

## C A S E R E P O R T

## A young man with persistent dyspepsia: the unexpected virtue of proton-pump inhibitors

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**Summary.** A 26-year-old man was referred to our department for a 3-year history of dyspepsia responsive to oral pump-inhibitors therapy. During the last year, he underwent a gastroscopy, a colonoscopy and a computed tomography enterography that failed to reveal an underlying organic disease: a diagnosis of functional dyspepsia was made. Because of the persistence of symptoms, he came to our ambulatory where we performed an abdominal ultrasound that revealed the presence of multiple bi-lobar lesions of the liver suspected for metastases and a hypoechoic solid lesion of the pancreas body, confirmed by a contrast enhanced computed tomography. Laboratory tests showed high chromogranin A and gastrin level, and a liver biopsy was consistent with a metastatic pancreatic neuroendocrine tumor. This report aims to underlie the diffuse heterogeneous diagnostic management of some common gastrointestinal symptoms, such as dyspepsia, that are too often approached with the prescription of proton pump inhibitors. ([www.actabiomedica.it](http://www.actabiomedica.it))

**Key words:** dyspepsia; proton pump inhibitor; neuroendocrine tumor; abdominal ultrasound

### Background

The management of dyspepsia represents a challenging issue in clinical practice, since it may underlie an extended spectrum of conditions ranging from a serious organic disease to a chronic disorder of altered peristalsis of the upper digestive tract (functional dyspepsia). Since some malignant diseases may present with dyspepsia, thought rarely, a reasoned diagnostic approach, that includes a complete history, physical examination, and appropriate imaging, is usually warranted, especially in the presence of alarm symptoms.

### Case presentation

A 26-year-old man was referred to our department for an annoying persistent dyspepsia started three years before. In the last few months, nausea, vomiting, and watery diarrhea developed.

Therefore, his primary care physician requested a gastroscopy, a colonoscopy and, after gastroenterology consultation, a computed tomography enterography without administration of concomitant intravenous contrast agent (due to a reported episode of angioedema). All the examinations resulted negative. Notably, the patient reported that only treatment with oral proton pump inhibitors (PPIs) was able to lead all the symptoms, including diarrhea, to complete remission. A diagnosis of functional dyspepsia was made.

The history of the patient was noteworthy for Gilbert syndrome and beta-thalassemia minor. Two years before admission he received an uncertain diagnosis of idiopathic urticaria/angioedema syndrome. He was a non-smoker and took no medication other than omeprazole.

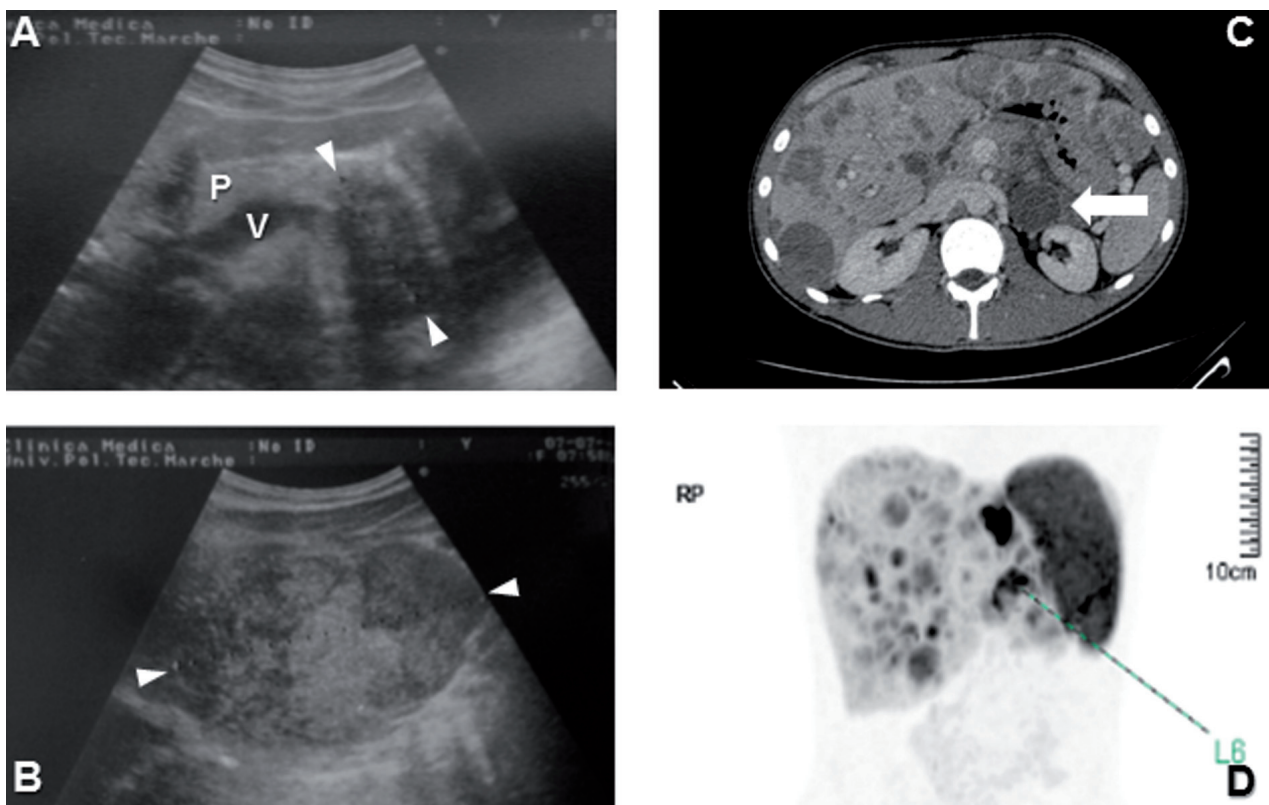
Upon the first ambulatory visit, routine laboratory tests were within normal range, except for elevated serum chromogranin A and gastrin levels (1826 ng/ml

and 428 pg/ml respectively), while he was taking omeprazole. Physical examination was unremarkable, except for a mild splenomegaly. We, therefore, performed bedside ultrasonography of the abdomen, that revealed a mild liver enlargement with the presence of multiple bi-lobar hypo-isoechoic lesions (the largest of 5.7 cm, at the 7<sup>th</sup> segment – Fig. 1), and a dishomogeneous hypoechoic solid lesion of the pancreatic body of about 5 cm in diameter (Fig. 1A-B). The patient was admitted for further evaluation. The findings of the abdomen ultrasound were confirmed by contrast enhanced computed tomography, which also revealed thrombosis of the portal venous system, involving the splenic vein and the portal junction (Fig. 1C). We, therefore, requested a percutaneous liver biopsy and the histological examination documented the proliferation of monomorphic cells organized in cordon pattern. On immunohisto-

chemical analysis, those cells were highly positive for cytokeratin (CAM 5.2) and focally for chromogranin A, with a Ki-67 index of 30%. The findings were consistent with metastatic pancreatic neuroendocrine tumor (G3). In order to complete the stadiation before starting therapy, a 68-Ga-DOTATOC PET/CT scan confirmed a dishomogeneous moderate tracer uptake of the pancreatic lesion and a mild uptake of the liver metastases (Fig. 1D).

## Discussion

Pancreatic neuroendocrine tumors (PNETs) are rare neoplasms, accounting for about 7% of all neuroendocrine tumors (NETs), and in up to 90% of the cases they are silent and non-functional (1). The inci-



**Figure 1.** Panel A-B: Epigastric B-mode ultrasonographic scan showing (A) the primary lesion in the pancreatic body (*arrowheads*; *P*, pancreatic head; *V*, portal vein) and (B) the largest metastasis involving and modifying the liver profile (*arrowheads*). Panel C: Contrast enhanced abdomen CT scan: the pancreatic tumor (*white arrow*) localized in the body-tail region and the diffuse liver metastatic disease. Panel D: The 68-Ga-DOTATOC PET/CT scan shows multiple focal tracer uptake, reflecting the presence of somatostatin-expressing cells, with the highest signal in the pancreatic region

dence of PNETs has increased over the last decades: in the Canadian population of Ontario, it raised up from 0.1 to 0.6 per 100,000 persons between 1994 and 2009, and only in part this is related to an increased incidental discovery (1). Furthermore, PNETs exhibited the lowest 5-year survival of all gastroenteropancreatic NETs (about 37.6%) (2). Considering that the incidence of PNETs significantly increases after the age of 40, our patient was exceptionally young at diagnosis, with the disease being already at the highest grading and staging, thus burdened with a poorer prognosis. PNETs are characterized by an unacceptable diagnostic delay (5-7 years on average), despite the development of modern imaging and biochemical tests (3).

The case depicted is useful to discuss relevant issues in clinical practice, including the primary care management of dyspepsia, which for our patient represented the first and most prominent symptom. From epidemiological studies, we know that dyspepsia is one of the most common problems encountered in everyday clinical practice, as it may affect approximately 20 to 25% of the adults in the Western Countries (4). Dyspepsia has been classified into organic, due to an underlying disease such as peptic ulcer or gastroesophageal reflux disease (GERD), and *functional*, a heterogeneous group with complex pathophysiological mechanisms not yet fully understood. According to the ROME III Consensus, our patient fulfilled diagnostic criteria for functional dyspepsia (5). Apparently, he did not report any *alarm* symptom such as unexplained weight loss, anemia or dysphagia (5). Nevertheless, when he reported the recent onset of nausea, vomiting and watery diarrhea, the primary care physician further investigated by requesting second-level studies such as gastroscopy, colonoscopy and CT enterography. Moreover, the latter was inappropriately performed without intravenous contrast for the previous non-pruritic urticarial rash more likely a misunderstood paraneoplastic manifestation associated to PNET than idiopathic or drug-related.

The widespread off-label use or, better, the abuse of PPIs is another emergent medical problem. PPIs are usually considered harmless drugs but they are not. The incidence of serious adverse events related to the chronic use of PPIs such as hypomagnesemia, increased risk of osteoporosis-related bone fractures

and infections, as well as relevant drug interactions, is probably under-recognized (6). The primary indications for their therapeutic use are mainly gastric and duodenal ulcer disease, erosive esophagitis, refractory GERD and gastric hypersecretion (i.e. Zollinger-Ellison syndrome). In the latter case, the administration of PPIs probably has the highest clinical benefit. Our patient strongly emphasized the inverse correlation between his symptoms and PPI treatment, which is uncommon for functional dyspepsia in which the relief from symptoms from PPI use is rarely thus prominent (6). Indeed, his pre-test probability of an underlying malignant disease was very low and could correctly justify a *wait and see* approach. Nevertheless, the unexpected complete remission of symptoms, including those which were less likely to respond to PPIs use, rightfully represented the clue for further investigations. However, the prescription of second level or invasive tests without a preconceived and reasoned diagnostic approach was harmful, since it did not allow considering alternative hypotheses when facing the disappointing negative results of these tests. The inexpensive bedside ultrasound examination revealed to be the right choice at the right time.

## Conclusion

In the 21<sup>st</sup> century's medicine, diagnostic and therapeutic tools are increasing faster than the physician's capability to keep up-to-date. As a result, every effort should be made in questioning non-specific symptoms – such as dyspepsia – or the widespread prescription of *harmless* medications – such as PPIs – by applying a thorough clinical method, supported by the best evidence, in order to reconsider unlikely but unfavorable alternative hypotheses.

## References

1. Cloyd JM, Poultsides GA. Non-functional neuroendocrine tumors of the pancreas: Advances in diagnosis and management. *World J Gastroenterol* 2015 Aug 28; 21(32): 9512-25.
2. Lawrence B, Gustafsson BI, Chan A, et al. The epidemiology of gastroenteropancreatic neuroendocrine tumors. *Endocrinol Metab Clin North Am* 2011 Mar; 40(1): 1-18, vii.

3. Modlin IM, Oberg K, Chung DC, et al. Gastroenteropancreatic neuroendocrine tumours. *Lancet Oncol* 2008 Jan; 9(1): 61-72.
4. Oustamanolakis P, Tack J. Dyspepsia: organic versus functional. *J Clin Gastroenterol* 2012 Mar; 46(3): 175-90.
5. Tack J, Talley NJ. Functional dyspepsia--symptoms, definitions and validity of the Rome III criteria. *Nat Rev Gastroenterol Hepatol* 2013 Mar; 10(3): 134-41.
6. Pinto-Sanchez MI, Yuan Y, Bercik P, Moayyedi P. Proton pump inhibitors for functional dyspepsia. *Cochrane Database Syst Rev* 2017 Mar 8; 3: CD011194.

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