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Case Report

# Gastric Mixed Neuroendocrine/Non-Neuroendocrine Neoplasia (MINEN) in a 48-Year-Old Female Patient: Evidence for a Common Precursor Cell Origin

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**Abstract**

A 48-year-old female patient consulted medical advice after noticing unspecific symptoms like obstipation, followed by b-symptoms. The patient underwent a CT scan and gastroscopy, during which a polypoid tumor in corpus ventriculi was observed. Subsequently an endoscopic submucosal dissection (ESD) was performed. Histological examination, along with immunohistochemistry, led to the diagnosis of a mixed neuroendocrine/non-neuroendocrine neoplasia (MINEN). The sequencing of both tumor components allows the assumption that both neoplasms derived from a common precursor cell.

**Keywords:** Mixed Neuroendocrine/Non-Neuroendocrine Neoplasia (MINEN); Composite tumor; Common Precursor Cell; Endoscopic Submucosal Dissection (ESD);

## Case Presentation

A middle-aged female presented to the clinic with malaise, significant unintended weight loss and night sweats. Physical examination and the initial blood test revealed no abnormalities.

## Radiology

Hence, a radiological assessment was requested. Contrast-enhanced hydro-multidetector computed tomography (MDCT) of the stomach after oral administration of 1500 ml of water showed a hypervascular polypoid mass in the gastric body (Figure 1) as well as two hypervascular lymph nodes close to the greater curvature. Findings were corroborated by somatostatin receptor analogue (68Ga DOTANOC) PET/CT, which demonstrated not only the hypermetabolic gastric tumor, but also two lymph nodes adjacent to the stomach with an SUVmax of 6.6 (Figure 1). MDCT and PET/CT features were consistent with the presence of a NET, without demonstrating the morphology of another tumor entity. Radiologically, there were no signs of transmural infiltration of the gastric wall.

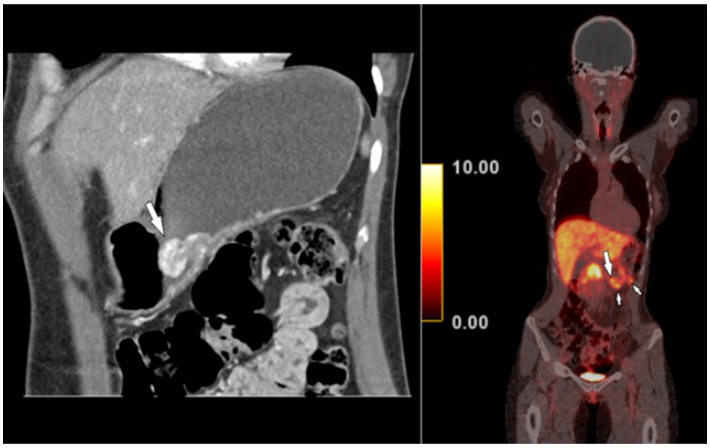


**Figure 1:** Left: Contrast-enhanced MDCT (paracoronal 3D-reconstruction) of the stomach demonstrates a polypoid hypervascular mass at the greater curvature (arrow). Right: subsequent somatostatin receptor analogue PET/CT shows not only the hypermetabolic mass in the in the stomach (large arrow), but also two metastatic lymph nodes outside the stomach (small arrows).

## Gastroscopy

Initially, it was recommended to perform a gastroscopy with endoscopic ultrasound, during which a biopsy specimen was taken from the exophytic part of the gastric tumor.

## Biopsy: Histological Report

Histological assessment classified the tumor lesion as a gastric adenoma, intestinal type, with high-grade dysplasia. The surrounding background in the biopsy specimen showed H. pylori-negative chronic atrophic gastritis of autoimmune type, with distinct atrophy of the gastric glands and intestinal metaplasia.

## Further blood test examination

A subsequent blood test revealed seropositivity for anti-parietal-cell antibodies at 45 U/mL [<7 U/mL]. The seropositivity for anti-parietal-cell antibodies confirmed the histological diagnosis of autoimmune gastritis.

## Treatment: Endoscopic submucosal dissection (ESD)

An interdisciplinary team managed the case and advised that an elective endoscopic intervention should be performed as a minimally invasive resection option. While the potentially polypoid tumor component was excised via a conventional endoscopic snare procedure, the main tumor component was subsequently resected via Endoscopic Submucosal Dissection (ESD). This involved the marking of the circumferential resection margin with coagulation marks, injection of Indigocarmin, circumferential mucosa incision with a Dual Knife, partial dissection, snaring and complete resection (Figure 2).

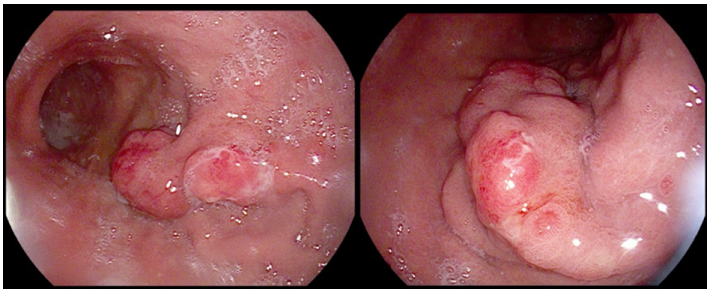

**Figure 2:** Endoscopic Imaging.

## ESD-Specimen: Histological Report (Figure 3-7)

## Gastric Adenocarcinoma

Histological examination revealed a gastric adenoma (intestinal type) with high-grade dysplasia, progressing into a well-differentiated gastric adenocarcinoma composed of loosely organized neoplastic glands infiltrating the gastric wall up to sections of submucosa. The neoplastic epithelium exhibited a high variability in nuclear size and shape, with nuclear pleomorphism and a vesicular to hyperchromatic appearance of the nuclei.

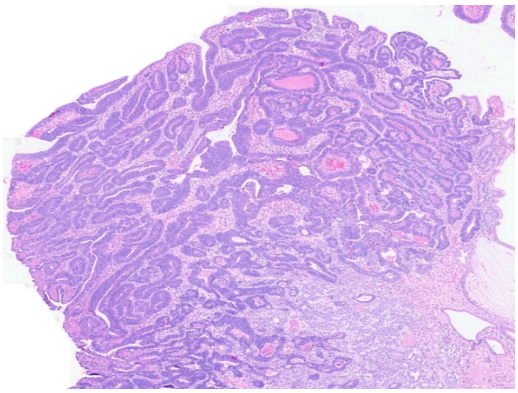

**Figure 3:** Gastric adenocarcinoma and its precursor lesion a gastric tubulovillous adenoma with high grade dysplasia next to formations of a neuroendocrine tumor (H&E, 40x).

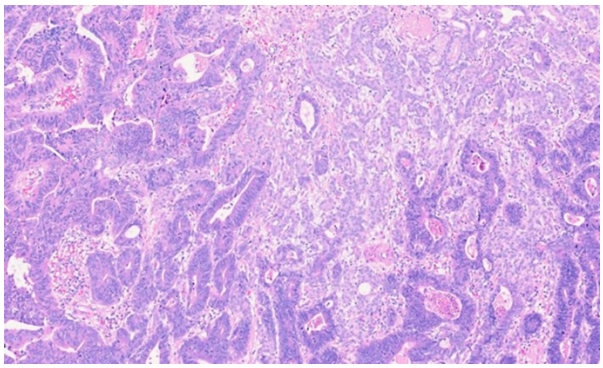

**Figure 4:** Gastric adenocarcinoma next to formations of a neuroendocrine tumor (H&E, 100x).

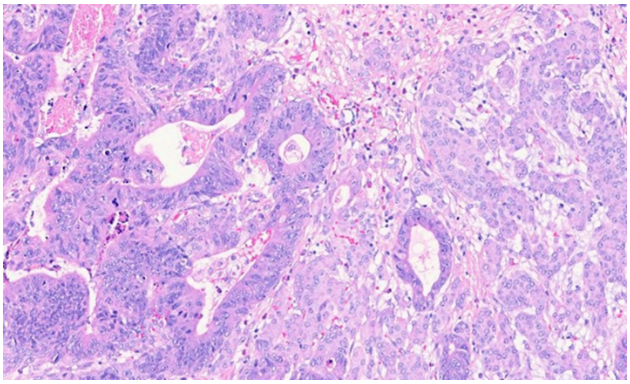

**Figure 5:** Gastric adenocarcinoma next to formations of a neuroendocrine tumor (H&E, 200x).

## Neuroendocrine Tumor (NET)

Moreover, another neoplastic cell population consisting of monomorphic neoplastic cells organized in nests and trabeculae was observed, indicating a neuroendocrine differentiation. This cell population displayed strong immunohistochemical expression of Synaptophysin and Chromogranin A. Similar to the formations of well-differentiated gastric adenocarcinoma, nests of the neuroendocrine tumor (NET) were detected in sections of the submucosa. The proliferation index (Ki67) of the neuroendocrine differentiated tumor component exhibited considerable heterogeneity, with an average value of 5-10%.

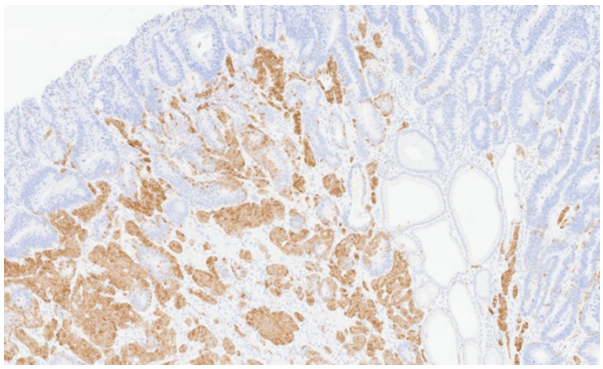

**Figure 6:** Immunohistochemistry – Synaptophysin (SYN, 100x).

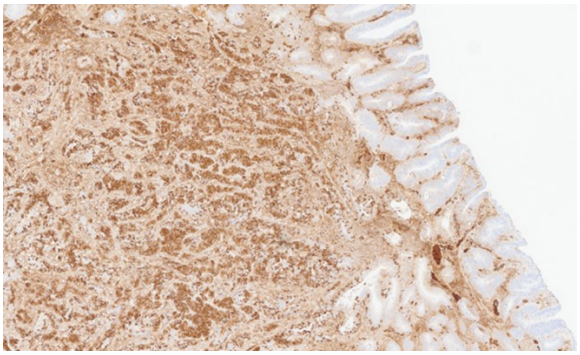

**Figure 7:** Immunohistochemistry – Chromogranin A (CgA, 40x).

## Immunohistochemistry

Further immunohistochemical investigations revealed that the formations of well-differentiated gastric adenocarcinoma strongly expressed several mismatch repair proteins (MLH1, PMS2, MSH2, MSH6), making the presence of microsatellite instability (MSI) unlikely. HER2 was negative (HER2: 0, faint membrane reactivity in <10% of tumor cells).

## Molecular Pathology

A TruSight™ Oncology 500 (TSO 500) assay was performed to assess the molecular profile of both the neuroendocrine and non-neuroendocrine differentiated tumor components separately. TSO 500 is a DNA and RNA NGS assay that targets 523 genes. Areas

where only one tumor component was present and minimal tumor intermingling was observed were selected. The area was marked on H&E slides and the percentage of tumor cells was estimated. Subsequently a macrodissection of tumor tissue was performed. The neuroendocrine tumor (NET) revealed a frameshift mutation in a tumor suppressor gene, namely MEN1 (p.P498Qfs*61). This molecular alteration is predicted to be inactivating and oncogenic. MEN1 is involved in the surveillance of gene transcription, signal transduction and genome integrity. Whereas germline loss-of-function mutations in the MEN1 gene are associated with MEN1 syndrome, an autosomal dominant tumor syndrome characterized by tumors in the pituitary, parathyroid, lung, intestine, and pancreas, somatic mutations and deletions in MEN1 can also be observed in a variety of sporadic neuroendocrine tumors (NET) [1,2]. The gastric adenocarcinoma exhibited a variety of mutations including MEN1 (p.P498Qfs*61), next to molecular aberrations in critical tumor suppressor genes such as APC (p.N1546Rfs*9), TP53 (p.V122Efs*29) and FBXW7 (p.R540*). In both tumor components microsatellite instability (MSI) was not observed and the tumor mutational burden (TMB) was low (<10 mutations/Mb).

## Background

### Atrophic autoimmune gastritis (AIG), ECL-cell hyperplasia & neuroendocrine tumors (NET)

Advanced autoimmune atrophic gastritis (AIG) leads to reduced or absent acid production, namely gastric hypo- or achlorhydria which is a stimulating factor for sustain gastrin secretion by antral G cells. ECL-cell proliferation is triggered through induced Hypergastrinemia and can appear linear (earliest lesion), nodular or adenomatous. Neuroendocrine proliferations with a diameter of more than 5mm are classified as neuroendocrine tumors (NET) [3,4]. Neuroendocrine tumors (NET) are lesions that are known to arise in the background of autoimmune atrophic gastritis. A hypothesis has been proposed that gastric adenocarcinoma in patients with AIG may be associated with undetected previous or current H. pylori comorbidity [5].

## Mixed neuroendocrine/non-neuroendocrine neoplasms (MINEN)

According to the World Health Organization (WHO), mixed neuroendocrine/non-neuroendocrine neoplasms (MINEN) are defined by the presence of both components, with each representing at least 30% of the tumor lesion, assuming that a neoplastic cell population below this threshold does not impact the behaviour of the tumor [6,13].

## Composite & collision tumors

Collision tumors as well as composite tumors are defined by the presence of two neoplastic cell populations with diverging morphology and immunohistochemical expression profiles coexisting within a single organ. In contrast to collision tumors cellular intermingling is observed in composite tumors. Whereas composite tumors are believed to arise from a common driver mutation, the phenomenon of collision tumors is interpreted as a result of a coincidental neoplastic change [7,8].

## Discussion

Radiological and endoscopic examinations and interventions, along with histological and immunohistochemical assessments, led to the diagnosis of a gastric mixed neuroendocrine/non-neuroendocrine neoplasia (MINEN) in a 48-year-old female patient. The tumor lesion was composed of two heterogeneous, intermingling differentiation types. In addition to a well-differentiated gastric adenocarcinoma, intestinal type, and its precursor lesion, a gastric tubulovillous adenoma with high-grade dysplasia, formations of a neuroendocrine tumor (NET) were observed. The surrounding non-neoplastic mucosal background exhibited histological features consistent with chronic atrophic gastritis of autoimmune type, fitting well with seropositivity for anti-parietal-cell antibodies.

## Autoimmune Gastritis and NET

Neuroendocrine neoplasms and their potential precursor, namely enterochromaffin-like cell (ECL) hyperplasia, are strongly associated with autoimmune atrophic gastritis. Regarding gastric adenocarcinoma in patients with AIG, there is a hypothesis that it is actually associated with unrecognized previous or coexisting H. pylori infections.

Rugge et al included 211 H. pylori negative patients with autoimmune gastritis (AIG) in a prospective long-term follow-up study to assess the associated risk of gastric cancer [5]. AIG was confirmed by histology together with serological assessment [5]. The enrolled patients were then followed up prospectively with paired biopsies and were histologically divided into atrophic and non-atrophic AIG [5]. ECL hyperplasia was classified as diffuse and adenomatous [5]. Progression of ECL status from diffuse to adenomatous hyperplasia/dysplasia was observed [5]. A few patients developed a neuroendocrine tumor (NET) during follow-up, always accompanied by extensive oxyntic gland atrophy and ECL adenomatous hyperplasia/dysplasia [5]. In their study, Rugge et al concluded that there is no increased risk of gastric cancer in patients with AIG and suggested that gastric adenocarcinoma in patients with AIG may be the result of unrecognized previous or current H. pylori comorbidity [5]. Miceli et al. described similar findings in their long-term follow-up observation of 498 patients with AIG [9]. Their objective was to assess the incidence of neoplastic complications over the follow-up period in patients with AIG and negative H. pylori status. The patients were stratified according to disease stage, including potential AIG, early AIG,

florid AIG, and end-stage AIG [9]. A neoplastic complication was observed in 8.5% of all enrolled patients. Of these 51.2% developed a neuroendocrine tumor (NET), G1, 4.9% showed formations of NET, G2 and 43.9% had epithelial dysplasia (low-grade & high-grade) [9]. No gastric adenocarcinoma was observed during follow-up time [9].

## Collision versus composite tumor

Although areas containing only neuroendocrine or non-neuroendocrine tumor components are observable, cellular intermingling of both tumor cell types can be seen, which does not correspond to the definition of a collision tumor.

To demonstrate that both components of the MINEN arise from the same driver mutation, molecular testing was performed on each tumor component separately. A MEN1 mutation was identified in both tumor components. However, molecular alterations of APC, TP53 and FBXW7 were only observed in the non-neuroendocrine part of the tumor, particularly within the gastric adenocarcinoma. Recent studies suggest that both neuroendocrine and non-neuroendocrine differentiated tumor cells in MINEN originate from a single precursor cell. It is proposed that this single precursor cell has the potential for dual differentiation during the process of tumorigenesis [10]. It is hypothesized that both tumor components share molecular aberrations in critical oncogenes, followed by activation of separate genetic pathways at some point [10]. Farooq et al. reported on a patient with trilinear-differentiated gastric MINEN and examined the molecular profiles of all three tumor components separately [11]. In addition to an adenocarcinoma and a neuroendocrine tumor, a lineage exhibiting squamous cell differentiation was also identified [11]. Their findings support the hypothesis that MINENs arise from a common precursor cell, as similar molecular aberrations in genes established as drivers of oncogenesis were observed in all three different lineages [11]. All three tumor components exhibited similar alterations in KRAS, NF1, CDKN2A, and TP53 [11]. In a study by Scardoni et al., six cases of MINENs in both the gastrointestinal tract and pancreas were examined to determine whether the exocrine and endocrine components of these tumors exhibited similar genetic aberrations [12]. It was reported that in five out of six cases, the endocrine and exocrine tumor components exhibited an overlapping mutational profile, which was linked to a monoclonal origin [12].

## Conclusion

Several interdisciplinary diagnostic approaches led to the diagnosis of a gastric mixed neuroendocrine/non-neuroendocrine neoplasia (MINEN) in a 48-year-old female patient with autoimmune atrophic gastritis. Our next-generation sequencing results are consistent with the postulated hypothesis that MINENs derive from a common precursor cell with the potential for dual differentiation.

## Declarations

**Contributors:** All authors contributed to planning, literature review and conduct of the case report. All authors have reviewed and agreed on the final manuscript.

**Competing interests:** None.

**Patient consent for publication:** Informed consent was obtained from the patient, consent form available upon request.

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