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Gastroenteropancreatic neuroendocrine neoplasm – a complex presentation in imaging methods

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Abstract

Neuroendocrine neoplasms comprise an ever greater ratio of primary gastrointestinal tract tumors, thanks to the improving diagnostics. The clinical presentation can be quite diverse depending on the type of the tumor. Imaging methods – both the spectrum of radiological methods and methods of nuclear medicine - are an integral part of the diagnostics. This article presents a case report of a 65-year old female patient, whose routine abdominal US scan performed as part of a preventive check-up revealed a suspicious liver incidentaloma. The case report presents the image of the pathology in various imaging modalities, radiologic and molecular/hybrid methods used in the differential diagnostic process of the lesion, as well as findings in follow-up examinations after histological verification of the lesion and an outline of further approach and treatment.

CASE REPORT

INTRODUCTION

Gastroenteropancreatic neuroendocrine neoplasms (GEP-NEN) present a diverse group of tumors originating from diffuse neuroendocrine system cells. They vary by their biological nature and are characterized by a wide range of clinical symptoms. Together with bronchopulmonary NEN, they belong to the most common neuroendocrine neoplasms (Sahani *et al.* 2013; Kuracinova *et al.* 2018; Ambrosini & Fanti 2016).

GEP-NEN are considered relatively rare, with incidence of about 3-7/100 000 people, however lately their incidence is increasing and neuroendocrine tumors are therefore becoming the second most common type of gastrointestinal tract tumors (after the colorectal carcinoma). For example, their incidence in the USA in years 1997 to 2012 has increased six times, with the incidence of localised NEN or NEN with locoregional spread increasing more than the incidence of NEN with distal metastases. This trend of earlier detection can be attributed to the advancement of imaging methods and diagnostic opportunities as a whole (Ambrosini & Fanti 2016; Kinová *et al.* 2010; Pavel *et al.* 2020).

Regarding the presence or absence of the clinical syndrome originating from production or secretion of bioactive substances, GEP-NEN can be divided into functional and nonfunctional ones.

Histologically, according to the 2019 WHO classification, they can be divided into well differentiated NET G1, G2 and G3, poorly differentiated neuroendocrine carcinoma G3 (NEC) and mixed neuroendocrine-nonendocrine carcinoma MiNEN, based on the Ki-67 index and the number of mitoses (Kuracinova *et al.* 2018; Tsoli *et al.* 2000)

According to the localisation, GEP-NEN can be divided into pancreatic and extrapancreatic ones, with pancreatic NEN accounting for 7–30% (Sahani *et al.* 2013; Kuracinova *et al.* 2018; Pavel *et al.* 2020).

CASE REPORT

A 65-year old female patient was referred for an abdominal ultrasound examination by her diabetologist while followed for LADA- type diabetes, in June 2018. Subjectively, the patient had no complaints, no other significant illnesses in her history, no pathology in the laboratory findings. In the past history, peripartal hysterectomy with left-sided adnexectomy and a breast surgery for fibroadenoma was noted.

The ultrasound examination documented 4 pathological findings – a simple cortical cyst of the left kidney, a homogeneous hyperechogenic, well-circumscribed lesion underneath the anterior abdominal wall, a cystic lesion in the area of right adnexa and a 1.5 cm large spherical lesion in the liver segment S8. The liver lesion had a central isoechogenic part with a hypoechogenic rim - it was interpreted as suspicious, a follow-up ultrasound with contrast agent administration (CEUS) was recommended.

On CEUS examination the lesion was markedly and rapidly enhancing post contrast administration, with wash-out in portovenous and delayed phase – it was concluded to be a markedly hypervascularized lesion, probably of malignant character, most likely a hypervascularized metastasis.

Due to suspicion of a disseminated tumor, a CT examination of the chest, abdomen and small pelvis with multiphase imaging of the liver was performed in July 2018. The dominant findings were also quick arterial lesion enhancement, with isodensity of the lesion compared to the surrounding parenchyma on the portovenous and delayed phase. No other changes like the appearance of a primary tumor or other signs of tumor dissemination were found. The finding was concluded as indeterminate, with a follow-up liver MR to be considered. In the meantime, the patient underwent a laparoscopic removal of the remaining cystic adnexa and the lesion underneath the anterior abdominal wall with benign findings - a serous cystadenoma and a fibrous lipoma. Perisurgically examined liver and the entire abdominal cavity were without pathological findings, without any signs of tumor lesions.

In November 2018, an MR examination of the liver with hepatospecific contrast agent was performed. The lesion showed no signs of growth, the signal characteristics in individual sequences were not in keeping with a specific tumor type. The dynamic postcontrast examination mirrored the CEUS image, that is an early arterial enhancement with rapid lesion wash-out; in the hepatospecific phase the lesion did not absorb the contrast agent - the image was ambiguous. The differential diagnosis included atypical adenoma or well-differentiated, slow-growing hepatocellular carcinoma besides a hypervascularised metastasis of unknown

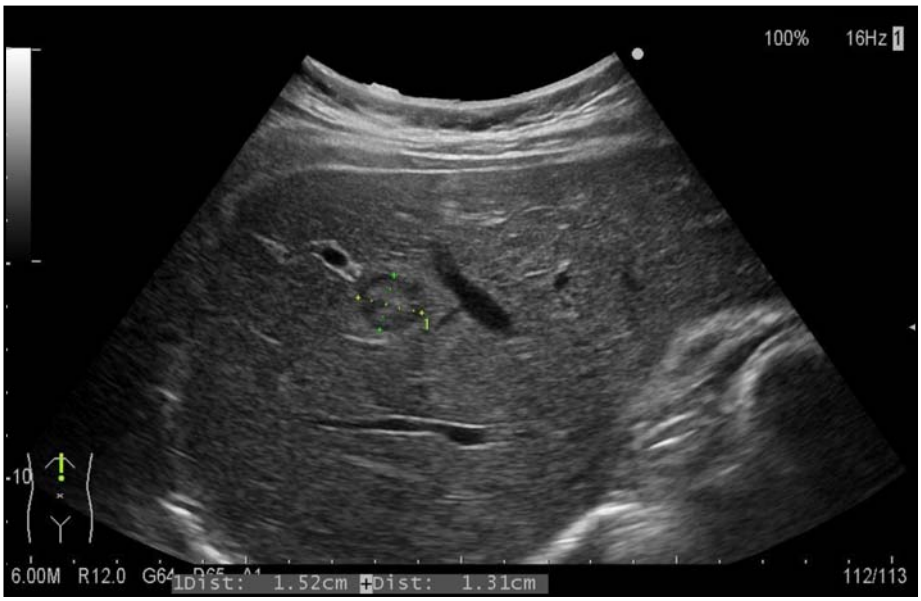

Fig. 1. First ultrasound examination visualized a round lesion with target appearance - a hyperechoic central area and a hypoechoic peripheral rim - in the central part of right liver lobe.

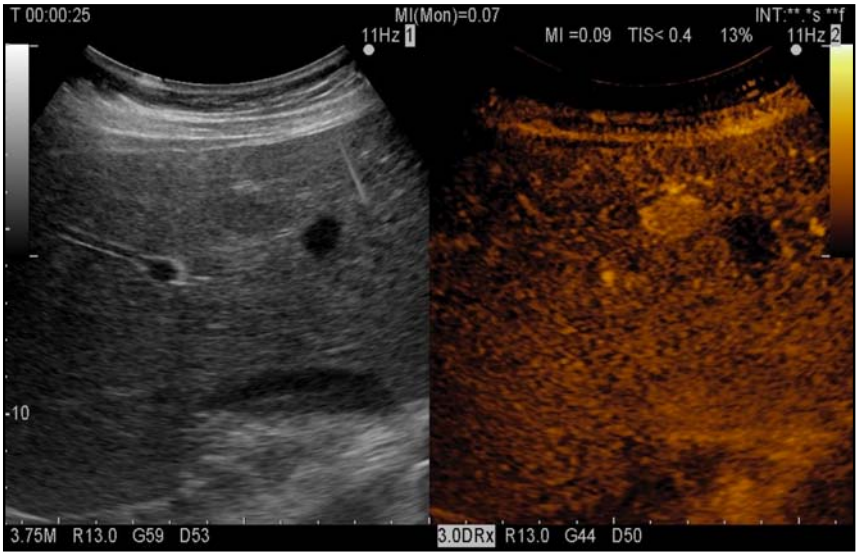

Fig. 2A. CEUS examination – arterial phase: A marked lesion enhancement is visible 25 seconds after the injection of the contrast agent.

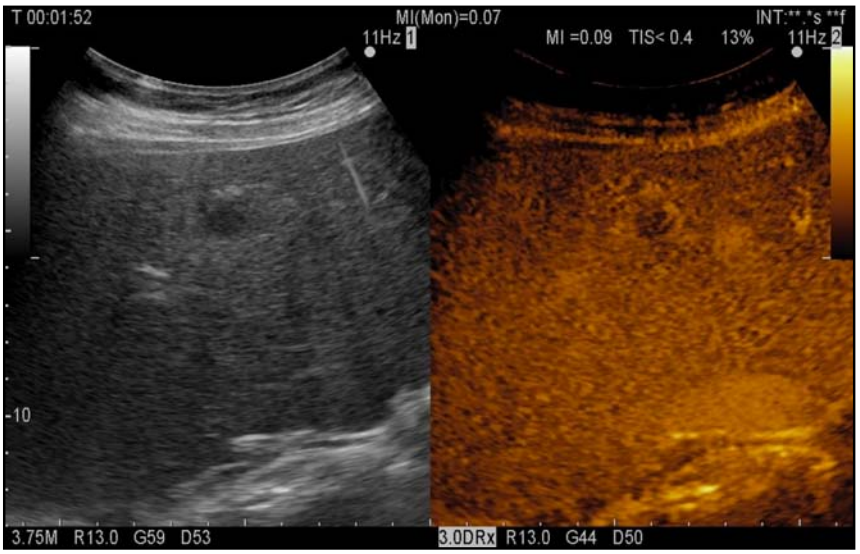

Fig. 2B. CEUS examination - venous phase: The lesion shows signs of contrast agent washout in the second minute, it is hypoechoic compared to liver parenchyma.

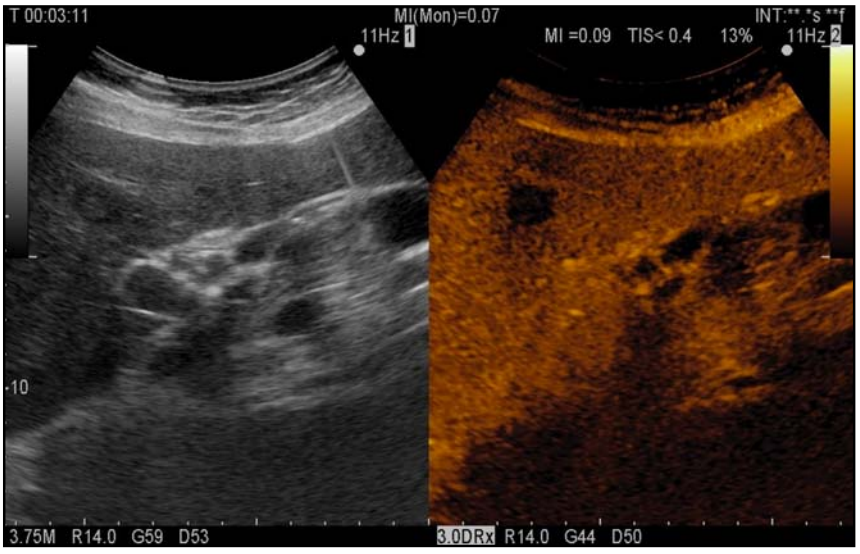

Fig. 2C. CEUS examination - delayed phase: There is significant contrast agent washout in the fourth minute, the lesion is markedly hypoechoic.

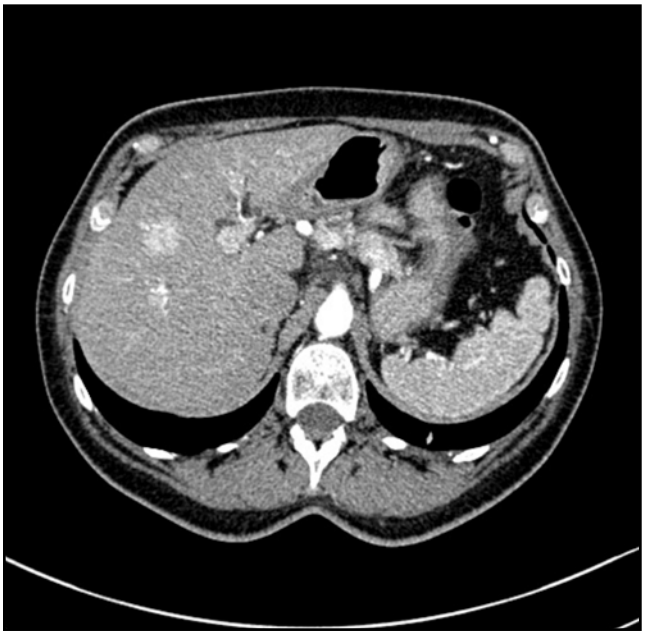

Fig. 3A. CT scan with contrast agent: In the arterial phase a marked enhancement of the lesion compared to the rest of the liver parenchyma is seen, which is typical for hypervascularized lesions.

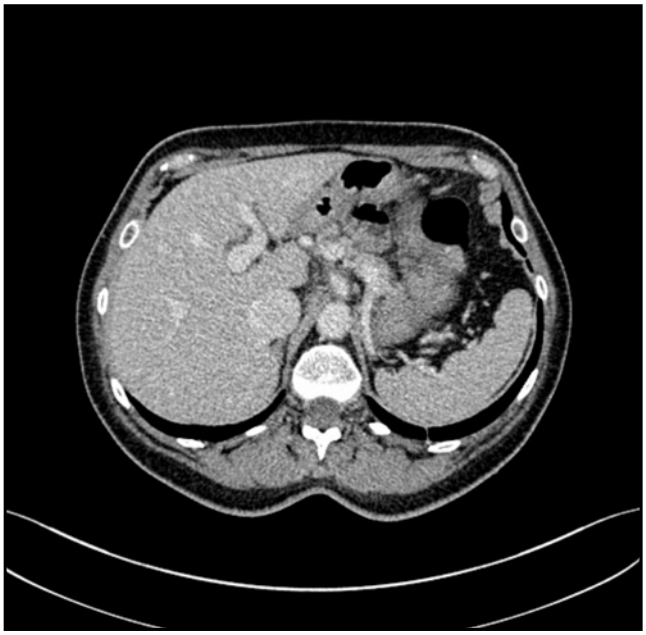

Fig. 3B. CT scan with contrast agent: In the venous phase of the CT scan there is no contrast agent washout contrary to the CEUS image, the lesion is isodense to the rest of the paremchyma.

origin, as well as less common findings such as peliosis hepatis or an inflammatory pseudotumor.

Due to inconclusive findings, the patient was referred to a PET/CT examination with the ^{18}F-FDG (^{18}F-fluorodeoxyglucose) radiopharmaceutical, which was performed in December 2018. A standard imaging of the body in portovenous phase was preceded by a liver-focused arterial phase, during which the known vascularised lesion was revealed, with an increased metabolic activity in the PET/CT image with a semiquantitative value SUVmax of 5.9 (standard uptake value). The metabolic activity of the lesion clearly surpassed the metabolic activity of liver parenchyma. The finding was interpreted as most likely malignant – the differential included HCC, NET, sarcoma or a vascularised metastasis. Other pathological lesion in the imaged range of the body was not found. A biopsy or extirpation of the lesion and additional testing for chromogranin A levels was recommended.

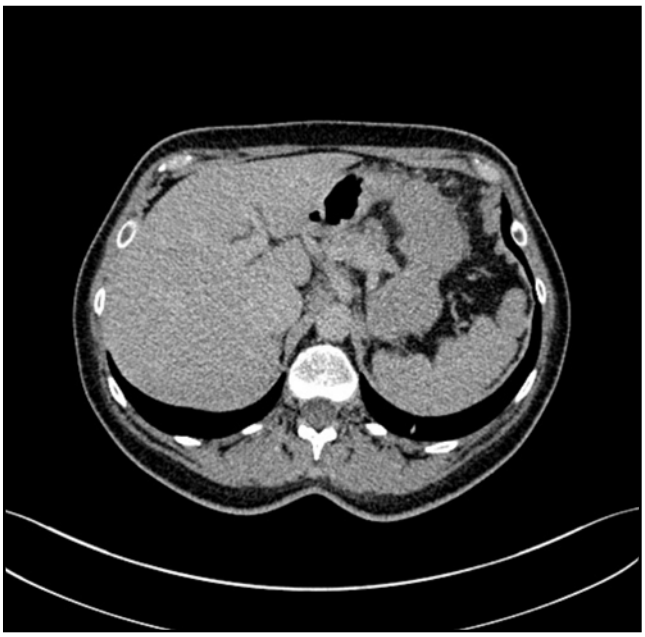

Fig. 3C. CT scan with contrast agent: In the delayed phase of the CT scan there is still no contrast agent washout.

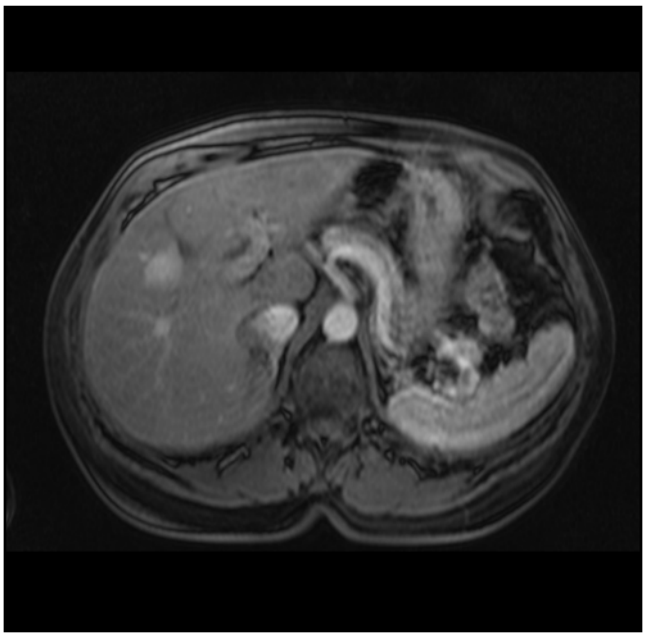

Fig. 4A. MR examination of the liver with hepatospecific contrast agent: In the arterial phase, a significant enhancement of the lesion compared to the rest of the liver parenchyma is also visible, indicating hypervascularised character of the lesion.

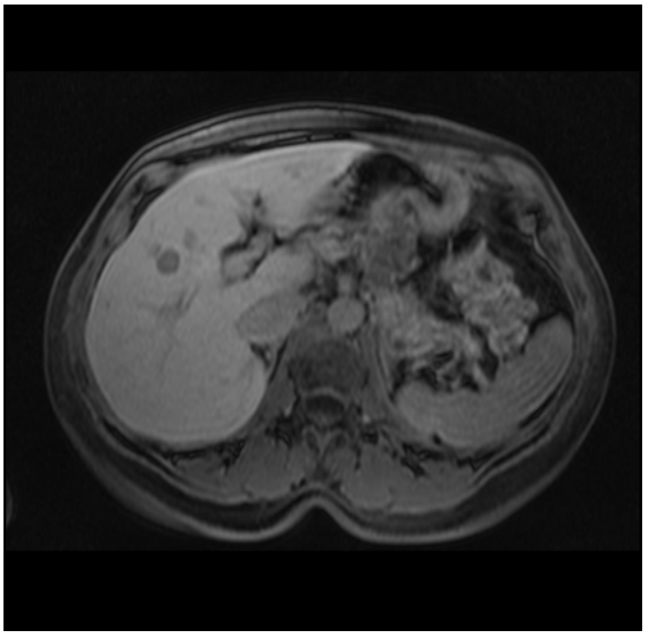

Fig. 4B. MR examination of the liver with hepatospecific contrast agent: In the venous phase, visible contrast agent washout occurs.

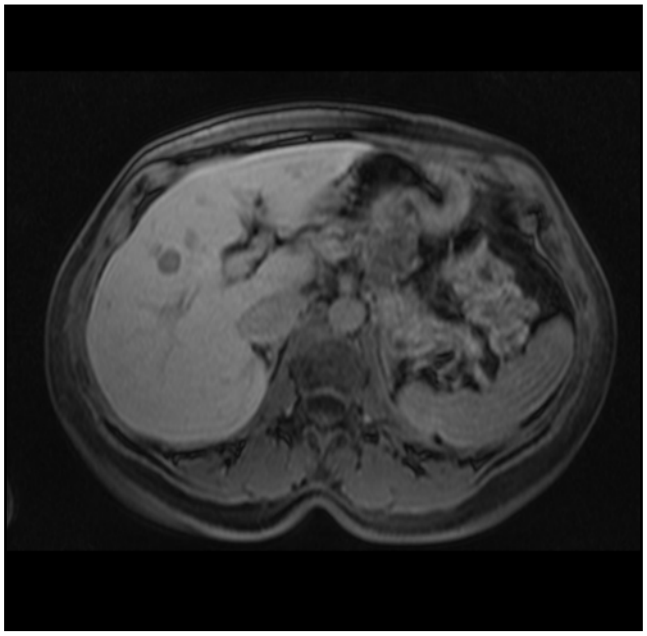

Fig. 4C. MR examination of the liver with hepatospecific contrast agent: In the hepatospecific phase, there is no cellular absorption of the contrast agent by the lesion.

Despite the fact that the liver lesion was solitary, relatively small in size, with no growth and no primary origin found, suspicion of a malignant aetiology persisted. In April 2019 a surgical resection of the lesion was therefore arranged, with the intention of a curative treatment. Persurgically the lesion was not palpable in the liver parenchyma, so a peroperative ultrasound was performed and the lesion was completely extirpated. A peroperative revisal of the entire abdominal cavity was also negative. The quick peroperative histological examination suspected a metastasis of a neuroendocrine tumor, which was confirmed by the definitive histology. The lesion was concluded as grade I, because the proliferative index Ki-67 was very low, less than 1 percent. The primary origin was thought to be in/from the area of pancreas or the small bowel. On that basis, a second reading of all prior imaging methods focused on the aforementioned areas was performed, without finding the primary lesion. During laboratory results, elevation of chromogranin A (CgA) to 680 μg/l was noted, neuron specific enolase (NSE) and 5-hydroxyindoleacetic acid (5-HLAA) remained within normal parameters. Neither endoscopic examination of upper gastrointestinal tract nor colonoscopy found the primary tumor.

Therefore, the endocrinologist recommended a CT examination focused on the small bowel - an enterography or enteroclysis, which was performed in June 2019. The patient refused a nasojejunal tube, so the examination was performed as an enterography – after fractional intake of 2 liters of a 10% manitol solution with subsequent intravenous application of a parasympatolytic. Due to the repeated findings of marked arterial enhancement, the protocol was slightly adjusted in order to image the early arterial phase to differentiate a highly vascularised tissue - the arterial phase scanning was started 4 seconds earlier after bolustracking than in the standard protocol. The examination found 4 small (4-5mm) markedly hypervascularised lesions in the area of the small bowel. Based on the morphology of the individual bowel loops (the height of Kerckring folds) in the area of those lesions, the bowel segments appeared to be parts of ileum.

During the next endocrinologic follow-up in July 2019, a PET/CT examination of somatostatine re-ceptors with the radiopharmaceutical ^{68}Ga-DOTA-TOC (^{68}Ga-DOTA-labelled peptids) was indicated in order to obtain approval for treatment with somatostatine analogues. For peroral contrast, diluted Manitol (without application of a spasmolytic) was chosen. The examination was performed in the portovenous phase. On PET scans, 4 small lesions with elevated expression of SSR (somatostatine receptors) in the area of the ileum were imaged, with the measured SUVmax value of 11.3 (clearly higher than level of SSR expression in normal liver parenchyma). On the CT scan there were no clear corresponding lesions. The findings were therefore consistent with the previous examination – CT enteroclysis and evaluated as „stable disease" by the indicating physician.

The patient preferred conservative approach instead of surgical resection, therefore the endocrinologist began treatment with a somatostatine analogue – Sandostatin. The next liver ultrasound follow-up after six months found no new metastatic lesions. Clinically the patient remained well, in laboratory findings there

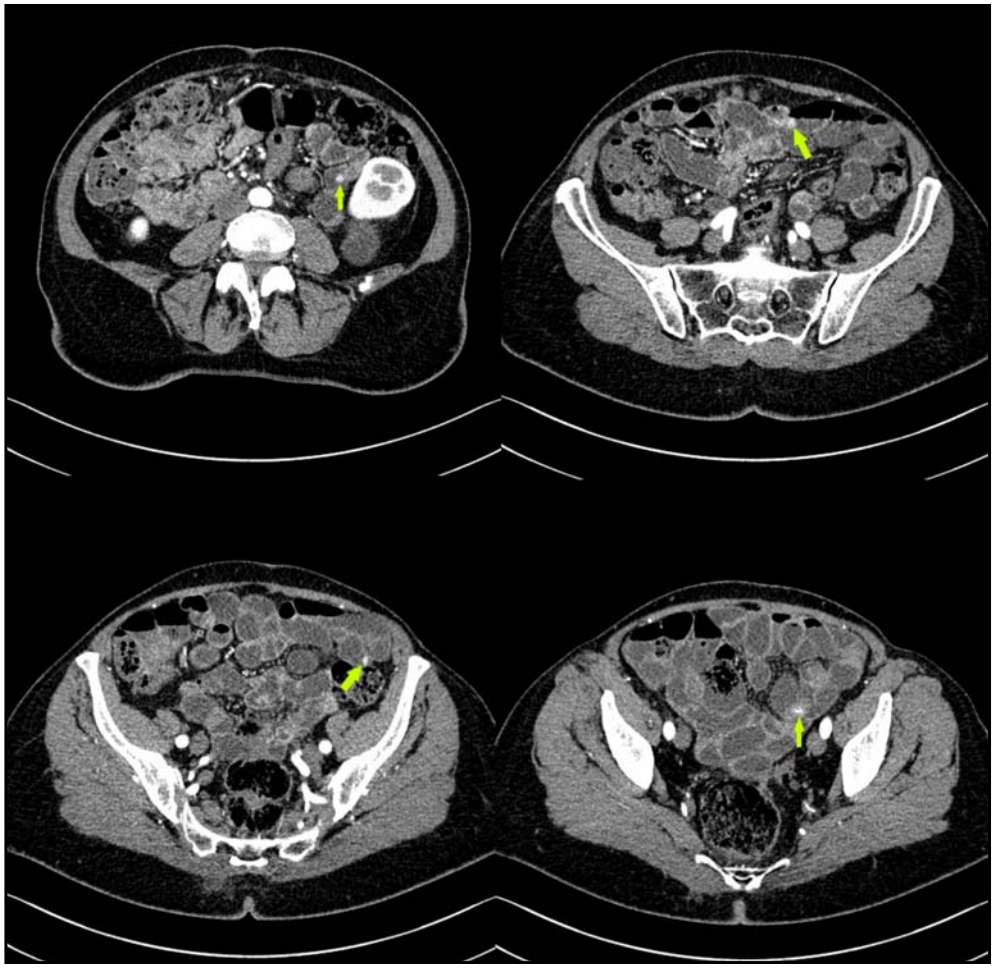

Fig. 5. CT enterography: The scans show a very early arterial phase - there are four small lesions visible in the wall of the small bowel - the ileus, which enhance markedly, more than the bowel wall itself. The enhancement is akin to that of the kidney cortex (left upper corner).

was notable decrease in CgA levels to 72μg/l, mild elevation of NSE to 21μg/l, 5-HIAA levels remained normal. A follow-up PET/CT examination with ^{68}Ga-DOTA-TOC was performed in October 2020, on which there was no disease progression. The 4 small lesions in the loops of ileum persisted with heightened SSR expression and with measured SUVmax value of 4.7–6. In comparison to the previous examination, there was decreased SSR activity, which might be a sign of treatment effect. No new lesions were found.

DISCUSSION

NEN of the small bowel are usually sporadic, manifest in the 6th to 7th decade as small hypervascularized polypoid or intramural lesions, often multiple (in 26 to 40% of cases), with the most common localisation being the ileum (30 to 49.9%). Most commonly, they are well differentiated with a low grade and slow growth with indolent course (Sahani *et al.* 2013; Kuracinova *et al.* 2018; Pavel *et al.* 2020; Xavier *et al.* 2016; Louthan 2009).

NEN of the small bowel can be accompanied by symptoms of carcinoid syndrome – the typical symptoms are sweating, flush or diarrhoe. Functional NEN of the small bowel, however, constitute only a minor ratio. As a matter of fact, 82 to 92% of patients have no clinical symptoms and a liver metastasis as the first sign is not unusual – as was the case in our patient. Liver metastases at the time of diagnosis are present in 20% of cases, which attests to the metastatic potential of even very small NEN of the small bowel lesions (Sahani *et al.* 2013; Ambrosini & Fanti 2016; Xavier *et al.* 2016).

The diagnostic approach is multidisciplinary. It is based on imaging methods – radiological methods and methods of nuclear medicine, laboratory diagnostics, invasive methods, histopathology and also clinical symptoms (if present). Despite advances in diagnostics, 20-50% of primary extrapancreatic GEP-NEN are challenging to locate (Sahani *et al.* 2013).

The laboratory diagnostics consists mainly of testing for specific markers – chromogranine A (CgA) and neuron specific enolase (NSE) in blood and 5-hydroxyindoleacetic acid (5-HIAA) in urine as sero-

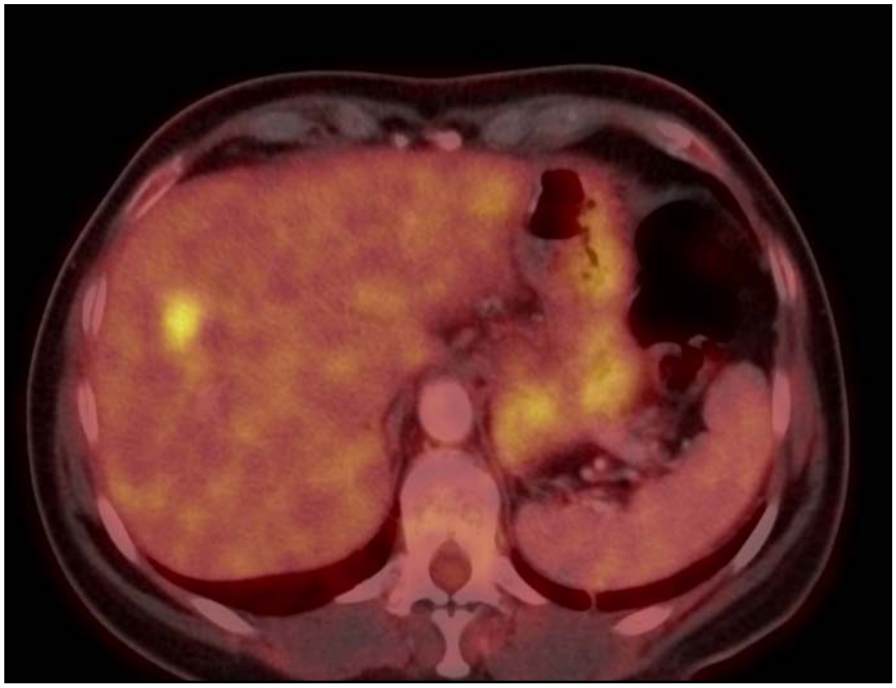

Fig. 6. Fusion PET-CT scan after administration of radiopharmaceutical 68Ga-DOTA-TOC - the lesion in the liver shows high metabolic activity.

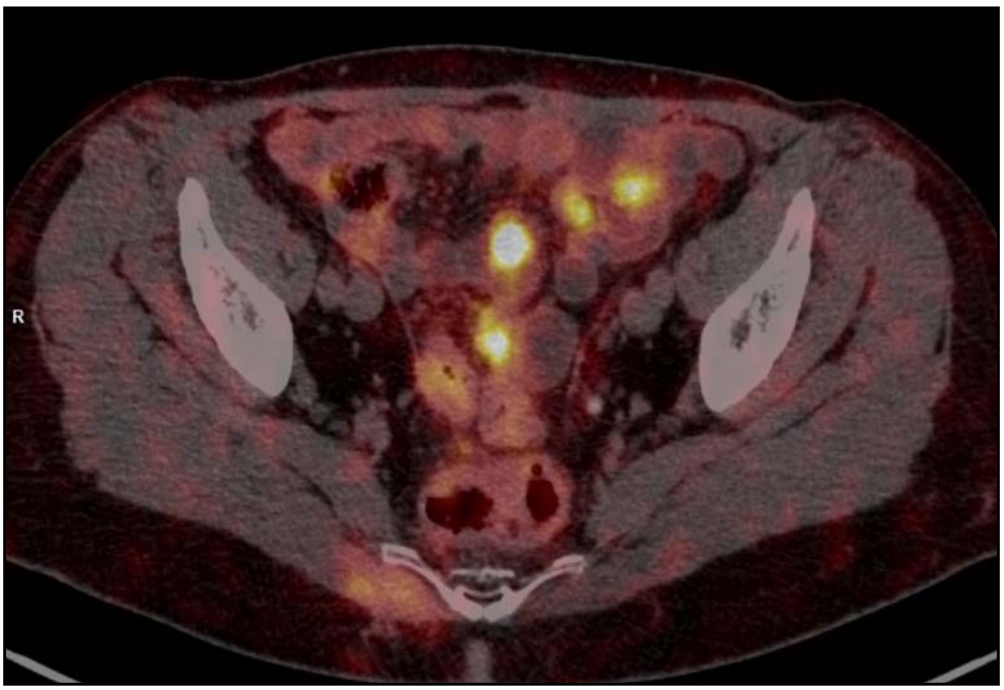

Fig. 7. Fusion PET-CT scan after administration of radiopharmaceutical 68Ga-DOTA-TOC - the scan exhibits small hypermetabolic lesions in the ileum.

tonine metabolic products (Kinová *et al.* 2010; Xavier *et al.* 2016).

In terms of radiology, we can consider CT to be the most commonly used imaging method in GEP-NEN diagnostics. It serves for finding the primary lesion as well as the eventual metastatic spread, or staging. The choice of protocol is based on the often hypervascularised character of NEN lesions – therefore a multiphasic postcontrast examination is needed, with an early arterial and then portovenous phase. Despite this, the identification of the primary lesion can be difficult and the examination can be falsely negative – as was the case in the first whole body scan of our patient. Another important parameter is also the suspected primary localisation – in our case, only enterography with adjusted time parameters of the arterial phase performed on the basis of searching for a suspected origo in the small bowel, led to finding the small bowel

lesions. Performing CT enterography or enteroclysis on suspicion of a tumor located in the small bowel is also recommended by literary sources – in the Kamaoui *et al.* study (2010) the sensitivity and specificity of enteroclysis reached 100% and 96.2%, respectively. A desmoplastic reaction of the mesentery can be observed relatively often in NEN of the small bowel, but that was not the case in our patient (Sahani *et al.* 2013; Pavel *et al.* 2020; Kamaoui *et al.* 2010; Ramage *et al.* 2012; Reznek *et al.* 2006).

An MR examination can also be used to find primary lesions of GEP-NEN, metastatic spread or to differentiate an indeterminate CT finding. According to some studies, an MR is more sensitive, particularly when it comes to detecting liver metastases (especially when a hepatospecific contrast agent is used). Overall, the MR or variants like MR enterography, are considered mainly as an alternative to the CT with all the usual benefits and limitations arising from an MR examination. This mirrors the situation in our case report – the MR examination of the patient produced practically the same information as the previous whole body CT scan and therefore was practically redundant in the diagnostic process (Sahani *et al.* 2013; Pavel *et al.* 2020; Reznek *et al.* 2006; Bader *et al.* 2001).

The use of US in NEN of the small bowel is limited, mostly to imaging liver metastases as in our case (Sahani *et al.* 2013).

In terms of nuclear medicine, two principles are usually used for imaging NEN. The first is imaging the increased expression of somatostatine receptors with radiactively labelled somatostatine analogues (the original scintigraphic method was in the past years replaced at several departments by the newer and more sensitive method of PET/CT with ^{68}Ga-DOTA-labelled-peptids). The second approach is imaging the increased glucose metabolism with the radiopharmaceutical ^{18}F-FDG (the most commonly used radiopharmaceutical in oncological indications). Both types of imaging have their advantages and their limitations (Ambrosini & Fanti 2016; Balogová & Noskovičová 2017).

Indications for molecular imaging include primary tumor localisation, metastases detection, evaluating treatment effect or biochemical recurrence. PET/CT with 68Ga-DOTA-labelled-peptids is also used to select patients for treatment with somatostatine analogues while these can be also radioactively labelled. The advantages of hybrid imaging include higher detection rate of lymph node or skeletal involvement (for example metastatic involvement of unenlarged lymph nodes or bone marrow metastases). According to the literary data, ^{68}Ga-DOTA-TOC PET/CT has a 92% sensitivity and a 95% specificity in detection of NEN (Ambrosini & Fanti 2016; Pavel *et al.* 2020; Balogová & Noskovičová 2017; Tsoli *et al.* 2018).

Usually well differentiated low grade NEN have higher SSR expression and lower level of glucose metabolism and therefore should be better imaged using ^{68}Ga-DOTA-TOC. However, NEN of intermediate and higher grade or poorly differentiated NEN should have a decreased SSR expression and higher glucose metabolism, therefore they should be imaged using ^{18}F-FDG or both methods. The accumulation of ^{18}F-FDG is considered a poor prognostic factor and is associated with higher tumor aggression (Balogová & Noskovičová 2017; Tsoli *et al.* 2018; Koranda *et al.* 2011).

In our case report, the low grade NEN liver metastatic lesion showed increased accumulation of ^{18}F-FDG, which is not common according to literature. ^{68}Ga-DOTA-TOC PET/CT was performed after extirpation of the liver metastasis and imaged 4 small primary NEN lesions in the ileum with increased SSR expression, which corresponds with the histology of the liver metastasis. On the first ^{18}F-FDG examination the lesions in ileum were not imaged, most likely due to "superimposition" of the lesions with physiologic accumulation of FDG in the bowel loops.

CONCLUSION

The presented case report shows a case of clinically asymptomatic neuroendocrine neoplasm of the ileum, where the first finding of a distant metastasis as a liver incidentaloma led to the diagnosis. The metastasis was better identifiable on imaging than the primary lesion - a situation which is common for GEP-NEN. Due to the epidemiological data of their increasing incidence, as well as the fact that metastatic spread is possible even in lesions of only several millimetre size, it is necessary to think of NET in differential diagnostics of hypervascularised liver incidentalomas and adjust the recommendations of other diagnostic procedures accordingly. Neuroendocrine tumors constitute an illness with a typically multidisciplinary approach regarding the diagnostic modalities, because of the important role of both radiological modalities and modalities of nuclear medicine or hybrid modalities as well as laboratory or histological modalities. Regarding the diagnostic process in this case report practically all modalities were utilized, some more or less redundantly. However, thanks to this it was possible to demostrate the complete image of the pathology in terms of both radiology and nuclear medicine.

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