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REVIEW

Neuroendocrine neoplasms in the context of inherited tumor syndromes: a reappraisal focused on targeted therapies

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Abstract

Purpose Neuroendocrine neoplasms can occur as part of inherited disorders, usually in the form of well-differentiated, slow-growing tumors (NET). The main predisposing syndromes include: multiple endocrine neoplasias type 1 (MEN1), associated with a large spectrum of gastroenteropancreatic and thoracic NETs, and type 4 (MEN4), associated with a wide tumour spectrum similar to that of MEN1; von Hippel-Lindau syndrome (VHL), tuberous sclerosis (TSC), and neurofibromatosis 1 (NF-1), associated with pancreatic NETs. In the present review, we propose a reappraisal of the genetic basis and clinical features of gastroenteropancreatic and thoracic NETs in the setting of inherited syndromes with a special focus on molecularly targeted therapies for these lesions.

Methods Literature search was systematically performed through online databases, including MEDLINE (via PubMed), and Scopus using multiple keywords' combinations up to June 2022.

Results Somatostatin analogues (SSAs) remain the mainstay of systemic treatment for NETs, and radiolabelled SSAs can be used for peptide-receptor radionuclide therapy for somatostatin receptor (SSTR)-positive NETs. Apart of these SSTR-targeted therapies, other targeted agents have been approved for NETs: the mTOR inhibitor everolimus for lung, gastroenteropatic and unknown origin NET, and sunitinib, an antiangiogenic tyrosine kinase inhibitor, for pancreatic NET. Novel targeted therapies with other antiangiogenic agents and immunotherapies have been also under evaluation.

Conclusions Major advances in the understanding of genetic and epigenetic mechanisms of NET development in the context of inherited endocrine disorders have led to the recognition of molecular targetable alterations, providing a rationale for the implementation of treatments and development of novel targeted therapies.

Keywords Neuroendocrine neoplasms · MEN1 · Von Hippel–Lindau (VHL) syndrome · Neurofibromatosis 1 (NF-1) · Tuberous sclerosis (TSC) · MEN4 · Targeted therapies

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Introduction

About 5% of neuroendocrine neoplasms (NENs) arise in the context of an inherited tumor syndrome. These are usually well-differentiated, low-proliferating (mitotic count < 20 HPFs and/or Ki-67 index < 20%) NENs, called neuroendocrine tumors (NETs), to be distinguished from poorly differentiated, highly proliferating NENs, called neuroendocrine carcinomas (NECs) [1, 2]. While NECs are aggressive, fast growing neoplasms that are usually sporadic [3], NETs are generally rather indolent, slowly growing neoplasms that produce peptide hormones or biogenic amines causing functional clinical syndromes, and can be associated with hereditary tumor syndromes [4], impacting on quality of life [5–7]. Among these predisposing genetic syndromes, some are associated with a limited spectrum of tumors, specifically localized in an organ or in the digestive tract, while others are associated with a very broad spectrum of neoplastic lesions, affecting either endocrine and non-endocrine organs [4, 8, 9].

The present review is specially focused on syndromes predisposing to gastroenteropancreatic (GEP) and thoracic NETs. They include: multiple endocrine neoplasias type 1 (MEN1), associated with a large spectrum of GEP and thoracic NETs, and type 4 (MEN4), associated with a wide tumor spectrum similar to that of MEN1; von Hippel–Lindau syndrome (VHL), tuberous sclerosis (TSC), and neurofibromatosis 1 (NF-1), associated with pancreatic NETs (pNETs). Other rare syndromes include glucagon cell hyperplasia neoplasia (GCHN), involving only the pancreas, and familial small-intestinal NETs (SI-NETs) (Table 1).

Surgery remains the only curative approach for localized NETs even in this setting, whereas systemic therapy is the standard of care for locally advanced or metastatic NETs and includes chemotherapy regimens, targeted agents, and radiopharmaceuticals [10]. Somatostatin analogues (SSAs) traditionally represent the mainstay of systemic treatment for NETs, given their efficacy to control hormonal production excess and tumor growth [11, 12]. Also, the innovative peptide-receptor radionuclide therapy (PRRT) with radiolabelled SSAs, that delivers targeted radiation to neuroendocrine neoplastic cells expressing somatostatin receptors (SSTRs), has been demonstrated to be effective and safe for SSTR-positive NETs [13]. Beyond these SSTR-targeted therapies, novel targeted therapies have been developed in the last decades, as the knowledge of genetic and molecular targetable alterations involved in NEN tumorigenesis has been improved. Nowadays, two other targeted agents have been approved for NETs. Everolimus, an inhibitor of the mammalian target of rapamycin (mTOR) pathway, is approved for GEP, lung and unknown origin NET, while sunitinib, an antiangiogenic tyrosine kinase inhibitor, is adopted in pancreatic NET (pNET) [14–16].

We propose a reappraisal of the genetic basis and clinical features of NETs in the clinical setting of inherited syndromes with a special focus on molecularly targeted therapies for these lesions.

Materials and methods

This narrative review was conducted focusing on papers published over the last years. Literature search was systematically performed through online databases including MEDLINE (via PubMed), and Scopus using multiple keywords combinations. The entree terms included "neuroendocrine neoplasms", "neuroendocrine tumors", "inherited tumor syndrome" "multiple endocrine neoplasia syndrome", "MEN1", "MEN4", "Von Hippel-Lindau syndrome", "tuberous sclerosis complex", "Glucagon cell hyperplasia neoplasia", Familial small-intestine neuroendocrine tumors", "Familial Insulinomatosis", Bronchopulmonary Neuroendocrine Tumors" and Thymus Neuroendocrine Tumors" in combination with "Molecularly targeted therapies", "somatostatin analogues", "peptide-receptor radionuclide therapy", "mTOR inhibitors", "everolimus", and "tyrosine kinase inhibitors". This was complemented by a carefully handsearching reference to find additional studies and expand the search. Literature search was performed up to June 2022.

The articles were selected on the basis of relevance of title and abstract in the topic. Primary studies and case series dealing with patients affected by NETs in the context of inherited tumor syndromes and reporting data on therapeutic approaches were included. Also systematic and narrative review focused on therapies and outcomes of NETs associated with inherited predisposing syndromes was identified. We included in the present review the articles matching the following inclusion criteria: English language and publication in peer-reviewed journals. We excluded articles for irrelevance to the topic, duplicates, and papers written in other languages apart from English.

Syndromes predisposing to gastroenteropancreatic neuroendocrine tumors (GEP-NET)

Multiple endocrine neoplasia type 1 (MEN1)

Genetic and clinical features of the syndrome

MEN1 or Wermer syndrome (OMIM *131100) is an autosomal dominant genetic syndrome with a high degree of

Table 1 The spectrum of neoplasms associated with the main inherited syndromes predisposing to gastroenteropancreatic and thoracic NENs

Syndrome	Inheritance pattern/frequency	Gene/genetic alteration	Protein function	Neuroendocrine tumor associated	Frequency (% of pts)
MEN1	Autosomal dominant 1:30,000	MEN1 is a tumor-suppressor gene located at 11q13 (10 exons). It encodes for a 610 amino acid protein, menin Heterozygous mutation; frameshift and nonsense variants, which generate a truncated menin protein, are the most frequent alterations	Menin localizes to the nucleus and is involved in several important cell functions including transcriptional regulation, genome stability, and cell proliferation	Primary HPT Often multiglandular	Over 90%
				Pituitary adenomas Prolactinoma (20%) GHoma (10%) ACTHoma (< 5%) Non-functional (< 5%)	30–40%
				GEP-NETs Non-functional (~ 50%) Gastrinoma (up to 40%) Insulinoma (~ 10%) Glucagonoma (< 1%) VIPoma (< 1%)	Up to 70%
				Bronchial/thymic carcinoids	10%
				Adrenal tumors Pheochromocytoma Cortical adenomas (mostly non-functioning)	10–40%
MEN4 (MENX)	Autosomal dominant 0.02–0.2:1000	CDKN1B, cyclin-dependent kinase (CDK) inhibitor 1b gene, located at 12p13 It encodes for the 196 amino-acid CDK1 inhibitor $p27^{Kip1}$ Heterozygous mutation; Missense mutations	p27 regulates the transition from cell cycle phase G0/G1 to S and is implicated in cellular proliferation, motility and apoptosis	Primary HPT	80–90%
				Pituitary adenoma Non-functional GH-omas (10%) ACTH-omas (5%)	50%
				GEP-NETs Non-functional Gastrinoma	25%
				Reproduction organ tumors Testicular cancer cervical carcinoma	NA
				Adrenal + renal tumors Carcinoid	NA

Table 1 (continued)

Syndrome	Inheritance pattern/frequency	Gene/genetic alteration	Protein function	Neuroendocrine tumor associated	Frequency (% of pts)
Von Hippel–Lindau disease (VHL)	Autosomal dominant 1–9:100,000	VHL gene is a tumor-suppressor gene located at 3p25 (3 exons plus a coding sequence of 639 nucleotides). It encodes a 232 amino acid protein (pVHL) Heterozygous mutation The most common type of mutation is a missense mutation. However, microdeletions/insertions, frameshift nonsense mutations, large deletions, and splice-site mutations were described	pVHL exerts many regolatory functions, involving cellular responses to hypoxia, cell growth, angiogenesis, energy metabolism The best-known function is targeting the HIFα, that in turn regulates the expression of several hypoxia-inducible genes Loss-of-function of the suppressor pVHL causes neoplastic transformation	P-NETs Non-functioning (98%) Pheochromocytomas/Paragangliomas	10–17% ~25%
Neurofibromatosis 1 (Von Recklinghausen's Disease) (NF-1)	Autosomal dominant 1: 3000	NF1 gene, a tumor-suppressor gene located on chromosome 17q.11.2, encoding for the 2485 amino acid protein neurofibromin Heterozygous mutation; missense mutations, frameshift, nonsense mutations	Neurofibromin affects cell proliferation/growth and metabolism by regulating the activation of p21 Ras, modulating adenylate cyclase activity, binding microtubules, and interacting with the cellular cytoskeleton	GEP-NET Somatostatinomas, mostly duodenal Gastrinomas Insulinomas NF-pNENs Pheochromocytomas	0–10% 2%
Tuberous sclerosis complex (TSC)	Autosomal dominant 1:20,000	TSC1 gene at 9q34 encoding the 1164 amino acid protein, hamartin TCS2 gene at 16p13.3 encoding the 1807 amino acid protein, tuberin TSC2 mutations are 2.5–5 times more common than TSC1 mutations Heterozygous mutation; deletion, insertion, missense mutation	Hamartin and tuberin interact with mTor pathway, which plays a key role in cell growth, differentiation and survival, energy regulation, response to hypoxia Loss of function of TSC1 or TSC2 leads to aberrant mTOR pathways, which promote tumorigenesis	P-NETs Non-functioning (~98%) Insulinomas Gastrinomas Glucagonomas	1–9%
Glucagon cell hyperplasia neoplasia (GCHN)	Autosomal recessive 4 per million	Glucagon receptor gene (GCGR) at 17q25 Homozygous mutations; two missense mutations or two heterozygous alterations, all determining decreased or absent GCGR activity	GCGR, integral component of plasma membrane, is a G-protein-coupled receptor, involved in several processes, including glucose homeostasis, regulation of glycogen metabolic process, cellular response to starvation and positive regulation of gene expression	P-NENs Silent glucogonomas NF-pNENs	NA

Table 1 (continued)

Syndrome	Inheritance pattern/frequency	Gene/genetic alteration	Protein function	Neuroendocrine tumor associated	Frequency (% of pts)
Familial small-intestine neuroendocrine tumors (SI-NENs)	Autosomal dominant	Inositol polyphosphate multikinase (IPMK) gene	IPMK protein is a key enzyme for inositol phosphates synthesis, and regulates many aspects of cell physiology, including metabolic and p53-related apoptotic pathways	Enteric (ileum and jejunum) NENs Non-functioning Carcinoid syndrome	NA
Familial insulinomatosis	Autosomal dominant Unknown	MAFA (β V-Maf avian musculoaponeurotic fibrosarcoma oncogene homolog A) gene at 8q24.3 Heterozygous mutation; missens mutations	MAFA protein, a transcription factor that is a key coordinator of β-cell insulin secretion	P-NENs Multiple insulinomas	NA

GEP-NEN gastroenteropancreatic neuroendocrine neoplasm, *HIFα* hypoxia-inducible transcription factor α, *HPT* hyperparathyroidism, *NEN* neuroendocrine neoplasm, *pNEN* pancreatic NEN, *NA* not available, insufficient numbers reported to provide prevalence/frequence information

penetrance, such that more than 95% of patients develop clinic manifestations of the disorder by the fifth decade and 75% of 20-year-old patients has at least one tumor [17]. It has an estimated prevalence of 1:30,000 inhabitants and affects men and women equally [18]. The disorder can affect all age groups; although the first symptoms often appear in people in their early 20 s, most people are diagnosed as having MEN1 in their 40 s. It is clinically suspected by the association of at least two diseases among: parathyroid glands hyperplasia and primary hyperparathyroidism (HPT) (90%), GEP-NETs (30–70%), especially non-functioning tumors (NF, 20–55%) and gastrinomas (30–40%), and anterior pituitary adenomas (30–40%), especially prolactinomas (20%) [19]. In addition, patients may also develop other neuroendocrine (i.e., bronchopulmonary NET in less than 2% of cases and pheochromocytoma in less than 1% of cases) and non-endocrine tumors (angiofibromas, 85%; collagenomas, 70%; lipomas, 30%; meningiomas, 8%) [20] (Table 1). Uncommon neoplasias like parathyroid carcinoma, mammary cancer, or adrenocortical carcinoma have also been reported [21–23].

MEN1 syndrome is caused by a mutation in the MEN1 gene, located on chromosome 11q13. The gene is composed of 10 exons, encoding the protein menin, which acts at different levels to regulate cellular proliferation, even if its specific role is still debated (Table 1) [24]. Menin acts as scaffold protein, and is also involved in epigenetic regulation of gene expression via histone methylation, facilitating or silencing transcriptional activity of target genes. MEN1 is a tumor-suppressor gene, whose inactivation should be biallelic to conduct to tumorigenesis: thus, following the Knudson's "two-hit" model, a somatic mutation of the MEN1 wild-type allele should occur, and it has been found in 90% of tumors from MEN1 patients, most commonly through large deletion [25, 26]. MEN1-associated tumors harbor germline and somatic mutations, consistent with Knudson's two-hit hypothesis. Anyway, no correlation between genotype and fenotype has been clearly established [27, 28].

MEN1-associated NETs

Epidemiology, clinical, and pathological features

The age-related penetrance (i.e., the proportion of gene carriers manifesting symptoms or signs of the disease by a given age) has been ascertained, being greater than 50% by 20 years of age and greater than 95% by 40 years [13, 14].

In young patients, the frequency of non-functioning pNET (NF-pNET) has increased up to 42, thanks to screening program, while functioning NETs remain rare in this age group [21, 29, 30]. Young patients with MEN type 1 and an exon 2 mutation have a twofold greater risk for developing a pNET [31].

Also, in adults, NF-pNET are the most frequent NETs, followed by gastrinomas (up to 40%), insulinomas (11–15%), and rare functioning pNETs like glucagonoma, VIPoma, and GHRH-oma (Table 1). In small percentage, also bronchopulmonary NET (BP-NET), pheochromocytoma, and type 2 gastric NETs are detected [21]. Insulinomas, thymic NET, and gastrinomas have the worst prognosis and the highest mortality [5]. Clinical symptoms are related to tumor secretion, since GEP-NETs can be associated with symptoms due to ectopic secretion of hormones (functioning NETs) or either do not secrete any hormones or the products secreted do not cause a clinical syndrome (non-functioning, NF-GEP-NET) (Table 2) [32–35].

MEN1-associated tumors may be larger, more aggressive, and resistant to treatment than sporadic endocrine tumors. Available data suggest that metastatic rate of some pNET histotypes can be higher in MEN1 patients rather than in sporadic ones: for example, metastases are reported in up to 50% of patients with MEN1-associated insulinomas, but less than 10% of non-MEN1 insulinomas [36, 37]. Recent studies identified metastatic spread and related complications of pNETs as the major cause of MEN1-specific mortality [38, 39].

Therapies and outcomes

Surgical treatment is indicate for localized sporadic NF-pNET > 2 cm or for functional pNET, but MEN1 patients often have multiple, multifocal tumors that occur over time, making surgery not always a viable option [40].

MEN1-related NETs can express all 5 somatostatin receptors (SSTR), but SSTR2 and SSTR5 are the most frequently found subtypes [41]: this is the pathogenetic base of somatostatin analogue (SSA) antisecretory and antiproliferative effects and of the possible use of radionuclide therapy (PRRT). Octreotide and lanreotide, SSAs that specifically bind SSTR2, proved to be effective and safe in MEN-1 related NETs either at localized or advanced stages [42] In a study of 5 MEN1 patients with metastatic GEP-NENs and hypergastrinemia, a 3 month treatment with SSAs administrated at standard dose (100 microg subcutaneously, three times daily) reduced both gastrin secretion with symptomatic relief and the size of liver metastases [42]. Octreotide has reported to stabilize disease in MEN1 patients in approximately 80% of cases [43]. Lanreotide has been compared to active surveillance in a prospective observational study in which it was administrated at standard dose in 23/42 MEN1 patients with p-NETs < 2 cm: the rate of tumor progression was significantly lower in treated than in untreated patients; 17% of treated patients had an objective response, while 65% of them had stable disease [44]. These data suggest a comparable efficacy of SSAs for inherited and sporadic pNENs, but a higher rate of tumor shrinkage in MEN1, supporting their early use in these patients [42]. No similar data are available for pasireotide, an SSA that binds SSTR1, SSTR2, SSTR3, and SSTR5 with different

Table 2 The main endocrine syndromes associated with functioning gastroenteropancreatic neuroendocrine tumors: clinical features and therapeutic options

F-NET syndrome	Main symptoms/sign	Initial medical treatment	Secondary/other medical treatment
Gastrinoma (Zollinger–Ellison syndrome)	Pain (26–98%), GERD (0–56%), GI bleeding (8–75%)	PPI	SSA
Insulinoma	Hyoglicemia: confusion (51%), Sweating (43%), Tremulousness (23%)	Frequent small feedings, diazoxide	SSA, PRRT, Everolimus
Carcinoid syndrome	Diarrhea (58–100%), flushing (67%), carcinoid heart disease (27%)	SSA	PRRT, telotristat
VIPoma (pancreatic cholera)	Severe and profuse diarrhea (95%), hypokalemia (89%), dehydration (78%), flushing (22%)	SSA, fluid/electrolyte replacement	PRRT, glucocorticoids, loperamide, sunitinib, indomethacin
Glucagonoma	Diabetes (22–90%), diarrhea (17–73%), dermatitis (NME) (54–90%)	SSA, amino acid infusion	Parenteral infusion, PRRT
Ectopic Cushing's syndrome	Cushingoid habitus, diabetes, hypertension, hypokalemia, osteoporosis, recurrent infections	Steroidogenesis inhibitors	Mitotane, dopamine agonists, SSA, PRRT
SSoma	Diabetes, diarrhea, gallbladder disease, weight loss	SSA	PRRT
GRHoma/GHoma	Acromegaly	SSA	PRRT
Paraneoplastic hypercalcemia	Hyperparathyroidism	SSA + cinacalcet, rehydration	Bisphosphonates, PRRT

F-NET functioning neuroendocrine tumors, *GI* gastrointestinal, *GERD* gastroesophageal reflux disease, *PPI* proton-pump inhibitors, *SSA* somatostatin analogues, *PRRT* peptide-receptor radionuclide therapy, *VIPoma* vasoactive intestinal polypeptide secreting neuroendocrine tumor, *SSoma* somatostatinoma, *GRHoma* growth hormone-releasing factor secreting neuroendocrine tumor, *NME* necrolytic migratory erythema

affinity. NETs express also some tyrosine kinases (TKs) receptors that can be targeted, like vascular endothelial growth factor receptor (VEGFR), insulin-like growth factor 1 receptor (IGF1R), and platelet-derived growth factor receptor (PDGFR). The multikinase inhibitor sunitinib has been proved to improve progression-free survival (PFS) in sporadic NETs of about 6 months compared to placebo [14], but no data were obtained in MEN1 patients [45]. Another possible targeted therapy involves the mTOR inhibitor everolimus, that is approved for advanced pNETs, with an increase of PFS of about 11 months [46]. In a multicentric retrospective study involving patients with both sporadic and MEN1-related pNETs, disease control rate with everolimus was numerically higher in MEN1-related compared to sporadic ones (87.5% vs. 68.4%), in terms of both PFS (33.1 vs 12.3 months, $P=0.383$) and time to treatment failure (TTF, 16.1 vs 9.9 months, $P=0.888$), suggesting a possible role of this germline mutation in treatment response [45]. Anyway, generally tumors find out escape pathways to avoid everolimus effect, and a novel mTOR inhibitor, sapanisertib, has being studied for everolimus-resistant pNETs. In a recent work, pNET-xenografts were implanted in mice, than treated with sapanisertib or with everolimus; when mice became resistant to everolimus, they were cross-over to sapanisertib, which showed high shrinkage potential, even in MEN1 mutated tumors [47]. Interesting pre-clinical results have also been reported about the role of nitric oxide synthase inhibitor using its vasoactive effect [48].

Multiple endocrine neoplasia type 4 (MEN4)

Genetic and clinical features of the syndrome

Multiple endocrine neoplasia type 4 (MEN4) is the latest member of MEN syndromes and shares a similar phenotype spectrum to MEN1 with negative MEN1 gene mutations (Table 1). In MEN4, there is a mutation in the cyclin-dependent kinase inhibitor 1b gene (CDKN1B), located in chromosome 12p13 [49]. The CDK inhibitor p27 (also known as KIP1), a 196 amino-acid protein encoded by the CDKN1B gene, regulates the transition from cell cycle phase G0/G1 to S and is implicated in cellular processes like proliferation, motility, and apoptosis [50, 51]. Pellegata and coworkers first described mutations in CDKN1B gene causing a p27 deficiency and a new MEN-like phenotype in rats and humans, further on named MEN4 (or MENX) syndrome [52, 53] (Fig. 1).

MEN4-associated NETs

Epidemiology, clinical, and pathological features

The incidence of CDKN1B mutations in patients with MEN1-related neoplasia is difficult to estimate, but it is likely to be around 3% [49]. Due to very few cases of MEN4 being reported and many being undiagnosed, there are uncertainties regarding the exact incidence and prevalence of MEN4.

The most common and early presentation in MEN4 syndrome is primary HPT due to parathyroid adenomas/hyperplasia, followed by pituitary tumors (functional and nonfunctional) and GEP-NETs (Table 1) [54].

Primary HPT has been reported in up to 80%-90% of cases with MEN4 [19]. It occurs at a later age in MEN4 compared to MEN1 patients, with a female predominance [53]. The second most common presentation is pituitary adenoma (either nonfunctional or functional) [55] (Table 1). The prevalence of NETs in MEN4 is approximately 25%, that is much lower than MEN1. These include duodeno- or gastric-pNETs, that could be non-functioning or associated with various clinical syndromes, depending on the main substances secreted. The most common functioning NET is gastrinoma, causing the so-called Zollinger–Ellison syndrome due to excess release of gastrin and subsequent secretion of gastric acid (Tables 1 and 2). Up to date, there are no reported cases of insulinoma, VIPoma, glucaconoma, and ectopic-ACTH secreting NET.in MEN4 [55]. Adrenal tumors, testicular cancer, cervical carcinoma, papillary

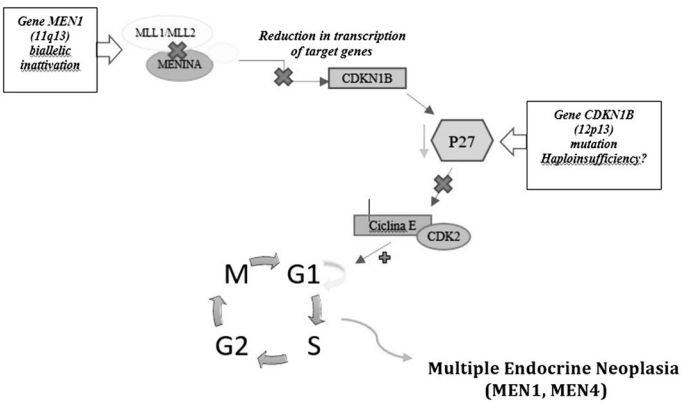

Fig. 1 Exemplification of the aberrant regulation/expression of signaling pathways downstream the mutated genes in MEN1 (MEN1 gene) and MEN4 (CDKN1B gene) syndromes

thyroid cancer, colon cancer, carcinoid, and meningioma are also reported [55, 56].

Therapies and outcomes

The management approach for either nonfunctional or functional neuroendocrine GEP-NETs is similar to MEN1 [49]. In gastrinomas, medical treatment includes proton-pump inhibitors and SSAs (Table 2), whereas surgical resection may be curative in small, localized and not metastatic tumors that may be fully excised [57]. Currently, there are no established druggable targets to reactivate or increase p27 expression in cancers, respective GEP-NETs. The E3 ubiquitin ligase S-phase kinase-associated protein 2 (Skp2) is an important mediator of ubiquitination of various proteins including p27, rendering them to subsequent proteasomal degradation. Small-molecule inhibitors of the E3 ubiquitin ligase Skp2 might be a promising future therapeutic approach in and then might also be worth to be investigated in GEP-NETs [58–60].

Von Hippel–Lindau (VHL) syndrome

Genetic and clinical features of the syndrome

Von Hippel-Lindau (VHL) disease is an autosomal dominantly hereditary tumor syndrome with an incidence of 1:36,000 newborns and estimated prevalence in Europe about 1–9/100,000. It is caused by germline mutations in the VHL tumor-suppressor gene located on the short arm of chromosome 3 (3p25.3) with lots of roles ranging from targeting hypoxia-inducible factor α (HIFα) for degradation and suppression of aneuploidy to microtubule stabilization (Table 1) [61–63]. The VHL protein (pVHL) acts as a subunit of a multiprotein ubiquitin ligase that negatively regulates expression of a large number of hypoxia-inducible genes controlled by HIFα. Downstream genes are involved in regulation of angiogenesis, cell proliferation, energy metabolism, and tumor progression, and include vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), transforming growth factor α (TGFα), epidermal growth factor (EGFR), and erythropoietin (EPO), to mention a few. pVHL acts as a tumor suppressor by binding to HIFα, preventing inappropriate expression of these hypoxia-inducible genes. Loss of pVHL results in high HIFα levels and subsequent overproduction of these growth factors, such as VEGF, PDGF, and TGFα, favoring tumorigenesis and neoangiogenesis (Table 1) [61–63].

The VHL syndrome is associated with an increased risk of developing various benign and malignant tumors [64, 65]. These include retinal capillary hemangioblastomas (RCH), central nervous system haemangioblastomas, phaeochromocytomas, renal cysts and clear cell renal cell carcinomas (ccRCC), endolymphatic sac tumors (ELST), cystadenomas of the epididymis and the broad ligament, as well as pancreatic cysts and pNET (Fig. 2). The disease penetrance is high, and more than 90% of patients harboring a VHL mutation develop clinical symptoms before the age of 65 years (100% by age 75 yrs) [64]. As a consequence, if a diagnosis of VHL disease is established, patients should undergo an

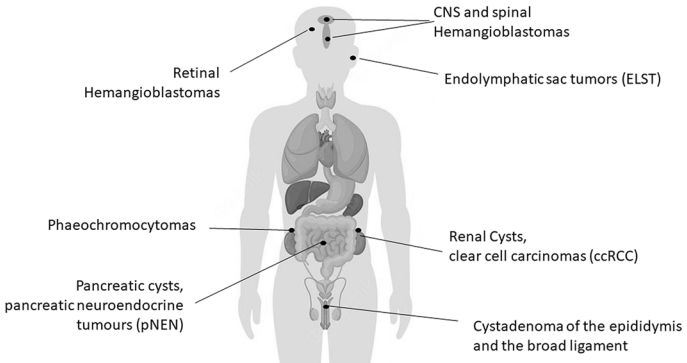

Fig. 2 Location of the most common benign and malignant tumors in patients with Von Hippel–Lindau (VHL) disease

Table 3 Routine surveillance protocol for VHL disease

Annual ophthalmic examination (direct and indirect ophthalmoscopy) beginning at age 1 to screen for retinal hemangioblastoma
Contrast-enhanced MRI of brain and full spine to screen for CNS hemangioblastomas beginning at age 12. Annual or biennial depending on clinical manifestations
MRI examination of the abdomen every 12 months to screen for renal cell carcinoma and pancreatic tumors beginning from the age of 12 years
Annual blood pressure monitoring and 24-h urine studies for catecholamine metabolites starting at age 4 to screen for pheochromocytoma. Alternatively, measuring plasma free metanephrines
Biennial audiogram starting at age 16 to screen for endolymphatic sac tumours

annual screening program [66] (Table 3). Tumor location and dynamics of development, disease severity, as well as age at first symptoms are considerably variable [66]. RCH and RCC are associated with a high morbidity and mortality due to potential blindness, life-threatening elevation of intracranial pressure, paraplegia, and metastases.

The overall life expectancy of VHL patients used to be limited with a median survival of around 50 years [64]. However, the introduction of clinical screening leads to significantly improved disease management with 10 year additional life expectancy [67].

VHL syndrome-associated NETs

Epidemiology and clinical features

pNETs were established as VHL component tumors in 1998 [68]. They are observed in 10–17% of VHL patients (Table 4, adapted from [69]) with a mean age at presentation of 35 years for solid lesions and a mean age of 37 years for cystic lesions [70, 71].

These tumors are usually asymptomatic, non-functional, multifocal and distributed throughout the pancreas [11] with a slow-growing pattern and favorable prognosis compared to sporadic tumors [72]. Although pNETs are an uncommon cause of mortality, they have malignant potential [73]. Interestingly, missense mutations in exon 3, especially of codons 161/167 are at enhanced risk for metastatic pNETs [74]. Additional risk factors for malignant VHL-associated pNETs include tumor size greater than 3 cm, short tumor diameter doubling time (less than 500 days), and other genetic factors [75–78].

Table 4 Lifetime risks of von Hippel–Lindau syndrome (VHL)-associated tumors

Tumor	Risk	Mean age at diagnosis (youngest age)
CNS hemangioblastoma	60–80%	30 (9) years
Cerebellar	44–72%	31 (9)
Brainstem	10–25%	32 (9)
Spinal	13–50%	33 (8)
Retinal angioma/hemangioblastoma	25–60%	25
Renal	25–75%	39 (12)
Cyst	42%	37 (12)
Clear cell carcinoma	17–70%	44 (44)
Pheochromocytoma	10–25%	27 (2)
Endolymphatic sac tumor	10–15%	22 (6)
Pancreatic	35–75%	36 (5)
Cyst	21%	33 (5)
Neuroendocrine tumor	10–17%	35 (16)
Papillary cystadenoma		
Epididymis	25–60%	24 (16)
Broad ligament	10%	NA (16)

*Adapted from Gläsker, H. P.H. Neumann, C. A. Koch, A. Vortmeyer, K. R et al. Von Hippel–Lindau disease Endotex 2018 [45]

Therapies and outcomes

Tumors with a diameter over 2.8 cm should be treated surgically to avoid metastasis in accordance to a recent multicenter study [74]. According to the new VHL disease guidelines for diagnosis and surveillance [79], medical treatment should follow the guidelines for non-functioning -pNETs: patients with disseminated disease, grade 1 and 2 NET and Ki67 index < 10% can be treated with SSA, and patients with disseminated disease, grade 2 NET (Ki6710–20%) or NEC (Ki67 > 20%) may be treated with conventional chemiotherapies (temozolomide + capecitabine, strptozotocin + 5FU or carboplatin + etoposide) or with molecular targeted therapies, including everolimus and sunitinib.

Data from small retrospective studies or case reports have suggested the promising efficacy of sunitinib for patients with VHL disease, including for VHL-related pNET [45, 80–83]. Noteworthy, a single drug could treat more than one neoplastic manifestation of VHL. However, larger prospective clinical trials are warranted to determine the efficacy in VHL-related pNET.

Less data are available about everolimus in VHL-related pNET. The only study available failed to provide conclusive data about its efficacy due to the low number of patients examined [45]. Finally, pVHL is a negative regulator of HIF1α that can act as a potential drug target for cancer therapy. Also, the downstream growth factor VEGF, that is typically overexpressed in VHL-related neoplasms, may be therapeutically relevant using the neutralizing anti-VEGF antibody, bevacizumab. Drugs that modulate the downstream targets of the pVHL/HIF pathway, including sunitinib, sorafenib, temsirolimus, and bevacizumab, have proven benefit in treating ccRCC and RCH [84, 85], but no data are available on their use/efficacy in VHL-associated NET.

Finally, PRRT has been proven to be an effective systemic treatment in the management of patients with advanced metastatic, or, inoperable slowly progressing NETs with high SSTR expression (86, 87).

Tuberous sclerosis complex (TSC)

Genetic and clinical features of the syndrome

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder characterized by hamartomas and mostly benign neoplasms involving multiple organs, such as brain, skin, kidneys, heart, lungs, and eyes [88]. The estimated

incidence is approximately 1 in 6000 to 1 in 10,000 live births, while the prevalence is 1 in 20,000 [89]. The underlying genetic alteration is a germline mutation in TSC1 (9q34) or in TCS2 (16p13.3) genes, which encode for hamartin and tuberin respectively, TSC2 mutations being 2.5–5 times more common than TSC1 mutations [90]. Loss of function of TSC1 or TSC2 leads to aberrant mTOR pathways, which promote tumorigenesis by interfering with cell growth, differentiation and survival [90, 91]. Due to the significant inter and intra-familial variability, TSC exhibits a wide spectrum of clinical features including also potentially malignant tumors such as NETs [88].

TSC-associated NETs

Epidemiology, clinical, and pathological features

The majority of NETs in the setting of TSC are represented by pNET with an overall prevalence ranging from 1 to 9% [88, 92–95]. The association between TSC and other NETs in the gastrointestinal tract remains still largely unknown [96]. It is difficult to assess the natural course and the risk of aggressive behavior of pNETs in this cohort of patients. Accumulating evidence suggest that TSC-associated pNETs usually appear well-differentiated, benign and indolent [96, 97]. However, rare cases of pNETs with local or distant metastasis and one case of recurrence after surgery were reported [86, 88, 98, 99]. Moreover, a more frequent association of pNETs with TSC2 germline mutations is observed, but no clear genotype–phenotype correlations have been identified. The majority of TSC-related pNETs are non-functional, and so far, no cases of functional transformation were found in literature [88]. Functional pNETs are predominantly insulinomas, but rare cases of gastrinomas or glucagonomas were also documented [96, 97]. Compared to the general population, pNETs in TSC individuals present an earlier age at onset [88, 93] and a major trend to arise as cystic lesions [95, 100]. TSC-related pNETs tend to be predominantly solitary and not multifocal [95]. However, two cases of multiple pNETs in SCT patients were detected [88, 92].

Therapies and outcomes

At present, there are no guidelines for management of NETs in TSC and current clinical practice may follow standardized recommendations for sporadic NETs. Surgical resection represents the first-line treatment for localized GEP-NETs and as most of the NETs occurring in TSC patients appear to be well-differentiated, surgery alone may be curative with a favorable prognosis [97]. A more accurate knowledge of TSC and NETs' pathogenesis have encouraged the exploration of targeted agents such as the mTOR inhibitors (mTORi) for TSC-associated NETs. The theoretical rationale in favor for the use of these novel drugs is provided by the demonstrated driver role of aberrant TSC1/TSC2/mTOR pathways in sporadic NETs tumorigenesis [91, 95, 97, 101] and by the documented efficacy of mTORi therapy both in sporadic and TSC-associate NETs [101–104]. Schrader et al. investigated the role of everolimus as a first-line adjuvant therapy for a metastatic pNETs associated to TSC and documented a partial remission of liver metastasis after 3 months of mTORi therapy and a 46% reduction of liver tumor burden after 6 months [105]. In a case series of TSC-related nonfunctional pNETs by Mowrey et al., tumor growth rate appeared slightly reduced in the 8 patients who received mTORi treatment (oral everolimus or sirolimus) in comparison with their non-mTORi counterparts, despite the difference was not statistically significant [88]. In the retrospective study of Koc et al., two individuals with TSC-associated pNET were treated with everolimus as a first-line therapy and their tumor decreased in size or remained stable. A favorable response with NET size reduction was also observed in a third patient who was submitted both to surgical resection of the tumor and to everolimus treatment initiated for other benign tumors related to TSC [94]. Ishida et al. documented a singular case of a neuroendocrine carcinoma (NEC) of the esophagogastric junction occurred in a TSC patient, already on sirolimus, an mTOR inhibitor, due to lymphangioleiomyomatosis (LAM). Despite multiple chemotherapy regimens, in combination also with targeted drugs such as Nivolumab (anti-PD-1) and Ramucirumab (anti-VEGFR-2), the patient deceased 23 months after diagnosis due to disease progression. Considering the occurring of NEC despite the inhibition of the AKT/mTOR oncogenic cascade, this case may be suggestive of the significant heterogeneous pathogenesis of NETs and NECs also in the setting of TSC [106]. Table 5 summarizes the above-mentioned publications, which provide preliminary evidence in favor for the use of mTORi in TSC-associated pNETs. However, further rigorous research is required to assess the efficacy of mTORi for NETs in this cohort of patients and to investigate whether the use of these drugs should be a potential pharmacological strategy as an alternative to surgery [88].

Neurofibromatosis 1 (NF-1) or von Recklinghausen's disease

Genetic and clinical features of the syndrome

NF-1 syndrome is an autosomal dominant tumor predisposition syndrome occurring in 1:3000–4000 live births [107]. It is caused by germline mutations in the NF-1 gene, a tumor-suppressor gene located on chromosome 17q, which encodes for the neurofibromin protein, that is especially expressed in the nervous system (Table 1) [108]. Neurofibromin acts as

Table 5 Summary of the studies providing preliminary evidence in favor for the use of mTOR inhibitors in TSC-associated NENs

Publication	Age at NEN diagnosis (yo)	Sex	TSC1/TSC2	Location	Dimension (mm)	Target therapy	Surgery	Outcome
Mowrey et al. 2021 [88]								
#1	8	M	TSC1	Pancreas-head	10	mTORi (everolimus or sirolimus)	No	Slightly reduced tumor growth rate vs non-mTORi counterparts
#2	13	M	NA	Pancreas-tail	14	mTORi (everolimus or sirolimus)	No	
#3	16	F	TSC2	Pancreas-body	7	mTORi (everolimus or sirolimus)	No	
#4	21	F	TSC2	Pancreas-body	17	mTORi (everolimus or sirolimus)	No	
#5	6	M	NA	Pancreas-tail	20	mTORi (everolimus or sirolimus)	Yes	
#6	10	F	NA	Pancreas-body	10	mTORi (everolimus or sirolimus)	Yes	
#7	9	F	TSC2	Pancreas-head	16	mTORi (everolimus or sirolimus)	No	
#8	32	M	NA	Pancreas-head	38	mTORi (everolimus or sirolimus)	NA	
Schrader et al. 2017 [105]	41	NA	TSC2	Pancreas-tail	NA	Everolimus	Yes	46% reduction of liver tumor burden after 6 months of everolimus
Koc et al. 2017 [94]								
#1	19	F	NA	Pancreas-body	27	Everolimus	No	Stable tumor size
#2	13	M	NA	Pancreas-tail	40	Everolimus	No	Decreased tumor size
#3	5	M	NA	Pancreas-tail	26	Everolimus	Yes	Decreased tumor size on everolimus, then surgical resection
Ishida et al. 2020 [106]	46	F	NA	Esophagogastric junction	NA	Everolimus, then nivolumab and ramucirumab in combination to multiple cytotoxic chemotherapy regimens	No	Patient's decease at 23 months after diagnosis due to disease progression

TSC tuberous sclerosis complex, *mTORi* mTOR inhibitors, *NA* not available, *yo* years old

a tumor suppressor, affecting cell proliferation/growth and metabolism by regulating the activation of p21 Ras, modulating adenylate cyclase activity, binding microtubules, and interacting with the cellular cytoskeleton. Sinergistically with tuberin, the TSC2 gene product, neurofibromin regulates mTOR pathways [109].

NF-1 affects multiple organs and tissues, with highly variable expressivity, but it is predominantly characterized by nervous system involvement and cutaneous findings, including *cafe au lait* spots (> 99%), neurofibromas (cutaneous > 99%, deep-seated-44%), skinfold freckling or Crowe's sign (85%), and iris Lisch hamartomas (> 95%) [110, 111]. Multiple neoplasms may arise in different organs and tissue, mainly the connective tissue and the central nervous system, and represent an increased cause of death. Indeed, NF-1 patients have a 10–15 year decrease in life-span (median ageof death—59 years), the most common cause of death being malignancy [112]. Pheochromocytomas (2%) and an increase risk of hypertension are clinically relevant in some patients [110].

NF-1-associated NETs

Epidemiology, clinical, and pathological features

GEP-NET tumors are reported in up to 10% of patients with NF-1 syndrome, most frequently somatostatinomas arising from the duodenum (Table 1) [113–117]. These duodenal somatostinomas are almost always hormonally silent and do not cause a functional syndrome, but they typically

occur in the periampullary region, often leading to obstructive symptoms and signs (biliary dilatation, pain, nausea, bleeding or vomiting, pancreatitis). Metastases to liver and/or lymph nodes occur in up to 30% of cases. Rarely, NF-1 patients have been diagnosed with pancreatic somatostatinoma, gastrinoma, insulinoma, or NF-pNETs, while it has been increasing the number of patients with gastrointestinal (GI) stromal tumors, that are becoming the most common NF-1-associated GI tumor [110].

Therapies and outcomes

NETs are not a significant cause of mortality, but do increase morbidity (risk for obstruction because of their prevalent periampullary location) in patients with NF-1. Taking into account the risk of obstruction, the possible malignancy (up to 30%) and the frequent preoperative understaging of the tumor, surgery is recommended, particularly for pNETs > 2 cm [110, 118]. The role of pharmacological therapy warrants further research.

Other rare syndromes

Glucagon cell hyperplasia neoplasia (GCHN)

Glucagon cell hyperplasia and neoplasia (GCHN) has been recently recognized as a distinct pathological entity according to 2017 World Health Organization Classification (WHO) of Tumors of Endocrine Organs [119]. GCHN is genetically and clinically heterogeneous and is classified into three variants: functional, non-functional, and reactive GCHN. Functional GCHN is characterized by hyperglucagonemia associated to glucagonoma syndrome, while non-functional GCHN by normal levels of glucagonemia. The pathogenesis of these two types remains still unclear [120]. The familial endocrine tumor syndrome is represented by the reactive variant, also known as Mahvash disease, an autosomal recessive disorder caused by inactivating mutations of the glucagone receptor gene (GCGR) (Table 1) [120]. To date, 9 GCGR pathogenic alterations have been identified, all determining decreased or absent GCGR activity [121]. Mahvash disease is characterized by hyperglucagonemia without glucagonoma syndrome in association to coexisting histological features of diffuse alfa cell hyperplasia, dysplasia, micro-pancreatic neuroendocrine tumors (pNET), and gross pNET [120]. This disorder is rare and probably under-recognized with an estimated prevalence of 4 per million [120]. It presents full penetrance and affects both sexes with an average age at diagnosis ranging from 25 to 74 years [120]. Given the rarity of GCHN, its natural history has not been well defined yet [121]. Accumulating data suggest that pNETs in Mahvash disease appear to be slow-growing tumors, predominantly glucagonomas and clinically non-functioning [120]. The gross pNETs may arise anywhere in the pancreas with size varying from 1 to 8 cm [120]. In most cases, no recurrence of pNETs after surgery has been identified during a follow-up period of 2–13 years [120, 122–125]. So far, only one case of distant metastasis to the liver was reported by Tang et al. [121, 123]. Due to the limited clinical evidence on Mahvash disease, current management may be extrapolated by the guidelines used for the treatment of other inherited pNET syndromes such as MEN1 [120]. Specifically, nonfunctional pNETs less than 2 cm may be monitored by active surveillance, whereas functional or pNETs larger than 2 cm may be submitted to surgical resection. The role of pharmacological therapy warrants further research. The benefits of SSAs are difficult to assess, since they may improve hyperglucagonemia, but are associated with a major risk of hypoglycemia [121]. Moreover, also one case of recurrent liver failure was reported by Robbins et al. after octreotide administration in a patient with Mahvash disease [126]. Due to the limited data and the rarity of the disorder, the efficacy of other target therapies remains unclear. Since mTOR activation might present a possible role in the pathogenesis of alpha cells' proliferation induced by high levels of amino acids in reactive GCHN, a potential use of mTOR inhibitors therapy may be investigated in this cohort of patients [119]. Novel drugs such as pharmacological chaperones are under current exploration, since the chaperones deputed to transport mutant GCGR to the plasma membrane may reduce glucagon levels and improve GCHN [120, 121, 127].

Familial small-intestinal NETs

Familial small-intestine neuroendocrine tumors (SI-NETs) represent a relatively new inherited disorder, defined as at least two cases in first-degree relatives not associated with other genetic syndromes [128]. Hereditary SI-NETs are rare with an estimated prevalence among all SI-NETs of 2.6–3.7% [129]. Epidemiological evidence in European and US families suggest an autosomal dominant inheritance with incomplete penetrance (Table 1) [128]. However, underlying molecular pathogenesis still remains unclear. Inositol polyphosphate multikinase (IPMK) gene alterations are considered potential driver mutations for tumorigenesis by causing aberrant p53 apoptotic pathways and increased survival of neoplastic cells [130]. Additional predisposing abnormalities not associated with IPMK-sequence may be involved and may not differ from those of sporadic SI-NETs (Table 1) [129]. Familial SI-NETs are commonly well-differentiated, slow-growing and present similar clinic-pathological features to the sporadic variants [129]. The disease course initially is paucisymptomatic with the onset of abdominal pain, intestinal obstruction, or carcinoid syndrome usually at advanced stages. Compared

to the sporadic counterparts, familial SI-NETs often present an earlier age at diagnosis and occur more frequently as multiple synchronous primary tumors with most lesions located in the ileum and secondly in the jejunum [128, 131]. Familial SI-NETs seem to be more often associated with distant metastasis and carcinoid syndrome than the sporadic ones [129]. Nevertheless, no evidence of a worse prognosis of the hereditary variant has been demonstrated [132]. To date, there are no standardized screening programs for asymptomatic at-risk family members. However, for earlier diagnosis, active surveillance should be provided for asymptomatic relatives extended for at least a 2–3-year period of time due to the indolent nature of SI-NETs. If familial SI-NET occurs, a multidisciplinary approach is essential to evaluate personalized treatment strategies. Given the rarity of the disorder and lacking guidelines for therapeutic management of hereditary SI-NETs, current clinical practice may follow the actual recommendations regarding sporadic SI-NETs. In the setting of a locoregional disease, surgical resection of the primary tumor with extensive lymph-node dissection represents the only curative approach [132, 133]. When metastatic disease occurs, primary tumor(s) resection should be considered, since it appears associated with better survival outcomes [128, 133, 134]. In case of unreseactable metastatic SI-NET, several target therapies may be evaluated [128, 135–137]. SSAs represent so far the first-line systemic therapy, which leads to a major control of carcinoid syndrome and to tumor growth inhibition [34, 128, 134]. The antiproliferative effects of SSAs were confirmed in GEP-NETs by trials such as PROMID and CLARINET [11, 12, 138]. The mTOR inhibitor everolimus may be a potential second-line treatment, which appears associated to a major progression-free survival as documented by RADIANT-4 trial [103]. Another important second-line therapy is represented by PRRT. The landmark trial NETTER-1 demonstrated a significantly longer progression-free survival and a higher response rate of 177Lu-Dotatate compared with high-dose octreotide LAR in patients with advanced midgut NET [137]. Other novel agents investigated in metastatic SI-NETs such as tyrosine kinase inhibitors: sunitinib, sorafenib, and pazopanib revealed in phase 2 trials' disease stabilization and improvement of progression-free survival [134, 139–142]. Another potential therapeutical option, although less preferred than the former strategies, is interferon alpha, which is associated with a reduced risk of tumor progression documented in some studies [134] when administered alone or combined with other targeted drugs. Also bevacizumab, a VEGF inhibitor, was explored confronted with interferon alpha both drugs in combination to octreotide. A higher radiological response rate was reported in the bevacizumab group; however, the difference was not statistically significant [103, 134].

Familial insulinomatosis

First described in 2009 by Anlauf et al. [143], adult-onset familial insulinomatosisis is a rare disorder characterized by recurrent, severe hypoglycemia caused by multiple insulin-secreting pancreatic tumors. It occurs more frequently in females, and the mean age at the diagnosis is 39.5 years [144–146]. Up to date, a few cases have been reported in the literature, so that the prevalence/incidence of the disorder in the general population cannot be estimated. In large studies, insulinomatosis is responsible for less than 5% of all patients with hyperinsulinemic hypoglycemia [143, 147].

The cause of the disorder is represented by loss-of-function mutations in the β V-Maf avian musculoaponeurotic fibrosarcoma oncogene homolog A (MAFA) gene, encoding for a transcription factor, the MAFA protein, that is a key coordinator of β-cell insulin secretion [145, 146, 148] (Table 1).

Typically, along to few macrotumors (usually 0.5–1 cm), multiple microtumors are found throughout the entire pancreas, all secreting insulin. Although these multifocal insulinomas are usually benign, rare occurrence of metastases has been reported. Due to the small size and the multicentric occurrence of the tumors, surgical intervention is often not curative as hypoglycaemia might recur from unresectable microscopic functional lesions, or potential occult metastases (Snaith et al., 2020). No data are available on the use/efficacy of targeted therapies in this disorder.

Syndromes predisposing to thoracic neuroendocrine tumors

Thoracic neuroendocrine tumors can occur in MEN1: both bronchopulmonary (B-NET) and thymus (T-NET) NET are reported [149, 150], generally in adulthood with a penetrance of 2% under 40 years [151].

Bronchopulmonary neuroendocrine tumors

The WHO classification of B-NETs is reported in Table 6. B-NETs are diagnosed in 4.7–6.6% of MEN1 patients [152–154] between 20 and 69 years with no sex prevalence or correlation with smoking and MEN1 genotype [153–155]. Most of the B-NET are well-differentiated bronchial carcinoma (BC). Specifically, BC are present in the 5% of MEN1 patients in both sex [150], usually typical carcinoid [156]. BC could be silent or associated with carcinoid syndrome (most common clinical syndrome), ectopic Cushing syndrome, or paraneoplastic syndrome of inappropriate antidiuretic hormone secretion (pSIADH) (Table 2) [157, 158]. B-NET local

Table 6 WHO classification of Bronchial neuroendocrine tumors (NETs)

Classification	Mitotic rate and necrosis
Well-differentiated	
Typical carcinoid, NET G1	Mitotic rate < 2 and absence of necrosis
Atypical carcinoid, NET G2	Mitotic rate 2–10 and/or presence of necrosis
Poorly differentiated	
Neuro-endocrine carcinomas Small-cell type Large-cell type	Mitotic rate > 10

symptoms include dyspnea, cough, and hemoptysis, but are often absent [152–154].

The main treatment for BC is surgery, if localized [138, 159, 160]. If surgery is not feasible (occult or not resectable primary tumor) and in advanced BC, first-line therapy is represented by SSA, to control both hormonal secretion and tumor growth [161]. PRRT has been proposed in advanced and/or metastatic BC in progression with SSAs therapy, and in particular [176], Lu-DOTATATE monotherapy seems the best [162, 163]. Other targeted therapies are poorly studied in this type of tumor, everolimus being the only approved according to a phase III clinical trial [164]. Novel targeted therapies with antiangiogenic agents and immunotherapies have been also under evaluation [103, 139, 142].

Thymus neuroendocrine tumors

T-NET are rare and silent tumors, present in only the 2–8% of MEN1 patients [152, 165–167], generally male (male to female ratio 4:1), but with a high mortality [168] and with 10-year survival of 33.3% [149]. Indeed, T-NET are causative of 19% of deaths related to MEN1 [169]. The mortality is associated with the following predictor factors: presence of metastasis, age (> 43 years), and diameter of tumor > 5 cm [149]. In addition, men and smoker are more affected, principally in Asia than Europa and USA where the adjuvant therapy following the surgery [149].

Thus, T-NET represent a crucial feature of the MEN1 syndrome [149], to the extent that a computed tomography or a magnetic resonance imaging of the chest is recommended every 1 to 2 years [17]. The treatment is based on surgery as soon as possible to reduce the incidence of metastasis [123, 125, 126], while radiotherapy and/or chemotherapy are indicated in advanced/metastatic tumors [135]. A phase 2 study is evaluating whether the TKI lenvatinib plus pembrolizumab benefits patients with type B3 thymoma or thymic carcinoma [170].

From the molecular alteration to the targeted therapy: the role of the pathologist

The development of novel drugs targeting specific genes/proteins and molecular pathways involved in tumor cell growth, survival, and spread must be coupled with identification of theranostic biomarkers that predict response tothose drugs and provide a rationale for their use in clinical practice (for instance, SSTRs, druggable pathways such as PI3K/AKT/mTOR and the angiogenetic VEGF/VEGFR pathway). As a consequence, in recent years, the competence of the pathologist was enriched with the introduction of predictive markers aimed at evaluating the immunohistochemical expression of drug targetable proteins.

A best-known feature of neuroendocrine neoplasms, mainly well-differentiated forms, is the overexpression of SSTRs, mainly subtype 2, that is homogeneously distributed at the surface of neoplastic cells. Due to the suppression of hormone release, antiproliferative, and antiangiogenic effects, the SSAs were introduced into the therapeutic protocol for neuroendocrine neoplasms. Although their action can be exerted also by indirect mechanisms, the effective efficacy of the therapy depends on the tumor expression of the specific receptor [171, 172]. Furthermore, besides having a predictive role, SSTR2 was shown to be a valuable prognostic marker: high immunohistochemical expression of this receptor was associated with longer overall survival (OS), and it proved to be a stronger prognostic indicator than the Ki-67 score [173, 174]. A specific immunohistochemical score based on membrane cellular staining was shown to correlate well with SSTR scintigraphy [175]. In the last years, the pathologist has also been making use of digital image analysis that could provide a good alternative for predicting response to SSAs in evaluating SSTR2 immunoreactivity of GI-NETs [171]. In a recent study by Mennetrey et al. focusing on a group of 108 MEN1-affected patients, it was demonstrated that SSTR-based imaging is superior and

complementary to conventional imaging in the vast majority of cases in the assessment of lymph-node or distant metastases, independently from the disease stage [176].

Most of the knowledge on the biology of NETs concerns the pancreatic forms. It was demonstrated that several molecular pathways are involved. In most pNET, TSC2 and PTEN genes, which are key inhibitors of the mTOR pathway, are underexpressed. Everolimus is the only inhibitory drug approved for the treatment of this pathology, but currently patient selection is not based on the expression of a predictive marker [15].

In non-functioning pNETs, DAXX and ATRX gene changes are associated with abnormal alternative telomere lengthening (ALT) status and poor prognosis [177]; hence, the assessment of their immunohistochemical expression (178) could be a valuable and practical tool as an alternative to more complex techniques (e.g., FISH analysis).

The resistance to alkylating agents in MGMT (O6-methylguanine DNA methyltransferase)-proficient cells is well known in neuroendocrine tumors; less clear is the best way to assess MGMT methylation status. It was tested by immunohistochemistry [179], by PCR or next-generation sequencing [180], but no one of them is supported for routine use.

Finally, NETs are highly vascularized and have an increased expression of proangiogenic factors and their receptors, which can represent both valuable prognostic markers of tumor growth and aggressiveness and a valid target for drugs directed against VEGF/VEGFR pathway [181, 182].

Conclusions and perspectives

Gastroenteropancreatic and thoracic NETs can occur in the context of a large number of hereditary predisposition syndromes. Some of these are well known and routinely screened in clinical practice, while others have been recently described and not fully known to date, and others are probably to be discovered yet. The general hallmarks of a hereditary predisposition syndrome include: multiple primary tumors (in the same or different organs), rarity of the disorders, young age of diagnosis (usually under the age of 40), and characteristic pattern of cancer within families. These syndromes are monogenic, highly penetrant with all carriers exhibiting at least part of the phenotype, and display variable expressivity with affected individuals showing different presentations of the disorder.

Recognizing NETs in the setting of inherited syndromes has significant implications for patient's outcomes and provides opportunity for early detection and appropriately timed treatment. Indeed, these syndromes are typically associated to early onset of tumors in childhood/adolescence, lifelong risk for further tumors development and multi-organ involvement. Additionally, the natural history of NETs in the setting of a hereditary condition may be different than would be expected in a sporadic form of the disease. For example, in some circumstances, the risk of metastatic disease is lower, and the disease displays an indolent course, while in others, the tumor is more aggressive and metastatic spread more frequent than commonly seen. Genetic counseling and testing is mandatory for a correct diagnosis in all patients with a suspicion for a hereditary endocrine neoplasia syndrome, and should be offered to close family members for risk stratification and appropriate management. Comprehensive molecular testing of all targetable alterations is critical to ensure that patients receive the most appropriate care. Experienced pathologists can also contribute to the diagnosis and management of these patients, all reason to support referral to high-volume centers.

Whereas genetic diagnosis to identify individuals with germline mutations has facilitated appropriate targeting of clinical approach to this high-risk group of patients, increased knowledge and understanding of genetic and epigenetic mechanisms and targetable alterations of related tumors may provide a rational and molecular basis for implementation of treatments and development of novel targeted therapies.

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Informed consent Written informed consent was obtained from the patients for publication of this case series.

Research involving human participants and/or animals No animals were used for this study.

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