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Case Report
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An Unusual Case of Chronic Diarrhea due to a Hidden Neuroendocrine Tumor

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Abstract

Gastroenteropancreatic-Neuroendocrine Neoplasms (GEP-NEN) are a heterogeneous group of rare tumors with annual incidence of less than 5 cases per 100,000 inhabitants. GEP-NEN is often mistaken for other disorders. The primary cancer site is unknown in about 13% of patients diagnosed with GEP-NEN. We report a case of a 71-years Caucasic old man, admitted at the Internal medicine unit because of a chronic intermittent watery diarrhea. Extensive laboratory analysis, imaging and colonoscopy were not helpful to make a diagnosis. Plasma levels of chromogranin A were elevated; metanephrines, normetanephrines, urinary 5-hydroxy indolacetic acid were within the normal range. The chromogranin values prompted the suspicion of GEP-NEN, and then a ^{68}Gallium-DOTATOC PET/CT was performed. The imaging exams showed a 9 mm-diameter nodule expressing somatostatin SSTR2-5 receptors, localized in the peripancreatic adipose tissue that we diagnosed as a GEP-NEN.

Keywords: GEP-NEN; Diarrhea; ^{68}Gallium-Dotatoc PET/CT; Chromogranin A

Introduction

Gastroenteropancreatic-Neuroendocrine Neoplasms (GEP-NEN or NETs) are rare tumors arising from the diffuse neuroendocrine system. Their annual incidence is less than 5 cases per 100,000 inhabitants [1].

NETs are classified as non-functional or functional tumors. The latter have a better prognosis and are associated to hormonal syndromes. Their clinical presentation can be characterized by non-specific symptoms, such as diarrhea, weight-loss, hypoglycemia, rectal bleeding, or can be related to the carcinoid syndrome, characterized by diarrhea, flushing and wheezing/asthma-like symptoms. Manifestations of non-functional tumors are mainly related to compression of neighboring anatomical structures [2,3]. Because of their non-specific symptoms, NETs are initially misdiagnosed. In about 13% of patients diagnosed with GEP-NEN, the primary site is unknown and the ^{68}Gallium-DOTATOC PET/CT represent the gold standard imaging test for the identification of tumor sites [4]. With this case of a chronic intermittent watery diarrhea, we want to underline how a simple clinical sign may hide a complex diagnosis.

Case Presentation

The present case-report describes 71-years Caucasic old man admitted at the Internal medicine unit due to a chronic intermittent watery diarrhea, started one year earlier. The diarrhea was accompanied by a significant weight loss (around 16 kg in one year), not related to diet habits. The diarrheal episodes lasted for about 2 to 3 weeks with up to 8 diarrhea attacks per day, afterward they spontaneously stopped. Patient's medical history was characterized by Rheumatoid Arthritis (RA) (CDAI score: 24) [5], high blood pressure, smoking. His therapeutic background was based on steroids to treat arthritis; beta-blocker, ace-inhibitor and hydrochlorothiazide to manage hypertension.

At the admission at the Internal Medicine Division, he presented body temperature of 37.2°C and diarrhea (5 diarrheal attacks per day). Scratch marks on the lower limbs due to sporadic itching were detected. Blood tests showed a slight increase in serum PCR (13.9 mg/L) and slight hypereosinophilia (12.3%) found (Table 1). An abdomen-CT (Computed-Tomography) revealed diffuse thickening of the sigma, mycrocalcifications of the hooked-tail process of the pancreas

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Table 1: Laboratory findings at the hospital admission.

Test	Value	Normal Value
Red blood cell (10^6/µL)	4.17	4.2-5.5
Hb (g/dL)	11.8	12-18
Ht (%)	35.9	34.7
MCV (Fl)	86.1	80-99
White blood cell (10^3/µL)	8.79	04-11
Neutrophil (%)	42.8	40-74
Lymphocyte (%)	25.7	20-48
Monocyte (%)	17.9	03-11
Eosinophil (%)	12.3	0-8
Basophil (%)	1.3	0-1.5
Platelets (10^3/µL)	254	150-450
Urea (mg/dL)	71	10-71
Creatinine (mg/dL)	1.76	0.67-1.17
Sodium (mg/dL)	139	132-146
Potassium (mg/dL)	4.53	3.7-5.4
Calcium (mg/dL)	9.11	8.6-10.2
Aspartate-Aminotransferase (U/L)	20	0-37
Alanine transaminase (U/L)	12	0-41
Lipase (U/L)	37	13-60
Amylase (U/L)	89	28-10
Bilirubin (mg/dL)	0.81	<1.2
Albumin (g/dL)	3.4	3.5-5.2
Alkaline Phosphatase (U/L)	90	40-129
GGT (U/L)	39	0-61
Iron (µg/dL)	49	59-150
Ferritin (ng/mL)	443	30-400
C-reactive protein (mg/L)	13.42	<5
TSH (mIU/L)	0.65	0.27-4.2
Activated partial thromboplastin time (sec)	28	24-36
Prothrombin time (PT)/ PT ratio (INR) (sec)	1.22	0.8-1.2
Cromogranine A (mcg/L)	913	<100

Laboratory findings at the hospital admission and during hospitalization

(Figure 1). Infectious and malabsorption causes of diarrhea were excluded by microbiological examination, immunoassay for coeliac disease, elastase, chymotrypsin and chemical examination of feces. Because of RA, corticosteroids (methylprednisolone 4 mg daily) were administered and contributed partially to a reduction in the number of diarrheal discharges. While in treatment with steroids, a flushing was observed.

To investigate a possible Inflammatory Bowel Disease (IBD), colonoscopy with biopsy was performed: At the sigma level, eosinophilic infiltrate in the lamina propria was revealed, suggesting non-specific inactive colitis. An entero-CT didn't reveal an upper localization of IBD. Tumor markers (CA 19-9, CEA, CA 125, and NSE) were not significant for neoplastic disease. TSH, FT3-FT4 was within the normal range.

Ruled out the most common causes of chronic diarrhea, NETs were considered. We tested the blood levels of Chromogranin A (CgA), which was significantly increased (913 mcg/L, NV <101.9 mcg/L). A

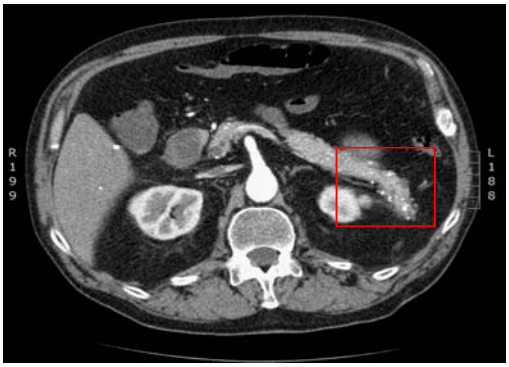

Figure 1: CT abdomen without contrast medium.
CT abdomen without contrast medium at the hospital admission depicting microcalcification of the hooked-tail process of the pancreas (red square). No tissue formations were detected.

chest-CT scan found a voluminous thyroid formation in the left lobe. Calcitonin, anti-Thyroperoxidase (TPO), anti- Thyrotropin Receptor (TSH-R), anti-Thyroglobulin (Tg) were normal. The thyroid echo showed an uneven consistency and nodular architecture. The needle aspiration of the nodular lesions showed thyrocytes aggregated in flaps and nodules, excluding overt abnormalities.

Therefore, the suspicion of NETs couldn't be confirmed. Urine was collected during 24 h after an amine-free diet to search for 5-Hydroxy Indolacetic Acid (5-HIIA), metanephrines, normetanephrines, catecholamines, homovanillic and vanillylmandelic acids, but the results were within the normal range.

Despite inconclusive urine tests and imaging, the diarrhea features strongly made us suspect a GEP-NEN. We decided to proceed further in the diagnostic ITER with ^{68}Gallium-DOTATOC PET/CT test. This exam reported a 9-mm nodule in the peripancreatic adipose tissue, with elevated receptor expression for SSTR2-5 (Figure 2). This finding allowed us to make diagnosis of "Atypical Carcinoid Syndrome" given by NET [6].

Once the diagnosis was defined, the patient started a treatment with the long-acting somatostatin analogue –Lanreotide - and he was admitted to evaluation for a surgical radical approach.

Discussion

NETs are a heterogeneous group of rare tumors, comprising less than 2% of all malignancies [7]. Neuroendocrine cells are distributed among multiple organs, so that the central nervous system, respiratory tract, Gastrointestinal (GI) tract, thyroid, and urogenital system may be involved. NET may be asymptomatic or may manifest themselves by secretion of either a peptide hormone or biogenic amine and, depending on that, they are classified in non-functional or functional NET, respectively [8,9]. So, because of their non-specific clinical presentation, a diagnostic delay often leads to discover an already metastasizing disease, no longer susceptible to surgery [10]. Commonly, first level investigations for NETs include imaging and biochemical tumor markers: Serum CgA and 5-HIAA [11]. According to the current guidelines [6], the presence of symptoms, high serum levels of CgA and urinary 5-HIAA define the "Typical Carcinoid Syndrome"; on the contrary, symptoms, high serum levels of CgA, despite negative urinary 5-HIAA, define the "Atypical Carcinoid Syndrome".

Most case-series of NETs describe, as initial symptoms, weight-

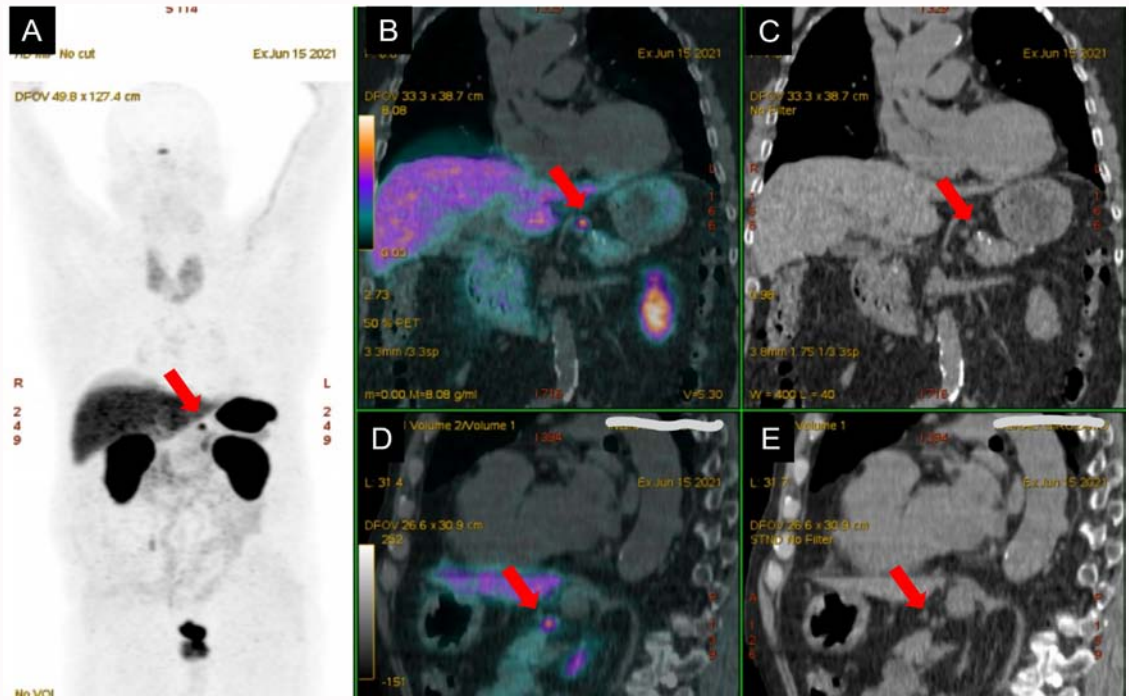

Figure 2: 68- Gallium-DOTATOC PET/CT.
Gallium-DOTATOC PET/CT showing a 9 mm tissue formation located in the adipose space between the body of the pancreas and the cardias, with elevated receptor expression for SSTR2-5. Panel A) whole body, Panels B and C) frontal view, and Panels D and E) lateral view. Identified lesion as red arrows.

loss, GI-bleeding and vomit [12]. Albishi et al. [7] described appendicitis and intestinal obstruction as acute manifestation of GEP-NEN.

Our case-report mentions watery diarrhea alone as a predominant clinical manifestation of GEP-NEN. Approximately 20% of patients with NETs develop carcinoid syndrome, characterized by flushing and diarrhea. In different cases, diarrhea has a multifactorial origin. In the review of Khan et al. [13], analyzing 44 case series of GEP-NEN, diarrhea was due to both NETs both to pancreatic enzyme insufficiency and small intestinal bacterial overgrowth.

In front of a suspicion of diarrhea caused by GEP-NEN, biochemical and first level- instrumental investigations (colonoscopy, abdominal-CT or RMI) allow to reach the diagnosis [14]. When the primary site tumor remains unknown, the ^{68}Gallium-DOTATOC PET/CT represents the gold standard imaging test [4].

In our case-report the diagnosis was made by the ^{68}Gallium-DOTATOC PET/CT, only performed on the basis of the clinical suspicious, despite the absence of first level investigations compatible with the diagnosis of GEP-NEN. Up to date, to the best of our knowledge, no other similar case-reports have been reported.

Our patient was affected by RA. This was the first confusing element in the diagnostic flow-chart: Diarrhea was initially referred to an inflammatory discomfort; the episodes of facial-neck flushing were adscripted to the steroidal therapy that also induced the remission of itching. The slight eosinophilia relieved spontaneously in three days. Moreover, the various instrumental investigations did not reveal the presence of nodules and/or masses together with the negativity of tumor markers. The hospitalization and the refractoriness to the different treatments led us to strongly suspect a neuroendocrine origin of the patient's syndrome.

The first diagnostic element was the CgA assay, found to be significantly increased (913 mcg/L, NV <101.9 mcg/L). CgA assay is considered as weak marker of NETs: It may be elevated in multiple conditions, such inflammatory diseases and can be increased by proton pump inhibitors. CgA usually correlates with tumor burden and its value over 200 pg/L is often associated to a bad prognosis [15]. Therefore, caution should be applied in making diagnosis of NETs only by the interpretation of CgA high serum level [6]. On the contrary, urinary 5-HIAA is a highly specific marker, albeit with lower sensitivity compared to CgA. Recent studies demonstrate that urinary 5-HIAA becomes elevated only at late disease stages, when metastases have already occurred [16]. Since in our case it could have been an early stage of NET, the negativity of 5-HIAA didn't prevent us from continuing the investigation.

We focused only on the clinical elements exhibited by our patient, considering that probably the intermittent diarrhea was due to pushed releases of hormones and that the absence of specific NETs markers could be related to the temporary tumor inactivity [17]. We made a definite diagnosis by the ^{68}-Gallium DOTATOC PET/CT scan, which reported a tissue nodule with elevated SSTR2-5 receptor expression.

Therefore, according with current guidelines [6], we made diagnosis of atypical carcinoid syndrome caused by a GEP-NEN, characterized by watery diarrhea, flushing and negativity for specific NET markers.

In our case report, an early diagnosis allowed our patient to be treated for his syndrome, achieving an improvement in his quality of life, allowing him to recover definitively by a surgery treatment.

Conclusion

Making an early diagnosis of NET represents a challenge for the Internist. In front of a suspicion of diarrhea caused by NET,

biochemical and first level- instrumental investigations allow to discover the primary site of the tumor in most of the cases. When the primary tumor remains unknown, the ^{68}-Gallium DOTATOC PET/CT represent the gold standard test. In the presence of a strong clinical suspicion and symptoms suggestive of NET, negative preliminary investigations should not stop the diagnostic process. Instead, the clinical work-up should continue by designing a second-line investigation approach.

References

1. Scott AT, Howe JR. Evaluation and management of neuroendocrine tumors of the pancreas. Surg Clin North Am. 2019;99(4):793-814.
2. Falconi M, Eriksson B, Kaltsas G, Bartsch DK, Capdevila J, Caplin M, et al. Consensus guidelines update for the management of functional p-NETs (F-p-NETs) and non-functional p-NETs (NF-p-NETs). Neuroendocrinology. 2016;103(2):153-71.
3. Ito T, Lee L, Jensen RT. Carcinoid-syndrome: Recent advances, current status and controversies. Curr Opin Endocrinol Diabetes Obes. 2018;25(1):22-35.
4. Menda Y, O'Dorisio TM, Howe JR, Schultz M, Dillon JS, Dick D, et al. Localization of unknown primary site with 68Ga-DOTATOC PET/CT in patients with metastatic neuroendocrine tumor. J Nucl Med. 2017;58(7):1054-7.
5. Gavrilă BI, Ciofu C, Stoica V. Biomarkers in rheumatoid arthritis, what is new? J Med Life. 2016;9(2):144-8.
6. AIOM for Neuroendocrine Tumors Guide Line 2020.
7. Albishi AM, Mostafa AMM, Ali HM, Alhagawi YA, Bazeed MF, Hussein MRA, et al. Incidence of gastrointestinal neuroendocrine tumor: Case series, armed forces hospital southern region, hospital-based tumor board registry. Case Rep Oncol Med. 2020;2020:8819392.
8. Oronsky B, Ma PC, Morgensztern D, Carter CA. Nothing but NET: A review of neuroendocrine tumors and carcinomas. Neoplasia. 2017;19(12):991-1002.
9. Davies K, Conlon KC. Neuroendocrine tumors of the pancreas. Curr Gastroenterol Rep. 2009;11(2):119-27.
10. Naraev BG, Halland M, Halperin DM, Purvis AJ, O'Dorisio TM, Halfdanarson TR. Management of diarrhea in patients with carcinoid syndrome. Pancreas. 2019;48(8):961-72.
11. Kapoor R, Bhattacharyya T, Gupta R, Mittal BR, Kalra N. A systematic review of management of neuroendocrine tumors: An experience from a tertiary care centre from India. Clin Cancer Investig J. 2014;3(5):363-72.
12. Ahmed M. Gastrointestinal neuroendocrine tumors in 2020. World J Gastrointest Oncol. 2020;12(8):791-807.
13. Khan MS, Walter T, Buchanan-Hughes A, Worthington E, Keeber L, Feuilly M, et al. Differential diagnosis of diarrhoea in patients with neuroendocrine tumours: A systematic review. World J Gastroenterol. 2020;26(30):4537-56.
14. Thompson AA, Suhail FK, Mirchia K, Rawlins SR. A case of profound secretory diarrhea revealing 2 primary neuroendocrine tumors. ACG Case Rep J. 2021;8(7):e00625.
15. Dam G, Grønbæk H, Sorbye H, Evensen ET, Paulsson B, Sundin A, et al. Prospective study of chromogranin A as a predictor of progression in patients with pancreatic, small-intestinal, and unknown primary neuroendocrine tumors. Neuroendocrinology. 2020;110(3-4):217-24.
16. Wedin M, Mehta S, Angerås-Kraftling J, Wallin G, Daskalakis K. The role of serum 5-HIAA as a predictor of progression and an alternative to 24-h urine 5-HIAA in well-differentiated neuroendocrine neoplasms. Biology (Basel). 2021;10(2):76.
17. Cai B, Broder MS, Chang E, Yan T, Metz DC. Predictive factors associated with carcinoid syndrome in patients with gastrointestinal neuroendocrine tumors. World J Gastroenterol. 2017;23(40):7283-91.