiency can also result in vitamin B12 deficiency. Patients who adhere to a vegan or strict vegetarian diet are prone to becoming cobalamin-depleted. Agents that block or impair absorption or metabolism of vitamin B12 such as neomycin, biguanides (metformin), PPIs (omeprazole), H2 receptor antagonists (cimetidine) and nitrous oxide (N_2O) used for anaesthesia or recreationally[7] can cause low vitamin B12 level.

Well-differentiated NETs arise most commonly from the gastrointestinal tract and lungs, and rarely from the genitourinary system. What was previously called 'carcinoid' is now called NET or neuroendocrine neoplasm (NEN)[1,2]. Carcinoid syndrome encompasses a constellation of symptoms mediated by humoral factors. Main symptoms of carcinoid syndrome include flushing and diarrhoea, yet these symptoms are rare, occurring only in functioning tumours. Despite being a rare entity, the incidence of NETs is increasing remarkably, and this is attributed to early endoscopic detection and frequent use of radiographic imaging[6]. Median age at diagnosis is 63 with a preponderance to males[2], and NET diagnosis is mostly incidental during endoscopy. Most patients are asymptomatic, and some may present with vague and non-specific symptoms such as recurrent upper abdominal pain and discomfort[8].

NETs originate from ECL cells (neuroendocrine cells) of the aerodigestive tract. ECL-harbouring cells stain with

potassium chromate when they contain serotonin[1,2]. The clinical behaviour of NETs is closely dictated by both histological grade and level of differentiation[4]. Grade represents the proliferative activity of tumorous cells and is measured by mitotic rate, which is the number of mitotic figures per 10 high-powered fields, or the Ki-67 index. Differentiation describes the extent to which neoplastic cells resemble their non-neoplastic counterparts. The World Health Organization divides NETs into two broad subgroups: well-differentiated and poorly-differentiated[5,7]. Well-differentiated NETs are classified into three types: low-grade (G1), intermediate (G2) and high-grade (G3), according to proliferative rate. Low and intermediate-rate NETs have an indolent behaviour, whereas high-grade tumours tend to assume aggressive behaviour. Poorly-differentiated NETs are high-grade carcinomas with a biologically aggressive behaviour resembling G3 well-differentiated NETs[1,2,6]. For instance, the Ki-67 is a mitotic index with higher values reflecting a poorer differentiation of neoplastic cells. Staging of gNETs follows the tumour, node, metastasis system and is determined by both biopsy results and imaging studies. Computered tomography (CT) scan, magnetic resonance imaging (MRI) and octreotide scintigraphy are commonly utilised imaging modalities for the staging of gNETs[3].

Immunohistochemical staining remains the cornerstone for the diagnosis of gNETs, with CgA and synaptophysin being the most specific diagnostic markers[5,7]. gNETs fall into four categories: types 1, 2, 3 and 4. *Table 1* summarises characteristics of all four gNET subgroups. Type 1 gNETs encompass around 70 to 80% of all gNETs. They are associated with chronic atrophic gastritis and pernicious anaemia, and are commonly found in females[3,4]. Endoscopically, they are usually less than 1 cm in size and they are portrayed as multiple polypoid lesions with small ulceration. They are derived from ECL cells, which transform into NETs through chronic stimulation by increased serum gastrin level in patients with atrophic gastritis[5]. Notably, patients with gNETs due to chronic atrophic gastritis are in their 60s to 70s[4,6].

Type 1 gNETs are non-functioning and benign tumours with a benign behaviour. Their propensity to metastasise is less than 10% when the size of the lesion is less than 2 cm[1,3].

Type 2 NETs are associated with Zollinger-Ellison syndrome in the setting of multiple endocrine neoplasia type 1 (MEN-1). They represent around 5% of gNETs and they also arise from ECL cells stimulated by increased serum gastrin levels. They behave similarly to type 1 NETs by assuming an indolent course and they are multifocal[4].

Type 3 gNETs are sporadic because they arise in the absence of atrophic gastritis, Zollinger-Ellison or MEN-1 syndrome. They represent around 20% of gNETs and are the most aggressive in terms of behaviour. Patients diagnosed with type 3 NETs exhibit either a local or hepatic metastasis in around 65% of cases. Unlike type 1 and 2 NETs, fasting serum gastrin level is normal in type 3 NETs[6,7].

The fourth type of gNET stems from usage of PPIs, which increases serum gastrin levels. Type 4 gNETs are often solitary. Pathologically, they are recognised by parietal cell and ECL cell hyperplasia without atrophic gastritis. Mucosal changes seen in type 4 gNETs are induced by hypergastrinemia in the absence of gastrinoma[1].

NETs have a propensity to metastasise to the liver, and liver metastases cause symptoms related either to tumour burden or hormonal induction[5,7]. Pain, jaundice and early satiety are symptoms caused by tumour burden, whereas flushing and diarrhoea are symptoms mediated by hormonal secretion.

Products of well-differentiated NETs are classified into three categories: amines, polypeptides and prostaglandins. Serotonin, 5-hydroxytryptophan, norepinephrine, dopamine and histamine are examples of amines-secreting NETs. Kallikrein, bradykinin, motilin, somatostatin, gastrin, vasoactive intestinal peptide and CgA exemplify polypeptides-secreting NETs. For instance, flushing is mediated by kallikrein and histamine whereas diarrhoea, cramping and valvular lesions are mediated by serotonin[3].

Physiologically, gastric epithelial G cells secrete gastrin, which stimulates ECL cells to secrete histamine. This creates positive feedback on gastric parietal cells, which further secrete hydrochloric acid and results in increased acid secretion. This process triggers a negative feedback mechanism on D cells that secrete somatostatin, which reduces the secretion of gastrin[1,2].

Incidence of metastasis is closely related to the size of the primary NET[2]. In other words, the bigger the size of the primary tumour, the higher the incidence of nodal and distant metastasis.

Our patient was found to have gNET type 1; this evokes the rarity of the case because it is only the second case to be mentioned in medical literature. It follows the case of Dhruv et al. that was reported in 2021, where in patients with a background of chronic atrophic gastritis, the annual incidence of type 1 gNET is around 0.4%[5]. Furthermore,

Characteristic	Type I	Type II	Type III	Type IV
Associated condition	Chronic atrophic gastritis and pernicious anaemia	Zollinger-Ellison syndrome and MEN-1	Sporadic	PPI
Serum gastrin	Elevated	Elevated	Normal	Elevated
Biological behaviour	Indolent	Indolent	Aggressive	Indolent

Table 1. Classification and general features of gNETs.

Dhruv et al. stated that around 22.2% of type 1 gNETs range between 0.5 mm and 5 mm, which make them invisible and not readily detected by upper endoscopy[5]. This is why type 1 gNET was not seen on EGD in our patient and was solely identified by random gastric biopsies. This fact highlights the importance of random gastric biopsies in uncovering entities that may be overlooked by direct endoscopic visualisation.

It is worth noting that our patient should be referred for an endoscopic surveillance every 6 to 12 months, and imaging studies when clinically indicated. Endoscopic surveillance is advised every 6 to 12 months because the patient will likely exhibit ECL cell hyperplasia and mucosal changes due to sustained hypergastrinemia[3,6]. The progression of type 1 gNET to a malignant phenotype is rare with a metastatic likelihood of less than 10% if the lesion is less than 2 cm. Aggressive surgical therapy is warranted in case of an extensive involvement of the gastric wall, a tumour size of more than 2 cm and emergent bleeding[5,6].

Types 1 and 2 gNETs usually have a good prognosis with close surveillance, whereas type 3 NET is associated with a 5-year mortality rate between 75% and 87%[2,7]. Tumours arising from chronic PPI usage appear to behave in a less malignant fashion than true-sporadic tumours[7].

The role of non-hormonal biomarkers, such as CgA and 5-hydroxyindolacetic acid (5-HIAA), the main metabolite of serotonin, is not recommended as a standard routine surveillance strategy because employing them to monitor disease recurrence is debatable in medical literature[5]. For instance, recommendations for follow-up after resection of a well-differentiated gastric NET have limited evidence.

CgA, a secretory protein released from the cytoplasmic chromaffin granules into the blood, aids in the diagnostic confirmation of carcinoid tumours. Serum CgA is the most commonly used biomarker to assess the tumour load[9]. However, the contribution of CgA to the detection of recurrent disease is limited, and the role of CgA in surveillance remains controversial. Furthermore, certain medications such as PPI can falsely elevate the CgA level[5].

In general, some tumours are unlikely to produce serotonin, which makes 24-hour measurements of urinary 5-HIAA counterintuitive for postoperative surveillance. Similarly, 5-HIAA measurement requires strict adherence to dietary restrictions before and during urine collection[5]. Therefore, consensus-based guidelines have increasingly de-emphasised the role of both CgA and 5-HIAA as standardised routine surveillance modalities. One study suggested that platelet serotonin is more sensitive than urinary 5-HIAA for detecting carcinoid tumours secreting small amounts of serotonin and not exhibiting the usual symptoms of carcinoid syndrome such as diarrhoea and flushing. As this is relevant in our case, using this test could have been of value in our patient[10].

Concerning the diagnostic role of imaging, CT scans represent the best modality for staging, surveillance and monitoring the therapeutic outcomes of NET. However, as in our case, CT scans have a limited role in gNET, which is usually diagnosed by endoscopy[11]. MRI can be used when CT scans are non-diagnostic. Some trials even found that MRI has a higher sensitivity than CT scans in the case of well-differentiated gastroenteropancreatic NETs (GEP-NETs), leading to the belief that MRI is the diagnostic procedure of choice in detecting metastatic NETs[12]. The positron emission tomography (PET)/CT imaging has an advantage over both CT and MRI in screening the whole body in one study[13]. Two types can be used: 68Ga-DOTA, which uses somatostatin analogue labelled with gallium-68 as a tracer marker to detect somatostatin receptors on NETs, and ^{18}F-FDG, which uses metabolic markers as a tracer. Ga-DOTA PET scans are used for high-grade NET and are considered superior to CT scans in the case of bone metastasis. On the other hand, ^{18}F-FDG PET CT is more useful for NETs with a high Ki-67 index and high cellular proliferation where somatostatin receptor expression is decreased leading to a decreased uptake by ^{68}Ga-DOTA PET/CT, along with an increased uptake of glucose by the tumour cells, detected by ^{18}F-FDG PET[11,13]. Imaging techniques therefore provide an important tool for incidental finding of asymptomatic carcinoid tumours in patients undergoing imaging for different reasons.

CONCLUSION

This case describes a rare type of gastric malignancy, type 1 gNET, that physicians ought to keep in their differential diagnosis among gastric cancers. gNETs are challenging to diagnose since they are mostly silent and asymptomatic. Incidence of gNETs is trending up due to the popularisation of endoscopy with its technical refinements and a frequent usage of PPIs. gNETs exhibit different therapeutic and surveillance strategies whereby each type defines survival and tailors' therapy, and endoscopic diagnosis and histopathological classification dictate management strategies. An evidence-based surveillance regimen should be sought for gNETs given the rarity of the disease and to trigger future perspectives on the diagnosis and treatment of gNETs.

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