Case Report

Mixed High-Grade Neuroendocrine Carcinoma with Villous Adenoma in the Duodenum: A First Case Report

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Mixed neuroendocrine non-neuroendocrine neoplasm (MiNEN) represents a rare diagnosis in the gastrointestinal tract. Only a few cases of MiNEN occurring in the small bowel had been previously reported. Here we report the first case of mixed high grade neuroendocrine carcinoma with villous adenoma arising in the duodenum. The patient is an 87-year-old female who presented for management of a 3.4 cm polypoid-like duodenal mass that was noted on a prior abdominal CT scan. PET scan showed intense uptake within the second portion of the duodenum consistent with a neoplasm. A biopsy previously performed showed tubulovillous adenoma. The patient had a remote history of breast cancer. Esophagogastroduodenoscopy was performed which showed fungating mass occupying 50% of the duodenal lumen and polypectomy was done. Grossly, the duodenal mass appeared as a pink-tan polypoid fragment of tissue. Microscopically, a villous adenoma is seen with focal area of high-grade dysplasia. Admixed with the villous adenoma, there are sheets of homogeneous small cells with high nuclear-cytoplasmic ratio, nuclear molding, high mitotic activity, and finely granular chromatin which stained positive for synaptophysin, CD56, CAM5.2, and CK8/18 while stained negative for chromogranin A, CK7, CK20, and CDX2. These findings support the diagnosis of high-grade neuroendocrine carcinoma arising in a background of villous adenoma. We report a first case of mixed high grade neuroendocrine carcinoma with villous adenoma arising from the duodenum.
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Key Words: *High-Grade Neuroendocrine Carcinoma, Villous Adenoma, Mixed neuroendocrine non-neuroendocrine neoplasm (MiNEN)*

INTRODUCTION

Neoplasms displaying a combination of neuroendocrine and conventional non-neuroendocrine morphologies of variable proportion are a well-known occurrence in various organs.[1] The nomenclature of such tumors has been inconsistent and changing a lot over the years.[2] In 2017, the WHO classification of tumors of the digestive system has termed this neoplasm as mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN).[3] MiNEN represents an extremely rare diagnosis and few single case reports and small case series are available in the literature describing this entity.[4-6] Therefore, the data on its epidemiology is limited. One systemic review suggests that MiNEN has incidence below 0.01/100,000 per annum.4 Moreover, MiNEN incidence and prevalence in the duodenum and small intestine remains unknown. Here we report the first case of mixed high-grade neuroendocrine carcinoma with villous adenoma occurring in the duodenum and we review the literature for the clinical and histopathological features of similar neoplasm.

CASE PRESENTATION

The patient is an 87-year-old female who presented our hospital for management of a duodenal mass that was noted on a prior abdominal CT scan performed 10 months earlier. The CT showed a 3.4 polypoid-like duodenal filling defect with marked dilation of both the common bile duct and the main pancreatic duct. MRI confirmed these findings and PET scan showed intense uptake within the second portion of the duodenum consistent with a neoplasm arising from duodenum, ampulla, or pancreas. A biopsy was performed which showed tubulovillous adenoma. At the time of presentation, the patient complained of fatigue, decreased appetite, and occasional lightheadedness that improved after iron infusions. The patient has also medical history of breast cancer status post mastectomy in 2011, atrial fibrillation on Rivaroxaban, hypertension, hyperlipidemia, and iron deficiency anemia. Esophagogastroduodenoscopy was performed which showed fungating mass occupying 50% of the duodenal lumen (**Figure 1A**). Polypectomy was done with sphincterotomy and placement of a stent in the common bile duct. The patient tolerated the procedure well and was discharged on the same

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day without complications. Grossly, the duodenal mass appeared as a pink-tan polypoid fragment of tissue measuring 2.2 cm in greatest dimension. Microscopically, a villous adenoma was seen predominantly consisting of finger-like projections lined by neoplastic cells with elongated hyperchromatic nuclei and focal area of high-grade dysplasia. Admixed with the villous adenoma, there were sheets of homogeneous small cells with high nuclear to cytoplasmic ratio, nuclear molding, high mitotic activity, and finely granular chromatin (**Figure 1B-1D**). These cells were positive for neuroendocrine markers synaptophysin and CD56 but were negative for chromogranin A. Additionally, both these neuroendocrine cells and the villous adenoma cells were positive for CK8/18 and Cam5.2. The neuroendocrine cells also were positive for TTF-1 immunostain which has been reported to be positive in 14% of neuroendocrine carcinomas.7 Unlike the cells of the villous adenoma, the neuroendocrine cells were negative for CDX2, CK7, and CK20. Given the patient's history of breast cancer, the breast markers GATA3 and GCDFP15/mammaglobin immunostains were performed, which turned out to be negative for both villous adenoma and neuroendocrine cells. Ki67 index was approximately 90% in neuroendocrine cells (**Figure 2**). These findings support the diagnosis of high-grade neuroendocrine carcinoma arising in a background of villous adenoma with focal high-grade dysplasia.

The patient was followed up in March 2021. One small ulcer was identified on duodenal mucosa without mass lesion.

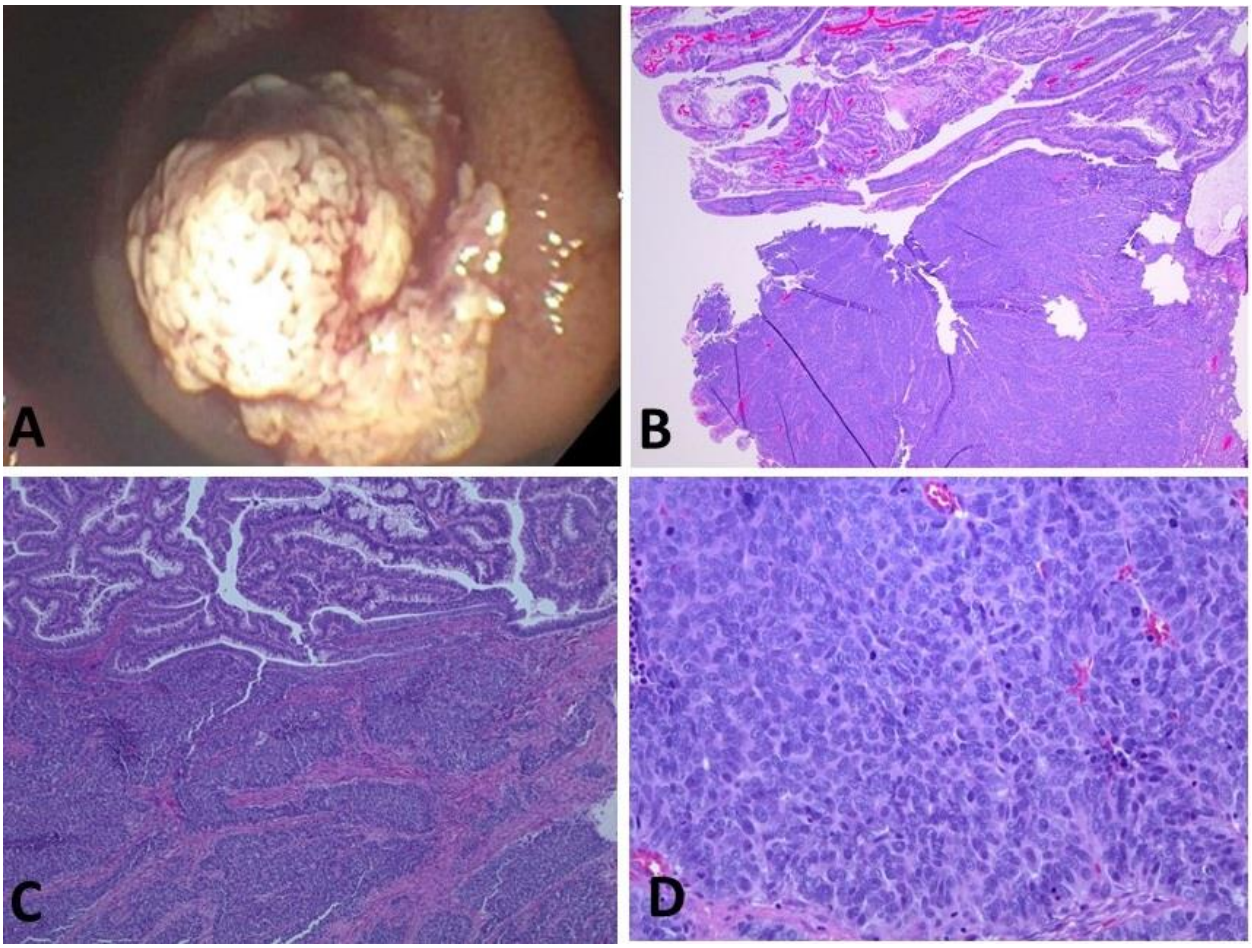

Figure 1. A. Esophagogastroduodenoscopy showing exophytic polypoid-like mass occupying 50% of the duodenal lumen. **B.** H&E 2X magnification showing sheets of small cells of neuroendocrine neoplasm in the submucosa next to surface villous adenoma, **C.** H&E 4X magnification showing villous adenoma juxtaposed the neuroendocrine carcinoma cells, and **D.** H&E 20X magnification showing high grade neuroendocrine carcinoma with multiple mitotic figures, nuclear molding, and finely granular chromatin.

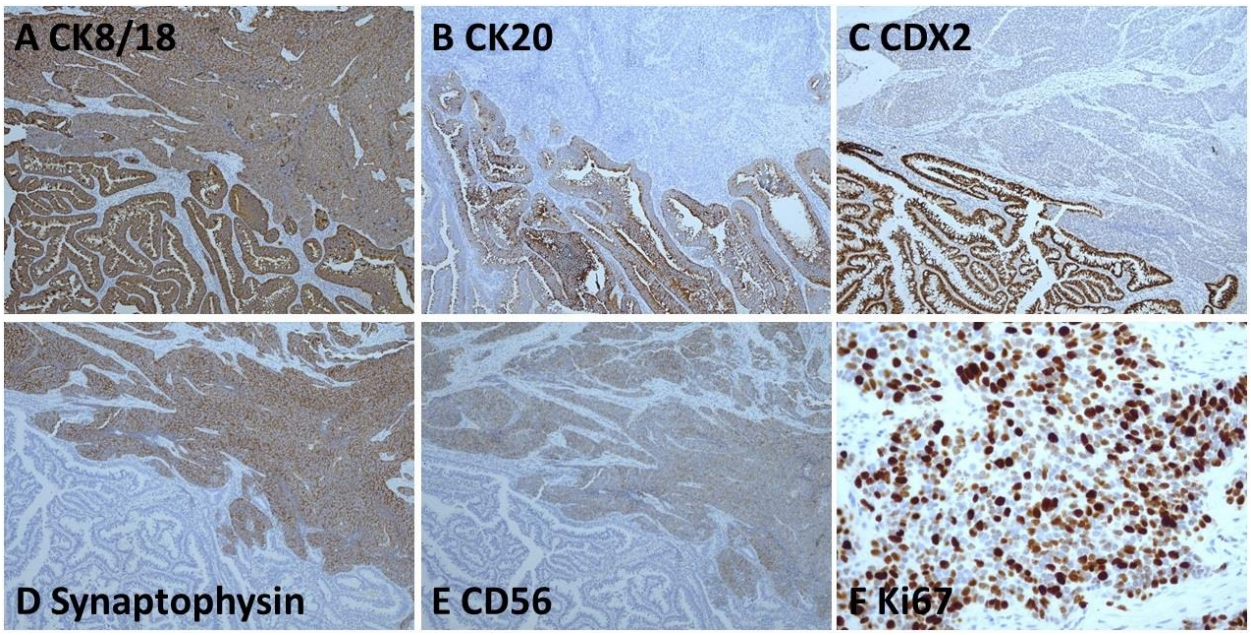

Figure 2. Immunohistochemical staining of the polyp. **A.** CK8/18 positive for both villous adenoma and high-grade neuroendocrine carcinoma (NEC); **B.** CK20 only positive for villous adenoma; **C.** CDX2 only positive for villous adenoma; **D.** Synaptophysin only positive for NEC; **E.** CD56 only positive for NEC; **F.** Ki67 index showing 90% positive for NEC.

DISCUSSION

MiNEN represents an extremely rare diagnosis and has incidence below 0.01/100,000 per annum in a system review.[4-6] It was first classified by the WHO as a separate entity in 2010 and used to be known as mixed adeno-neuroendocrine carcinoma. In 2017, the mixed neuroendocrine-non-neuroendocrine neoplasm was named by WHO to include all combinations of neuroendocrine and non-neuroendocrine neoplasms including adenoma, adenocarcinoma, squamous cell carcinoma and acinar cell carcinoma.[1,4] Morphologically, the neuroendocrine and exocrine components can occur in separate areas of the same lesion or can be diffusely admixed. Only a few case reports and small retrospective studies are available in the literature which has led to limited data about its epidemiology or pathogenesis.[5] According to a recently published meta-analysis study by Frizziero et al., a total 91 publications about MiNEN were identified in the English literature, out of which only 13 were from North America and only one case had the tumor originated in the small intestine.4 We searched PubMed and found total 17 MiNEN reported in duodenum,[8-17] but some cases are in non-English literature.[9,11,13]

Of 17 MiNEN in duodenum, 11 cases showed mixed adenocarcinoma with high-grade neuroendocrine carcinoma and 6 cases showed mixed adenoma with well-differentiated neuroendocrine tumor. However, mixed adenoma with high-grade neuroendocrine carcinoma in duodenum has not been reported. In our case, the neuroendocrine component developed as solid sheets of small cell carcinoma growing in the center of non-neuroendocrine villous adenoma component with each component constituting at least 30% of the tumor which fits the definition for the diagnosis of MiNEN. In addition, we tried to rule out the metastatic breast cancer. The tumor cells were negative for GATA3 and GCDFP15/mammaglobin immunostain. The primary breast cancer was a ductal carcinoma without high grade neuroendocrine components. Therefore, it is the first case report with mixed adenoma and high-grade neuroendocrine carcinoma originating in the duodenum.

Although MiNEN in the digestive system is more frequently composed of an adenocarcinoma-NEC combination, it can also encompass a wide spectrum of different combinations between epithelial tumors (including adenoma, adenocarcinoma, squamous cell carcinoma, and other carcinomas) and neuroendocrine neoplasms. MiNEN usually is an aggressive entity with a high-grade neuroendocrine component in the majority of cases and it has poor survival outcomes similar to those of pure NECs.2,5 In a large retrospective cohort of patients in 5 European centers, 69 patients with diagnosis of MiNEN were studied. The median overall survival is 28.6 months in localized cases but 9.0 months in advanced cases.5 However, a small group of MiNEN which is composed of a combination of adenomas with well-differentiated neuroendocrine tumor show favorable prognosis. In one study, La Rosa et al. reported that 12 cases with mixed adenoma and well-differentiated NET were alive and free of disease after a mean follow-up time of 9 years (range 1 to 27 years).[8] These cases are an indolent disease that needs to be distinguished from aggressive high-grade MiNENs. La Rosa et al. suggested classifying MiNEN into three grades (high, intermediate and low) according to the

grade of each of its components. Low grade MiNENs which are combinations of well-differentiated NETs with any adenoma are a heterogeneous group with different morphology, clinical behavior, and possible biology, which can be called mixed adenoneuroendocrine tumor (MANET). They also reviewed literature and identified 59 previously reported MANETs. Total 6 cases were in duodenum, but none of them show mixed adenoma with high-grade NEC.

In conclusion, it is a first case to report the NEC component developed as sheets of solid growth in the center of non-neuroendocrine villous adenoma component. The presence of high-grade NEC component confers poor prognosis.

CONFLICT OF INTEREST AND FINANCIAL DISCLOSURES

All authors do not have Conflicts of Interest and Financial Disclosures.

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