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Paraneoplastic Endocrine Syndromes Associated with Neuroendocrine Neoplasms in Adults: A Case Report and a Contemporary Review

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ABSTRACT

Neuroendocrine neoplasms are distinguished by their remarkable biosynthetic capacity to synthesize and secrete a diverse array of biologically active peptides, amines, and hormones. While a significant proportion of neuroendocrine neoplasms remain clinically non-functional, a subset exhibits systemic endocrine phenomena that significantly impact morbidity and mortality. These manifestations range from classic functional syndromes intrinsic to neuroendocrine differentiation to rare, complex paraneoplastic endocrine syndromes driven by ectopic hormone secretion or immune-mediated mechanisms.

We describe a complex case of a 33-year-old female with a pancreatic neuroendocrine tumor that demonstrated extreme secretory plasticity through the sequential emergence of three distinct ectopic hormones. The clinical course began with Zollinger-Ellison syndrome, which progressed into refractory ectopic Cushing syndrome. The disease further evolved into hypercalcemia of malignancy driven by the simultaneous dual secretion of parathyroid hormone-related protein and 1,25-dihydroxyvitamin D. Despite the implementation of aggressive multimodal therapies, including somatostatin analogs, peptide receptor radionuclide therapy, and targeted systemic agents, the tumor exhibited profound biochemical evolution and clinical aggression.

Distinguishing this work from previous literature, this article provides a definitive mechanistic taxonomy that categorizes over 22 paraneoplastic endocrine syndrome phenotypes based on their underlying molecular drivers, such as epigenetic de-repression and alternative RNA splicing. While prior reviews have traditionally offered static clinical catalogs, this synthesis introduces the framework of secretory escape to explain the functional switching and tumor heterogeneity observed in high-grade neuroendocrine neoplasms. Emerging biomarkers and advances in functional imaging, such as gallium-68 DOTATATE positron emission tomography/computed tomography, have improved the recognition of these syndromes; however, managing multifaceted ectopic secretion remains a formidable challenge. This review underscores that a high index of clinical suspicion and a coordinated multidisciplinary approach are essential for navigating the prognostic implications and optimizing therapeutic outcomes in the era of modern precision oncology

Introduction

Neuroendocrine neoplasms (NENs) are a heterogeneous family of epithelial tumors arising from diffuse neuroendocrine cells distributed throughout the body. These cells share the capacity for amine precursor uptake and decarboxylation and possess neurosecretory granules capable of hormone storage and regulated exocytosis.[1] The majority of NENs arise within the gastroenteropancreatic or bronchopulmonary systems, although primary tumors have been described in virtually every organ.[2]

Based upon the 2022 World Health Organization (WHO) classification, NENs are divided into three main categories: Well-differentiated NENs (neuroendocrine tumors [NETs]), poorly differentiated NENs (neuroendocrine carcinomas [NECs]), and mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs). Well-differentiated NETs are graded by proliferative activity into grades 1, 2, and 3 based on the Ki-67 proliferation index and mitotic count (per $2mm^2$). Grade 1 lesions have a Ki-67 index of <3% and <2 mitoses/$2mm^2$; grade 2 lesions have a Ki-67 index of 3%–20% and 2–20 mitoses/$2mm^2$; and grade 3 lesions have a Ki-67 index of >20% and >20 mitoses/$2mm^2$. If the Ki-67 index and mitotic activity are discrepant, the higher of the two grades is reported. Poorly differentiated NENs usually exhibit very high proliferative activity, with Ki-67 indices >20% and >20 mitoses/$2mm^2$ and are subclassified as either small-cell or large-cell types. This distinction carries major prognostic and therapeutic implications and has influenced the interpretation of hormone-mediated clinical syndromes.[3]

One of the defining characteristics of NENs is their ability to produce bioactive substances, such as hormones, peptides, and cytokines, which can modulate the tumor microenvironment via autocrine and paracrine signaling or induce systemic phenomena through endocrine pathways. In some cases, hormone secretion corresponds to the normal physiological repertoire of the cell of origin. In other instances, tumors express substances that are not typically associated with the tissue lineage (ectopic), thereby producing paraneoplastic endocrine syndromes (PNES). The term paraneoplastic refers to systemic manifestations caused by tumor-derived factors rather than by direct tumor invasion, compression, or metastasis. PNES may precede tumor detection, dominate the clinical presentation, complicate oncologic treatment, and influence prognosis.[4]

The incidence of NENs is 6–8 cases per 100,000 individuals annually in many Western countries.[5] Improved diagnostic sensitivity, aging populations, and increased incidental detection during imaging have contributed to this rise. While many NENs remain nonfunctioning throughout their course, endocrine manifestations occur in approximately 10–40% of patients, depending on tumor site, grade, and metastatic status. PNES are most common in well-differentiated NENs of the midgut and pancreas, although bronchial NETs and high-grade NECs may also produce clinically significant endocrine phenomena.[6]

We describe a patient with an ultrarare multihormonal pancreatic NEN characterized by the sequential secretion of gastrin, adrenocorticotropic hormone (ACTH), parathyroid hormone-related protein (PTHrP), and 1,25-hydroxyvitamin D. The concurrent presentation of Zollinger-Ellison syndrome, ectopic Cushing syndrome, and hypercalcemia of malignancy in a single patient is seldom documented and represents a significant hormonal escape. Although the tumor had a lower-grade histology, its behavior was that of a highly aggressive tumor with multihormonal secretory phenotypes. Ultimately, this case emphasizes the necessity for vigilant, longitudinal hormonal monitoring in metastatic pancreatic NENs, as shifting biochemical profiles can precipitate metabolic crises that necessitate urgent intervention.

The primary strength of this review lies in its presentation of a definitive mechanistic taxonomy (Table 1), which offers a significant advancement over previous literature. While earlier reviews have traditionally focused on static, lineage-consistent hormone production or provided descriptive catalogs of individual syndromes, this article introduces a novel framework for understanding the temporal and secretory evolution of NENs. We move beyond established surveys to address the phenomenon of secretory escape, a critical clinical sentinel where a functional hormonal switch signals underlying clonal evolution and genomic instability before anatomical progression occurs. By categorizing more than 22 distinct syndromes based on specific molecular drivers, such as epigenetic de-repression and alternative RNA splicing, this work provides the deep-dive necessary to bridge the gap between classic clinical descriptions and the modern biological understanding of paraneoplastic phenomena. Consequently, this review serves as a superior contemporary reference for clinicians navigating the increasingly complex, plastic neuroendocrine phenotypes in the era of modern precision oncology.

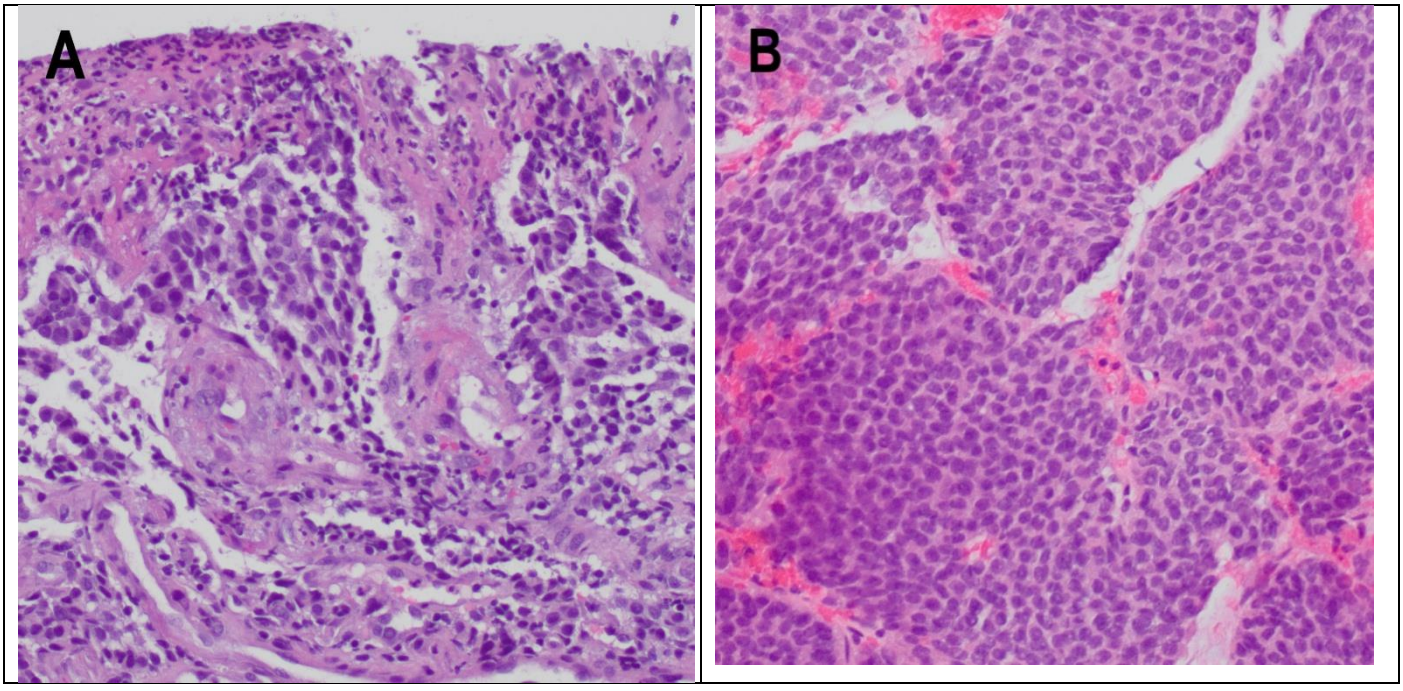
Table 1: Mechanistic taxonomy of paraneoplastic endocrine syndrome

Secretory Category	Syndrome / Hormone	Molecular Mechanism	Clinical Significance
I. Lineage-Consistent (Eutopic)	Carcinoid Syndrome (serotonin, histamine, tachykinins, kallikrein, prostaglandins) Gastrinoma Insulinoma Glucagonoma Somatostatinoma PPoma	**High Lineage-Fidelity:** Preservation of tissue-specific proprotein convertases and mature secretory granules	Baseline functional state: the tumor maintains the identity of its progenitor cell

Secretory Category	Syndrome / Hormone	Molecular Mechanism	Clinical Significance
II. Lineage-Inconsistent (Ectopic/Plasticity)	Ectopic Cushing (ACTH / CRH) Hypercalcemia (PTHrP / 1,25-dihydroxyvitamin D NICTH (Big-IGF-2) Acromegaly (GHRH) SIAD (Vasopressin / Oxytocin)	**Epigenetic De-repression:** DNA hypomethylation and loss of gene silencing allows for forbidden hormone synthesis	Signals clonal evolution and high-grade biological aggression
III. Vasoactive & Gut-Peptide Switches	VIPoma Neurotensinoma Motilinoma CCKoma Incretinomas (GLP-1 / GLP-2) Ghrelinoma	**Secretory Plasticity:** Shift in peptide processing or co-secretion due to tumor heterogeneity	Often presents as biochemical mimics (e.g., CCKoma mimicking ZES) or preservation of appetite/BMI
IV. Rare Axis & Systemic Drivers	Spontaneous OHSS (FSH/LH) Hyperprolactinemia Osteomalacia (FGF23) Erythrocytosis (EPO) Hypertension (renin) Hypercalcitoninemia	**Ectopic Axis Activation:** Direct synthesis of complex glycoproteins and renal-targeting hormones by the NEN	Requires specialized biochemical testing to rule out primary organ-specific disease
V. Immune & Cytokine Mediated	Inflammatory Syndrome (IL-6, TNF-α, IL-1) Procalcitonin / CGRP / GRP Secretion	**Cytokine Signaling:** Direct release of pro-inflammatory mediators by the neoplastic clone	Causes Systemic Inflammatory Response; often a marker of advanced disease

Case Presentation

A 33-year-old woman with chronic diarrhea presented with postprandial epigastric pain, melena, and anemia. An initial esophagogastroduodenoscopy (EGD) revealed a 2-cm duodenal ulcer with an adherent clot, treated with epinephrine, cautery, and pantoprazole. A follow-up EGD showed a 1.5-cm residual ulcer, with biopsies confirming a low-grade neuroendocrine tumor (NET) positive for synaptophysin and chromogranin A (CgA) (Figure 1A). Subsequent biochemical testing confirmed a gastrinoma phenotype, with a serum gastrin level of 2,705 pmol/L and a CgA of 181 nmol/L.



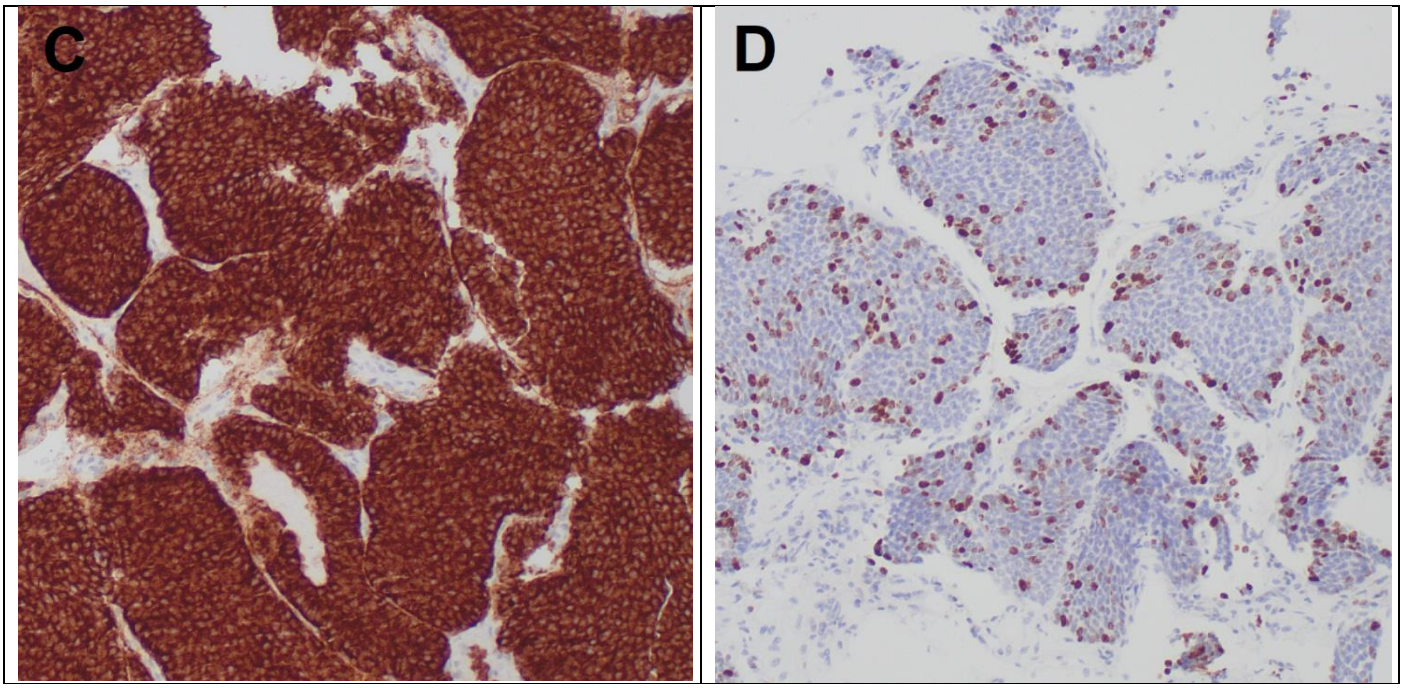


Figure 1. Photomicrographs of the well-differentiated pancreatic neuroendocrine tumor.
(A) 200x H&E stain: Low power view of the duodenal ulcer with the underlying NET.
(B) 100x H&E stain: The liver biopsy identified nests of monotonous regular cells with round to oval nuclei and salt and pepper chromatin. Mitoses are absent in this photo.
(C) 100x synaptophysin immunostain: The metastatic tumor cells have diffuse, strong cytoplasmic staining.
(D) 100x Ki67 immunostain: 10-15% of the tumor cells have positive staining consistent with an intermediate or grade 2 well-differentiated NET.

Staging via CT and gallium-68 DOTATATE PET/CT revealed a 6.8 x 5.5 cm hypervascular mass in the pancreatic head and dozens of DOTATATE-avid hepatic metastases (Figure 2A). Despite monthly Sandostatin LAR 30 mg, the disease demonstrated rapid progression. A liver biopsy confirmed a metastatic well-differentiated NET, grade 2 (of 3) with a mitotic index of 1 mitosis per 2mm^2 and a Ki-67 proliferation index of 10–15% (Figure 1B-D). The clinical course was soon complicated by rapid weight gain, facial puffiness, supraclavicular fat accumulation, and proximal muscle weakness. Laboratory workup (Table 2A) confirmed Cushing syndrome. Immunohistochemistry (IHC) on the liver biopsy was negative for ACTH; corticotropin-releasing hormone (CRH) staining could not be performed. However, the rapid clinical evolution, coupled with a confirmatory biochemical profile and normal pituitary MRI, established the diagnosis of ectopic Cushing syndrome (ECS).

Table 2A

Date	Serum Cortisol (nmol/L)	24h UFC (nmol/24h)	DHEAS (µmol/L)	ACTH (pmol/L)	Gastrin (pmol/L)	CgA (nmol/L)
10/2022	--	--	--	--	2,705	181
05/2023	2,020	15,701	8.3	87.9	9,439	833
07/2023	--	--	--	128.9	--	843
12/2024	--	--	--	--	--	249
08/2025	--	--	--	2,374	36,934	1311

Abbreviations: 24h UFC: 24-hour urinary free cortisol (Normal: <124 nmol/24h); DHEAS: dehydroepiandrosterone sulfate (Normal: 1.2–7.3 µmol/L); ACTH: adrenocorticotropic hormone (Normal: 1.6–13.9 pmol/L); Gastrin (Normal: <48 pmol/L); CgA: Chromogranin A (Normal: <9.4 nmol/L).

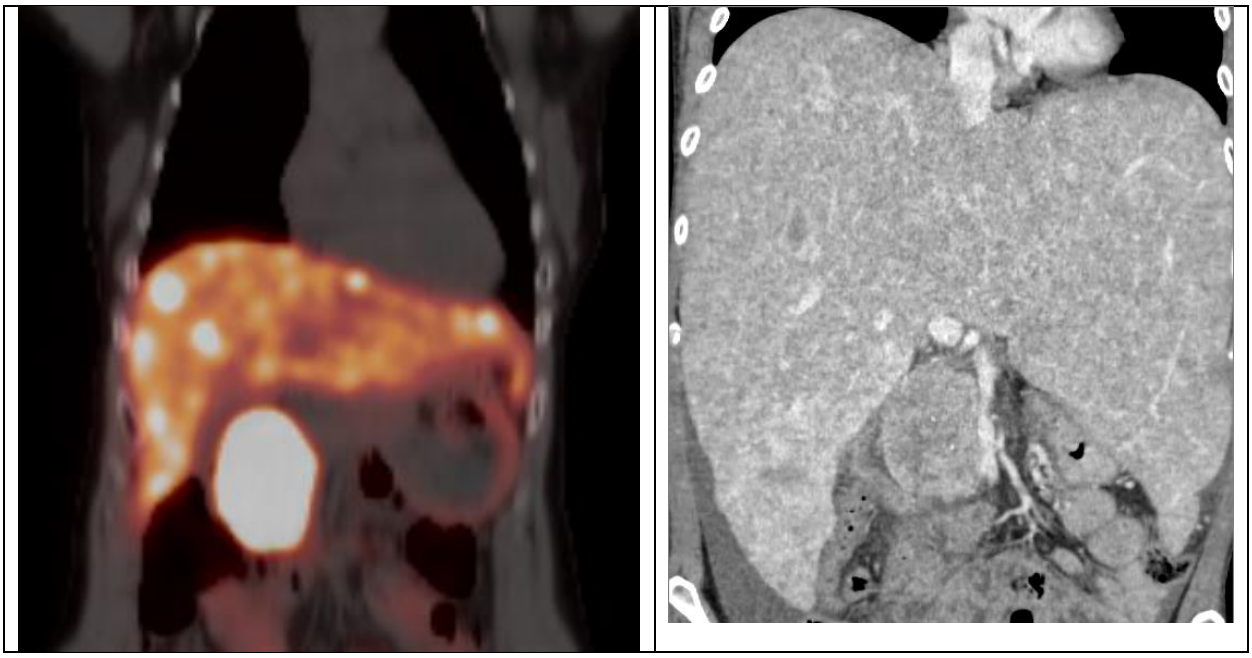


Figure 2. Initial staging and disease progression of the pancreatic neuroendocrine tumor
(A) Ga-68 DOTATATE PET/CT showing intense, diffuse tracer uptake in the primary pancreatic head mass and multiple scattered hepatic metastases, confirming high SSTR expression.
(B) Axial contrast-enhanced CT showing marked progression of metastatic burden with massive hepatomegaly.

Despite escalating doses of ketoconazole and metyrapone, the patient's hypercortisolemia remained refractory, leading to worsening hypertension, hyperglycemia, and hypokalemia. Consequently, a salvage bilateral adrenalectomy was performed to achieve definitive hormonal control; histopathology of the adrenal glands confirmed benign cortical hyperplasia.

The course was marked by a parathyroid hormone (PTH)-independent hypercalcemic crisis (Table 2B). Biochemical analysis attributed this to the simultaneous secretion of both PTHrP and 1,25-dihydroxyvitamin D. Management required intravenous fluids, calcitonin, and zoledronic acid. Molecular profiling via Caris Molecular Intelligence® (Caris Life Sciences, Irving, TX) identified a low mutation burden and was negative for microsatellite instability, while germline genetic testing using the Invitae Common Hereditary Cancers Panel (Invitae Corporation, San Francisco, CA), which includes the multiple endocrine neoplasia 1 (MEN1) gene, was negative.

Table 2B

Date	Corr. Ca (mmol/L)	Phos (mmol/L)	Cr (µmol/L)	25-OH Vit D (nmol/L)	PTH (pmol/L)	PTHrP (pmol/L)	1,25-$(OH)_2$ Vit D (pmol/L)
06/2023	2.73	0.65	71	32	<0.6	82.6	--
08/2023	3.70	0.87	116	--	<0.6	44.0	1,256
01/2024	2.43	0.97	65	--	--	--	--
12/2024	2.70	1.13	71	--	--	116.0	--
08/2025	2.68	0.78	80	--	<0.6	85.0	842

Abbreviations: Corr. Ca: corrected calcium (Normal: 2.1–2.6 mmol/L); Phos: phosphorus (Normal: 0.8–1.5 mmol/L); Cr: creatinine (Normal: 62–106 µmol/L); 25-OH Vit D: 25-hydroxyvitamin D (Normal: >50 nmol/L); PTH: parathyroid hormone (Normal: 1.1–6.9 pmol/L); PTHrP: parathyroid hormone-related protein (Normal: <2.0 pmol/L); 1,25-$(OH)_2$ Vit D: 1,25-dihydroxyvitamin D (calcitriol) (Normal: 43–173 pmol/L).

The malignancy was refractory to multiple lines of systemic therapy, including capecitabine/temozolomide, ^{177}Lu-DOTATATE, everolimus, cabozantinib, and sunitinib. Palliative radiation was administered to the duodenum to control recurrent hemorrhage. Surveillance imaging showed massive hepatomegaly and further enlargement of the pancreatic primary (Figure 1B).

Proposed Integrated Model of Neuroendocrine Secretory Evolution

The clinical behavior of NENs is best understood through a unified model that correlates morphological differentiation with secretory fidelity. In this framework, well-differentiated NETs represent a state of high lineage-fidelity; these cells possess the mature organellar machinery, specifically well-formed neurosecretory granules and proprotein convertases, to facilitate lineage-consistent (eutopic) secretion.[7] Because these tumors retain vestigial regulatory receptors, their hormonal output, while excessive, often maintains the functional phenotype of their progenitor cells.[8]

As the neoplasm moves toward a high-grade state, this lineage-fidelity is lost in favor of lineage-inconsistent (ectopic) secretion and paraneoplastic complexity.[9] This transition is precipitated by profound epigenetic dysregulation. As the tumor genome undergoes global

hypomethylation and loses chromatin-stabilizing proteins, silenced genetic loci are de-repressed.[10] This genomic instability allows the cell to bypass its tissue-specific constraints and begin the synthesis of ectopic peptides. In this stage, the cell has essentially relinquished its origin, adopting a plastic, multilineage secretory profile that is often refractory to standard inhibitory feedback loops.

Finally, the most aggressive end of the spectrum, represented by NECs and MiNENs, demonstrates a complete breakdown of the secretory apparatus. In these cases, the rapid rate of proliferation outpaces the cell's ability to package and process complex peptides. This leads to the secretion of biologically active but structurally immature pro-hormones or a complete loss of secretory function altogether. Therefore, the emergence of a PNS, particularly one that is lineage-inconsistent, should be viewed not merely as a metabolic complication, but as a clinical marker of clonal evolution and dedifferentiation. This integrated model suggests that a shift in a patient's secretory phenotype may serve as a liquid biopsy, signaling a transition in the tumor's underlying molecular grade before it becomes visible on standard imaging.[11]

Most common paraneoplastic endocrine syndromes

CARCINOID SYNDROME

Carcinoid syndrome (CS) affects 30–40% of patients with well-differentiated midgut or bronchial NETs, and occurs less commonly in those with pancreatic, ovarian, or thymic primaries.[7] The syndrome's clinical constellation is driven by the systemic release of serotonin alongside an array of vasoactive mediators, including histamine, tachykinins, kallikrein, and prostaglandins. Normally, serotonin released into the portal circulation is metabolized by the liver. However, when hepatic metastases are present or when primary tumors drain directly into systemic circulation, vasoactive mediators reach the systemic circulation in sufficient concentrations to cause symptoms. Although liver metastases are present in 90% of patients with CS, 10% of cases can develop in the absence of liver metastases, particularly if the primary tumor arises from the ovary, testis or if a large burden of retroperitoneal tumor is present.[12]

Patients classically present with episodic cutaneous flushing, secretory diarrhea, and abdominal cramping, occasionally accompanied by bronchospasm. Chronic exposure to supraphysiological serotonin levels facilitates the formation of plaque-like fibrous deposits on the endocardial surfaces and right-sided heart valves; this predominantly affects the tricuspid and pulmonary valves, resulting in valvular regurgitation or stenosis and the development of carcinoid heart disease (CHD).[13] Clinical management is further complicated by the risk of carcinoid crisis, a life-threatening hemodynamic instability, and the metabolic diversion of tryptophan toward serotonin synthesis, which can precipitate niacin deficiency (pellagra) and malabsorption of fat-soluble vitamins (A, D, E, and K) and B12.[14]

Biochemical diagnosis relies on elevated 24-hour urinary 5-hydroxyindoleacetic acid (5-HIAA) levels, a serotonin metabolite. A 24-h urine 5-HIAA >131 µmol is strongly indicative of CS, although levels >46.8 µmol, the upper limit of normal, in patients with compatible symptoms, are considered suggestive of a serotonin-producing tumor. Serum 5-HIAA, a more convenient and equally efficacious alternative, has also been used, with an optimal diagnostic threshold of 139.4 nmol/L.[15] Plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) has emerged as a critical screening biomarker for CHD. In patients with elevated 5-HIAA or suggestive clinical symptoms, an NT-proBNP level >31 pmol/L needs further evaluation with echocardiography.[13]

The diagnostic evaluation of CS necessitates a multimodal imaging approach, to localize the primary tumor and quantify metastatic burden. Endoscopic ultrasound or capsule endoscopy are reserved for localizing small bowel or pancreatic primaries that remain anatomically elusive.

The therapeutic management of CS includes systemic control of hormone-mediated symptoms and reduction of total tumor burden. SSAs, such as octreotide and lanreotide, represent the first-line standard of care. These agents bind with high affinity to somatostatin receptor subtype 2 (SSTR2), effectively inhibiting the release of serotonin and other vasoactive peptides in over 70% to 80% of patients.[12] For those with refractory secretory diarrhea, the oral tryptophan hydroxylase inhibitor telotristat ethyl is indicated to specifically block the rate-limiting step of serotonin synthesis, significantly reducing bowel movement frequency and improving quality of life.[16]

In cases of progressive disease or high-volume hepatic metastases, locoregional therapies, including hepatic arterial embolization (HAE), chemoembolization (TACE), or radioembolization (TARE), are highly effective in achieving both cytoreduction and symptomatic relief. Furthermore, PRRT with ^{177}Lu-DOTATATE has demonstrated significant improvements in progression-free survival and hormonal control for SSTR-positive midgut NENs.[17] For patients with significant valvular involvement, early surgical valve replacement is the definitive intervention for CHD, provided the systemic disease is relatively stable. Finally, clinicians must remain vigilant for carcinoid crises during invasive procedures, necessitating the prophylactic and intraoperative use of intravenous octreotide infusions to mitigate life-threatening hemodynamic instability.[18]

HYPERCALCEMIA OF MALIGNANCY

Hypercalcemia of malignancy (HCM) occurs in fewer than 5% of NEN cases, particularly pancreatic NETs and bronchial carcinoids, and is predominantly driven by the ectopic secretion of PTHrP.[19,20] This peptide shares significant structural homology with the N-terminal domain of native PTH, allowing it to bind and activate the PTH1 receptor (PTH1R) in bone and kidney tissues. This activation stimulates osteoclast-mediated bone resorption and enhances renal tubular calcium reabsorption, leading to hypercalcemia despite suppressed levels of endogenous PTH.[19]

A secondary, albeit rarer, mechanism of HCM in NETs involves the ectopic production of 1,25-dihydroxyvitamin D. This mechanism, more characteristic of lymphomas but documented in some well-differentiated NETs, involves the tumor-expressed enzyme 1α-hydroxylase, which converts 25-hydroxyvitamin D into its active form. The resulting increase in intestinal calcium absorption and bone resorption contributes to a hypercalcemic state.[21]

The presence of PTH-independent hypercalcemia and elevated plasma PTHrP and/or 1,25-dihydroxyvitamin D levels establish the diagnosis. Acute management involves aggressive intravenous isotonic saline and intravenous bisphosphonates (zoledronic acid) or the RANK-ligand inhibitor denosumab.[22] However, definitive control of hypercalcemia is fundamentally dependent on reducing the tumor burden through surgical resection, SSAs, or targeted radionuclide therapies.

SYNDROME OF INAPPROPRIATE ANTIDIURESIS

Syndrome of inappropriate antidiuresis (SIAD) is characterized by euvolemic hyponatremia due to inappropriate arginine vasopressin (AVP) secretion. While SIAD is most frequently identified in small-cell lung cancer (SCLC), occurring in approximately 7% to 16% of cases, it is also a recognized complication of well-differentiated NETs arising in the gastrointestinal tract, pancreas, and bronchial tree (23). These tumor cells autonomously synthetize AVP leading to the constitutive activation of vasopressin V2 receptors (V2R) in the renal collecting ducts. The subsequent insertion of aquaporin-2 water channels facilitates excessive free-water reabsorption, resulting in hypoosmolar hyponatremia and inappropriately concentrated urine.

From a molecular perspective, the ectopic production of AVP in NENs is driven by the derepression of the AVP gene, often accompanied by the expression of its carrier protein, neurophysin II.[24] In SCLC, the tumor microenvironment and specific oncogenic drivers promote a high volume of AVP mRNA transcription.[25] Clinically, the degree of hyponatremia often serves as a surrogate marker for tumor burden and biological aggressiveness. Furthermore, the escape from fluid restriction in these patients often signals disease progression or the development of resistance to systemic chemotherapy.[25]

The management of SIAD requires aggressive treatment of the primary NEC and symptomatic correction of the electrolyte imbalance. While fluid restriction remains the first-line intervention, its efficacy is often limited in patients with high urinary osmolality or those requiring high-volume intravenous chemotherapy. In such refractory cases, vasopressin receptor antagonists (vaptans), such as tolvaptan, provide a targeted mechanism to induce aquaresis without depleting electrolytes.[26]

Ectopic oxytocin secretion has also been documented in SCLC and certain bronchial carcinoids. These tumor cells autonomously produce mature oxytocin, which shares significant structural homology with AVP, and can cross-react with the V2R in the renal collecting ducts.[27] At high concentrations, this hormone induces a clinical state indistinguishable from ectopic AVP excess. While oxytocin is associated with uterine contractions and the let-down reflex, these patients rarely endorse these symptoms, likely due to the lack of oxytocin receptor density in non-pregnant patients. Notably, many NENs co-secrete oxytocin along with AVP, potentially synergizing the severity of hyponatremia.[24]

ECTOPIC CUSHING SYNDROME

Ectopic Cushing syndrome (ECS) due to ectopic ACTH secretion (EAS) accounts for 15–20% of ACTH-dependent Cushing syndromes. Bronchial carcinoids, thymic NETs, pancreatic NETs, high-grade NECs, and pheochromocytomas/ paragangliomas are recognized etiologies.[28]

The pathogenesis of EAS is characterized by the loss of tissue-specific gene silencing and the subsequent autonomous production of bioactive peptides. In a physiologic state, the expression of the proopiomelanocortin (POMC) gene is strictly regulated and largely restricted to pituitary corticotrophs. The neoplastic transformation induces DNA hypomethylation of the POMC promoter region.[29] This epigenetic shift allows for aberrant gene transcription in non-pituitary tissues, driven by alternative transcription factors rather than the classic pituitary-specific factors like T-box transcription factor (Tpit).[30]

The clinical severity of EAS is often dictated by the tumor's post-translational processing efficiency. While pituitary cells utilize the enzyme prohormone convertase 1/3 to cleave the POMC precursor into mature ACTH (1–39), SCLC exhibits impaired enzymatic machinery, resulting in the secretion of large, biologically inactive POMC precursors and pro-ACTH.[31] Despite their lower affinity for the melanocortin 2 receptor (MC2R), their sheer volume can saturate adrenal receptors, leading to massive, unregulated cortisol production and bilateral adrenal hyperplasia.

A defining feature of EAS is the relative or absolute resistance to glucocorticoid-mediated negative feedback. In pituitary-dependent Cushing's disease, adenomas typically retain some sensitivity to high-dose glucocorticoids. In contrast, ectopic tumors often manifest glucocorticoid receptor (GR) abnormalities, such as reduced receptor density or overexpression of the dominant-negative GRβ isoform. This molecular autonomy ensures that ACTH secretion persists unabated despite profound systemic hypercortisolemia, a phenomenon that provides the rationale for the high-dose dexamethasone suppression test in clinical differentiation.[30]

Furthermore, the rapid and extreme elevations of cortisol in EAS frequently overwhelm the capacity of the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which converts cortisol to inactive cortisone at the renal tubule level, protecting the mineralocorticoid receptor.[32] When this enzymatic shuttle is saturated, cortisol acts as a potent mineralocorticoid agonist, resulting in the hypokalemic metabolic alkalosis and severe hypertension that often distinguish this condition from more indolent forms of Cushing syndrome.[32]

Diagnostic evaluation includes measurement of serum, urine, and salivary cortisol and ACTH, dexamethasone suppression testing, and diagnostic imaging studies. Inferior petrosal sinus sampling may be required to distinguish pituitary from ectopic sources.[30] Localization of small bronchial NETs can be challenging and may necessitate functional imaging. Management involves prompt control of hypercortisolism using steroidogenesis inhibitors, followed by definitive tumor-directed therapy when feasible. In cases of uncontrolled hypercortisolism, bilateral adrenalectomy may be considered.[33]

In rare clinical presentations, ECS is mediated by the autonomous secretion of CRH. Ectopic CRH production is primarily associated with bronchial carcinoids, pancreatic NETs, and, less frequently, MTC. In these instances, the ectopic CRH binds the CRHR1 receptors of the anterior pituitary causing diffuse corticotroph hyperplasia and leading to the overproduction of pituitary ACTH and subsequent adrenal hypercortisolemia.[34]

NON–ISLET CELL TUMOR HYPOGLYCEMIA

Non-islet cell tumor hypoglycemia (NICTH), while more commonly linked to mesenchymal tumors, has been well-documented in high-grade NECs and certain bronchial carcinoids.[35,36] It is characterized by severe fasting hypoglycemia driven by the autonomous tumor secretion of "big" insulin-like growth factor 2 (big-IGF-2), an incompletely processed, high-molecular-weight precursor of IGF-2. Under physiological conditions, IGF-2 is sequestered in large ternary complexes with IGF-binding protein-3 (IGFBP-3) and an acid-labile subunit (ALS), which limits its bioavailability. In NICTH, however, the tumor-derived "big" IGF-2 fails to form these complexes, leading to an excess of free, bioactive IGF-2 that readily crosses the capillary endothelium to reach target tissues.[37]

The structural homology between IGF-2 and insulin allows "big" IGF-2 to bind and activate the insulin receptor (IR-A isoform) and the type 1 IGF receptor (IGF-1R). This activation induces a potent insulin-like effect, stimulating massive glucose uptake in skeletal muscle and adipose tissue while simultaneously inhibiting hepatic gluconeogenesis and glycogenolysis.[37] Furthermore, the elevated free IGF-2 exerts negative feedback on the pituitary-hypothalamic axis, suppressing the secretion of growth hormone (GH). This suppression leads to a secondary decline in hepatic IGF-1 and ALS production, further increasing the amount of "big" IGF-2 and exacerbating the hypoglycemia.[37]

The diagnosis of NICTH is based on the presence of hypoglycemia alongside suppressed levels of insulin, C-peptide, and proinsulin, which distinguishes it from insulinoma. A definitive diagnosis is supported by an elevated IGF-2 to IGF-1 ratio (typically >3:1 or 10:1 depending on the assay).[37,38] Management of NICTH is notoriously difficult; while acute glucose requirements can be astronomical, long-term stabilization often requires high-dose glucocorticoids, which stimulate gluconeogenesis and increase the clearance of "big" IGF-2. Ultimately, surgical cytoreduction or targeted radionuclide therapy remains the only definitive means of correcting hypoglycemia.[38]

ACROMEGALY

Ectopic secretion of growth hormone-releasing hormone (GHRH) accounts for less than 1% of all cases of acromegaly.[39] Unlike classic acromegaly, which is caused by a primary pituitary adenoma, ectopic GHRH-mediated acromegaly results from the autonomous production of GHRH by bronchial carcinoids (approximately 60% of cases) and pancreatic NETs.[39] The circulating GHRH binds to the GHRH receptors (GHRHR) on somatotroph cells, causing diffuse somatotroph hyperplasia and GH hypersecretion, which in turn stimulates hepatic production of IGF-1.

These patients present with acral overgrowth, coarsening of facial features, and metabolic dysfunction, associated with a hyperplastic pituitary gland on MRI. This pituitary enlargement can be misidentified as a primary GH-secreting adenoma, leading to unnecessary and ineffective transsphenoidal surgery. The biochemical signature that distinguishes ectopic GHRH from pituitary-dependent acromegaly is a markedly elevated plasma GHRH concentration (typically >49.6-59.5 pmol/L), whereas GHRH is usually undetectable in patients with primary pituitary adenomas.[40,41]

Management of the resulting acromegaly focuses on the surgical resection of the primary tumor, which typically leads to a rapid normalization of both GHRH, GH and IGF-1 levels. In cases of unresectable disease, SSAs serve as the primary pharmacological intervention by directly inhibiting GHRH release from the tumor and reducing GH secretion from the hyperplastic pituitary somatotrophs.[42]

Rare paraneoplastic endocrine syndromes

HYPERTHYROIDISM

While human chorionic gonadotropin (hCG) secretion is classically associated with gestational trophoblastic disease and germ cell tumors, its role in NENs is more nuanced. Although some high-grade NENs exhibit plurihormonal potential to secrete the common α-subunit, they lack the capacity to synthesize the specific TSH-β-subunit required for functional TSH assembly. Consequently, while certain malignancies induce paraneoplastic hyperthyroidism through massive hCG production, which cross-reacts with TSH receptors due to structural homology,[43] this specific mechanism remains largely undescribed in the context of NENs.

While ectopic TSH secretion is a recognized cause of central hyperthyroidism, documented cases are almost exclusively restricted to ectopic pituitary NETs (PitNETs) arising from embryological remnants in locations such as the nasopharynx or sphenoid sinus.[44] True TSH production by non-pituitary NENs remains clinically elusive and lacks definitive validation in modern literature.

SPONTANEOUS OVARIAN HYPERSTIMULATION SYNDROME

While most gonadotroph-secreting neoplasms are of pituitary origin, ectopic follicle-stimulating hormone (FSH) production represents a rare but clinically significant paraneoplastic manifestation of NENs.[45] This phenomenon is characterized by the autonomous secretion of FSH, which bypasses the hypothalamic-

pituitary-gonadal regulatory axis to drive spontaneous ovarian hyperstimulation syndrome (OHSS).

Clinical presentations typically involve profound hyperestrogenism and the development of bilateral multicystic ovaries, particularly in premenopausal women. Diagnostic confirmation is supported by the resolution of the hyperstimulatory state following surgical cytoreduction of the primary tumor, most notably documented in cases of large mediastinal carcinoids. IHC profiles in these tumors often demonstrate intense, diffuse cytoplasmic reactivity for CgA, frequently accompanied by focal or weak FSH expression, confirming the tumor as the bioactive source of the gonadotropic stimulus.

Interestingly, FSH receptors have also been identified on the neoplastic cells of some pancreatic NETs, suggesting potential autocrine or paracrine signaling pathways that may influence tumor biology.[46]

Ectopic LH secretion has also been associated with pancreatic NETs. The ectopic LH binds directly on the LHCGR in the gonads, stimulating the excessive production of sex steroids causing anovulation and virilization.[47,48]

HYPERPROLACTINEMIA

While prolactin (PRL) is primarily synthesized by lactotrophs of the anterior pituitary, its production extends to diverse extra-pituitary sites under both physiological and pathological conditions. Pathological ectopic PRL secretion is most formally recognized in ectopic PitNETs, neoplasms histologically identical to pituitary adenomas but lacking anatomical continuity with the sella turcica or pituitary stalk. These tumors arise from Rathke's pouch remnants and are frequently localized in peri-pituitary regions such as the sphenoid sinus, clivus, or nasopharynx. Beyond these embryological derivatives, ectopic PRL secretion has also been documented in extracranial non-pituitary-derived neoplasms, representing a rare but clinically significant cause of hyperprolactinemia.[49]

In the rare extracranial cases, the clinical presentation often involves profound elevations in serum PRL, sometimes exceeding 60 times the upper limit of normal, accompanied by classic symptoms such as galactorrhea and oligomenorrhea. Small cell neuroendocrine carcinomas (SCNEC) of the ovary have been implicated, with IHC analysis revealing peri-nuclear dot-like PRL positivity. This staining pattern is significant as it signifies hormone localization within the Golgi complex, confirming active synthesis rather than passive absorption.[50]

Furthermore, hyperprolactinemia may occur as part of a multi-hormonal paraneoplastic profile. In cases of MTC, tumors have demonstrated the capacity to simultaneously produce ACTH-like peptides and PRL-stimulating factors, leading to concurrent Cushing's syndrome and galactorrhea. In such instances, the complete resolution of paraneoplastic symptoms following surgical resection serves as definitive evidence of the tumor's secretory role.[51]

HYPERTENSION

While most renin-secreting tumors are primary renal juxtaglomerular cell tumors (reninomas), ectopic renin production has been documented in NENs. Cases associated with pancreatic NECs have demonstrated plasma renin activity (PRA) elevations exceeding ten-fold above baseline, with tumor tissue assays revealing renin concentrations significantly higher than physiological levels.[52]

Molecular evidence has confirmed that these poorly differentiated cells are capable of *de novo* hormone synthesis rather than simple sequestration. For instance, the identification of renin mRNA within ileal small-cell NEC tissue, identical in size to renal renin mRNA, verifies active synthesis pathways in extra-renal sites.[53] Clinical presentations often include severe, refractory hypertension and hypokalemic alkalosis that may fail to respond to standard dietary sodium manipulation.[54]

In contrast, ectopic aldosterone secretion is not currently classified as a standard paraneoplastic syndrome. Evidence suggests that most documented cases of ectopic aldosterone arise from aberrant adrenocortical tissue (accessory adrenal glands) rather than true neuroendocrine lineage.[55]

HYPERCALCITONINEMIA

Calcitonin secreting-extra-thyroidal NENs present a significant diagnostic challenge, as they can secrete calcitonin at concentrations identical to those seen in MTC. This biochemical overlap is compounded by the fact that these malignancies, mainly SCLC and LCLC, can be histologically and immunohistochemically indistinguishable from MTC.[55,56] Consequently, these and other extra-thyroidal sources such as pancreas, parathyroid glands, larynx, esophagus, thymus, lung, small intestine, liver, and bladder frequently lead to a diagnostic dilemma, where the biochemical signature of hypercalcitoninemia is misattributed to a thyroid primary, potentially resulting in unnecessary surgical interventions.[57]

In some high-grade NECs, the tumor may secrete procalcitonin, the larger precursor molecule, which serves as a highly sensitive marker for tumor burden and treatment response.[58]

From a management perspective, the presence of ectopic calcitonin does not require hormone-specific therapy, as it is generally biologically inert in adults. However, it serves as an invaluable surrogate biomarker for monitoring disease progression and the efficacy of cytoreductive surgeries or SSAs.

ECTOPIC CALCITONIN GENE-RELATED PEPTIDE

Medullary thyroid cancer (MTC) originates from thyroid parafollicular C-cells, which represent the physiological site for the synthesis of both calcitonin and calcitonin gene-related peptide (CGRP). While CGRP functions as a neuropeptide within the central and peripheral nervous systems, it is constitutively expressed in C-cells via tissue-specific alternative RNA splicing of the *CALCA* gene. Consequently, CGRP production in MTC is classified as

eutopic, reflecting an up-regulation of the native secretory profile of the progenitor cell line rather than ectopic hormone expression.[59]

In contrast, the expression of CGRP in non-thyroidal NENs and lung malignancies, such as bronchial carcinoids, represents a shift in secretory fidelity.[60] In high-grade NENs, CGRP often manifests as part of a complex, multi-hormonal paraneoplastic profile. This biochemical diversity is clinically relevant in cases where occult primary lung lesions remain undetectable while producing systemic co-secretion of ACTH, gastrin-releasing peptide (GRP), and CGRP from metastatic sites.[61]

Furthermore, the presence of CGRP in tumors like pheochromocytomas underscores the sophisticated nature of alternative peptide processing in neoplastic cells. Although CGRP and calcitonin share a common genetic origin, certain tumors exhibit a highly specific secretory phenotype—producing CGRP-like immunoreactivity (comprising both α and β isoforms) in the absolute absence of calcitonin.[62] This phenomenon highlights a significant loss of lineage-fidelity, where alternative RNA splicing pathways are prioritized over the production of traditional hormones. Clinically, identifying CGRP expression serves as a specific immunohistochemical tool for confirming neuroendocrine lineage, particularly when the primary tumor is anatomically elusive.[62]

VERNER–MORRISON SYNDROME

While approximately 90% of VIPomas are intrapancreatic, the remaining 10% manifest as ectopic tumors, often originating from neural crest-derived tissues, including pheochromocytomas, ganglioneuroblastomas, and MTC.[63,64]

Patients usually present with large tumors that cause WDHA syndrome (watery diarrhea, hypokalemia, and achlorhydria), often with delayed diagnosis due to the vasodilatory effects of VIP masking catecholamine-induced hypertension.[64,65] While surgical resection is effective for localized disease, metastatic cases lack standardized treatment, although emerging therapies like sunitinib have shown success in managing tumor burden and symptoms.[66]

ECTOPIC GLUCAGON-LIKE PEPTIDE-1 AND GLUCAGON-LIKE PEPTIDE-2

Glucagon-like peptide-1 (GLP-1) and glucagon-like peptide-2 (GLP-2) are hormones co-secreted by intestinal L-cells from the proglucagon (GCG) gene following nutrient intake. GLP-1 acts as an incretin to regulate glucose and insulin, whereas GLP-2 is primarily intestinotrophic, promoting gut growth and repair. In the intestine and brain, PC1/3 cleaves the precursor into these two peptides, whereas in the pancreas, PC2 processing leads to glucagon production.[67]

In the context of NENs, a transition from diabetes to severe fasting hypoglycemia may signal a shift in this processing machinery. Metastatic pancreatic NENs have demonstrated the capacity to co-secrete GLP-1 alongside glucagon, where tumor-derived GLP-1 acts as a primary driver of hyperinsulinemic hypoglycemia. This paraneoplastic effect is mediated by the stimulation of endogenous β-cell hyperplasia and subsequent insulin release, a mechanism confirmed through *ex vivo* tissue cultures and bioassays.[68]

Furthermore, ectopic GLP-1 secretion can clinically mimic post-bariatric syndrome, presenting as post-prandial hypoglycemia even years after gastric bypass surgery. High intratumoral concentrations of glucagon frequently coexist with the co-secretion of GLP-1, insulin, and somatostatin.[69] Identifying these pancreatic NENs via functional imaging, such as octreotide scintigraphy, is critical, as surgical enucleation often results in complete biochemical and clinical remission.

The identification of GLP-2 as a potent intestinotrophic hormone originated from observations of a renal tumor reported by Gleeson et al[70] and subsequent glucagonomas described by Stevens et al[71] demonstrating that patients with these neoplasms exhibited significant small bowel enlargement and villous hyperplasia that regressed upon tumor resection. CT scanning later confirmed these structural changes in vivo.[72] While these cases established a link between proglucagon-derived peptides (PGDPs) and intestinal proliferation, the specific mediator remained elusive until Drucker et al identified GLP-2 as the bioactive intestinotrophic component.[73] This was further validated by Byrne et al, who documented a neuroendocrine carcinoma co-secreting GLP-1, GLP-2, and PYY, where massively elevated circulating GLP-2 levels directly correlated with jejunal mucosal hyperplasia and delayed intestinal transit.[74]

ECTOPIC GHRELIN

Ghrelin, the primary orexigenic hormone, is secreted by the stomach to stimulate appetite via the hypothalamic arcuate nucleus. By binding the GHS-R1a receptor, it triggers growth hormone release, increases gastric motility, and promotes fat storage. Its levels typically peak before meals to signal hunger and subside postprandially.[75]

In the context of metastatic NENs, ectopic ghrelin secretion creates a distinct clinical profile that may counteract the systemic effects of advanced malignancy. Patients with extreme hyperghrelinemia frequently maintain an obese BMI and preserved appetite. Notably, these patients often lack the cancer cachexia typically associated with metastatic disease, suggesting that tumor-derived ghrelin may provide a protective metabolic buffer against wasting syndromes.[76]

Despite ghrelin's role as a potent GH secretagogue, clinical evidence indicates that paraneoplastic hyperghrelinemia rarely results in acromegaly. Most documented cases, including those arising from gastric or pancreatic NENs, show maintained normal GH and IGF-I levels despite massive circulating ghrelin concentrations.[76,77] However, the metabolic consequences are significant; extreme hyperghrelinemia has been linked to the development of new-onset or worsening diabetes mellitus, likely secondary to ghrelin's inhibitory effect on insulin secretion and its promotion of hepatic glucose output.[76] IHC analysis in these cases typically

confirms intense ghrelin immunoreactivity co-expressed with pan-neuroendocrine markers such as synaptophysin and CgA.

ECTOPIC SOMATOSTATIN

Somatostatinomas are somatostatin-secreting NENs which can be localized in the pancreas (60%) or in the duodenum (40%).[78] Somatostatin-14 or somatostatin-28, which act as universal inhibitory peptides, bind to SSTR1–5 across multiple organ systems, suppressing the release of various hormones and digestive enzymes, bypassing the body's normal metabolic and gastrointestinal regulatory loops.[79] The resulting clinical profile, known as somatostatinoma syndrome, is defined by the triad of secondary diabetes mellitus, cholelithiasis, and steatorrhea. These features are direct consequences of the hormone's inhibitory reach: it suppresses insulin and glucagon secretion to cause dysglycemia, inhibits cholecystokinin to induce gallbladder stasis and gallstones, and blocks pancreatic exocrine function to cause fat malabsorption.

While most somatostatinomas are associated with the gastrointestinal tract, ectopic production has also been documented in ovarian neoplasms, such as stromal carcinoids arising within mature cystic teratomas. In these cases, the clinical presentation may deviate from the classic triad, manifesting instead as severe, erratic blood glucose fluctuations characterized by both hyper- and hypoglycemia. This metabolic instability results from the profound systemic inhibition of both insulin and counter-regulatory hormones.[80]

Biochemical confirmation is achieved through the detection of markedly elevated circulating somatostatin levels, which can exceed 8,000 pmol/L in active disease, followed by rapid normalization and clinical resolution upon surgical resection. IHC analysis typically confirms strong somatostatin expression within the tumor tissue, validating the neoplasm as the primary source of the inhibitory syndrome.[80]

CYTOKINE-MEDIATED SYNDROMES

The secretion of pro-inflammatory cytokines, specifically interleukin-6 (IL-6), TNF-α, and IL-1, is a recognized driver of systemic PNS in patients with pheochromocytomas and paragangliomas (PPGL).[81] A case series identified three such patients within a 422-person surgical cohort, contributing to the 42 cases of IL-6-producing PPGL reported to date. Despite this rarity, the actual incidence may be higher, as clinical signs like treatment-resistant fever, anemia, and elevated inflammatory markers (CRP and ESR) are often masked by catecholamine excess. Evidence suggests that IL-6 is likely secreted directly by neoplastic cells rather than as a secondary response to norepinephrine. While surgical resection is the only curative intervention to normalize laboratory values, preoperative management with NSAIDs or α-blockers (e.g., doxazosin) can effectively mitigate systemic symptoms.[82]

Paragangliomas and pheochromocytomas (PPGL) can present with a distinct inflammatory phenotype characterized by fever of unknown origin and elevated markers, driven by ectopic IL-6 secretion.[83] This cytokine-mediated syndrome can trigger systemic inflammatory response syndrome, causing symptoms like weight loss and renal dysfunction that resolve only upon tumor resection.[83]

In a study of 43 patients with well-differentiated gastroenteropancreatic NETs, researchers found elevated levels of cytokines including IL-1β, IL-6, IL-8, IL-18, and TNF, alongside decreased IL-10 compared to healthy controls. These cytokine levels correlated significantly with tumor grade, metastasis, and disease progression, indicating potential for a diagnostic and prognostic panel. A panel combining these markers could enhance the accuracy of current NET monitoring tools, suggesting a role for immune response profiling.[84]

ECTOPIC NEUROTENSIN

Ectopic neurotensin secretion is most frequently associated with pancreatic NETs and VIPomas. This 13-amino acid peptide acts as a potent vasodilator and modulator of gastrointestinal motility. The clinical hallmark of a neurotensinoma is vasodilatory flushing, hypotension, and increased intestinal secretion, often overlapping with the WDHA syndrome. Neurotensin often serves as a co-secreted peptide rather than a sole driver of symptoms, but its presence correlates with advanced metastatic disease and a higher proliferative index.[85]

Blackburn et al demonstrated that NETs, specifically VIPomas, can ectopically secrete neurotensin. The study found that roughly 28% of studied VIPomas contained neurotensin-like immunoreactivity, with some cases producing elevated plasma levels, though the clinical presentation was indistinguishable from standard VIPoma syndrome.[86]

ECTOPIC GASTRIN-RELEASING PEPTIDE

Gastrin-releasing peptide (GRP) is a 27-amino acid mammalian homolog of bombesin that regulates gastric acid secretion, satiety, and GI motility via its receptor, GRPR.[87]

IHC analysis of 85 human neoplasms confirmed that GRP is a prevalent marker of neuroendocrine differentiation. Intense cytoplasmic GRP immunoreactivity was most consistent in MTC (100%), as well as various carcinoids of the lung, pancreas, and intestine (61%). While also present in a subset of SCLC and PitNETs, it was absent in pheochromocytomas, neuroblastomas, and non-neuroendocrine tumors. The study further identified GRP in normal thyroid C-cells and bronchial Kulchitsky cells, establishing GRP as a specific immunohistochemical tool for identifying neuroendocrine lineage across multiple organ systems.[88]

Progastrin-releasing peptide (ProGRP) is a highly specific biomarker for SCLC, with a normal upper limit of 50 pg/ml. While levels can be elevated by renal impairment or certain non-SCLC malignancies (rarely exceeding 120 pg/ml), ProGRP shows significantly higher concentrations in SCLC compared to non-SCLC. It demonstrates a sensitivity of 60–70% in localized SCLC and 75–90% in extensive disease, outperforming neuron-specific enolase in diagnostic sensitivity. Although it lacks independent

prognostic significance in multivariate analyses, ProGRP is a valuable tool for monitoring treatment response in SCLC patients.[89]

ECTOPIC MOTILIN

Motilin acts on G-protein coupled receptors in the enteric nervous system to trigger the migrating motor complex. Patients typically present with severe upper gastrointestinal hypermotility, manifesting as chronic nausea, vomiting, and abdominal cramping.[90]

However, clinical evidence suggests that the presence of tumor-derived motilin does not always correlate with symptomatic dysmotility, even in the setting of high-grade metastatic disease. In some cases of motilin-secreting NENs, patients may remain asymptomatic with normal gastric emptying and gastroduodenojejunal motility despite extremely high intratumoral and circulating motilin concentrations.[91] These tumors, which may originate from various sites including the rectum, can exhibit an indolent clinical course spanning several decades.

Beyond its role in motility, motilin expression often coexists with other neuroendocrine markers such as somatostatin and PP, as confirmed by IHC analysis. The relative stability of these tumors in certain phenotypes underscores the utility of plasma motilin not only as a diagnostic indicator but as a supplemental biomarker for monitoring long-term disease progression in NENs.[91]

TUMOR-INDUCED OSTEOMALACIA

Tumor-induced osteomalacia (TIO) is a paraneoplastic syndrome driven by the ectopic secretion of fibroblast growth factor 23 (FGF23). While most commonly associated with benign phosphaturic mesenchymal tumors,[92] FGF23 secretion is a documented, albeit rare, feature of NENs.[93] Pathologically, elevated circulating FGF23 suppresses renal phosphate reabsorption and inhibits the activation of 1,25-dihydroxyvitamin D, resulting in severe hypophosphatemia and impaired bone mineralization. Patients typically present with progressive musculoskeletal pain, proximal muscle weakness, and multiple insufficiency fractures, often enduring a multi-year diagnostic delay due to the non-specificity of these symptoms. Because FGF23-secreting NENs frequently overexpress SSTRs, gallium-68 DOTATATE PET/CT has become the preferred imaging modality for localizing these typically small, occult lesions.[92] While complete surgical resection remains the only curative intervention, the anti-FGF23 monoclonal antibody burosumab offers an option for patients with unresectable or metastatic disease.[94]

ECTOPIC CHOLECYSTOKININ

Cholecystokinin (CCK) is synthesized and secreted by specialized enteroendocrine cells, known as I-cells, which are concentrated in the mucosal lining of the duodenum and proximal jejunum.[95] While rare, CCK-secreting NENs (CCKomas) present a unique clinical challenge due to their ability to mimic other functional syndromes. Extremely high circulating CCK levels, which can reach 1,000 times the physiological limit, act as a potent agonist for the gastrin-CCK2 receptor. This cross-reactivity drives gastric acid hypersecretion and peptic ulcer formation, creating a clinical phenotype nearly identical to ZES.[96]

Clinical presentations of CCKomas often include chronic diarrhea, severe weight loss, recurrent cholelithiasis, and refractory peptic ulcers. A critical diagnostic clue is the presence of ZES-like symptoms in the context of paradoxically normal or low serum gastrin levels. In metastatic disease, particularly when the primary tumor originates in the pancreas, liver metastases may serve as the dominant source of hormone production, with IHC analysis typically confirming diffuse CCK positivity.[96]

ERYTHROCYTOSIS (POLYCYTHEMIA)

While autonomous erythropoietin (EPO) production is more frequently associated with renal cell carcinomas or hemangioblastomas, it has been documented as a rare paraneoplastic manifestation of NENs, including pheochromocytomas[97] and MTC.[98] In the context of advanced MTC, ectopic EPO secretion can drive secondary polycythemia, appearing in coordination with extreme elevations of traditional tumor markers such as calcitonin and carcinoembryonic antigen (CEA).[98]

Clinical evidence suggests that the emergence of inappropriately elevated serum EPO levels in these patients often correlates with a high tumor burden and rapid disease progression. Consequently, while rare, monitoring for secondary erythrocytosis in patients with established NENs may provide a clinical indicator of high-grade secretory plasticity and advancing disease stage.[98]

GENERAL AND SPECIFIC BIOMARKERS

Chromogranin A: CgA is an acidic glycoprotein primarily stored in the secretory granules of neuroendocrine cells throughout the body. It is the most common circulating biomarker for NENs as it correlates with tumor burden, progression, and metastases, although its clinical value is limited by its lower sensitivity and specificity.[8] Higher CgA levels are found with midgut carcinoids and pancreatic NENs.[99] Falsely elevated values can occur with chronic atrophic gastritis, proton pump inhibitors, glucocorticoids, untreated hypertension, and liver, kidney, and heart. Conversely, falsely low levels can be seen with localized or nonfunctional NENs and during treatment with SSAs. CgA is generally considered a reliable marker to monitor disease progression and treatment response and for detection of relapses.[13]

Pancreastatin: Pancreastatin is a post-translational cleavage product of CgA that is ectopically processed and secreted by many gastrointestinal NENs. Its primary biological effect is the potent inhibition of insulin secretion and the stimulation of hepatic gluconeogenesis. Pancreastatin is increasingly recognized as a superior biomarker to CgA for predicting overall survival and monitoring response to somatostatin analog therapy, as it is less influenced by PPI use.[100]

Pancreatic polypeptide: PP is a hormone produced primarily by PP cells in the pancreas that serves as a

neuroendocrine differentiation biomarker and markedly elevated concentrations are associated with PPomas, insulinomas, and glucagonomas.[4] High levels can also occur with gastrointestinal disorders, diabetes and advanced age and low levels can be seen in obese individuals. When combined with CgA, their diagnostic utility for nonfunctional NENs significantly increases.[99,100]

Neuron-specific enolase: NSE, a glycolytic enzyme primarily found in neurons and neuroendocrine cells, is a sensitive indicator of neuronal damage and cell death that is also used to monitor treatment and detect recurrence in small cell lung cancer and various NENs.[8,100]

Serotonin and 5-HIAA: Serotonin is primarily synthesized by midgut NENs. Its metabolite, 5-HIAA, is the gold standard for diagnosing and monitoring carcinoid syndrome. In clinical practice, 24-hour urinary 5-HIAA has a specificity of ~90%, though plasma 5-HIAA is increasingly used for patient convenience.[15] Clinicians must account for false positives triggered by tryptophan-rich foods (e.g., bananas, walnuts) and false negatives in patients with renal insufficiency or those taking certain medications like SSRIs.

Insulin: Elevated fasting insulin in the presence of hypoglycemia (<3.1 mmol/L) is the biochemical hallmark of an insulinoma. Beyond mere insulin levels, a comprehensive diagnostic panel includes C-peptide and proinsulin to differentiate endogenous hyperinsulinism from factitious administration.

Gastrin: Hypergastrinemia in the presence of a gastric pH <2.0 confirms the diagnosis of ZES. Because common conditions like atrophic gastritis and PPI use also elevate gastrin, a secretin stimulation test is the definitive provocative tool; a paradoxical rise in gastrin (>95.3 pmol/L) following secretin administration is highly indicative of gastrinoma rather than secondary hypergastrinemia.[3]

Glucagon: Glucagonomas typically produce plasma glucagon levels exceeding 144–287 pmol/L (normal <43 pmol/L). The associated necrolytic migratory erythema is often the presenting symptom, thought to be caused by hypoaminoacidemia and zinc deficiency secondary to the tumor's catabolic state. Because glucagonomas are frequently metastatic at the time of diagnosis, this marker is critical for monitoring the burden of disease during systemic therapy.[7]

VIP: VIPomas secrete massive amounts of this peptide. Diagnostic confirmation requires a fasting plasma VIP level >59 pmol/L in a patient with secretory diarrhea that persists even during fasting.[63]

Somatostatin: Somatostatinomas are rare and often present incidentally during imaging or as part of MEN1 or neurofibromatosis type 1. While a plasma level >61.1 pmol/L is suggestive, many somatostatin-secreting tumors are non-functional and do not produce the classic inhibitory triad.[100]

EMERGING BIOMARKERS

NETest®: NETest® is a multianalyte liquid biopsy that measures the expression of 51 different genes associated with tumor signaling, proliferation, secretion, and neoplastic behavior utilizing real-time PCR and machine learning algorithms used to diagnose and monitor NENs.[99] The NETest® quantifies these genes and evaluates the amount of expression of certain gene clusters allowing its conversion to a percentage known as the NETest® score, which indicates the presence and activity disease level. It has high diagnostic accuracy, predictive response to treatment, and disease monitoring and correlates better than traditional markers with imaging, tumor grade, and ki67 index.[99] Higher scores are seen with more aggressive disease, with scores between 41 and 100% indicating progressive disease. Conversely, reductions in the NETest® score suggest successful treatment interventions (0-20%: no active disease; 21-40%: stable disease). Notably, the NETest® can detect recurrence and metastatic disease six months earlier than traditional biomarkers and radiological imaging.[100]

Circulating tumor cells: Circulating tumor cells (CTCs) represent intact neoplastic cells shed into the bloodstream, offering a minimally invasive liquid biopsy platform to detect and molecularly characterize NENs while quantifying tumor burden and histological grade. However, their clinical utility is frequently hampered by low diagnostic sensitivity, with detection rates ranging from only 21% to 50% in the metastatic setting, a significant limitation compared to the NETest®, which demonstrate superior performance in early-stage screening.[99] Consequently, current evidence suggests that the primary utility of CTCs lies in their prognostic value rather than as a frontline diagnostic modality. While CTC counts correlate with disease progression and overall survival, their precise integration into standardized clinical algorithms remains a subject of ongoing investigation to determine how they might best complement traditional imaging and tissue-based pathology.[99]

Circulating tumor DNA: circulating tumor DNA (ctDNA) represents a subset of cell-free DNA released by apoptotic or necrotic tumor cells into the bloodstream, serving as a highly specific liquid biopsy that captures the real-time genomic landscape of a NEN. Due to its short half-life and ability to reflect both spatial and temporal heterogeneity, ctDNA is increasingly used in clinical oncology for molecular residual disease detection, identifying emergent resistance mutations, and monitoring therapeutic efficacy.[101] While technical advancements in digital PCR and Next-Generation Sequencing (NGS) have significantly improved sensitivity, the field currently faces challenges regarding analytical standardization and the potential for false positives from clonal hematopoiesis. Integrating ctDNA into standard care marks a shift toward precision oncology, where treatment decisions, from surgical escalation to targeted therapy selection, are guided by a patient's unique and evolving molecular profile.[99]

MicroRNAs: microRNAs (miRNAs) are small, non-coding RNA molecules that post-transcriptionally regulate gene

expression that have emerged as stable and tissue-specific indicators of neuroendocrine tumorigenesis. Unlike fragile mRNA, miRNAs are highly resilient to degradation and can be reliably quantified in both formalin-fixed paraffin-embedded tissues and biofluids, where they are often encapsulated in exosomes or bound to protein complexes.[102] Profiling studies have identified distinct miRNA signatures, such as the upregulation of miR-21 and miR-10b, which correlate with increased tumor aggressiveness, metastatic potential, and poor clinical outcomes.[99] Furthermore, because specific miRNA clusters vary between pancreatic and small-intestinal NENs, they offer significant potential for differential diagnosis and the identification of primary tumor sites in cases of unknown origin. Despite their promise as liquid biopsies the transition of miRNAs into routine clinical practice requires further large-scale validation to address challenges in platform standardization and the confounding effects of systemic inflammatory responses.[102]

Proteomic biomarkers: Proteomic biomarkers represent a critical bridge between static genomic blueprints and dynamic clinical phenotypes, offering a more nuanced reflection of tumor behavior than traditional mono-analytes. High-throughput mass spectrometry and proteogenomic profiling have identified distinct protein signatures, including angiogenic factors like VEGF, inflammatory cytokines such as IL-8, and novel tissue-specific markers like INSM1 and ISL1, that provide superior diagnostic sensitivity and more precise site-of-origin determination.[103] These multifaceted proteomic landscapes not only facilitate more accurate histological grading but also enable the identification of immune-hot phenotypes, potentially predicting response to immunotherapy where traditional grading systems fall short.[99] As the field moves toward a multi-omics approach, the integration of these protein-based signatures into routine practice promises to refine risk stratification and allow for real-time monitoring of therapeutic resistance through the detection of evolving proteomic shifts.[100]

Soluble immune checkpoints and cytokines: A novel liquid biopsy platform utilizing a "minimal signature" of five key immunological factors (sCD25, sPD-L2, sTIM3, sLAG3, and Galectin-9) has demonstrated exceptional diagnostic precision for NENs. In a multicenter validation cohort, this panel achieved an accuracy exceeding 90% (AUC 0.94–0.99), providing a robust methodology for differentiating NEN subtypes and identifying patients at high risk for metastatic progression.[104]

ANATOMIC IMAGING

Multiphase contrast-enhanced computed tomography: CECT utilizing multidetector computed tomography (MDCT) technology remains the mainstay for initial staging, surgical planning, and longitudinal surveillance due to its widespread availability and superior spatial resolution. To maximize diagnostic yield, a multiphasic contrast protocol, encompassing late arterial, portal venous, and delayed phases, is mandatory, as most NENs are hypervascular and demonstrate characteristic intense enhancement during the arterial phase.[105] While MDCT provides critical anatomical detail for assessing vascular infiltration and mesenteric desmoplastic reactions, its sensitivity for detecting small primary lesions (particularly in the small bowel) and bone metastases is significantly lower than that of SSTR-PET/CT. Furthermore, while MDCT is the standard for assessing treatment response via RECIST 1.1 criteria, it is often limited by its inability to differentiate viable tumor from treatment-induced necrosis or fibrosis.[105] Consequently, MDCT is best utilized as a complementary tool to MRI for hepatic assessment and molecular imaging for whole-body staging, collectively forming a comprehensive diagnostic framework that bridges anatomical structure with biological activity.[106]

Magnetic Resonance Imaging: MRI is the premier anatomical modality for the detection and characterization of hepatic metastases, consistently outperforming CECT with sensitivity reaching 95%. This diagnostic superiority is driven by high soft-tissue contrast and the integration of functional sequences, specifically diffusion-weighted imaging, which identifies hypercellularity, and the use of hepatobiliary-specific contrast agents. These agents are selectively taken up by functional hepatocytes, leaving NEN metastases (which lack these transporters) as conspicuous dark lesions during the hepatobiliary phase, thereby enabling the detection of sub-centimeter deposits often missed by other modalities.[106] Furthermore, MRI is increasingly utilized for pancreatic NEN localization, where T2-weighted sequences and secretin-enhanced MRCP provide detailed ductal and parenchymal mapping essential for surgical parenchymal-sparing techniques. Despite its higher cost and longer acquisition times compared to CT, MRI's lack of ionizing radiation and unmatched sensitivity for the liver make it an indispensable component of the longitudinal surveillance and preoperative staging algorithm.[107]

FUNCTIONAL IMAGING

^{111}In-pentetreotide (Octreoscan™): Octreoscan has been largely superseded as the gold standard by SSTR-PET/CT. In contemporary clinical practice, Octreoscan is increasingly relegated to specific secondary roles or settings where PET technology is unavailable.[108]

SSTR-PET/CT: SSTR-PET/CT has fundamentally redefined the management of well-differentiated (G1 and G2) NENs. The technique utilizes various DOTA-conjugated peptides, primarily Ga-68 DOTATATE, Ga-68 DOTATOC, and Ga-68 DOTANOC).[109] With a pooled sensitivity of 90–96% and specificity of 85–100%, SSTR-PET/CT is significantly superior to both conventional CT/MRI and Octreoscan. Its high spatial resolution and sensitivity for small-volume disease allow for the detection of occult primary tumors and subtle metastases in the bone, lymph nodes, and peritoneum that are frequently missed by anatomical imaging.[110] Prospective studies have demonstrated that the integration of SSTR-PET/CT leads to a change in clinical management for 33–51% of patients, often by identifying previously unknown metastatic sites that preclude curative surgery or by confirming eligibility for targeted systemic therapies.[109] Beyond staging, SSTR-PET/CT serves as the essential theranostic companion to PRRT. Visualizing SSTR density via ^{177}Lu-DOTATATE PET/CT enables patient selection

for PRRT (Krenning Scale Grade 3/4 or high SUVmax). Combined with 18F-FDG PET/CT, this approach identifies aggressive, low-SSTR clones better managed with chemotherapy, ensuring tailored treatment strategies.[110]

18F-FDG PET/CT: While not routinely used for diagnosing slow-growing, well-differentiated NETs due to their low metabolic activity, 18F-FDG PET/CT is an essential tool for assessing tumor aggressiveness and predicting patient outcomes. This scan detects fast-growing, high-grade, or poorly differentiated cancer cells that consume high levels of glucose, making it particularly useful for staging G3 NETs and NECs.[111] A positive FDG PET result suggests the presence of non-SSTR-expressing cells that may need sequential or concurrent cytotoxic chemotherapy, is strongly associated with a higher risk of disease progression and shorter overall survival, often outperforming traditional grading systems like the Ki-67 index as a prognostic marker.[110]

Conclusions

The evaluation of a suspected PNES requires careful correlation of clinical features, biochemical testing, imaging, and histopathology. Therapeutic advances, including SSAs, targeted molecular therapies, and PRRT, have transformed the management of hormonally active NENs. Improved symptom control has translated into enhanced quality of life and prolonged survival. Multidisciplinary collaboration between endocrinologists, oncologists, radiologists, and surgeons is essential.'

The traditional dichotomy between functional and non-functional NENs is increasingly being replaced by a nuanced understanding of secretory evolution. As this review has detailed, the progression from lineage-consistent (eutopic) to lineage-inconsistent (ectopic) secretion serves as a clinical sentinel for dedifferentiation. The pathogenesis of these PNES, driven by epigenetic de-repression and the loss of pro-hormone processing, marks a transition toward a more primitive and aggressive biological state. Recognizing these functional switches early is paramount, as they often precede radiological evidence of tumor progression.

The most promising frontier in this field is the integration of multi-omics and liquid biopsies to monitor these secretory transitions and refine the classification of MiNENs. While traditional serum markers like CgA offer limited specificity, the detection of ctDNA for *TP53/RB1* mutations or exosomal miRNA profiles provides a non-invasive window into the tumor's molecular grade. By tracking these biomarkers alongside transcription factor mapping, clinicians can transition toward interventional endocrinology, where the biological fingerprint of the tumor guides personalized care and systemic therapies are adjusted at the first sign of molecular escape.

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References

1. Rindi G, Mete O, Uccella S, et al. The 2022 WHO classification of neuroendocrine neoplasms: a perspective on the major changes and their clinical implications. *Endocr Relat Cancer*. 2022;29(8):R115-R131. doi:10.1530/ERC-22-0131
2. Dasari A, Shen C, Halperin D, et al. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. *JAMA Oncol*. 2017;3(10):1335-1342. doi:10.1001/jamaoncol.2017.0589
3. Oronsky B, Ma PC, Morgensztern D, Carter CA. Nothing But NET: A Review of Neuroendocrine Tumors and Carcinomas. *Neoplasia*. 2017;19(12):991-1002. doi:10.1016/j.neo.2017.09.002
4. Kanakis G, Kaltsas G, Grozinsky-Glasberg S, et al. ENETS Guidelines for the Management of Patients with Digestive Neuroendocrine Neoplasms: Concept of Paraneoplastic Syndromes. *Neuroendocrinology*. 2016;103(2):144-152. doi:10.1159/000443170
5. Yuan C, et al. Current perspectives on neuroendocrine tumors: Epidemiology, classification, and clinical behavior. *Hlife*. 2024;2(3):112-125. doi:10.1016/j.hlife.2024.07.006
6. Halperin DM, Shen C, Dasari A, et al. Frequency of Carcinoid Syndrome at Diagnosis Among Patients With Gastrointestinal Neuroendocrine Tumors. *JAMA Netw Open*. 2020;3(5):e205470. doi:10.1001/jamanetworkopen.2020.5470
7. Cives M, Strosberg JR. Gastroenteropancreatic Neuroendocrine Tumors. *CA Cancer J Clin*. 2018;68(6):471-487.
8. Yao JC, et al. Chromogranin A and Neuron-Specific Enolase as Markers of Progressing Neuroendocrine Tumors. *J Clin Oncol*. 2011;29(15_suppl):4119-4119.
9. Diercks BP, et al. Paraneoplastic syndromes in neuroendocrine neoplasms: a systematic review and clinical guide. *Cancer Metastasis Rev*. 2021;40(2):589-605.
10. Pipinikas CP, et al. Epigenetic dysregulation and the evolution of neuroendocrine tumors. *Nat Commun*. 2015;6:8243.
11. Oberg K, et al. Circulating biomarkers for neuroendocrine tumors: If we can't measure it, we can't understand it. *Cancers*. 2023;15(15):3876. doi:10.3390/cancers15153876
12. Hofland J, Herrera-Martínez AD, Zandee WT, de Herder WW. Management of carcinoid syndrome: a systematic review and meta-analysis. Endocr Relat Cancer. 2019 Mar;26(3):R145-R156. doi: 10.1530/ERC-18-0495. PMID: 30608900.
13. Grozinsky-Glasberg S, et al. European Neuroendocrine Tumor Society (ENETS) 2022 Guidance Paper for Carcinoid Syndrome and Carcinoid Heart Disease. Journal of Neuroendocrinology. 2022;34(7):e13146.
14. Vitale G, Carra S, Alessi Y, et al. Carcinoid Syndrome: Preclinical Models and Future Therapeutic Strategies. International Journal of Molecular Sciences. 2023;24(4):3610. doi:10.3390/ijms24043610.
15. Kerolles M, Mulders MCF, Mirzaian M, et al. Serum 5-hydroxyindoleacetic acid measurements for the diagnosis and follow-up of carcinoid syndrome. The Journal of Clinical Endocrinology & Metabolism. 2025;110(12):e3980-e3988. doi:10.1210/clinem/dgaf26
16. Kulke MH, et al. Telotristat Ethyl in Carcinoid Syndrome: Safety and Efficacy of a Novel-Mechanism Action Agent (TELESTAR Trial). Journal of Clinical Oncology. 2017;35(1):14-23.
17. Strosberg J, et al. Phase 3 Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumors (NETTER-1). New England Journal of Medicine. 2017;376(2):125-
18. Marasco M, Romano E, Arrivi G, et al. Exploring carcinoid syndrome in neuroendocrine tumors: insights from a multidisciplinary narrative review. Cancers (Basel). 2024;16(22):3831. doi:10.3390/cancers16223831.
19. Goldner W. Cancer-Related Hypercalcemia. Journal of Oncology Practice. 2016;12(5):426-432. doi:10.1200/JOP.2016.011155
20. Faggiano A, Lania A, Ferolla P, et al. Hypercalcemia of Malignancy in Patients with Neuroendocrine Tumors: A Multicenter Study. Journal of Clinical Endocrinology & Metabolism. 2020;105(5):e1966-e1974. doi:10.1210/clinem/dgz303
21. Zagouri F, Kastritis E, Zografos G, et al. Ectopic 1,25-dihydroxyvitamin D Production in Neuroendocrine Tumors: Case Report and Review of the Literature. *Anticancer Research*. 2015;35(2):1121-1126. PubMed
22. Stewart AF. Cancer-Associated Hypercalcemia. *New England Journal of Medicine*. 2022;386(15):1443-1451. doi:10.1056/NEJMcp2113128
23. Grohé C, Berardi R, Burst V. Hyponatraemia—SIADH in lung cancer diagnostic and treatment algorithms. Crit Rev Oncol Hematol. 2015;96(1):1-8. doi:10.1016/j.critrevonc.2015.04.005
24. North WG. Gene regulation of vasopressin and oxytocin in small-cell lung cancer. Cancer Res. 1991;51(13):3513-3518.
25. Kallio T, Pasternack M, Saarela J, et al. Neuroendocrine tumor markers in small cell lung cancer. Front Endocrinol (Lausanne). 2017;8:94. doi:10.3389/fendo.2017.00094
26. Hansen O, Sørensen P, Hansen KH. Hyponatremia as a prognostic factor in non-small cell lung cancer: a systematic review and meta-analysis. *Transl Lung Cancer Res*. 2021;10(2):984-996. doi:10.21037/tlcr-20-820
27. Grant P, Ayuk J, Bouloux PM, et al. The role of tolvaptan in the management of hyponatremia in cancer patients. *Cancer Manag Res*. 2016;8:107-114. doi:10.2147/CMAR.S103525
28. Miao H, Lu L, Zhu H, et al. Experience of ectopic adrenocorticotropin syndrome: 88 cases with identified causes. Endocr Pract. 2021;27(9):866-873. doi:10.1016/j.eprac.2021.02.015
29. Newell-Price J. Proopiomelanocortin gene expression and DNA methylation: implications for the ectopic ACTH syndrome. Endocrinology. 2003;144(3):765-771. doi:10.1210/en.2002-221021
30. Isidori AM, Kaltsas GA, Pozza C, et al. The ectopic adrenocorticotropin syndrome: clinical features, diagnosis, management, and long-term follow-up. J

Clin Endocrinol Metab. 2006;91(2):371-377. doi:10.1210/jc.2005-1542
31. Stewart MF, Crosby SR, Gibson S, Twentyman PR, White A. Small cell lung cancer cell lines secrete predominantly ACTH precursor peptides not ACTH. Br J Cancer. 1989;60(1):20-24. doi:10.1038/bjc.1989.212
32. Uwaifo GI, Remaley AT, Stene MA, et al. The 11β-hydroxysteroid dehydrogenase type 2 enzyme shuttle is saturated in the ectopic adrenocorticotropin syndrome. Endocr Pract. 2002;8(3):190-200. doi:10.4158/EP.8.3.190
33. Landry JP, Clemente-Gutierrez U, Pieterman CRC, et al. Management of adrenocorticotropic hormone-secreting neuroendocrine tumors and the role of bilateral adrenalectomy in ectopic Cushing syndrome. Surgery. 2022;172(2):559-566. doi:10.1016/j.surg.2022.03.014
34. Clarin MM, Grotzki S, Mickisch O, et al. Ectopic CRH syndrome: a rare cause of Cushing's syndrome. Exp Clin Endocrinol Diabetes. 2011;119(02):112-114. doi:10.1055/s-0030-1262846
35. Orrego JJ, Chorny JA. Hypoglycemia from metastatic meningeal solitary fibrous tumor occurring over two decades after initial diagnosis. JCEM Case Rep. 2023;1(1):luad001. doi:10.1210/jcemcr/luad001
36. Pickering ME, Bouvier D, Puravet A, et al. Hypophosphatemia related to a neuro-endocrine tumor of the pancreas: a case report. Clin Biochem. 2022;104:62-65. doi:10.1016/j.clinbiochem.2022.03.006
37. Dynkevich Y, Rother KI, Whitford I, et al. Tumors, IGF-2, and hypoglycemia: insights from the clinic, the laboratory, and the historical archive. Endocr Rev. 2013;34(6):798-826. doi:10.1210/er.2012-1033
38. Bodnar TW, Acevedo MJ, Pietropaolo M. Management of non-islet-cell tumor hypoglycemia: a clinical review. J Clin Endocrinol Metab. 2014;99(3):713-722. doi:10.1210/jc.2013-3382
39. Daskalakis K, Chatzelis E, Tsoli M, et al. Endocrine paraneoplastic syndromes in patients with neuroendocrine neoplasms. Endocrine. 2019;64(2):384-392. doi:10.1007/s12020-018-1773-3
40. Borson-Chazot F, Garby L, Raverot G, et al. Acromegaly induced by ectopic secretion of GHRH: a review 30 years after GHRH discovery. Ann Endocrinol (Paris). 2012;73(6):497-502. doi:10.1016/j.ando.2012.09.004
41. Garby L, Caron P, Claustrat B, et al. Clinical characteristics and outcomes of 77 patients with ectopic growth hormone-releasing hormone secretion. Psychoneuroendocrinology. 2012;37(9):1483-1489. doi:10.1016/j.psyneuen.2012.02.001
42. Faglia G, Arosio M, Bazzoni N. Ectopic acromegaly. Endocrinol Metab Clin North Am. 1992;21(3):575-595.
43. Carcamo J, Wang S, Gosiengfiao K, Sapkota S. Paraneoplastic hyperthyroidism in a patient with b-hCG secreting gastric carcinoma. J Endocr Soc. 2023;7(Suppl 1):bvad114.1844. doi:10.1210/jendso/bvad114.1844
44. Kumar S, Phang CA, Ni H, Diamond T. A patient with an ectopic sphenoid bone TSH secretory adenoma: case report and review of the literature. Front Endocrinol (Lausanne). 2022;13:961256. doi:10.3389/fendo.2022.961256
45. Burgos J, Cobos P, Vidaurrazaga N, et al. Ovarian hyperstimulation secondary to ectopic secretion of follicle-stimulating hormone: literature review prompted by a case. Fertil Steril. 2009;92(3):1168.e5-1168.e8. doi:10.1016/j.fertnstert.2009.06.023
46. Sardella C, Russo D, Raggi F, et al. Ectopic expression of FSH receptor isoforms in neoplastic but not in endothelial cells from pancreatic neuroendocrine tumors. J Endocrinol Invest. 2013;36(3):174-179. doi:10.3275/8472
47. Hirshberg B, Conn PM, Uwaifo GI, et al. Ectopic luteinizing hormone secretion and anovulation. N Engl J Med. 2003;348(4):312-317. doi:10.1056/NEJMoa022384
48. Piaditis G, Angellou A, Kontogeorgos G, et al. Ectopic bioactive luteinizing hormone secretion by a pancreatic endocrine tumor, manifested as luteinized granulosa-thecal cell tumor of the ovaries. J Clin Endocrinol Metab. 2005;90(4):2097-2103. doi:10.1210/jc.2003-032029
49. Lu Y, Chen X, Ke X, et al. Hyperprolactinemia caused by extra-pituitary prolactin secretion: a systematic review. *Endocr Connect.* 2025;14(7):e250054. doi:10.1530/EC-25-0054
50. Gururaj S, Nisal K, Davies Q, Deen S, McNally PG. Ectopic prolactin secretion secondary to an ovarian tumour. *Endocrinol Diabetes Metab Case Rep.* 2013;2013:130016. doi:10.1530/EDM-13-0016
51. Birkenhäger JC, Upton GV, Seldenrath HJ, Krieger DT, Tashjian AH Jr. Medullary thyroid carcinoma: ectopic production of peptides with ACTH-like, corticotrophin releasing factor-like and prolactin production-stimulating activities. Acta Endocrinol (Copenh). 1976 Oct;83(2):280-92. doi: 10.1530/acta.0.0830280. PMID: 184633.
52. Langer P, Bartsch D, Gerdes B, Schwetlick I, Wild A, Brehm B, Erley C, Lamberts R. Renin producing neuroendocrine pancreatic carcinoma--a case report and review of the literature. Exp Clin Endocrinol Diabetes. 2002 Jan;110(1):43-9. doi: 10.1055/s-2002-19994. PMID: 11835125.
53. Saito T, Fukamizu A, Okada K, et al. Ectopic production of renin by ileal carcinoma. Endocrinol Jpn. 1989;36(1):117-124. doi:10.1507/endocrj1954.36.117
54. Hauger-Klevene JH. High plasma renin activity in an oat cell carcinoma: a renin-secreting carcinoma? Cancer. 1970;26(5):1112-1114. doi:10.1002/1097-0142(197011)26:5<1112::aid-cncr2820260521>3.0.co;2-5
55. Zhu J, Zhang J, Qin Y, et al. Ectopic adrenocortical adenoma causing malignant hypertension and hypokalemia: a case report. Am J Case Rep. 2025;26:e948022. doi:10.12659/AJCR.948022
56. Llewellyn DC, Srirajaskanthan R, Vincent RP, Guy C, Drakou EE, Aylwin SJB, Grossman AB, Ramage JK, Dimitriadis GK. Calcitonin-secreting neuroendocrine neoplasms of the lung: a systematic review and narrative synthesis. Endocr Connect. 2021 Apr

26;10(4):447-461. doi: 10.1530/EC-21-0071. PMID: 33764887; PMCID: PMC8111313.
57. Ansari UA, Ramirez CL, Feliberti EC, Vinik AI, Perry RR. Calcitonin-secreting pancreatic neuroendocrine tumor in a patient with multiple endocrine neoplasia type 1. Pancreas. 2016;45(3):e11-e12. doi:10.1097/MPA.0000000000000544
58. Itoga M, Tanaka H, Taima K, et al. Procalcitonin expression in patients with large cell neuroendocrine carcinoma of the lung. BMC Res Notes. 2021;14(1):25. doi:10.1186/s13104-021-05448-4
59. Steenbergh PH, Höppener JW, Zandberg J, Visser A, Lips CJ, Jansz HS. Calcitonin and calcitonin gene-related peptide genes are expressed in medullary thyroid carcinoma and pheochromocytoma. Cancer Res. 1986;46(2):813-817.
60. Tsutsumi Y. Immunohistochemical analysis of calcitonin and calcitonin gene-related peptide in human lung. Hum Pathol. 1989;20(9):896-902. doi:10.1016/0046-8177(89)90103-2
61. Ghatei MA, Stratton MR, Allen JM, Joplin GF, Polak JM, Bloom SR. Co-secretion of calcitonin gene-related peptide, gastrin-releasing peptide and ACTH by a carcinoid tumour metastasizing to the cerebellum. *Postgrad Med J*. 1987;63(736):123-130. doi:10.1136/pgmj.63.736.123
62. Conlon JM, McGregor GP, Gröndal S, Grimelius L. Synthesis of alpha- and beta-calcitonin gene-related peptide by a human pheochromocytoma. *Peptides*. 1989;10(2):327-331. doi:10.1016/0196-9781(89)90038-7
63. Said SI. Evidence for secretion of vasoactive intestinal peptide by tumours of pancreas, adrenal medulla, thyroid and lung: support for the unifying APUD concept. Clin Endocrinol (Oxf). 1976;5 Suppl:201S-204S. doi: 10.1111/j.1365-2265.1976.tb03828.x. PMID: 29733.
64. Yee SK, Meyer JH, Wong LL. Vasoactive Intestinal Peptide-Secreting Pheochromocytoma: A Case Report and Review of Literature. AACE Clin Case Rep. 2022 Apr 1;8(4):158-162. doi: 10.1016/j.aace.2022.03.003. PMID: 35959082; PMCID: PMC9363508.
65. Leibowitz-Amit R, Mete O, Asa SL, Ezzat S, Joshua AM. Malignant pheochromocytoma secreting vasoactive intestinal peptide and response to sunitinib: a case report and literature review. Endocr Pract. 2014 Aug;20(8):e145-50. doi: 10.4158/EP14093.CR. Erratum in: Endocr Pract. 2015 Jan;21(1):94. Lebowitz-Amit, Raya [corrected to Leibowitz-Amit, Raya]. PMID: 24936559.
66. Ghatei MA, Stratton MR, Allen JM, Joplin GF, Polak JM, Bloom SR. Co-secretion of calcitonin gene-related peptide, gastrin-releasing peptide and ACTH by a carcinoid tumour metastasizing to the cerebellum. Postgrad Med J. 1987;63(736):123-130. doi:10.1136/pgmj.63.736.123
67. Drucker DJ. Mechanisms of Action and Therapeutic Application of Glucagon-like Peptide-1. Cell Metab. 2018;27(4):740-756. doi:10.1016/j.cmet.2018.03.001
68. Todd JF, Wilding JPH, Thompson GR, Bloom SR. Glucagon-like peptide-1 and glucagon secretion from a pancreatic neuroendocrine tumor causing hyperinsulinemic hypoglycemia. J Clin Endocrinol Metab. 2012;97(9):3039-3044. doi:10.1210/jc.2012-1621
69. Guimarães M, Rodrigues P, Pereira SS, et al. GLP1 and glucagon co-secreting pancreatic neuroendocrine tumor presenting as hypoglycemia after gastric bypass. Endocrinol Diabetes Metab Case Rep. 2015;2015:150049. doi:10.1530/EDM-15-0049
70. Gleeson MH, Bloom SR, Polak JM, Henry K, Dowling RH. Endocrine tumour in kidney affecting small bowel structure, motility, and absorptive function. Gut. 1971;12(10):773-782. doi:10.1136/gut.12.10.773
71. Stevens FM, Flanagan RW, O'Gorman DJ, Buchanan KD. Glucagonoma syndrome demonstrating giant duodenal villi. Gut. 1984;25(7):784-789. doi:10.1136/gut.25.7.784
72. Drucker DJ, Erlich P, Asa SL, Brubaker PL. Induction of intestinal epithelial proliferation by glucagon-like peptide 2. Proc Natl Acad Sci U S A. 1996;93(15):7911-7916. doi:10.1073/pnas.93.15.7911
73. Byrne MM, Goke B, Arnold R, et al. Intestinal proliferation and delayed intestinal transit in a patient with a GLP-1-, GLP-2- and PYY-producing neuroendocrine carcinoma. Digestion. 2001;63(1):61-68. doi:10.1159/000051873
74. Wieriks J, van den Bosch MA, van Leeuwen MS. Villous hypertrophy of the small bowel in a patient with glucagonoma. J Comput Assist Tomogr. 1983;7(2):334-337.
75. Ibrahim Abdalla MM. Ghrelin—physiological functions and regulation. Eur Endocrinol. 2015;11(2):90-95. doi:10.17925/EE.2015.11.02.90
76. Tsolakis AV, Portela-Gomes GM, Stridsberg M, et al. Malignant gastric ghrelinoma with hyperghrelinemia. J Clin Endocrinol Metab. 2004;89(8):3739-3744. doi:10.1210/jc.2003-032118
77. Corbetta S, Peracchi M, Cappiello V, et al. Circulating ghrelin levels in patients with pancreatic and gastrointestinal neuroendocrine tumors: identification of a novel gastropancreatic tumor marker. J Clin Endocrinol Metab. 2003;88(7):3117-3120. doi:10.1210/jc.2002-021932
78. Tsoli M, Dimitriadis GK, Androulakis II, Kaltsas G, Grossman A. Paraneoplastic syndromes related to neuroendocrine tumors. In: Feingold KR, Anawalt B, Blackman MR, et al, eds. Endotext. MDText.com, Inc; 2020. Accessed March 16, 2026. https://www.ncbi.nlm.nih.gov/books/NBK279135/
79. Dimitriadis GK, Angelousi A, Weickert MO, Randeva HS, Kaltsas G, Grossman A. Paraneoplastic endocrine syndromes. Endocr Relat Cancer. 2017;24(6):R173-R190. doi:10.1530/ERC-17-0036
80. Sugiyama T, Nakanishi M, Hoshimoto K, et al. Severely fluctuating blood glucose levels associated with a somatostatin-producing ovarian neuroendocrine tumor. J Clin Endocrinol Metab. 2012;97(11):3845-3850. doi:10.1210/jc.2012-2091
81. Meijs AC, Schroijen MA, Snel M, et al. Interleukin-6 producing pheochromocytoma/paraganglioma: case series from a tertiary referral centre for pheochromocytomas and paragangliomas. J

Endocrinol Invest. 2021;44(10):2253-2259. doi:10.1007/s40618-021-01532-5
82. Angelousi A, Peppa M, Chrisoulidou A, et al. Malignant pheochromocytomas/paragangliomas and ectopic hormonal secretion: a case series and review of the literature. Cancers (Basel). 2019;11(5):724. doi:10.3390/cancers11050724
83. Siddiqui UM, Matta S, Wessolossky MA, Haas R. Fever of unknown origin: could it be a pheochromocytoma? A case report and review of the literature. Case Rep Endocrinol. 2018;2018:3792691. doi:10.1155/2018/3792691
84. Milione M, Maisonneuve P, Spada F, et al. Inflammation-related cytokines and their roles as prognostic markers in gastroenteropancreatic neuroendocrine neoplasms. *Gastroenterol Res Pract*. 2020;2020:8315174. doi:10.1155/2020/8315174
85. Srivastava A, Alexander J, Priest WM. Verner-Morrison syndrome with neurotensin production. Br Med J (Clin Res Ed). 1982;284(6320):941-942. doi:10.1136/bmj.284.6320.941
86. Blackburn AM, Bryant MG, Adrian TE, Bloom SR. Pancreatic tumours produce neurotensin. J Clin Endocrinol Metab. 1981;52(4):820-822. doi:10.1210/jcem-52-4-820
87. Ohki-Hamazaki H, Iwabuchi M, Maekawa F. Development and function of bombesin-like peptides and their receptors. Int J Dev Biol. 2005;49(2-3):293-300. doi:10.1387/ijdb.041913ho
88. Wolf HJ, Müller-Hermelink HK. Gastrin-releasing peptide (GRP-like) immunoreactivity in human neuroendocrine tumors. *Virchows Arch B Cell Pathol Incl Mol Pathol*. 1986;52(1):41-48. doi:10.1007/BF02889950
89. Molina R, Auge JM, Alicarte J, et al. Pro-gastrin-releasing peptide in patients with benign and malignant diseases: clinical comparison with CEA, SCC, CYFRA 21-1 and NSE in patients with lung cancer. *Anticancer Res*. 2005;25(3B):1773-1778.
90. Sanger GJ, Lee K. Motilin: towards a new understanding of the gastrointestinal system and therapeutic-potential. *Br J Pharmacol*. 2008;154(6):1147-1154. doi:10.1038/bjp.2008.204
91. Fiasse R, Deprez P, Weynand B, et al. An unusual metastatic motilin-secreting neuroendocrine tumour with a 20-year survival. Pathological, biochemical and motility features. Digestion. 2001;64(4):255-262. doi:10.1159/000048870
92. Bosman MSP, Florenzano P, Gafni RI, Collins MT. Tumor-induced osteomalacia: a systematic literature review. Endocr Connect. 2024;13(4):e240039. doi:10.1530/EC-24-0039
93. Lallemant B, Joubert J, Desmeules S, et al. FGF23-mediated tumor-induced osteomalacia in a patient with a pancreatic neuro-endocrine tumor. Clin Biochem. 2022;104:54-58. doi:10.1016/j.clinbiochem.2022.02.008
94. Jan de Beur SM, Miller PD, Weber TJ, et al. Burosumab for the treatment of tumor-induced osteomalacia. J Bone Miner Res. 2021;36(4):627-635. doi:10.1002/jbmr.4233
95. Rehfeld JF. Cholecystokinin and the hormone-receptor concept. J Clin Med. 2021;10(4):712. doi:10.3390/jcm10040712
96. Rehfeld JF, Federspiel B, Bardram L. A cholecystokinin-secreting pancreatic endocrine tumour (CCKoma) with liver metastases. N Engl J Med. 2004;351(13):1364-1365. doi:10.1056/NEJM200409233511326
97. Pare A, Tamilia M. A Case of Paraneoplastic Erythropoietin Secretion Secondary to Medullary Thyroid Cancer. *J Endocr Soc*. 2021;5(Suppl 1):A877–A878. doi:10.1210/jendso/bvab048.1792
98. Drénou B, Le Tulzo Y, Caulet-Maugendre S, et al. Pheochromocytoma and secondary erythrocytosis: role of tumour erythropoietin secretion. Nouv Rev Fr Hematol (1978). 1995;37(3):197-9
99. Franchina M, Cavalcoli F, Falco O, et al. Biochemical markers for neuroendocrine tumors: traditional circulating markers and recent development—a comprehensive review. Diagnostics (Basel). 2024;14(12):1289. doi:10.3390/diagnostics14121289
100. Kopylova M, Deskur A, Ziemniak P, et al. Circulating neuroendocrine tumor biomarkers: past, present and future. *J Clin Med*. 2022;11(19):5542. doi:10.3390/jcm11195542
101. Mandair D, Ensell L, Spanswick VJ, et al. Circulating tumor cells in neuroendocrine neoplasms: a systematic review and meta-analysis. *Endocr Relat Cancer*. 2020;27(1):R1-R18. doi:10.1530/ERC-19-0128Grolmusz VK, Kövesdi B, Rácz K, Patócs A. Role of microRNAs in the pathogenesis of neuroendocrine tumors. *Front Endocrinol (Lausanne)*. 2021;11:613143. doi:10.3389/fendo.2020.613143
102. Grolmusz VK, Kövesdi B, Rácz K, Patócs A. Role of microRNAs in the pathogenesis of neuroendocrine tumors. *Front Endocrinol (Lausanne)*. 2021;11:613143. doi:10.3389/fendo.2020.613143
103. Hermans BC, Derks JL, Thunnissen E, et al. Identifying the site of origin for neuroendocrine neoplasms: the role of IHC, proteomics and molecular profiling. *Cancers (Basel)*. 2022;14(15):3649. doi:10.3390/cancers14153649
104. Mata-Martínez P, Celada L, Cueto FJ, et al. A blood-based liquid biopsy analyzing soluble immune checkpoints and cytokines identifies distinct neuroendocrine tumors. *J Exp Clin Cancer Res*. 2025;44(1):82. doi:10.1186/s13046-025-03337-3
105. Hesami M, Blake M, Anderson MA, et al. Diagnostic anatomic imaging for neuroendocrine neoplasms: maximizing strengths and mitigating weaknesses. *J Comput Assist Tomogr*. 2024;48(4):521-532. doi:10.1097/RCT.0000000000001615
106. Maxwell JE, Howe JR. Imaging in neuroendocrine tumors: an update for the clinician. *Int J Endocr Oncol*. 2015;2(2):159-168. doi:10.2217/ije.14.40
107. Chamokova B, Bastati N, Poetter-Lang S, et al. The clinical value of secretin-enhanced MRCP in the functional and morphological assessment of pancreatic diseases. *Br J Radiol*. 2018;91(1084):20170677. doi:10.1259/bjr.20170677
108. Krenning EP, Kwekkeboom DJ, Bakker WH, et al. Somatostatin receptor scintigraphy with [111In-DTPA-

D-Phe1]- and [123I-Tyr3]-octreotide: the Rotterdam experience with more than 1000 patients. *Eur J Nucl Med*. 1993;20(8):716-731. doi:10.1007/BF00181765

109. Bozkurt MF, Virgolini I, Balogova S, et al. SNMMI procedure standard/EANM practice guideline for SSTR-PET/CT imaging in neuroendocrine tumors. J Nucl Med. 2023;64(2):204-213. doi:10.2967/jnumed.122.264701
110. Wang IE, SaTsu HA, Brooks AF, et al. Molecular imaging of neuroendocrine tumors: current applications and future trends. Diagn Interv Imaging. 2025;106(11):385-393. doi:10.1016/j.diii.2025.05.005.
111. Girod B, Prasad V. Advances in molecular imaging for neuroendocrine neoplasms. Cancers. 2025;17 (12):2013. doi:10.3390/cancers17122013