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BRIEF REPORT

Gastrinomas and non-functioning pancreatic endocrine tumors in multiple endocrine neoplasia syndrome type-1 (MEN-1)

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Introduction

Multiple endocrine neoplasia type-1 (MEN-1) is a rare hereditary autosomal dominant syndrome due to frameshift and non-sense mutations in the MEN-1 tumor suppressor gene localized on the long arm of chromosome 11 [1]. Also known as Wermer syndrome, it has a prevalence of 2–20/100,000 individuals who may develop multiple neoplastic lesions arising in the parathyroid (90–95%) as well as the pituitary glands (40–50%), the pancreatic islet cells (50–60%) and the duodenal wall (35–40%) [2].

While the most common clinical onset of patients affected by MEN-1 is due to primary hyperparathyroidism [3], pancreatic endocrine tumors (PNETs) represent the main cause of cancer-related death, which is most commonly due to non-functioning (NF) subtypes [4]. Indeed, these tend to have a more aggressive behavior compared to their sporadic counterparts with a malignant potential reported to be size-related with a cut-off value set at 2 cm [5–7]. Hence, active surveillance with endoscopic ultrasonography (EUS) combined with either contrast-enhanced multi-detector-CT (MDCT) [8] or magnetic resonance imaging [9] is strongly recommended in patients with MEN-1 syndrome.

As far as contrast-enhanced MDCT is concerned, recent advances suggest that contrast-enhancement patterns of PNETs may be indeed predictive of tumor grading defined as the rate of expression of the proliferation index *Ki-67* [10]. As most G1 (*Ki-67* <3%) tumors usually appear as hypervascular lesions, G2 (*Ki-67* 3–20%) or G3 (*Ki-67* >20%) tumors typically manifest as hypovascular lesions [11–13]. However, as PNETs in MEN-1 syndrome are usually multifocal [14], the co-existence of lesions with different contrast-enhancement patterns and different biological behavior may indeed occur in clinical practice.

Herein, we describe a case of 48-year-old male with a genetic diagnosis of MEN-1 syndrome who had a Zollinger–Ellison syndrome due to duodenal gastrinomas shown by an EUS and confirmed by contrast-enhanced MDCT, which also depicted loco-regional adenopathies and three other NF-PNETs with different contrast-enhancement patterns and biological behavior.

Case report

In 2009, a 48-year-old male affected by MEN-1 syndrome (frameshift mutation 317delC) was admitted to the Endocrinology and Metabolic Diseases Unit of our Institution with a history of relapsing peptic ulcers resistant to proton pump inhibitors and high levels of gastrinemia (489 pg/ml). The patient had been previously submitted to a total parathyroidectomy for primary hyperparathyroidism in 2005 and was under medical therapy with Cabergoline (0.5 mg pro die) for a prolactin-secreting pituitary adenoma.

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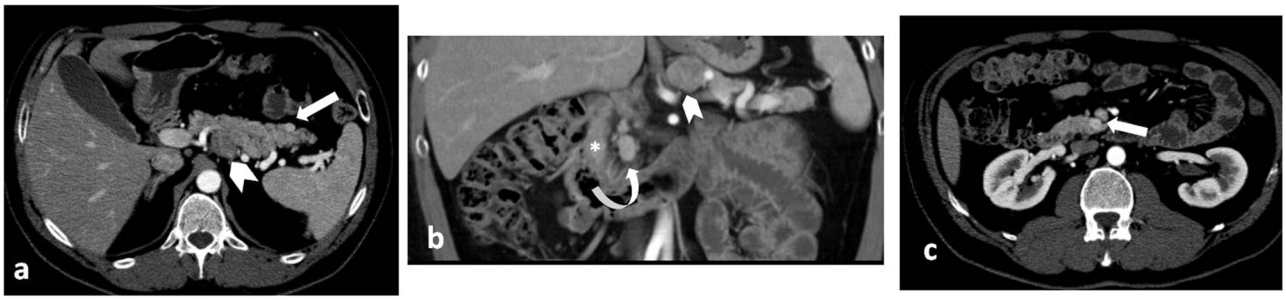

Fig. 1 Contrast-enhanced multi-detector CT in a 48-year-old male patient with MEN-1. Both arterial-phase transverse images (**a**, **c**) and a 3-mm-thick coronal reformatted image in the pancreatic phase (**b**) are shown. Peri-centimetric hypervascular nodules (arrows) are depicted at the level of the anterior margin of the pancreatic tail (**a**) as well as in the uncinate process (**c**) along with a 3.0 × 2.6 cm hypovascular nodule in the posterior aspect of the pancreatic body (arrow-head), the latter more conspicuous in the pancreatic phase (**b**) where inhomogeneous thickening of the medial duodenal wall (*) along with a cluster of nearby adenopathies (curved-arrow) can also be appreciated

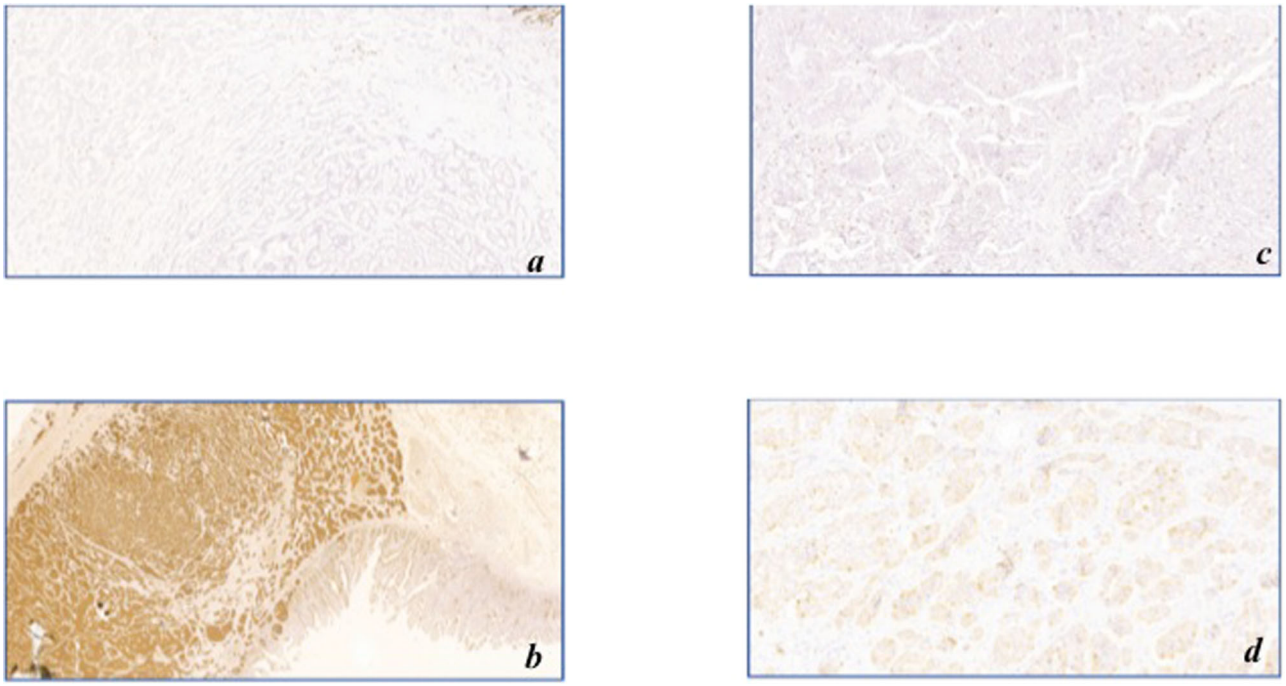

Fig. 2 Immuno-histochemical analysis performed after a pancreato-duodenectomy extended to the pancreatic body: formalin-fixed paraffin-embedded 4 µ sections of surgical specimens of the duodenal wall (**a**, **b**) and the pancreatic body (**c**, **d**) are shown. Tissue sections were tested for Ki-67 expression (**a**, **c**), gastrin (**b**) and glucagon (**d**). Immuno-histochemistry results were consistent with a NET G1 (Ki-67 <3%) gastrin-positive tumor of the duodenal wall (**a**, **b**) and a NET G2 (Ki-67 3–20%) glucagon-positive tumor of the pancreatic body (**c**, **d**)

The patient was first submitted to an EUS performed with a radial transducer (7.5–20 MHz, Olympus, GIF-UM130Q) which documented multiple hypoechoic nodules (2–12 mm) within the duodenal wall (not shown) and then underwent a contrast-enhanced MDCT (Aquilion 64, Toshiba, Japan) which was performed according to a multiphasic protocol [8] after i.v. bolus (4 ml/s) injection of 1.7 cc/kg of a nonionic iodinated contrast media (370 mgI/ml). Arterial-phase imaging depicted multiple hypervascular sub-centimetric nodules at the level of both the pancreatic tail (Fig. 1a) as well as the uncinate process (Fig. 1c) along with an inhomogeneous and asymmetric thickening of the medial duodenal wall and a cluster of duodeno-pancreatic adenopathies which were both better depicted in the pancreatic phase (Fig. 1b). In addition, a large (30 × 26 mm) hypovascular nodule could also be appreciated in the dorsal aspect of the pancreatic body, much more conspicuous in the pancreatic phase (Fig. 1b) than in the arterial phase (Fig. 1a).

The patient was then submitted to a pancreatoduodenectomy extended to the pancreatic body and the histopathological analysis revealed several ($n = 14$) gastrin-positive NET G1 tumors (Fig. 2a, b), the larger (*pT2,N1*) in

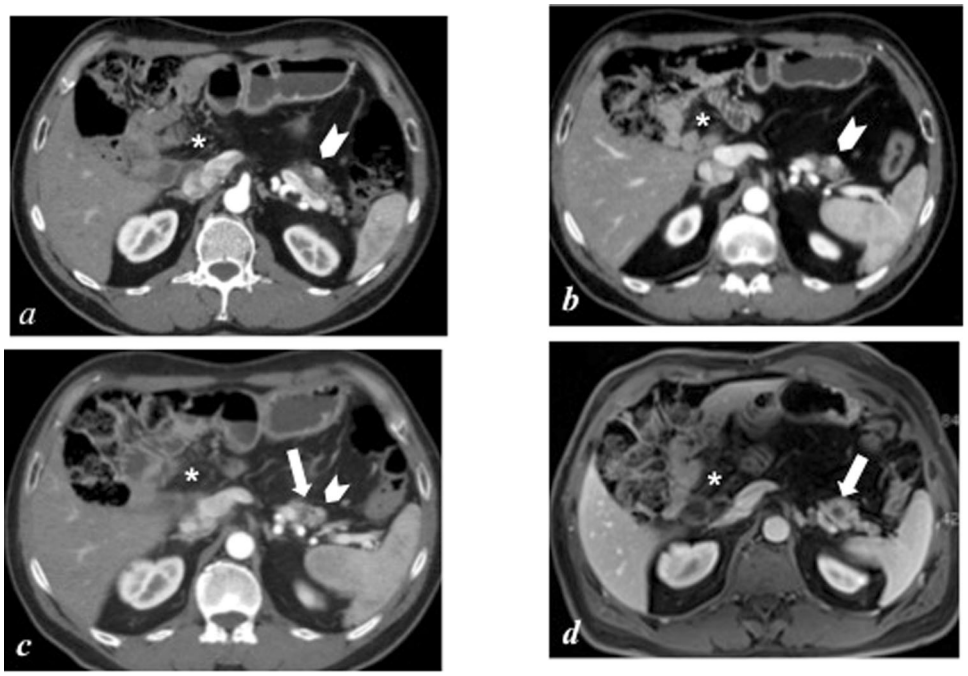

Fig. 3 Arterial-phase transverse images of follow-up MDCT examinations performed after pancreatoduodenectomy (*) in 2011 (**a**), 2013 (**b**), 2015 (**c**) are shown along with a T1-VIBE Gd+ fat-sat MR axial sequence acquired in 2017 (**d**). At contrast-enhanced MDCT (**a**–**c**), a small hypervascular nodule can be well appreciated on the anterior margin of the pancreatic tail appearing stable (7–9 mm) over a 6-year interval (arrow-heads). In 2015, a nearby hypovascular area could also be retrospectively appreciated (arrow) but it was prospectively overlooked. The nodule was much more conspicuous at Gd-enhanced MR (**d**) which also depicted a hypervascular lesion at the level of the V hepatic segment consistent with a liver met (not shown)

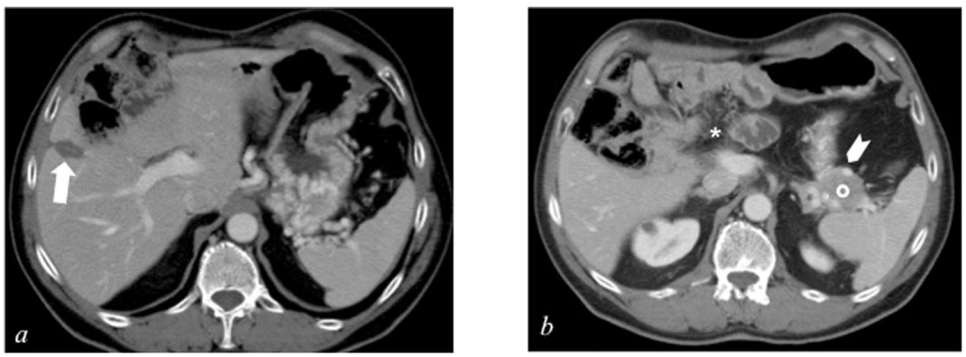

Fig. 4 Portal-venous phase transverse images of a follow-up MDCT examination performed after pancreatoduodenectomy (*) in 2019. An oval-shaped hypo-attenuating area (arrow) is well depicted at the level of the V hepatic segment (**a**) as a result of the coagulative necrosis induced by radiofrequency ablation along with the small hypervascular nodule at the level of the pancreatic tail (arrow-head). This is displaced anteriorly by a large hypovascular area (°) consistent with progressive disease which appears locally advanced with encasement of the splenic vessels (**b**) and engorgement of gastro-lienal veins (**a**)

the duodenal wall (Fig. 1b), a glucagon-positive NET G2 (*pT2, N0*) in the pancreatic body (Fig. 2c, d) and two well-differentiated G1 NETs in the pancreatic head (Fig. 1c) and in the pancreatic body (not shown). To preserve pancreatic endocrine function, the pancreatic tail was not removed.

The patient started somatostatin analogs (SSA) therapy (Sandostatin LAR 30 mg/28 days → Lanreotide Autogel 120 mg/28 days) and follow-up contrast-enhanced MDCT examinations, performed bi-annually, showed the hypervascular nodule in the pancreatic tail to be stable in size (7–9 mm) over 6 years (Fig. 3a–c).

In 2017, however, an abdominal ultrasound depicted a hypoechoic lesion at the level of the V hepatic segment which was confirmed by a VIBE-T1-w Gadolinium-enhanced MR performed at 3T (Somatom Trio, Siemens, Germany) and considered to be consistent with a liver metastasis (not shown) along with a small (9 mm) hypointense nodule at the level of the pancreatic tail (Fig. 3d) which had been prospectively overlooked at contrast-enhanced MDCT (Fig. 3c). Both the pancreatic lesion as well as the liver met showed focal uptake of the radiotracer at ^{68}Ga-DOTA-TOC PET/CT with a SUV_{max} of 6.3 and 29.5, respectively (not shown).

The patient was first shifted to high-dose SSAs therapy (Lanreotide LAR 120 mg/14 days) and then submitted to a radiofrequency ablation of the hepatic lesion in 2019 as shown by a contrast-enhanced MDCT follow-up study (Fig. 4a) which also documented progressive disease at the level

of the pancreatic tail (Fig. 4b) with a SUV_{max} of 30 at ^{68}Ga-DOTA-TOC PET/CT (not shown).

The patient was therefore scheduled for peptide receptor radionuclide therapy and received four cycles of ^{177}Lu-DOTATE 7.4 GBq (200 mCi) every 8 weeks between November 2020 and March 2021 with a cumulative dose of 29.6 GBq (800 mCi).

He is currently under clinical and instrumental follow-up with the last contrast-enhanced MDCT performed on May 2022 showing stable disease.

Discussion

Although both functional and NF-PNET may occur in patients with MEN-1 syndrome [4], only the latter are considered the main cause of cancer-related mortality as a result of their malignant potential, which has been reported to be size-dependent with a cut-off value set at 2 cm [5–7]. As a result, active surveillance is strongly recommended in patients with MEN-1 and is usually accomplished by a combination of EUS with either contrast-enhanced CT [8] or MR [9]. Dimension, however, is not the only feature that should be taken into account when evaluating either familial or sporadic PNET as recent studies have emphasized that contrast-enhancement patterns may indeed be predictive of their differentiation grade and biological behavior [11–13]. Indeed, an arterial-enhancement ratio <1.1, reported as the ratio between the attenuation of the tumor and that of the surrounding parenchyma, should be viewed with caution even in lesions smaller than 2 cm according to Belousova et al. [12]. In our patient, whereas the small hypervascular nodule depicted at the level of the pancreatic tail (Fig. 1b) had been stable over 10 years (Figs. 3 and 4) as a result of SSA therapy [15, 16], the nearby hypovascular lesion was metastatic at presentation despite being only 9 mm in its longest diameter (Fig. 3d). Even in the absence of a pathologic proof for both pancreatic lesions, we can reasonably argue that the hypervascular lesion was indeed a G1 NF-PNET as it showed the same attenuation pattern as the surgically removed nodule within the pancreatic head (Fig. 1) whereas the hypovascular nodule was likely an NF-PNET of a higher grade (G2/G3) as it showed a fairly low uptake (SUV_{max} 6.3) of the radiotracer at ^{68}Ga-DOTA-TOC PET/CT [17] and rapidly progressed under high-dose SSA therapy (Fig. 4b).

As far as the hypovascular nodule depicted by contrast-enhanced MDCT at the level of the pancreatic body (Fig. 1b) is concerned, despite it faintly immuno-stained for glucagon at histopathological analysis (Fig. 2d) it also has to be considered an NF-PNET. Indeed, this occurs quite often in patients with MEN-1, whereas true functioning glucagonomas are quite rare (<3%) tumors and have a worse prognosis compared to gastrinomas [18]. However, the Ki-67 proliferation index (Fig. 2c) was consistent with its hypovascular appearance indicating a G2 PNET (Fig. 1b) [12–14].

As far as duodenal gastrinomas are concerned, contrast-enhanced MDCT clearly depicted the asymmetric and the inhomogeneous thickening of the medial duodenal wall which corresponded to the larger tumor found at histopathology (*pT2*) but failed to detect the multiple submucosal nodules shown by EUS which is considered the gold standard as a result of its higher spatial and contrast resolution [8]. However, contrast-enhanced MDCT well depicted loco-regional adenopathies (Fig. 1b) which turned out to be true positive findings at histopathological analysis (*pT2,N1*).

Finally, this case arises a number of questions about the optimal surgical technique in patients with MEN-1 and PNETS [19, 20]. While there is a general consensus about surgical indications in NF-PNET >2 cm in view of their malignant potential [5–7], most surgeons favor a conservative approach to preserve endocrine function and offer the patient a better quality of life [19]. However, while such a conservative approach may be reasonable in patients undergoing a distal pancreatectomy, it can be considered debatable in those undergoing a pancreatoduodenectomy as this anecdotal case clearly shows. In retrospect, a total pancreatectomy would have spared the patient from a high-grade NF-PNET possibly assuring him a better prognosis. Indeed, a prophylactic pancreatectomy could be considered a reasonable option in patients with MEN-1 due to both the improved surgical techniques as well as pharmacologic advances in insulin-replacement therapies [20].

In summary, we have herein reported a 13 years observational study in a patient with MEN-1 syndrome who developed both functioning as well as NF-PNET with different contrast-enhancement patterns and biological behaviors. As current guidelines on active surveillance in patients with MEN-1 are mainly focused on lesions' diameters [7], this case shows that aside from dimension contrast-enhancement patterns of PNET should also be taken into account [11–13].

Author contributions L.C.: conceptual design and manuscript draft. F.B.: data collection and literature search. R.M.: referring physician. L.M.: histopathological analysis. A.F.: manuscript revision. V.R.: MR study. V.G.: PPRT. A.C.: manuscript revision. S.M.: manuscript revision. A.B.: manuscript editing.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Ethics approval This is an observational study. The Local Ethical Committee declared that no ethical approval is required.

Informed consent Written informed consent was obtained by the patient for both.

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