Endokrynologia Polska
DOI: 10.5603/EP.a2021.0052
Volume/Tom 72; Number/Numer 4/2021
ISSN 0423–104X, e-ISSN 2299–8306

Clinical challenges and dilemmas in the management of advanced pancreatic neuroendocrine tumour — the first manifestation of von Hippel-Lindau disease in a young patient

Karolina Morawiec-Sławek[1], *Marta Opalińska*[2], *Agnieszka Stefańska*[2], *Anna Sowa-Staszczak*[1], *Alicja Hubalewska-Dydejczyk*[1]

[1]*Chair and Department of Endocrinology, Jagiellonian University Medical College, Krakow, Poland*
[2]*Chair and Department of Endocrinology, University Hospital, Krakow, Poland*

Key words: *pNET; von Hippel-Lindau disease; somatostatin analogues*

Pancreatic neuroendocrine tumours (pNET) account for approximately 30% of all gastro-entero-pancreatic neoplasms [1]. Most pNETs occur as sporadic tumours, but 9% are components of hereditary syndromes [multiple endocrine neoplasia type 1, von Hippel-Lindau disease (VHL), von Recklinghausen disease]. Approximately 1% all pNETs are associated with VHL [1–3].

Somatostatin analogues (SSA) octreotide and lanreotide are recommended as first-line systemic treatments in non-functional pNETs with low proliferation index and good somatostatin receptor (SSTR) expression, due to their widely proven antiproliferative effect and limited toxicity [1, 3, 5]. Despite their similar mechanism of action, sequential therapy of one followed by another in patients with disease progression could still be effective in disease stabilisation.

This paper shows the clinical challenges and dilemmas in the management of advanced pNET in a young patient with VHL syndrome.

In February 2015, a 16-year-old female patient with a several-month-long history of abdominal pains, diarrhoea, and weight loss was admitted to the hospital due to cholestasis and jaundice. Contrast-enhanced CT showed a pancreatic head tumour 86 × 76 × 77 mm, with liver penetration and infiltration of the mesenteric vessels, and portal and splenic veins Additionally, enlarged paraaortic lymph nodes and liver metastases in segments V, VII, and IV were described. Pancreatoduodenectomy with cholecystectomy (Whipple procedure) accompanied by gastrointestinal anastomosis formation using the Traverso-Longmire method and resection of a metastatic liver lesion were performed.

Histopathological examination confirmed pNET G2 infiltrating small nerve trunks, blood vessels, the wall of the small intestine, and bile duct (Ki-67 5%, liver with lymph node metastases 2/7). Post-operative [^{99m}Tc]Tc-DOTA-TOC SPECT/CT identified pathological somatostatin receptor (SSTR) expression in a pancreatic head tumour (30 × 24 mm) and in liver metastasis (segment VII — 15 mm).

Genetic testing for the *MEN1* gene was negative. Because of the patient's young age and an aggressive tumour type, further genetic testing was conducted, finding an abnormality in the *VHL* gene. The analysis of the *VHL* gene mutation in parents and siblings was negative.

After obtaining approval from the National Health Fund (NHF), the adolescent patient was qualified for an off-label therapy with octreotide LAR every 4 weeks (starting with the dose of 20 mg and then 30 mg) causing stabilisation of the disease.

After 10 months of the therapy, in March 2016, a control [^{68}Ga]Ga-DOTA-TATE PET/CT followed by magnetic resonance imaging (MRI) showed the disease progression (increase pNET to 41 × 26 mm and new liver metastases all having good SSTR expression). Due to disease progression and again after obtaining a positive opinion from the NHF, octreotide LAR was changed to lanreotide Autogel (120 mg *s.c.* every 4 weeks).

From May 2016 until now the therapy has been continued, with good tolerance and without clini-

Alicja Hubalewska-Dydejczyk, Chair and Department of Endocrinology, Jagiellonian University Medical College, Krakow, Poland, tel/fax: (+48) 124002300/48 124002317; e-mail: alahub@cm-uj.krakow.pl

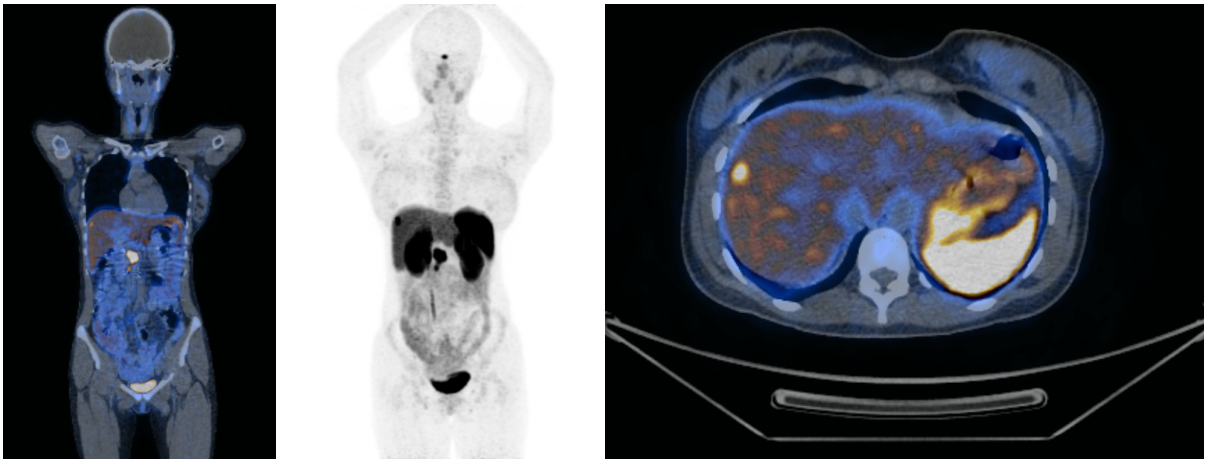

Figure 1. *[^{68}Ga]Ga-DOTA-TATE PET/CT — February 2021 — pathological SSTR expression in pancreatic head tumour and in liver metastases (segment VII/VIII and V)*

cally relevant adverse events. On the follow-up [^{68}Ga] Ga-DOTA-TATE PET/CTs (Fig.1) and MRI scans, no disease progression has been reported. Currently there are no other symptoms characteristic of VHL.

VHL is a hereditary autosomal dominant syndrome in which benign and malignant tumours develop in the central nervous system (CSN) and visceral organs. The disease incidence is 1/36,000 live births, and it results from mutations in the VHL tumour suppressor gene located on chromosome 3. The most characteristic tumours in VHL are hemangioblastoma of the retina and CSN, clear cell renal carcinoma (RCC), pheochromocytoma, and tumour of the inner ear or pancreas. Hemangioblastomas and RCCs are associated with high morbidity and mortality [2, 4]. Of all VHL patients, 10–17% develop pNET [1, 3]. pNET connected with VHL are generally non-functional (rarely cause symptomatic disease) and have metastatic potential, so they should be optimally operated before metastatic spread. Krauss et al. reported that significant risk factors of metastatic pNET potential are maximum tumour diameter ≥ 2.8 cm, tumour volume doubling time (≤ 24 months), and the mutation in exon 3 — especially of codon 161 and 167 [2, 4].

We present a very rare situation in which advanced, aggressive pNET is the first and only presentation of VHL syndrome. Additionally, the patient has a *de novo* mutation of the *VHL* gene (codon 161) and none of the other family members is affected by VHL syndrome. Management guidelines for aggressive VHL-pNETs are based on limited evidence, making this case more challenging.

The situation of young patient seemed difficult to treatment. At diagnosis, radical resection was impossible due to advance and dissemination of the disease, making systemic treatment necessary. The confirmation of SSTR expression in the remnant tumour mass enabled off-label SSA therapy in the adolescent patient. After pNET progression a simple switch to another SSA resulted in long-lasting disease stabilization.

In summary, the combination of a surgery and sequential therapy with long-acting SSA gave a very promising 6 years of stabilisation of aggressive VHL-pNET.

Author's statement

K.M.S. is the first author.

Conflict of interest

None declared.

Funding

None declared.

References

1. Kos-Kudła B, Hubalewska-Dydejczyk A, Kuśnierz K, et al. Consensus Conference, olish Network of Neuroendocrine Tumours. Pancreatic neuroendocrine neoplasms - management guidelines (recommended by the Polish Network of Neuroendocrine Tumours). Endokrynol Pol. 2013; 64(6): 459–479, doi: 10.5603/EP.2013.0031, indexed in Pubmed: 24431118.
2. Krauss T, Ferrara AM, Links TP, et al. Preventive medicine of von Hippel-Lindau disease-associated pancreatic neuroendocrine tumors. Endocr Relat Cancer. 2018; 25(9): 783–793, doi: 10.1530/ERC-18-0100, indexed in Pubmed: 29748190.
3. Falconi M, Eriksson B, Kaltsas G, et al. Vienna Consensus Conference participants. ENETS Consensus Guidelines Update for the Management of Patients with Functional Pancreatic Neuroendocrine Tumors and Non-Functional Pancreatic Neuroendocrine Tumors. Neuroendocrinology. 2016; 103(2): 153–171, doi: 10.1159/000443171, indexed in Pubmed: 26742109.
4. Ahmad S, Naber MR, Giles RH, et al. Diagnostic and management strategies for pNETs in Von Hippel-Lindau: a systematic review. Endocr Relat Cancer. 2021; 28(3): 151–160, doi: 10.1530/ERC-20-0469, indexed in Pubmed: 33512331.
5. Stueven AK, Kayser A, Wetz C, et al. Somatostatin Analogues in the Treatment of Neuroendocrine Tumors: Past, Present and Future. Int J Mol Sci. 2019; 20(12), doi: 10.3390/ijms20123049, indexed in Pubmed: 31234481.