The International Academy of Pathology
Hong Kong Division
HKIAP Scientific Congress 2026

Gastric ECL-Cell NETs

New Type 4 & Type 5 Subtypes

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Gastric NETs: ~20-Fold Rise in Incidence, 1975–2016

Age-adjusted incidence, per 1,000,000

1975

0.309

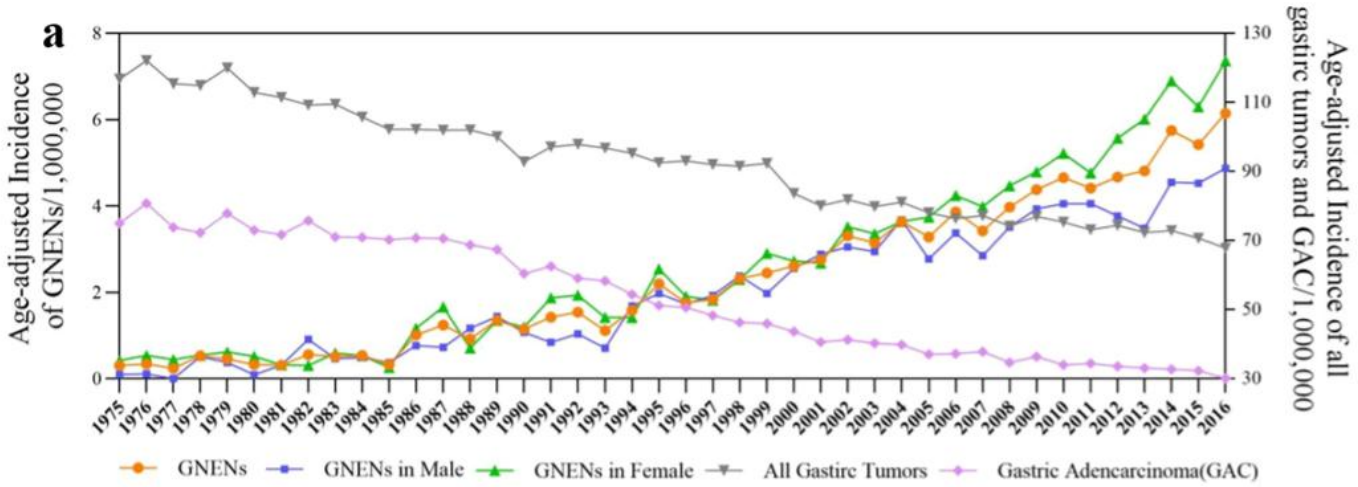
2016

6.149

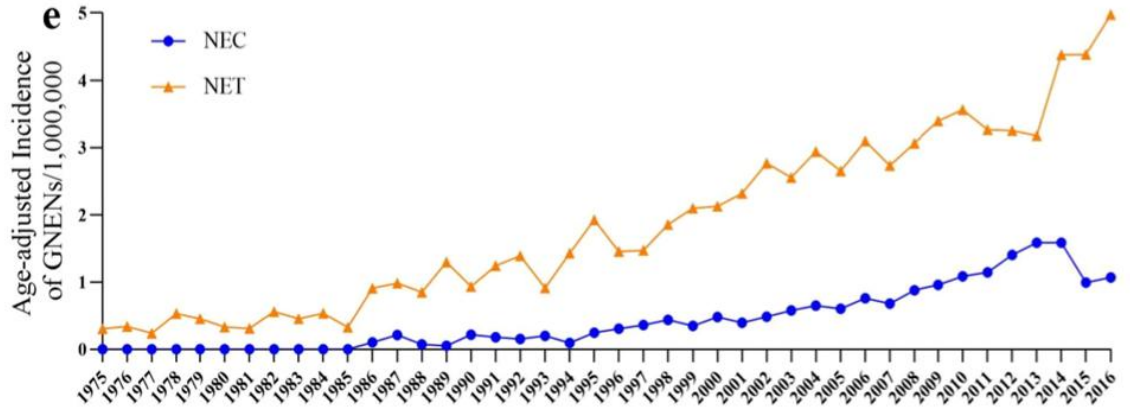
≈20× increase (calculated)

Females slightly > males

All gastric tumors and ACA **declined** over the same period



NEC vs NET



Hu P, et al. Gastric Cancer 2020;23:591–599 (CC BY 4.0)

Improved Detection vs True Increase in Incidence

1. **Endoscopic surveillance**
   More upper endoscopy finds small, asymptomatic lesions
2. **Biopsy of "simple" polyps**
   Small polyps now sampled rather than ignored
3. **Use of IHC**
   Neuroendocrine markers improve recognition
4. **Still under-counted?**
   Atypical or absent symptoms → Is true incidence higher?
5. **Contribution of long-term PPI use**
   Extent of contribution from PPI-related hypergastrinemia unproven

Hu P, et al. Gastric Cancer 2020;23:591–599 (CC BY 4.0)

Gastric NETs: Updated 2026 WHO Classification

ESTABLISHED SUBTYPES

NEW SUBTYPES (2026)

Type 1
Autoimmune
Atrophic Gastritis

Type 2
MEN1 / ZES
Gastrinoma

Type 3
Sporadic
(No Hypergastrinemia)

Type 4
Germline ATP4A
Mutation

Type 5
Chronic PPI
Use

Most gastric NETs arise from enterochromaffin-like (ECL) cells of the oxyntic mucosa

Gastric NETs: 3 Established Subtypes (pre-2026 WHO)

Type 1

~70–80%

Autoimmune atrophic gastritis

- Female predominance (~65%)
- Hypochlorhydria → hypergastrinemia → ECL-cell proliferation
- Atrophy of parietal and chief cells in gastric body
- Small (0.5–1.0 cm); multifocal (~70%), corpus
- Invasion usually superficial
- Nodal/distant metastasis very rare
- Managed endoscopically; good long-term prognosis

Type 2

~5%

Zollinger–Ellison / MEN1

- Male = female; mean age ~50 y
- Hypergastrinemia from a gastrinoma
- Nearly always MEN1
- Small (≤1.5 cm); multifocal (~100%)
- 10–30% metastasize
- Managed by treating the underlying gastrinoma

Type 3

~15–25%

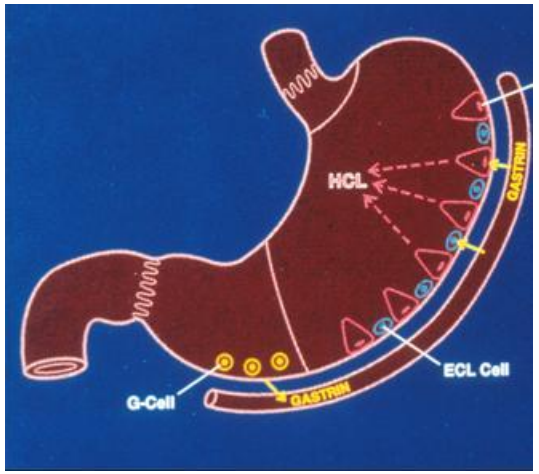
Sporadic, not gastrin-dependent

- Male predominance (~80%); mean age ~55 y
- Solitary (~100%)
- ~71% >2 cm with advanced stage
- Much higher malignant potential
- Typically radical gastrectomy
- Small localized tumors: advanced endoscopic resection

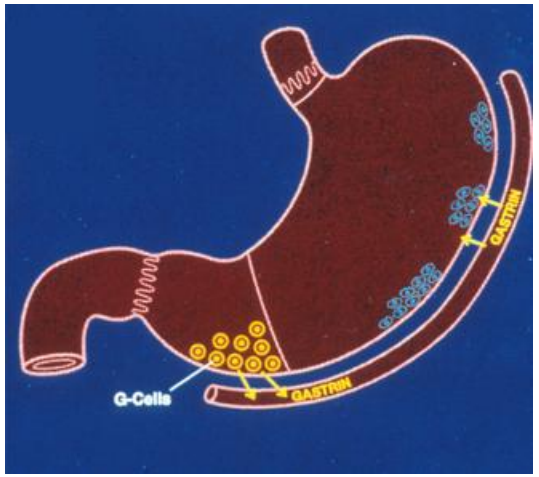
Adapted in part from the CAP Protocol for Neuroendocrine Tumors of the Stomach (v5.0.0.0)

Pathogenesis of Type 1 gastric NET in Autoimmune Gastritis

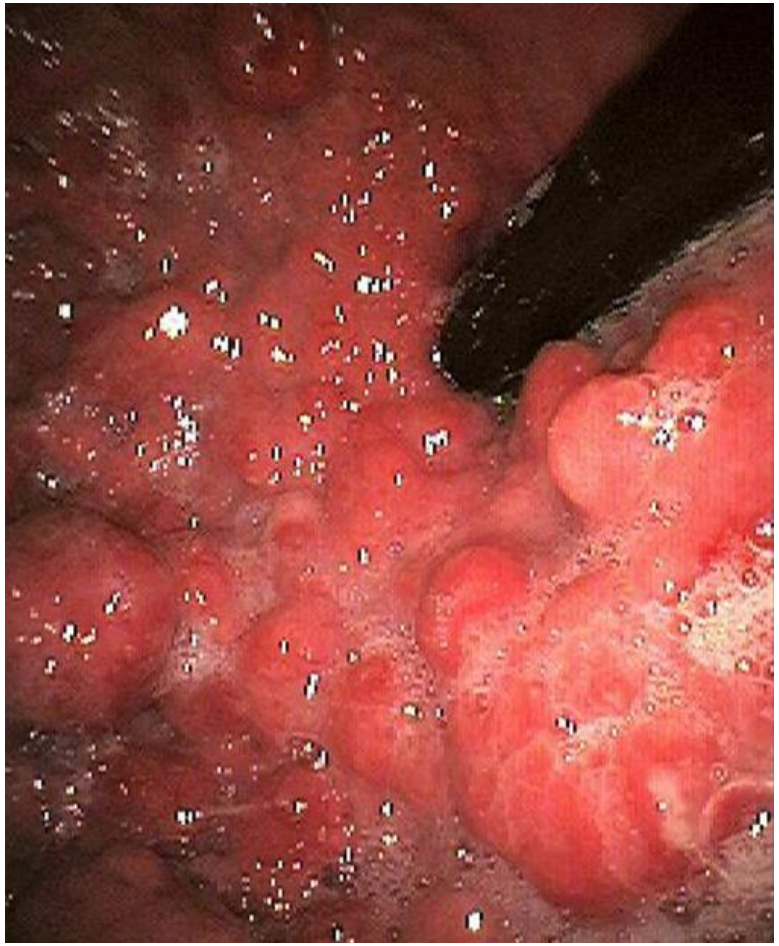
Normal



Autoimmune gastritis

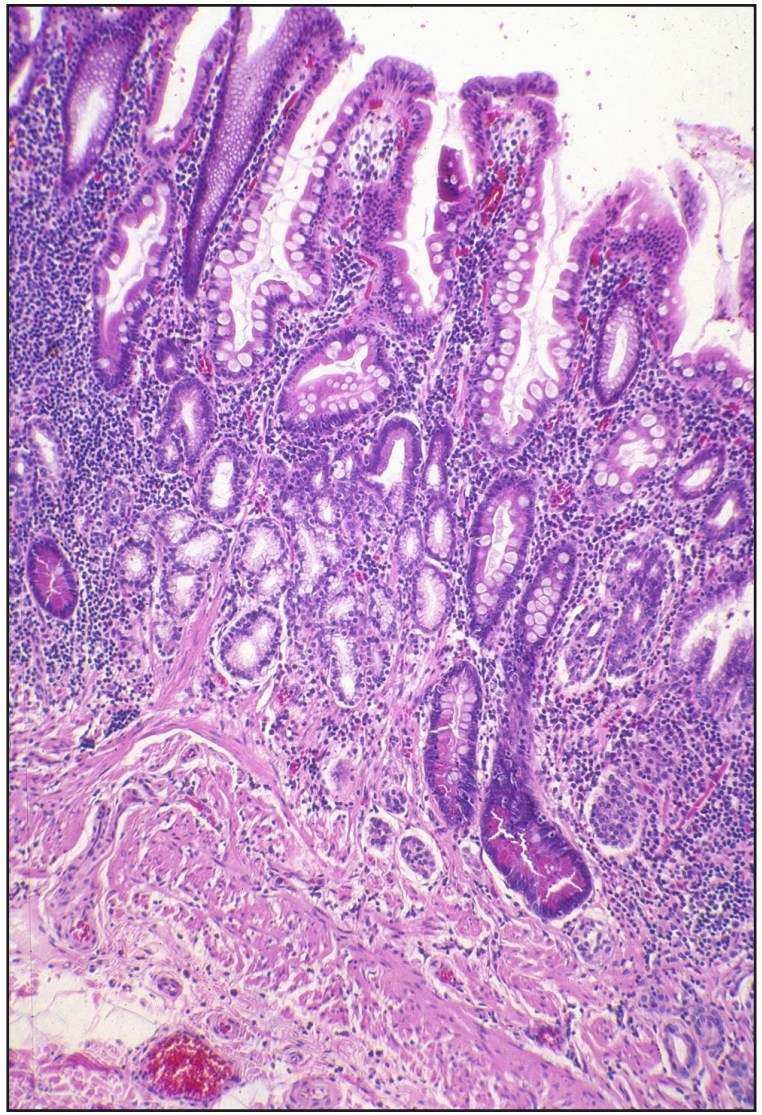


1. **Autoantibodies**
   Parietal cell H^+/K^+-ATPase, intrinsic factor
2. **Oxyntic atrophy → achlorhydria**
   ↑ Risk of enteric infections
3. **G-cell hyperplasia with secondary hypergastrinemia**
4. **ECL-cell hyperplasia**
   Trophic gastrin drive in oxyntic mucosa
5. **Type 1 gastric NET**
   Develops in a subset of patients

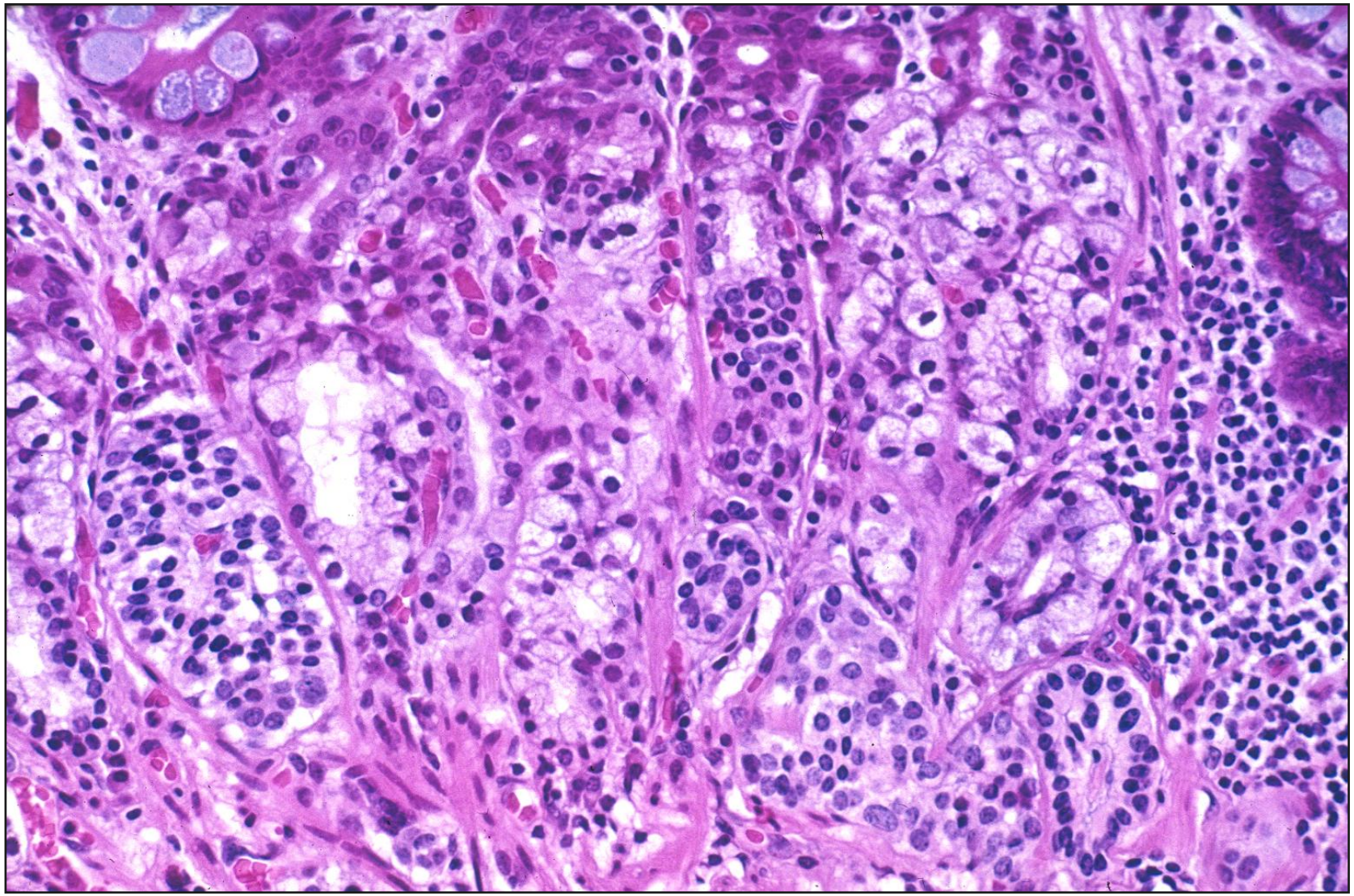


Endoscopy: multifocal polypoid lesions in the corpus

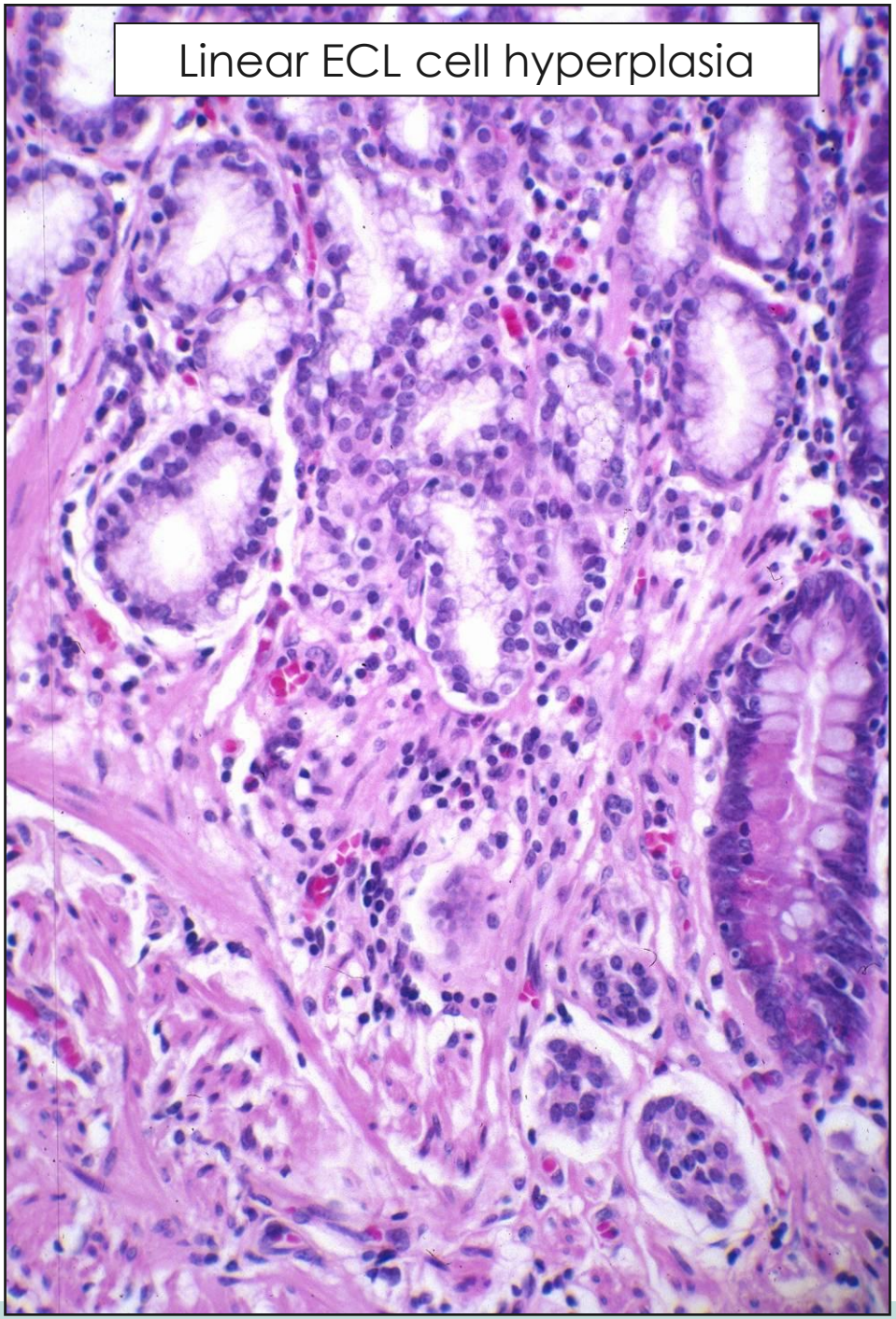
Chronic infl. centered around glands
Parietal & chief cell loss with atrophy

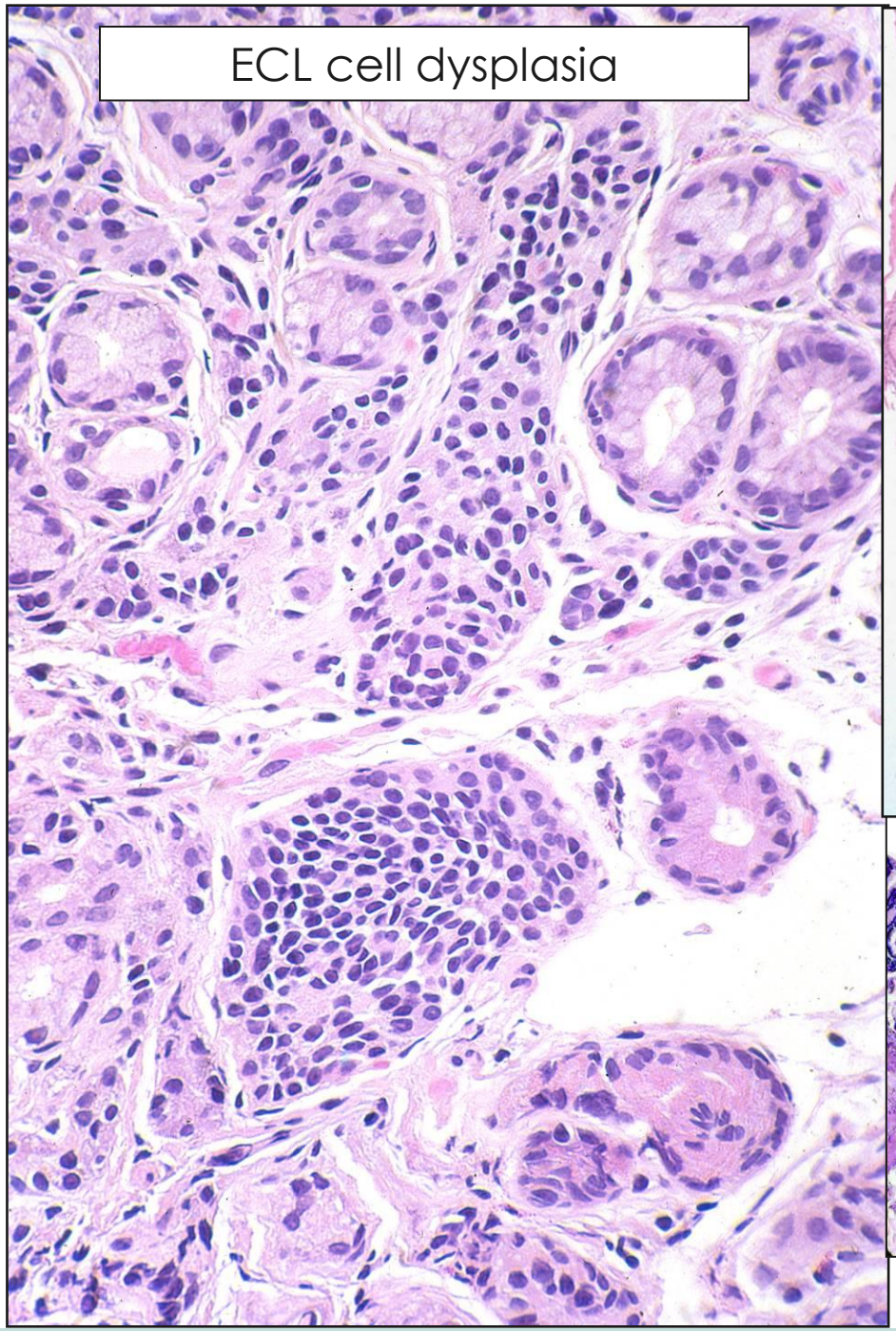


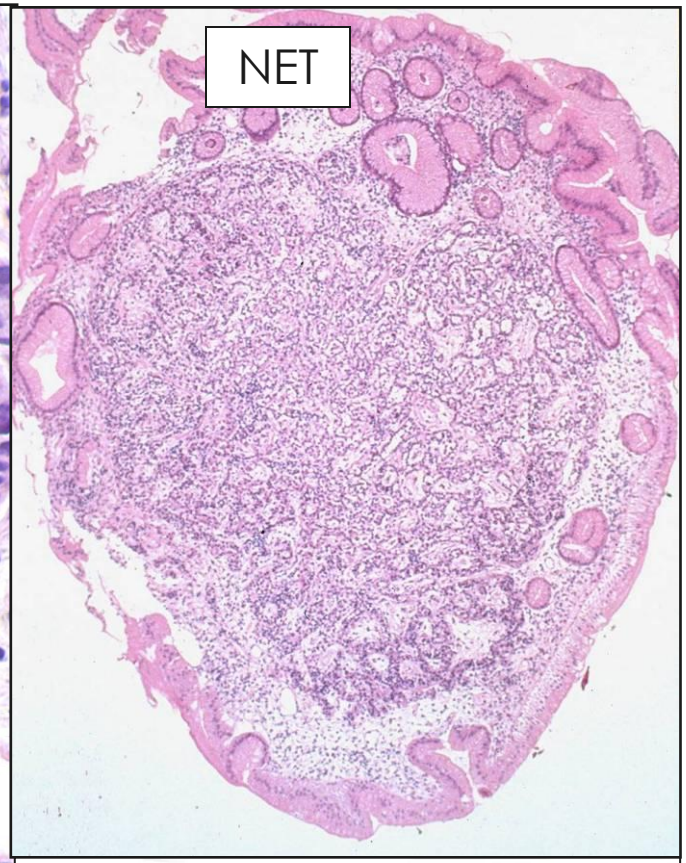
Pyloric and intestinal metaplasia

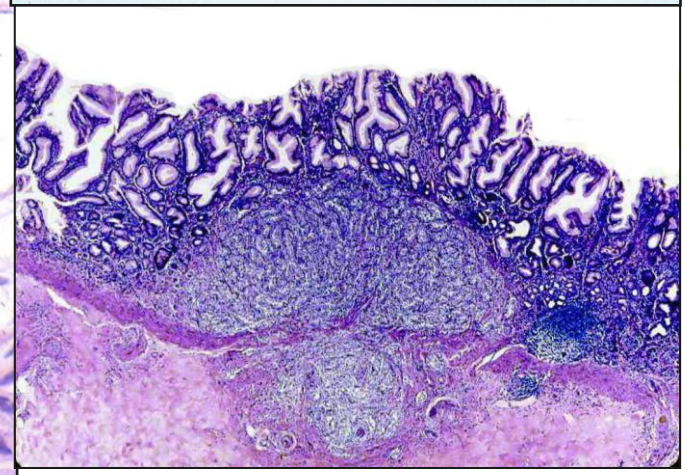


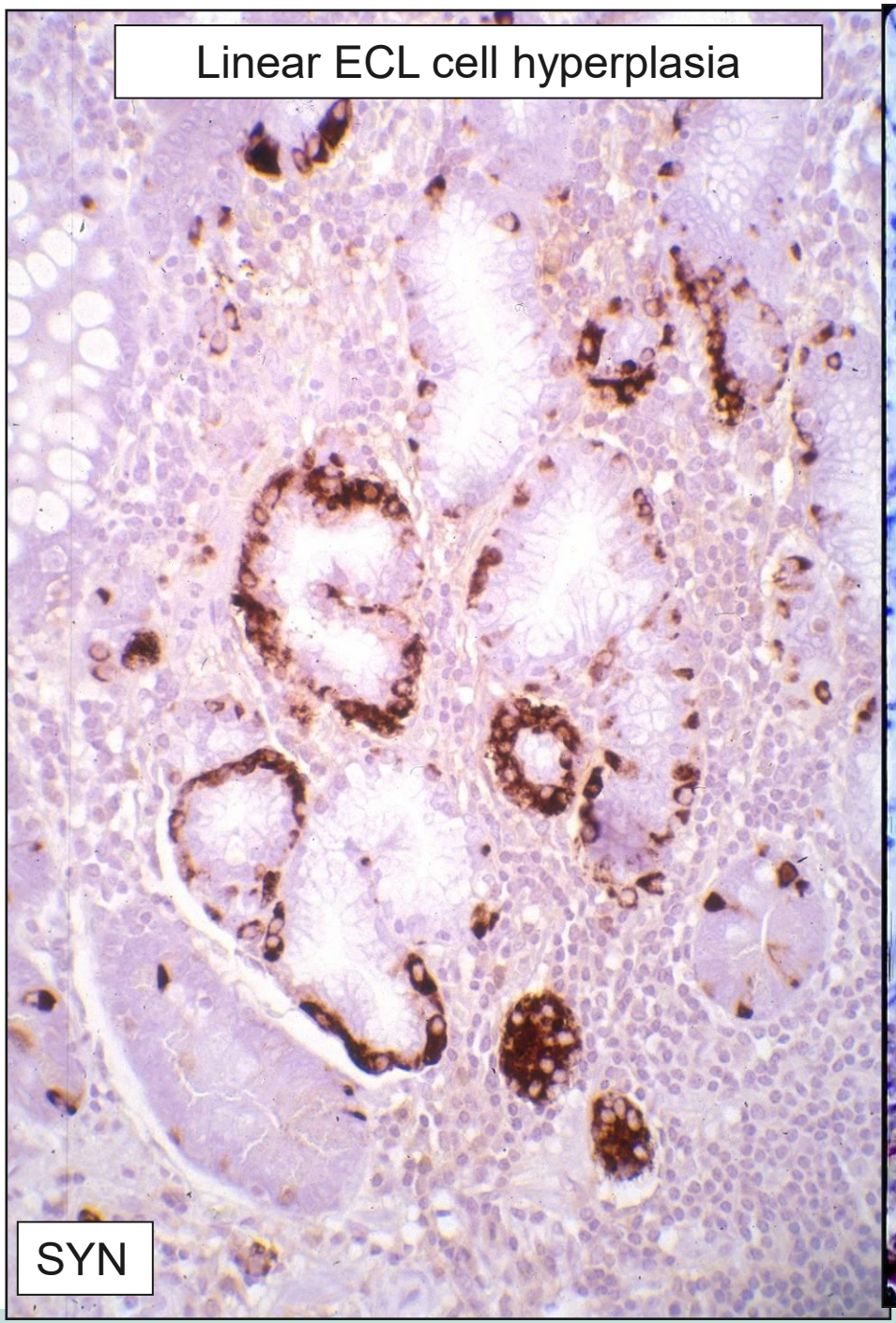
Endocrine cells hyperplasia.

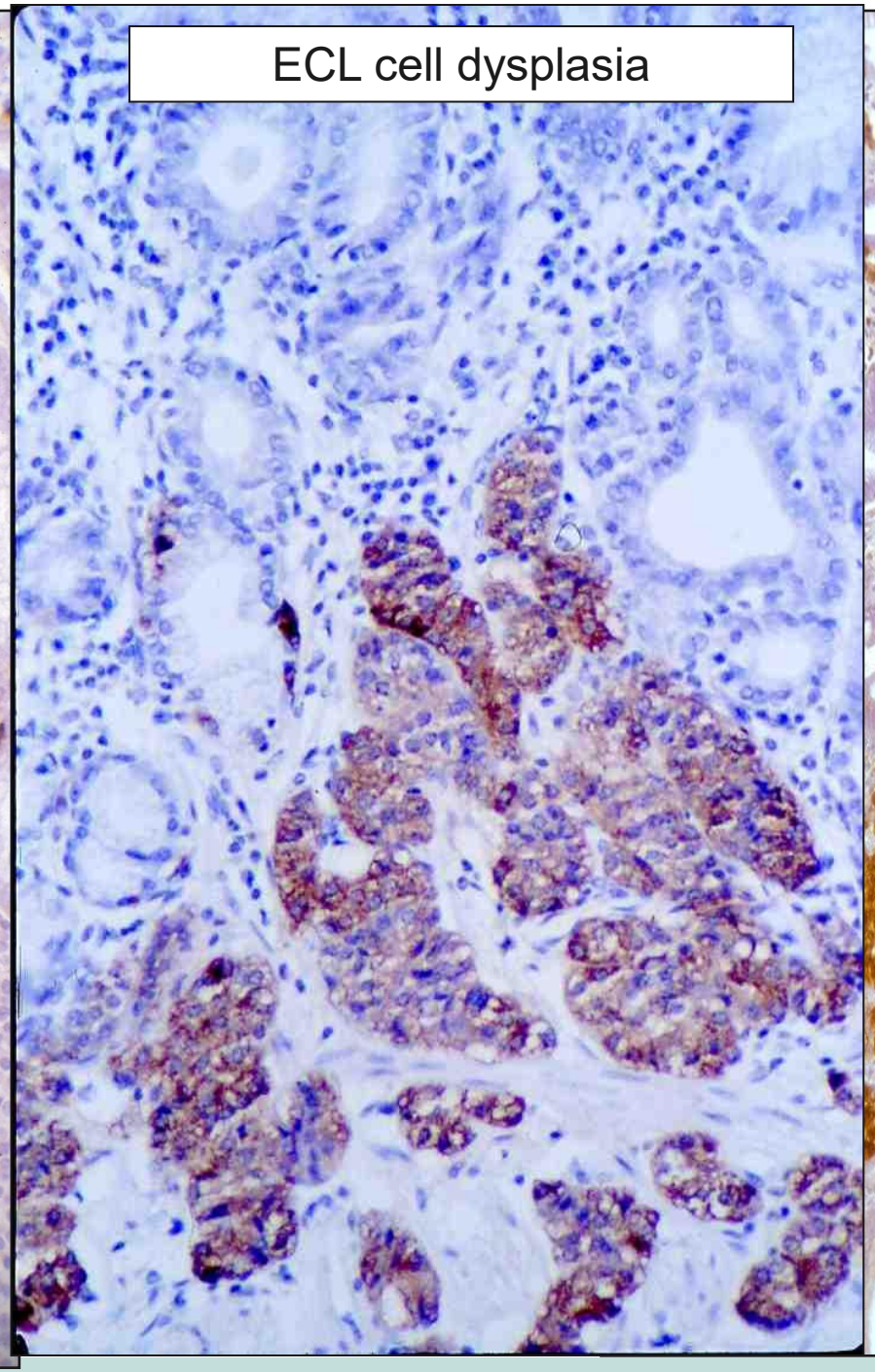

Linear ECL cell hyperplasia

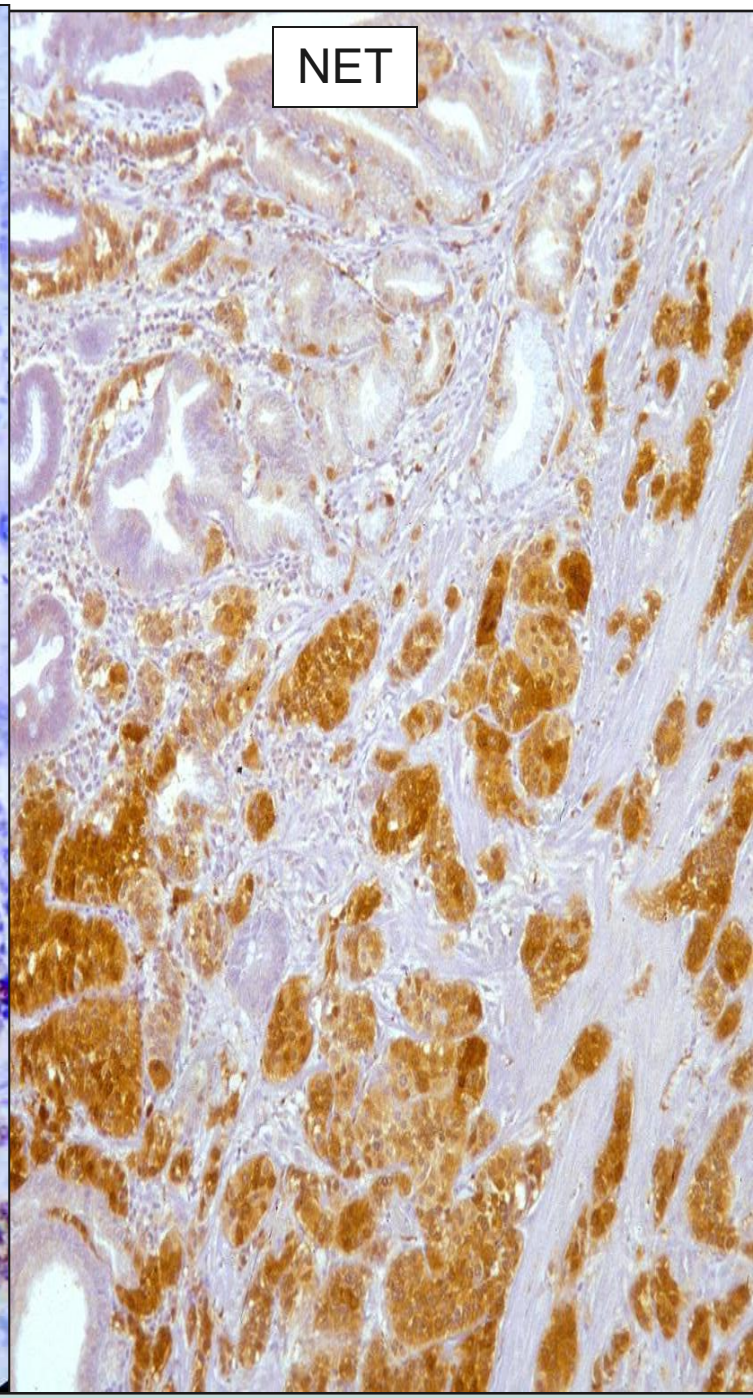

ECL cell dysplasia


NET




Linear ECL cell hyperplasia
SYN

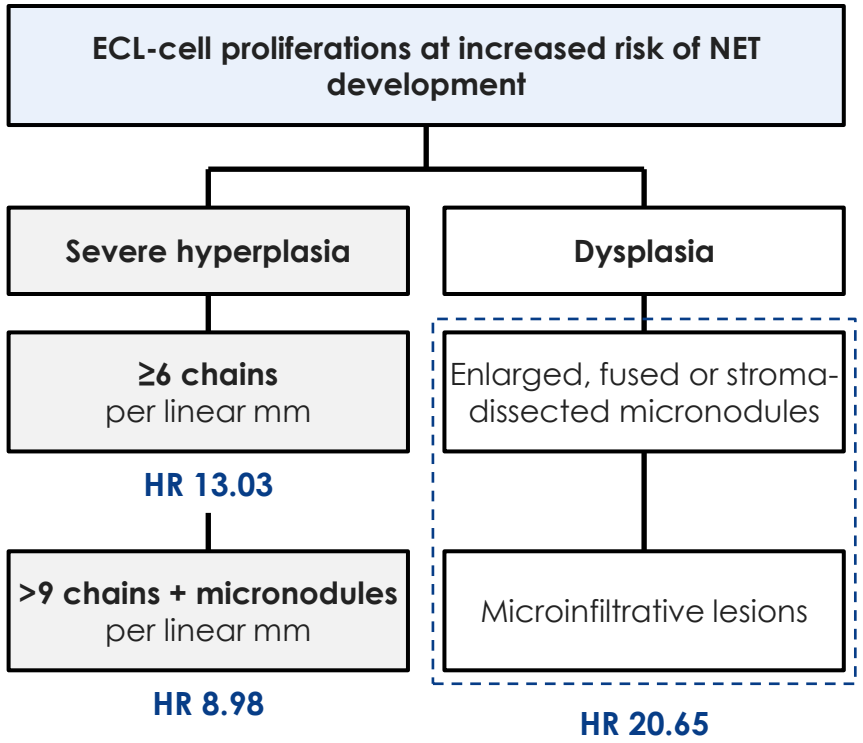

ECL cell dysplasia


NET

ECL-Cell Proliferations

Nomenclature & risk of precursor lesions

	Type	Number	Pattern	Size (µm)	Invasion
Hyperplasia	Linear	≤5 cells	Row	–	–
	Micronodular	≥5 cells	Cluster	100–150	
	Adenomatoid	≥5 cells	Micronodules (≥5)	100–150	L. propria
Dysplasia			Micronodules: A – enlarging/fusing B – microinvasive C – w/ newly formed stroma	<500	L. propria
Neoplasia	**Intramucosal**		**Solid**	**≥500**	**L. propria**
	Invasive		**Solid**	**≥500**	**Submucosa**



Chain = linear sequence of >5 ECL cells. HR = hazard ratio for dysplasia and/or NET (hyperplastic lesions) and for NET (dysplastic lesions).

PMID: 23642738

Types 2 & 3 Gastric NETs

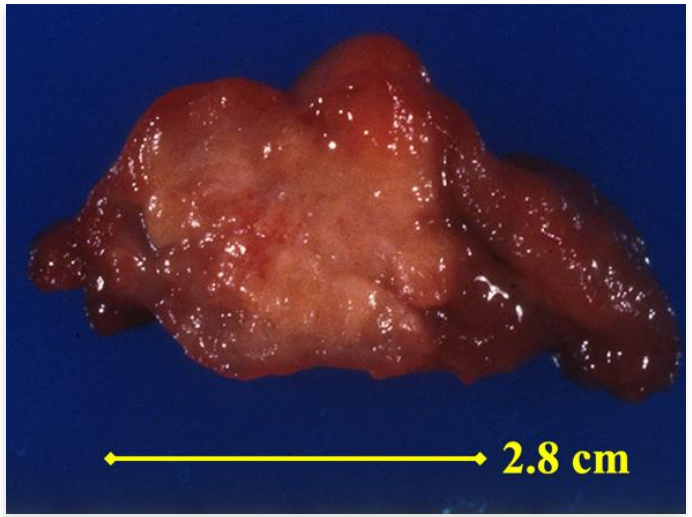
Type 2 (~5% of gastric NETs)

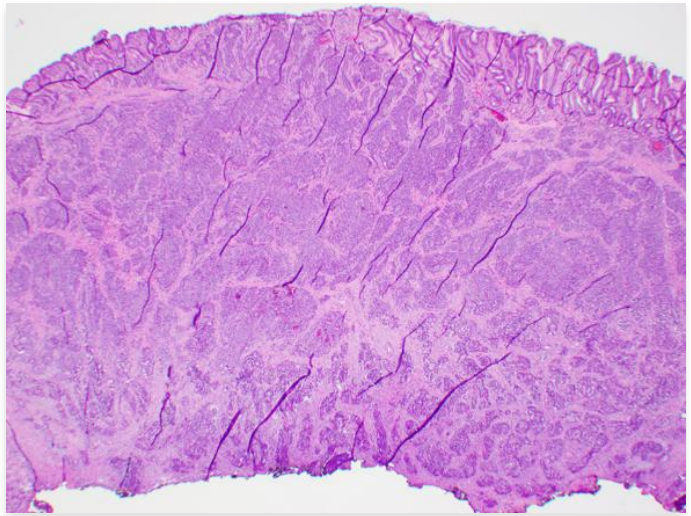
- Zollinger–Ellison syndrome; nearly always MEN1
- Hypergastrinemia from duodenal/pancreatic gastrinoma
- Hypertrophic hypersecretory gastropathy
- ECL-cell hyperplasia may be present
- Small (≤1.5 cm) and multicentric
- Male = female; mean age ~50 y
- Metastasis in 10–30%
- Management: control the underlying gastrinoma

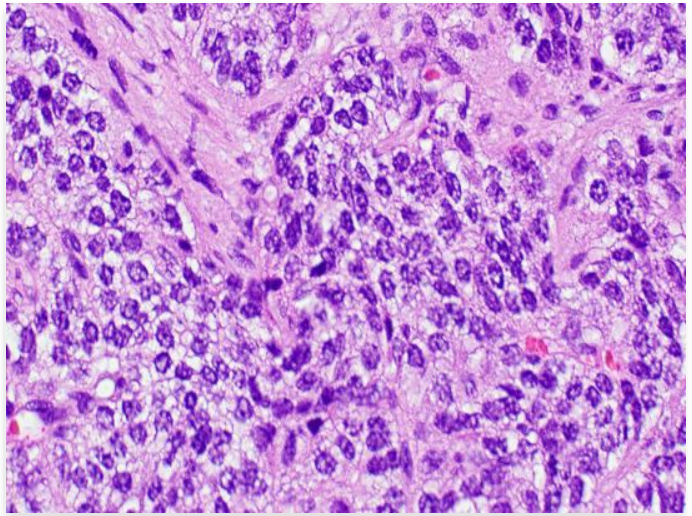
Type 3 (sporadic; ~15–25%)

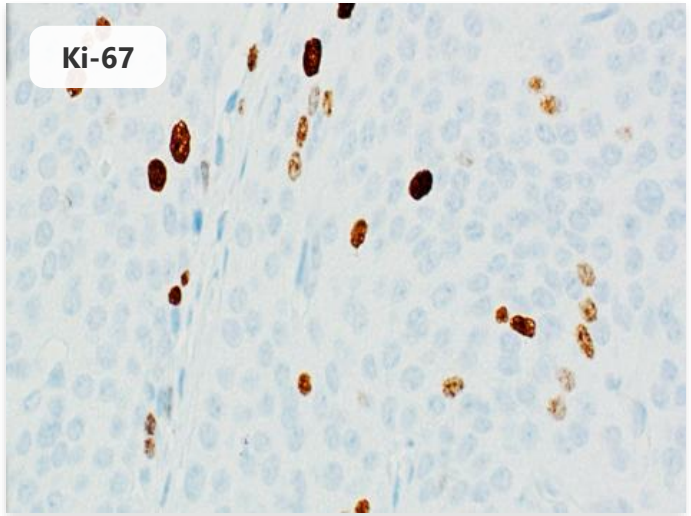
- Not associated with hypergastrinemia
- Typically solitary mass; usually non-functional
- No background ECL-cell hyperplasia
- Male predominance (~80%); mean age ~55 y
- ~71% >2 cm with advanced stage at diagnosis
- Much higher malignant potential
- Typically radical gastrectomy
- Small, localized tumors: advanced endoscopic resection possible

Type 3 Well-Differentiated NET: Case Example









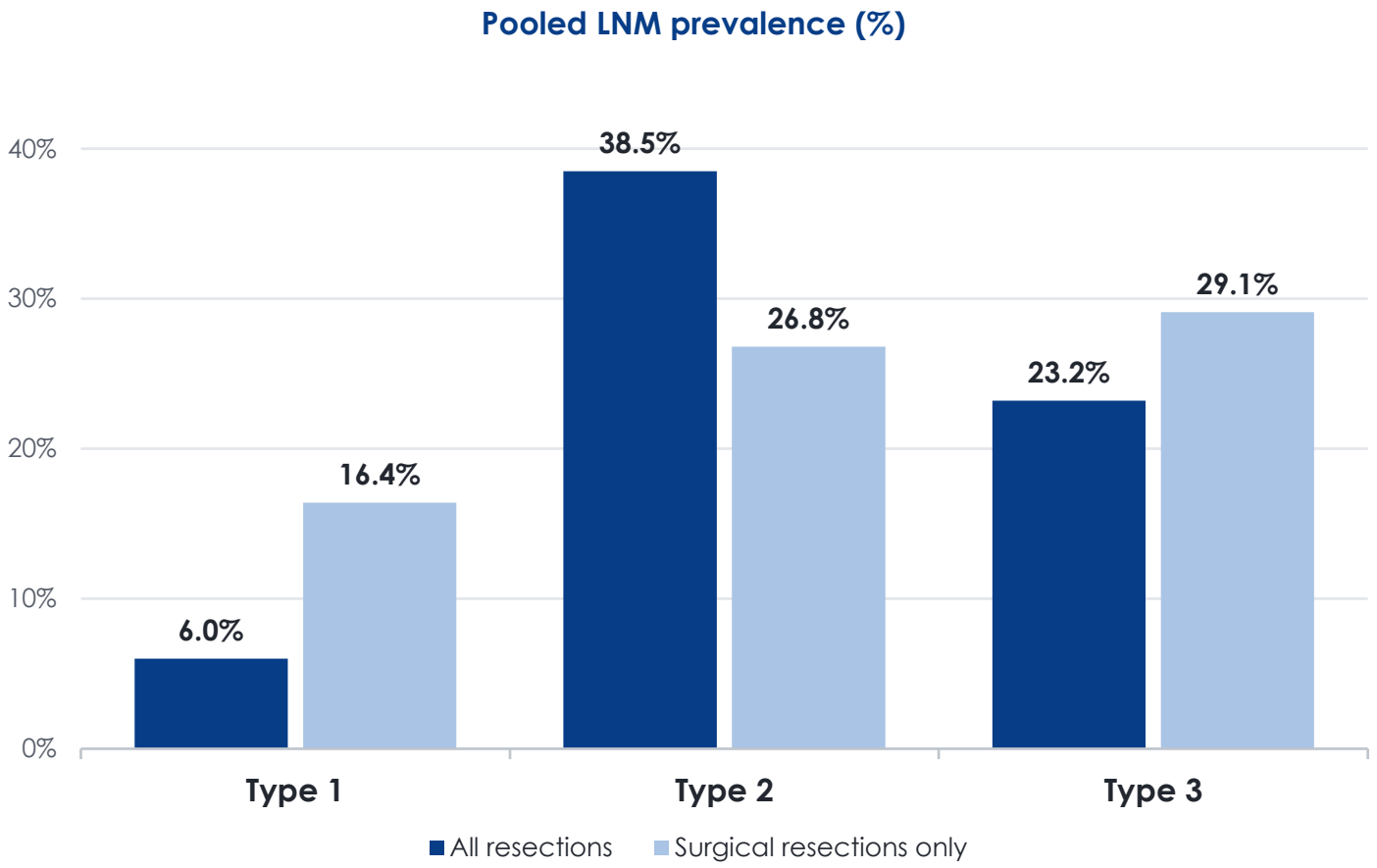
2.8 cm

Tumor size

Grade 2

Based on Ki-67 proliferation index

Lymph Node Metastasis by Subtype



Odds of LNM vs Type 1

11.5 OR
Type 2
95% CI 3.5–38.5 · n = 28 (5 studies)

6.9 OR
Type 3
95% CI 3.8–12.5 · n = 477 (14 studies)

0.54 OR
Type 2 vs 3
95% CI 0.19–1.50 · not significant

Ogata Y, et al. Dig Endosc 2025;37:834–843

2026 WHO 6th Edition: New Subtypes

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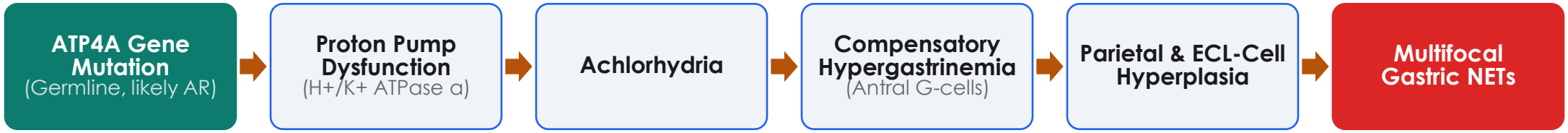
Type 5
Chronic PPI
Use

Unifying mechanism: proton pump dysfunction → achlorhydria/hypochlorhydria → compensatory hypergastrinemia → ECL-cell hyperplasia → NETs

Key distinction from Type 1:

- Type 1: Autoimmune destruction of parietal cells → mucosal **atrophy** with loss of parietal cells
- Types 4 & 5: Proton pump dysfunction → parietal cell **hyperplasia/hypertrophy** (parietal cells present but non-functional)

Type 4: Germline ATP4A Mutation (Intrinsic Proton-Pump Dysfunction)



Genetics & Clinical

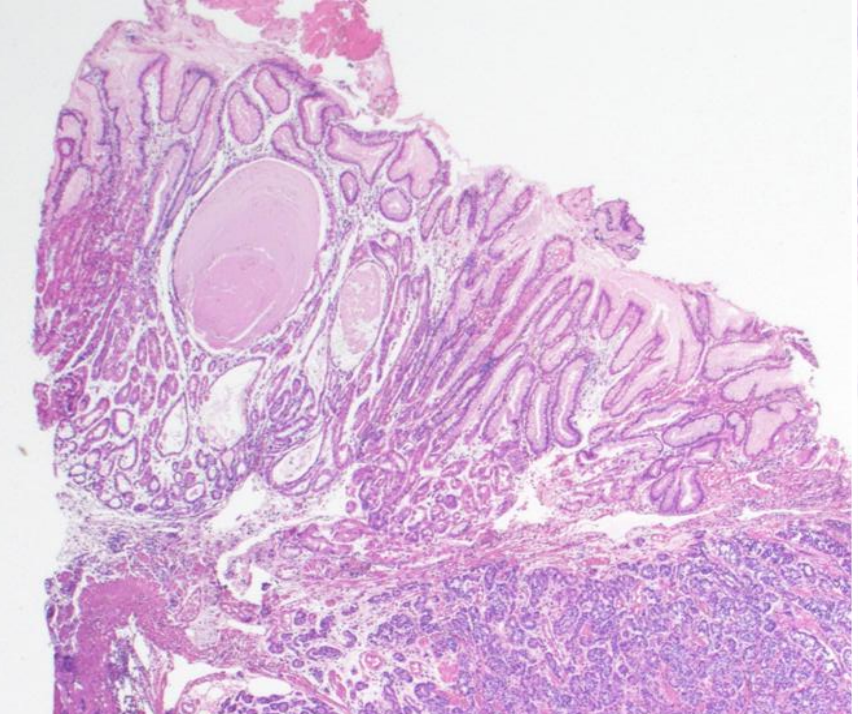
- Inactivating germline mutation of *ATP4A* gene (encodes H+/K+ ATPase a-subunit)
- Likely autosomal recessive inheritance
- Uncertain if ATP4A is the sole causative gene

Type 4 Gastric NET: Clinical Features

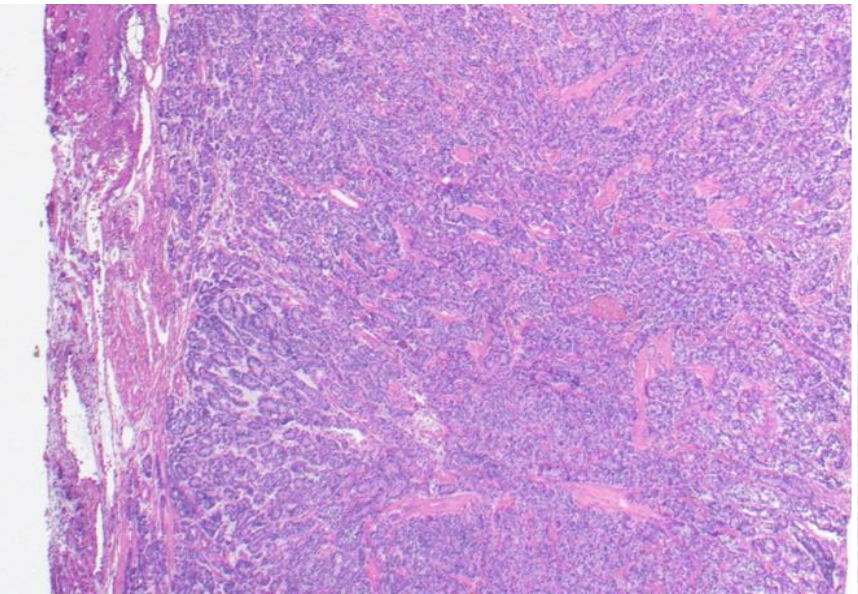
- Exceedingly rare; female predominance
- Multiple (often innumerable) tumors in body/fundus;.
- Typically <15 mm
- Most patients asymptomatic at diagnosis
- Gastrin markedly elevated (>1,000 pg/mL in most cases)
- Low malignant potential
- LN metastases in 4 reported patients: 3 from a consanguineous Spanish family (ATP4A c.2107C>T) and 1 micrometastasis
- Distant metastases: not reported
- Treatment: gastrectomy, antrectomy, EMR/ESD, somatostatin analogs, or observation

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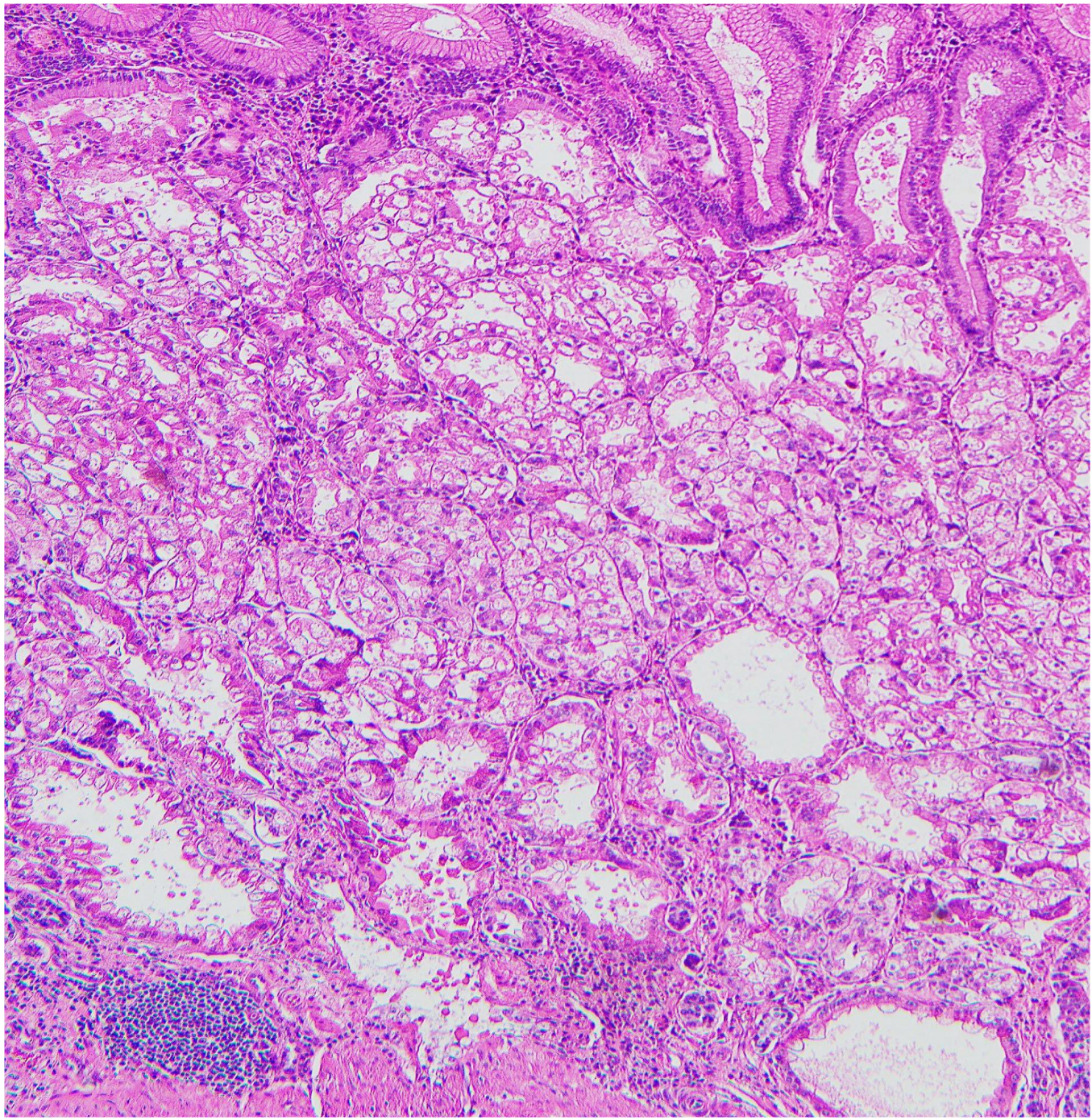
Hypertrophic/hyperfunctioning mucosa w/ dilated, protruding fundic glands



Characteristic eosinophilic secretions

Parietal cell *hypertrophy* with cytoplasmic vacuolization

IHC: **Negative** staining for α/β-subunits of H+/K+ ATPase



Type 4 Gastric NETs: Reported Cases (1 of 2)

First author/year	Age/sex	No. of tumors on endoscopy	Largest tumor size	Tumor grade	Gastrin (pg/mL)	Pathologic LN involvement	Distant metastases	Treatment	Genetic testing	ATPase α/β IHC staining
Ooi/1995	47/M	19	1.5 cm	ND	>800	None	None	Gastrectomy	ND	ND
Hinoshita/2005	52/F	Multiple	3 mm	ND	1820	None	None	EMR	ND	ND
Abraham/2005	54/F	Multiple	13 mm	1	1400	one micrometast.	None	Gastrectomy	ND	Weak α/β subunits
Hosoya/2008	30/M	Multiple	20 mm	ND	2400	None	None	Gastrectomy	ND	ND
Nakata/2010	50/F	Multiple	12 mm	ND	1400	None	None	Gastrectomy	ND	ND
Calvete/2015*	39/M	>100	ND	2	486	Yes	None	Gastrectomy	ATP4A c.2107C>T	ND
Calvete/2015*	37/M	>100	ND	1	398	Yes	None	Gastrectomy	ATP4A c.2107C>T	ND
Calvete/2015*	33/F	>100	ND	2	>1000	Yes	None	Gastrectomy	ATP4A c.2107C>T	ND
Calvete/2015*	23/F	50	ND	1	455	No	None	Gastrectomy	ATP4A c.2107C>T	ND
Calvete/2015*	27/F	50	ND	2	597	No	None	Gastrectomy	ATP4A c.2107C>T	ND

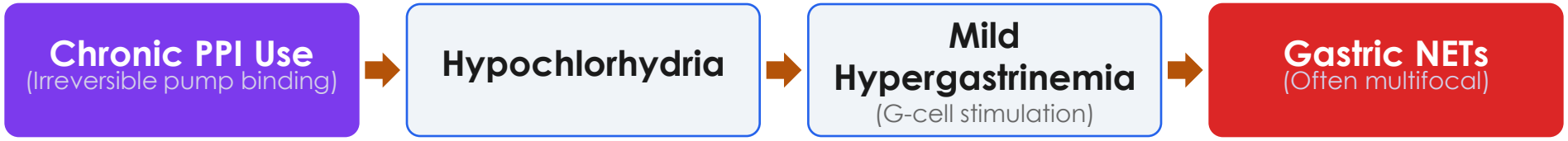
ND: not done; NA: not applicable (no lymph node sampling); EMR: endoscopic mucosal resection; ESD: endoscopic submucosal dissection; LAR: long-acting release

Type 4 Gastric NETs: Reported Cases (2 of 2)

First author/year	Age/sex	No. of tumors on endoscopy	Largest tumor size	Tumor grade	Gastrin (pg/mL)	Pathologic LN involvement	Distant metastases	Treatment	Genetic testing	ATPase α/β IHC staining
Ishioka/2019	37/M	Multiple	5 mm	ND	6800	NA	None	None	ND	Absent α/β subunits
Ishioka/2019	36/M	Multiple	Small	ND	2600	NA	None	Antrectomy	ND	Absent α/β subunits
Ihara/2020*	51/F	Multiple	11 mm	ND	4722	None	None	EMR	ATP4A c.598G>A and c.1993C>T	ND
Hirai/2022	62/F	Multiple	10 mm	1	770	NA	None	Octreotide LAR	ND	Positive α / absent β
Shiroma/2022	50/F	3	8 mm	2	>3000	NA	None	Gastrectomy	ATP4A c.1993C>T	Positive β / absent α
Abe/2022	69/F	6	5 mm	ND	11675	NA	None	None	ND	Absent α/β subunits
Sasaki/2024	47/F	Multiple	10 mm	2	4450	NA	None	ESD	ATP4A c.2108G>A	Absent α/β subunits

ND: not done; NA: not applicable (no lymph node sampling); EMR: endoscopic mucosal resection; ESD: endoscopic submucosal dissection; LAR: long-acting release

Type 5: Chronic PPI-Associated



- *Shared with Types 1 & 4: hypochlorhydria stimulates G-cell gastrin secretion, driving ECL-cell proliferation*

- Diagnosis requires documented PPI duration
- Longer PPI exposure (>5–10 years) increases diagnostic specificity
- Shorter PPI exposure: gastric NET more likely sporadic (Type 3)
- Biopsy of non-tumoral oxyntic mucosa is critical
- Hypergastrinemia relatively mild (vs marked in Type 4); tends to normalize after PPI discontinuation

Type 5: Clinicopathologic Features

- First human cases reported in the 1990s; incidence rising rapidly
- **Distinguishing Type 5 from Type 3 has major management implications**
- Histology: parietal/ECL-cell hyperplasia, parietal cell vacuolization, fundic gland polyps, foveolar hyperplasia
- Diagnosis supported by biopsy of background mucosa (away from tumor nodules) showing PPI-associated changes
- Hypergastrinemia relatively mild; normalizes with PPI discontinuation
- Often multifocal, but fewer tumors than Type 4
- Malignant potential low: higher than Type 1, lower than Type 3
- Grade: roughly equal Grade 1 and Grade 2; Grade 3 rare
- LN metastases uncommon; distant metastases exceedingly rare

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- Diagnosis supported by biopsy of background mucosa (away from tumor nodules) showing PPI-associated changes
- Hypergastrinemia relatively mild; normalizes with PPI discontinuation
- Often multifocal, but fewer tumors than Type 4
- Malignant potential low: higher than Type 1, lower than Type 3
- Grade: roughly equal Grade 1 and Grade 2; Grade 3 rare
- LN metastases uncommon; distant metastases exceedingly rare

PPI-Associated Gastric NETs: Published Series

First author/year	Duration of PPI use	No. of patients	Median age / % male	Multifocal tumors	Tumor size	Grade 1:2:3 (%)	LNM	DM	Surgical resection
Trinh/2020	>1 year (67% >3 years)	38	59 / 63%	NR	61% <1 cm	47/47/5	15%	3%	—
Rais/2022	>1 year*	17	68 / 41%	24%	77% <1 cm	35/65/0	6%	0%	6%
Logan/2023	>6 months	23	61 / 52%	24%	Mean 10 mm	39/43/0	4%	0%	9%
Egbert/2025	>1 year (median 9)	45	65 / 36%	22%	Median 6 mm	36/53/4	0%	4%	13%
Song/2025	NR	18	60 / 44%	28%	NR	50/33/0	NR	11%	28%
Al-Toubah/2026	≥5 years	45	NR / 49%	46%	Median 8 mm	40/54/4	9%	0%	16%
Azimpouran/2026	>1 year (median 9)	23	65 / 40%	30%	95% <1 cm	49/51/0	9%	0%	NR

LNM: lymph node metastases; DM: distant metastases; NR: not reported
**Only 15/17 patients suspected of chronic PPI use had documented PPI duration; —: not available*

Gastric NET Types 1–5: Pathogenesis

Feature	Type 1	Type 2	Type 3	Type 4	Type 5
Underlying mechanism	Autoimmune gastritis	Gastrinoma (ZES), usually MEN1	Sporadic	Endogenous parietal-cell proton-pump dysfunction	Chronic pharmacologic inhibition (e.g., PPI-associated)
Genetic association	None	MEN1	None	Germline ATP4A muation	None
Gastric acid status	Hypochlorhydria / achlorhydria	Hyperchlorhydria	Normal	Achlorhydria	Hypochlorhydria
Serum gastrin	Markedly elevated	Markedly elevated	Normal	Markedly elevated	Mild to moderately elevated (often reversible)
Parietal cells	Loss / atrophy	Hyperplasia	Preserved	Hypertrophy with cytoplasmic vacuolization (intrinsic pump dysfunction)	Hyperplasia with cytoplasmic vacuolization (reversible with PPI withdrawal)
ECL cell changes	Hyperplasia	Hyperplasia	None	Hyperplasia	Hyperplasia
Background oxyntic mucosa	Chronic atrophic metaplastic gastritis	Parietal cell hyperplasia ± fundic gland polyps	Normal / non-specific changes	Parietal cell hyperplasia ± fundic gland polyps with eosinophilic secretions	Parietal cell hyperplasia ± fundic gland polyps
H+/K+ ATPase IHC	NA	NA	NA	Negative	NA

ECL: enterochromaffin-like; IHC: immunohistochemistry; MEN1: multiple endocrine neoplasia type 1; NA: not applicable; PPI: proton pump inhibitor; ZES: Zollinger–Ellison syndrome

Gastric NET Types 1–5: Behavior & Management

Feature	Type 1	Type 2	Type 3	Type 4	Type 5
Tumor multiplicity	Multifocal	Multifocal	Solitary	Multifocal (often innumerable)	Often multifocal
Typical tumor size	Small (<15 mm)	Small	Larger, variable	Small (<15 mm)	Small to intermediate
Histologic grade	Usually G1	Usually G1	Often G2–G3	Usually G1	G1–G2 predominance
Lymph node metastases	Rare	10–30%	Common	Rare	Uncommon
Distant metastases	Very rare	Rare	Common	Never reported	Exceedingly rare
Overall malignant potential	Very low	Low to intermediate	High	Very low	Low to intermediate
Primary management approach	Endoscopic resection and surveillance	Treat gastrinoma ± endoscopic or surgical resection	Surgical resection	Individualized (ESD, SSA, surgery, or observation)	Endoscopic resection ± PPI cessation

ECL: enterochromaffin-like cell; LN: lymph node; ESD: endoscopic submucosal dissection; SSA: somatostatin analog; PPI: proton pump inhibitor

Conclusions & Future Directions

2026 WHO classification: five gastric NET subtypes

TYPE 1
Atrophic gastritis
Gastrin-dependent

TYPE 2
ZES / MEN1
Gastrin-dependent

TYPE 3
Sporadic
Aggressive → radical surgery

TYPE 4 NEW
Endogenous proton-pump dysfunction
Gastrin-dependent

TYPE 5 NEW
PPI-induced
Gastrin-dependent · rising

Subtype distinction is not academic: *it separates sporadic Type 3 (radical surgery) from gastrin-dependent Types 1, 2, 4, 5 (more indolent behavior).*

Key Take-Home Points

- Type 4 (endogenous proton-pump dysfunction) is exceptionally rare
- Type 5 (PPI-induced) is rapidly rising and may soon become the dominant subtype
- Both new subtypes are gastrin-dependent and far less aggressive than sporadic Type 3
- Background mucosa (parietal/ECL and foveolar hyperplasia) plus documented PPI duration are key to accurate subtyping

Future Directions

1. Larger studies with longer-term follow-up for Types 4 and 5
2. Genetic testing to define the full spectrum of Type 4 mutations
3. Surveillance strategies for long-term PPI users