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# Mixed adenoma–well-differentiated neuroendocrine tumor of the major duodenal papilla: Case report with review of literature

Yasuhiro Kubota, Yuki Fukumura, Yoshihiro Hirata, Yusuke Takasaki, Takashi Yao

## ABSTRACT

**Introduction:** Mixed adenoma–well-differentiated neuroendocrine tumor (MANET) is a recently introduced tumor entity, composed of an adenoma and a well-differentiated neuroendocrine tumor. It occurs infrequently in the colorectum, is very rare in the duodenum, and no case arising from the major duodenal papilla has been reported to date.

**Case Report:** We describe an extremely rare case of MANET arising from the major duodenal papilla in a woman in her 80s. The patient underwent endoscopic examination for abnormal liver function tests, which revealed a hypervascular, elevated lesion at the major duodenal papilla. Because ampullary carcinoma was suspected, subtotal stomach-preserving pancreaticoduodenectomy was performed. The 30 × 6 mm whitish tumor centered on the major papilla was histologically composed of three components: a pure adenomatous component, a pure neuroendocrine tumor component, and a mixed adenomatous-neuroendocrine component. The adenomatous component was predominantly high-grade, and the neuroendocrine component corresponded to grade 2. "Budding-off" and "ductuloinsular complex" patterns were frequently observed in the mixed component. Immunohistochemically, the neuroendocrine component was positive for serotonin and CDX2 in addition to neuroendocrine markers. Six months after surgery, the patient developed multiple metachronous liver metastases derived from the neuroendocrine component, and several metastatic foci were histologically diagnosed as grade 3 neuroendocrine tumor.

**Conclusion:** Although rare, considering the possibility of MANET in the major duodenal papilla is essential to avoid misdiagnosis as neuroendocrine carcinoma or adenocarcinoma. In this paper, we summarize the clinicopathological features of MANET based on a review of literature and discuss issues requiring further investigation.

**Keywords:** Major duodenal papilla, Mixed adenoma–well-differentiated neuroendocrine tumor, Mixed neuroendocrine–non-neuroendocrine neoplasm

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## INTRODUCTION

Mixed neuroendocrine–non-neuroendocrine neoplasm (MiNEN) is a rare tumor entity composed of both neuroendocrine and non-neuroendocrine components. This terminology was adopted in the 2017/2019 WHO classification of tumors of endocrine organs/digestive tumors [1, 2], and remains in use in the 2025/2026 WHO classification of tumors of endocrine organs/digestive tumors (beta version), respectively [3, 4]. These lesions were previously termed as mixed adenoneuroendocrine carcinomas (MANECs) in the 2010 WHO classification [5], but the terminology was revised to MiNEN to encompass the heterogeneity of mixed neoplasms, including adenomas, adenocarcinomas, squamous cell carcinoma, and acinar cell carcinoma for the non-neuroendocrine component, and differentiated and poorly differentiated neuroendocrine neoplasms for the neuroendocrine component.

Mixed adenoma–well-differentiated neuroendocrine tumor (MANET), a subtype of MiNEN, is extremely rare and is composed of an adenoma and a well-differentiated neuroendocrine tumor (NET). This tumor entity was first proposed by La Rosa et al. in 2012 [6], as MANET exhibits a far more indolent clinical behavior compared with MiNEN of other combinations. Although MANET-type tumors had been reported only rarely under various terms, such as "glandular–carcinoid tumors" [7], recent years have seen the publication of several case reports [8–11]. However, it is only recently that their clinicopathological features are clarified through case series [12, 13]. According to these reports, MANET most commonly arises in the colon, with fewer cases occurring in the stomach and small intestine. To date, only four cases of duodenal MANET have been reported and no MANET of the major duodenal papilla has been reported.

Herein, we report the first known case of MANET arising in the major duodenal papilla. The patient's clinical course, along with the histological and immunohistochemical findings, is presented with a review of the literature. The clinical behavior, potential diagnostic pitfalls, tumorigenesis, and issues requiring further investigation are also discussed.

## CASE REPORT

A woman in her 80s with no significant past or family history was referred to a local hospital because of abnormal liver function tests. Contrast-enhanced computed tomography (CT) showed dilatation of the common bile duct and main pancreatic duct. Upper gastrointestinal endoscopy identified a 14-mm hypervascular, elevated lesion at the major duodenal papilla (Figure 1A). A biopsy specimen suggested an epithelial neoplasm. Because ampullary carcinoma was clinically suspected, the patient was referred to our hospital and underwent subtotal stomach-preserving pancreaticoduodenectomy.

Grossly, the resected specimens showed a whitish, elevated papillary mass centered on the major papilla, measuring 30 × 6 mm (Figure 1B). Histologically, the tumor consisted of three components: a pure adenomatous component, a pure neuroendocrine component, and a mixed adenomatous-neuroendocrine component. The pure tubular adenomatous component, predominantly exhibiting high-grade dysplasia, was located in the mucosa of the major duodenal papilla (Ad), the ampullary bile duct (Ab), and ampullary common duct (Ac) (Figures 1C and 2A). The pure neuroendocrine component grew mainly in solid nests of various sizes, composed of cells with round nuclei and pale eosinophilic cytoplasm. It was predominantly located in the peripheral and deeper portions of the tumor, including the lamina propria to muscularis propria of the duodenal wall (Du), the sphincter of Oddi (Od), and the wall of the ampullary pancreatic duct (Ap) (Figures 1C, D and 2B). Both components intermingled at the Ab/Ac wall within the Od with transitioning into each other (Figures 1C, D and 2C). In the mixed component, "budding-off" of NET nests from the adenomatous component and a "ductuloinsular complex"-like transition pattern between the two components were frequently observed (Figure 2D–F). Immunohistochemically, the neuroendocrine component was diffusely positive for synaptophysin, chromogranin

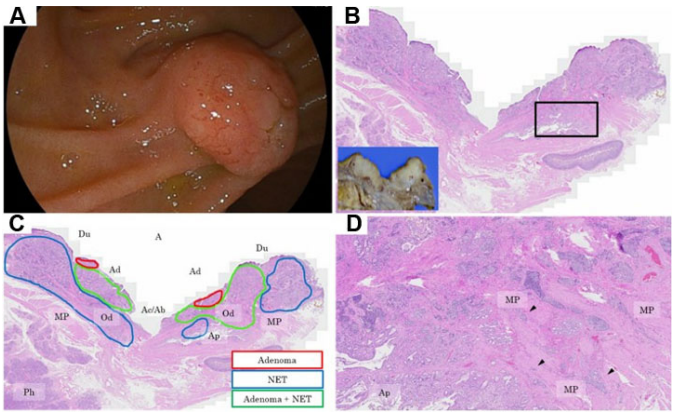


Figure 1: Endoscopic, macroscopic, and schematic microscopic views of MANET. (A) Upper gastrointestinal endoscopy showing a hypervascular, elevated lesion at the major duodenal papilla. (B) Rope view of the tumor centered on the major papilla (inset: macroscopic view of the cut surface). (C) Schematic microscopic view illustrating the distribution of each tumor component. The pure tubular adenomatous component (red) is located at Ad; the pure NET component (blue) is mainly present in the Du, Od, and Ap walls; and the mixed adenoma-NET component (green) is predominantly observed in the Ab/Ac walls and Od. *Abbreviations:* Ad, ampullary duodenal mucosa; Du, duodenal wall; Od, sphincter of Oddi; Ap, ampullary pancreatic duct; Ab, ampullary bile duct; Ac, ampullary common channel; Ph, pancreatic head; A, ampulla; MP, muscularis propria of the duodenum. (D) Schematic microscopic view showing NET invasion into the Ap (arrow) and MP (arrowhead). The Ap is outlined with a solid line, and accessory glands of the Ap are indicated by a dotted line. The entire area shown in panel D corresponds to the region enclosed in panel B.

A, CD56, INSM1, and serotonin, with retained nuclear ATRX/DAXX expression, and negative for insulin, glucagon, and somatostatin. The Ki-67 labeling index was 5.2%. In contrast, the adenomatous component was positive for CK7 and weakly positive for serotonin, but negative for the neuroendocrine markers (Figure 2G–J). The tumor was diagnosed as MANET composed of high-grade tubular adenoma and NET, G2.

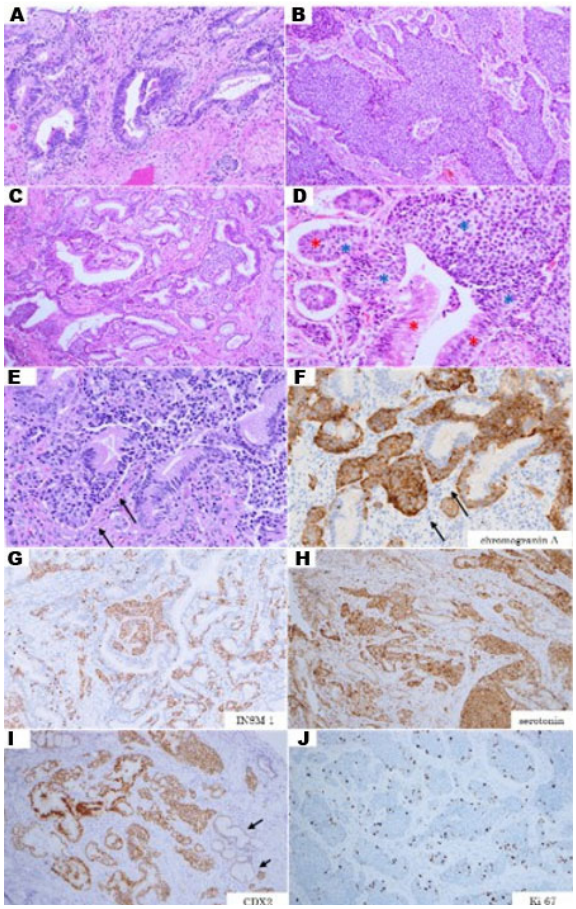


Figure 2: Representative microscopic views of MANET. (A) Pure adenomatous component composed mainly of tubular adenoma with high-grade dysplasia. (B) Pure neuroendocrine component showing a sheet-like growth pattern. (C–E) Mixed adenomatous and neuroendocrine components. Panel C shows a low-power view demonstrating the admixture of adenoma (tubular growth) and NET (sheet-like growth). Panel D shows a high-power view with "ductulo-insular complex"-like transition pattern between neuroendocrine nests (blue asterisks) and the adenomatous component (red asterisks) and Panel E shows a high-power view with "budding-off" of neuroendocrine nests (arrows) from the adenomatous component. (F) The "budding-off" of neuroendocrine nests (corresponding to panel E) are highlighted by chromogranin A staining (arrows). (G) The neuroendocrine component is positive for INSM1, whereas the adenomatous component is negative. (H) The neuroendocrine component is strongly positive for serotonin, whereas the adenomatous component shows weak positivity. (I) Both neuroendocrine and adenomatous components are positive for CDX2. Background accessory glands of Ac/Ab are negative for CDX2 (arrows). (J) Neuroendocrine components showing Ki-67 labeling index of 5.2%.

Six months after pancreatoduodenectomy, magnetic resonance imaging detected three metastatic lesions (8 × 8 mm, 6 × 6 mm, and 1.5 × 1.5 mm) in segment 4 of the liver, and the patient underwent partial hepatectomy. All three lesions were confirmed as metastatic NETs: one was NET G3 with a Ki-67 index of 40.5%, and the others were NET G2 (Figure 3A and B). The patient subsequently developed additional hepatic metastases and is currently receiving peptide receptor radionuclide therapy (PRRT) with Lutetium-177 dotatate, together with lanreotide acetate 120 mg, because the lesions demonstrated high somatostatin receptor uptake on scintigraphy. She is alive with disease 24 months after the initial surgery.

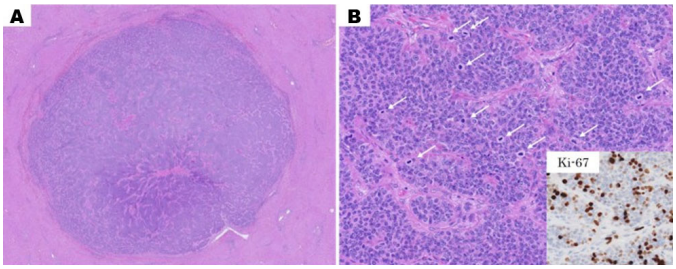


Figure 3. Microscopic views of the liver metastasis. Metastasis of neuroendocrine component at low (A) and high (B) magnification. Note the multiple mitotic figures (arrows) and high Ki-67 labeling index (40%, inset), consistent with NET G3.

## DISCUSSION

We reported a case of MANET arising in the major duodenal papilla. Recently, La Rosa et al. and Rokutan et al. summarized the clinicopathological features of MANET in the digestive system and stomach, respectively [12, 13]. According to La Rosa et al., most MANETs arise in the colorectum (71.4% of their own and reviewed cases, n=49). The frequencies at other sites were 18.4% in the stomach, 8.2% in the duodenum, and 0.2% in the ileum. After reviewing the original cited paper, we identified four previously reported duodenal cases on a per-patient basis, including the report by July et al., which described a single patient with recurrent MANETs in the duodenum [12, 14]. The female-to-male ratio was 21:28 (age range, 28–82 years). The NET grades were G1 (n=28), G2 (n=2), G3 (n=1), and not available (n=18). Clinical follow-up revealed "alive free of disease" (n=25), "alive with disease" (n=6), "died of other causes" (n=1), and not available or lost to follow-up (n=17), as reported by La Rosa et al.

Table 1 summarizes the previously reported duodenal MANETs (n=4), and the present case represents the fifth. Earlier reports did not specify the exact location within the duodenum; therefore, the relationship to the major duodenal papilla remained unclear. This is the first report to definitely identify the major duodenal papilla as the tumor site. Because the ampullary duodenum differs from the non-ampullary duodenum in histology and tumor staging, this case represents the first clearly documented MANET of the major duodenal papilla.

Table 1: Summary of previously reported duodenal MANET

| Case | Sex | Age | Site | Adenoma type and dysplasia[a] | NET infiltration (lp/mm/mp)[b] | NET grade | IHC hormones (5-HT/SST/ Ins/Glu)[c] | Metastasis | Outcome (years)[d] |
|---|---|---|---|---|---|---|---|---|---|
| #1 [12] | M | 75 | Duodenum | TVA, LG | mm | G1 | 5-HT, SST: – Ins, Glu:N/A | No | AFD(2) |
| #2 [12] | F | 77 | Duodenum | TA, LG | mm | G1 | 5-HT, SST: – Ins, Glu:N/A | No | AFD(1) |
| #3 [12] | F | 32 | Duodenum | TA, LG | lp | G1 | 5-HT: + SST: – Ins, Glu: N/A | No | AFD(2) |
| #4 [16] | F | 72 | Duodenum | TA, LG | lp | N/A | 5-HT, SST: – Ins, Glu:N/A | No | AWD(2) |
| Our case | F | 80 | Major duodenal papilla | TA, HG | mp | G2 | 5-HT: + SST: , Ins, Glu: – | Yes | AWD(1.8) |

[a]TA, tubular adenoma; TVA, tubulovillous adenoma; LG, low grade; HG, high grade.
[b]lp, lamina propria; mm, muscularis mucosae; mp, muscularis propria.
[c]5-HT, serotonin; SST, somatostatin; Ins, insulin; Glu, glucagon.
[d]AFD, alive free of disease; AWD, alive with disease.

To date, only two studies have summarized the clinicopathological features of MANET, and both emphasized its indolent nature. However, recently, Rao S has reported a gastric MANET composed of adenoma, adenocarcinoma, and grade 1 NET (Ki-67 index of 2.27%), which has shown aggressive behavior such as rapid growth and lymph node metastasis of NET component [8]. Hence, our case as well as Rao's case suggest that the prognosis of some MANETs may be poorer than previously recognized. In the series by La Rosa et al., all patients with follow-up data were alive and free of disease after a mean follow-up time of nine years, and the NET component was grade 1 for 90.3% of their patients [12]. Rokutan et al. reported that all their cases consisted of intestinal-type tubular adenoma with low- or focal high-grade dysplasia and grade 1 NET, and none developed recurrence after endoscopic resection during 2–94 months of follow-up. In contrast, the present case showed a grade 2 NET for the primary tumor and multiple liver metastases, including grade 3 lesions, indicating a more aggressive clinical course. The adenomatous component was also predominantly high grade. These findings suggest that, although MANET is more indolent than MiNEN of other combinations, some MANET may behave rather aggressively. Furthermore, it remains unclear whether MANET arising in the major duodenal papilla is inherently more aggressive than those at other sites.

We identified several potential pathological pitfalls in diagnosing MANET of the major duodenal papilla: (1) Because of its extreme rarity at this site, accurate diagnosis—particularly in biopsy specimens—can be challenging. When the adenoma is high grade, the neuroendocrine component may mimic invasive adenocarcinoma. (2) The NET component may be misdiagnosed as neuroendocrine carcinoma (NEC), especially when coexisting with high-grade adenoma, because most MiNENs consist of adenocarcinoma and NEC. (3) The histological complexity of the major duodenal papilla, including the mixed circular and longitudinal smooth muscle of the sphincter of Oddi, requires careful interpretation to avoid mistaking high-grade adenoma within the sphincter of Oddi for invasive adenocarcinoma with desmoplastic reaction. Although MANET is rare, careful evaluation of both components is essential, recognizing the possibility of MANET. Because the treatment differs markedly between well-differentiated NET and poorly differentiated NEC, avoiding overdiagnosis of MANET as MANEC is crucial.

Regarding tumorigenesis, we consider that the adenomatous component and neuroendocrine component in this case do not represent a collision tumor but instead share a common origin. The tumor consisted of three areas—pure adenomatous, pure NET, and mixed—and in the mixed areas, small NET nests frequently extended into the stroma from the base of adenomatous glands ("budding off"), similar to gastric adenoma with endocrine cell micronests and NETs [15, 16]. Combined nests of neuroendocrine and ductular cells ("ductuloinsular complex-like transitions"), reminiscent of pancreatic nesidioblastosis [17], further support a single tumor origin with bidirectional differentiation.

In this case, the NET component was diffusely positive for serotonin and negative for insulin, glucagon, and somatostatin. Although data on the hormonal profile of MANET remain limited, previous studies reported serotonin positivity in 85.7% (6/7) of gastric MANETs, 33.3% (1/3) of duodenal MANETs, and 25% (2/8) of colorectal MANETs [12, 13]. These findings suggest that the cellular origin of MANETs in the digestive system is

heterogeneous, whereas most gastric MANETs and the present case may originate from serotonin-producing enterochromaffin cells, as proposed by Rokutan et al. [13].

This case highlights several issues requiring further investigation: (1) Is the neuroendocrine component of MANET at the major duodenal papilla more aggressive than at other sites? (2) Is there a relationship between the grades of neuroendocrine component and non-neuroendocrine components-for example, does a high-grade adenomatous component correlate with a higher-grade NET? (3) Should the term MANET still be applied when the non-neuroendocrine component includes adenoma with invasive adenocarcinoma?

## CONCLUSION

We report an extremely rare case of MANET arising in the major duodenal papilla, thereby expanding the known anatomic spectrum of this entity. We summarized the clinicopathological features of MANET on a literature review and discussed potential diagnostic pitfalls and issues requiring further study.

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### Author Contributions

Yasuhiro Kubota – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the

version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Yuki Fukumura – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Yoshihiro Hirata – Acquisition of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Yusuke Takasaki – Acquisition of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Authors declare no conflict of interest.

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All relevant data are within the paper and its Supporting Information files.