RESEARCH ARTICLE

Neuroendocrine tumour located in the small intestine, diagnosed by an abdominal ultrasound reassessment of liver haemangiomas

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BACKGROUND: Neuroendocrine tumours (NETs) located in the gastrointestinal tract have had an increased incidence during the past 10 years. Well-differentiated tumour formations located in the small intestine have a slow evolution, with the patients being asymptomatic in the early stages and accidental diagnosis in most cases. Annual ultrasound screening and other procedures are essential in the detection of malignant tumours in the early stages.

In this paper we report the case of a 55-year-old female patient, with total thyroidectomy performed in 2010 for a papillary thyroid carcinoma, currently undergoing replacement therapy with Euthyrox (75µg / day), asymptomatic. During the ultrasound monitoring of some pre-existing liver haemangiomas, a solid formation was highlighted, vascularised at the level of the last ileal loop. Laboratory tests presented normal values, excepting serum serotonine level which was significantly increased. The investigations after the ultrasound, namely, the colonoscopy with examination of the terminal ileum on about 30 cm, PET-CT scan (positron emission tomography/computed tomography), morphological results correlated with the immunophenotypic ones (CHROMO, Synaptophysin, Ki67), have led to the diagnosis of a G1 neuroendocrine tumour located in the terminal ileum. At the same time, the PET-CT scan also showed a left lung nodule, minimally metabolically active, for which excision was recommended, in order to establish the certain diagnosis between a primary formation and a secondary metastasis.

In our case, in the absence of ultrasound annual monitoring of known liver haemangiomas, the neuroendocrine tumor located in the terminal ileum, would have been diagnosed in advanced stages, when the therapeutic management and the follow-up would have been difficult. Also, due to the fact that many years ago, the patient had a papillary thyroid carcinoma and endocrine malignancies are related to the appearance of NETs, the issue of the existence of a connection between the two types of neoplasms occurs.

Key Words: *Neuroendocrine tumour, terminal ileum, abdominal ultrasound, immunohistochemistr, PET-CT scan.*

INTRODUCTION

Small bowel neoplasms account for merely 3% of all malignant tumours of the gastrointestinal tract [1], the most common forms of which are neuroendocrine tumours with ileal location, followed by adenocarcinomas [2].

This low percentage is supported by the following pathogenic mechanisms [3,4]:

1) Low exposure to carcinogens (benzpyrene) due to the high concentration of benzpyrene in the small intestine which limits the conversion to toxic metabolites;
2) The protective effect of Ig A in large amounts in the small intestine
3) The reduced presence of pathogens (bacteria) at this level.

The average age for the diagnosis of neuroendocrine tumours is between 65 and 70 years [5], with male predominance (male/female = 1.5/1) [6].

Well-differentiated gastrointestinal tract NETs have a slow evolution, with a hypersecretion of vasoactive or hormonal substances, with their diagnosis being made by immunohistochemical and microscopic methods [7-9].

We report a clinical case of neuroendocrine tumour of the terminal ileum grade G1 in a 55-year-old woman, diagnosed by ultrasound (incidentally), with possible secondary metastasis.

METHODS AND MATERIALS

55-year-old female patient, diagnosed in 2010 with papillary thyroid carcinoma for which a total thyroidectomy was performed followed by one course of radioactive iodine, currently under replacement therapy with Euthyrox, in early February 2020 reported to a private clinic in Bucharest for *ultrasound* reassessment of pre-existing liver haemangiomas. The ultrasound result showed a slightly steatotic liver structure, the presence in the right lobe of several hyperechoic formations suggestive of infracentimetric haemangiomas, without solid focal processes primary or secondary in nature, a pancreas with lipomatous infiltration appearance, and in the terminal part of the last ileal loop, a solid polyp-like, vascularised formation about 1.5 cm in size (*Figures 1 and 2*). At the same time, an ultrasound of the soft parts, of the submandibular and parotid glands was performed, which showed a normal appearance without cervical lymphadenopathy, and the evaluation of the post-thyroidectomy thyroid lodge did not show any oncologically suspected local changes.

In ***March*** of this year, the patient underwent a *colonoscopy* that revealed

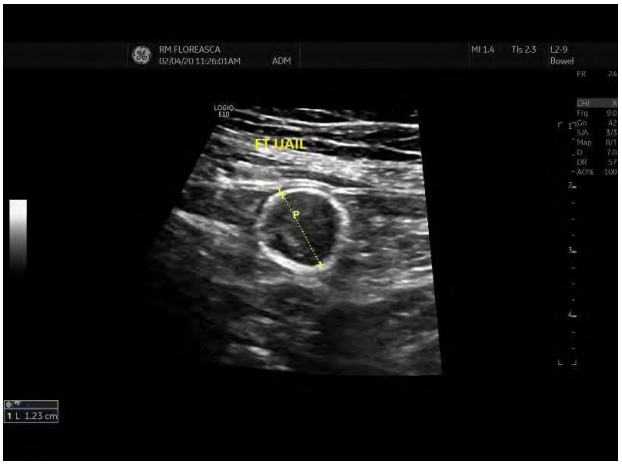

Figure 1. Neuroendocrine tumours (NETs) located in the terminal ileum (the patient's image from abdominal ultrasound)

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turgescent external and internal haemorrhoids, without bleeding traces, rectal ampulla, sigmoid colon, descending, transverse (additional loop, but with normal mucosa), ascending, to the ileocaecal valve of normal appearance. About 5-6 cm away from the ileocaecal valve, an oedematous, infiltrated, stiffened mucosa area was visualized, and adjacent to this area there was a protruding, muriform formation, about 15 mm in size, intensely vascularised, on the surface and in depth, with a wide implantation base, for which biopsies were taken *(Figures 3 and 4)* .

The histopathological examination described an ileal mucosa with preserved architecture, a villous to crypt ratio of 3:1, moderate oedema in the lamina propria and disseminated lymphocytic infiltrate with a vague tendency to subepithelial accumulation, reduced intraepithelial lymphocytosis. Adjacently, a mass of eumorphic red blood cells including tiny, torn fragments, consisting of medium-sized cells with monomorphic hyperchromic nuclei, with rare typical mitoses, with peripheral palisade outlines and rosette formation - an appearance suggestive of a ***low-grade neuroendocrine tumour (G1).***

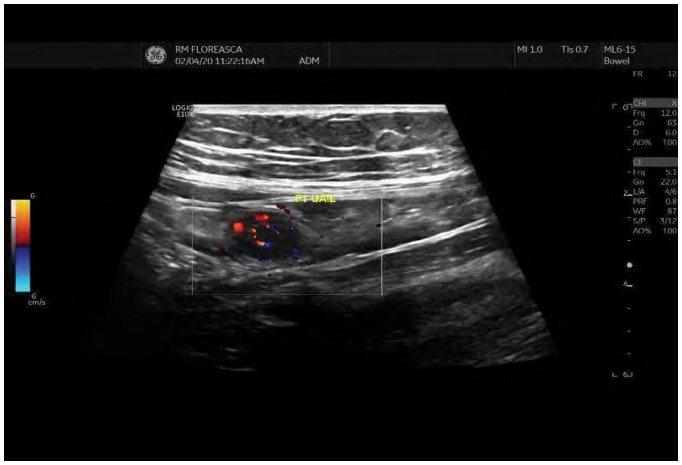

Figure 2. Neuroendocrine tumours (NETs) located in the terminal ileum (Doppler)- the patient's image from abdominal ultrasound

Figure 3. Patient's image from colonoscopy (biopsied tumor)

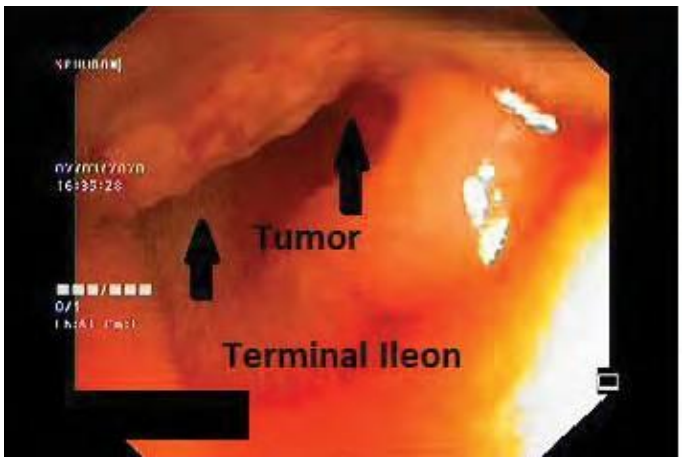

Figure 4. Patient's image from colonoscopy (the tumor located in the terminal ileon)

The immunohistochemical examination showed the following aspects:

- CHROMO (LK2H10): positive reaction in most tumour cells
- SYNAPTOPHYSIN (SP11): diffuse reaction in tumour cells
- Ki67(30-9): reaction present in very rare tumour cells (approximately 1%)

Thus, immunophenotypic data correlated with morphological data indicated and confirmed the diagnosis of *neuroendocrine tumour with histological grade G1.*

In **May** this year, the patient underwent a PET-CT scan 60 minutes after intravenous administration of 151 MBq F18 FDG (fluorodeoxyglucose) and oral ingestion of 10 ml of diluted iodine contrast agent 1/10 (Omnipaque). The investigation described in the left lung, in the lower apical segment, an ovoid node, solid and "matte glass" appearance, minimal F18-FDG uptake, with infiltrative contours and 0.8 / 0.8 cm diameters and radiotracer hypercapture at the level of the last distal ileal loop. Otherwise, no images of recurrence in the thyroid lodge, no lymphadenopathy in the cervical or supradiaphragmatic ganglion stations; liver, pancreas, spleen, gallbladder, kidneys, adrenal glands, uterus, appendages without metabolically active lesions, except for layered vertebral degenerative changes.

Recent laboratory tests did not indicate pathological changes: PTH (parathyroid hormone), TSH (thyroid-stimulating hormone), f T4 (thyroxine free), aldosterone/renine ratio, plasma free metanephrine and plasma free normetanephrine tests- normal values, neuron-specific enolase within normal limits). Also, Chromogranin A =50 ng/ml (20-100ng/ml) and urinary 5-HIAA = 2,42 (1-10mg/24 h) indicated normal values, while serum serotonine level was increased -553ng/ml (80-400ng/ml).

RESULTS

Following the investigations performed, in this case the tumour is well differentiated, low grade with rare typical mitosis and Ki67 reaction present in very rare tumour cells (1%), positive reactions of chromogranin (CgA) and synaptophysin in most tumour cells, increase in serum serotonine levels, making the malignant formation fall under the grade G1 NETs. Abdominal ultrasound, colonoscopy with examination of the terminal ileum, PET-CT (F-18 FDG) performed on the patient diagnosed and confirmed the presence of the tumour in the terminal ileum.

DISCUSSION

Neuroendocrine neoplasms of the gastrointestinal tract have locations at the jejunoileal, appendages, caecal, colon or rectal level, those located in the small intestine accounting for about half of the total malignancies at this level [10].

The pathogenic mechanisms of the jejunum and ileum NETs are characterized by the production of active amines (serotonin, histamines), polypeptides (somatostatin, neurokinin A, neurokinin B, β-endorphins) and prostaglandins [11].

From a clinical viewpoint, the most common symptom is intermittent abdominal pain followed by nausea accompanied by vomiting, diarrhoea, weight loss, fatigue and, less frequently, rectorage / hematochezia and fever [10]. In most cases, the symptoms occur when the disease is in an advanced stage. In the described case, the patient is asymptomatic, with the diagnosis of the malignant tumour formation being made at an early stage. (G1).

The WHO classified gastrointestinal NETs according to the histopathological appearance and proliferation rate as follows [12]:

- Low-grade = G1
- Intermediate – grade = G2
- High-grade = G3

From the viewpoint of the mitotic activity, the differentiation between G1 and G2 is extremely minor, only1 mitotic figure per 10-high –powered fields (HPF). The classification of the Ki-67 proliferation index was achieved

through the collaboration of ENETS (European Neuroendocrine Tumor Society), AJCC (American Joint Committee on Cancer) and WHO (World Health Organisation) (2017) as follows [13,14] *(Table 1)*:

- <3% → G1
- 3-20% →G2
- >20% →G3

The histopathological examination of the well-differentiated NETs reveals solid, trabecular tumours, well delineated in the submucosa or extended in the muscles, with the surface reflecting hypervascularization or increased lipid content, with glandular pattern with uniform cells, round or oval nuclei with chromatin in "salt and pepper "and finely granular, eosinophilic cytoplasm[15].

The diagnosis of neuroendocrine tumours located in the small intestine is achieved from an immunohistochemical viewpoint based on chromogranin (CgA) and synaptophysin [10], with our patient showing positive reactions of both tests in most tumour cells.

Other tests used to highlight the neuroendocrine origin and location of the primary tumour is:

- TTF-1 (Thyroid transcription factor-1)- manifested in well-differentiated neuroendocrine tumours originating in the lungs [16]
- CDX2 (Caudal Type Homeobox gene 2) – expresses well-differentiated NETs with intestinal origin [17]
- ISL1 (Insuline gene) – expresses the pancreatic origin [16]
- PAX 8 (Paired-box gene 8)– suggests duodenal and rectal origin [18]

Other laboratory tests with sensitivity and specificity for NETs are: (CgA) serological chromogranin A (the elevated value of which indicates an unfavorable prognosis), the high value of 5-HIAA (5-Hydroxyindoleacetic acid) with specificity for 24 h serotonin in urine (which shows the presence of a primary tumour at the jejunoileal level) and serotonin [10].

From the viewpoint of *imaging and other procedures*, NETs are diagnosed by the following:

1) Upper endoscopy and colonoscopy with examination of the terminal ileum [19] or double balloon enteroscopy [20]. The videocapsule with the evaluation of the small intestine is not recommended due to the obstruction given by the tumour and the retention of the capsule at that level[19]
2) CT (computed tomography) or MRI (magnetic resonance imaging) detect any mesenteric formation that indicates a primary tumour located in the small intestine
3) PET-CT (68-Ga DOTATATE and Ga-68 DOTATOC) is significantly more sensitive to the somatostatin receptor than Indium-111 pentetreotide scintigraphy (OctreoScan)
4) Abdominal ultrasound can detect a primary tumour of the small intestine and mesenteric lymphadenitis, as well as advanced liver metastases [10]

The potential for distant metastasis of the jejunoileal NETs depends on the size of the formation [21]:

- <1 cm → 5%
- 1-2 cm → 20%
- >2 cm → 47%, with the most damaged organ being the liver followed by the lungs, bones [11], breast, colon and skin [22].

From a *treatment* viewpoint, somatostatin analogues are effective in relieving symptoms and stabilizing tumour growth [23].

Surgery for the well-differentiated small bowel NETs, with <1.5 - 2 cm diameters, in the absence of adjacent lymph node invasion and mesoappendix, is the first therapeutic option [23].

Because approximately ½ of patients with gastrointestinal NETs have at least one other malignancy on this route, it is necessary to examine the entire digestive tract before surgery [24].

All the investigations performed on the patient diagnosed and confirmed the presence of the tumour in the terminal ileum, with a medium risk of metastasis in this case (about 20%) and surgical resection of the tumour formation as first-line therapeutic conduct.

TABLE 1
Classification and staging criteria for gastrointestinal tract NETs - WHO -2019.

Terminology	Differentiation	Clinical	Grade	Mitotic rate* (mitoses/2 mm2)	Ki-67 index* (percent)
NET, G1	Well differentiated	Slow clinical behaviour	Low	<2	<3
NET, G2	Well differentiated	Slow clinical behaviour	Intermediate	2 to 20	3 to 20
NET, G3	Well differentiated	Aggressive clinical course	High	>20	>20

TABLE 2
TNM staging of NETs located in the small intestine AJCC UICC

	1st stage	Second stage	Third stage	Fourth stage
TNM staging	T1N0M0	T2T3N0M0	T1N1N2M0 T2N1N2M0 T3N1N2M0 T4N0M0 T4N1N2M0	TXT0NXN0N1N2M1 T1NXN0N1N2M1 T2NXN0N1N2M1 T3NXN0N1N2M1 T4NXN0N1N2M1

The 10-year survival rate for jejunoileal NETs depends on the stage of the disease, according to the results of studies conducted by AJCC (American Joint Committee on Cancer) and National Cancer Institute Surveillances Epidemiology and End Results, as follows [25]*(Table2)*:

- 95% for the 1st and 2nd A stages
- 77% for the 2nd B and 3rd B stages
- 68% for the 3rd A stage
- 42% for the 4th stage.

Other markers used in the prognostic value of the NETs are [26]:

- Cytokeratin 19 (CK19)
- CD99 (cluster of differentiation) (4/54)
- $P27^{KIP1}$ (cyclin-dependent kinase inhibitor)

Monitoring of patients with post-surgical NETs of the small intestine is achieved by performing an abdominal ultrasound, MR enterography, chest CT scan and biochemical markers [27].

CONCLUSION

1. Annual ultrasound screening and other procedures are essential in the detection of malignant tumours in the early stages.
2. The peculiarity of the reported case is that, in the absence of ultrasound monitoring of pre-existing liver haemangiomas, terminal ileal NETs would have been diagnosed in advanced stages, when the therapeutic difficulty would have increased significantly and the prognosis would have been unfavorable with a low survival rate.
3. Due to the fact that 10 years ago, the patient had a thyroid carcinoma, and one of the causes of NETs is the presence of multiple endocrine malignancies (parathyroid glands, thyroid), the problem of the existence of a connection between the 2 types of neoplasms arises.
4. According to the PET-CT scan result, the left lung nodular formation may be a secondary metastasis distant from the NET (although the lung is not the most common organ at risk of metastasis) or a benign or malignant primary tumour.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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