# Case Report

# Mixed Small Cell Carcinoma and Mucinous Adenocarcinoma of Appendix: A Rare Case Report with Review of Literature

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## Abstract

Gastrointestinal mixed neuroendocrine non-neuroendocrine neoplasms (MiNEN) are a heterogeneous group of tumors showing different morphological and prognostic features. The biological behavior of MiNEN is mostly driven by its high-grade component. Due to limitations in diagnostic methods and poor awareness, the incidence of MiNEN may be underestimated. The pathogenesis of MiNEN remains controversial. Molecular studies point towards a common monoclonal origin of the two components. Mixed tumors of the appendix are quite rare compared with those occurring elsewhere in the gastrointestinal tract. Although the appendix represents a common site of intestinal neuroendocrine tumors, primary extrapulmonary small cell carcinoma of the appendix is a rare entity. We describe a unique case of primary combined adenocarcinoma and small cell carcinoma of the appendix.

***Keywords:***

*Appendix, mucinous adenocarcinoma, neuroendocrine non-neuroendocrine neoplasms, small cell carcinoma of the appendix*

## Introduction

Mixed neuroendocrine non-neuroendocrine neoplasms (MiNEN) are hybrid tumors comprising neuroendocrine and non-neuroendocrine components, with each component accounting for at least 30% of the tumor [1]. MiNEN may result from either the simultaneous proliferation of multiple cell lineages or the proliferation of stem cells capable of differentiating along multiple cell lineages. It is well known that goblet cell carcinoma of the appendix frequently exhibits both glandular and endocrine differentiation in the same tumor cells. By contrast, mixed tumors with separate epithelial and neuroendocrine components are quite rare in the appendix compared with those occurring elsewhere in the intestine [2, 3]. Herein, we describe a rare case of MiNEN of the appendix. Awareness of this unusual combination will help in accurate diagnosis and planning proper treatment.

## Case Report

A sixty-one-year-old male patient presented at an outside hospital with abdominal pain of one-week duration. On examination, there was tenderness in the right lower outer quadrant. A CT scan showed a 2.6 x 2.5 x 2.3 cm mass lesion in the tip of the appendix with solid and cystic areas and foci of calcification. Diagnostic laparoscopy and appendicectomy were performed. The patient was referred to our center, and we reviewed the slides. Microscopy showed a neoplasm consisting of two neoplastic components which were closely juxtaposed but not intermingled (Figure 1a, 1b). One component showed atypical cells in a glandular pattern with abundant extracellular mucin. This component mainly involved the luminal aspect and was focally seen infiltrating the muscularis propria with a stromal desmoplastic reaction. The second component mainly involved the muscularis propria, and the tumor cells were arranged in sheets and vague nests. The cells had scant cytoplasm, ovoid hyperchromatic nuclei with nuclear molding, finely dispersed chromatin, and inconspicuous nucleoli (Figure 1c). On immunohistochemical analysis, the second component showed diffuse moderate positivity for synaptophysin, dot-like positivity for chromogranin, and a 90% MIB1 labelling index (Figure 1d, 1e, 1f). Based on morphology and immunoprofile, a diagnosis of MiNEN of the appendix showing mucinous adenocarcinoma (Grade 2) and small cell carcinoma components was made. There was no perineural tumor infiltration or lymphovascular tumor emboli. The proximal part of the lesion showed features of acute suppurative appendicitis. The outer surface of the appendix was intact, and the base of the appendix was free of neoplasm. There were no lymph nodes.

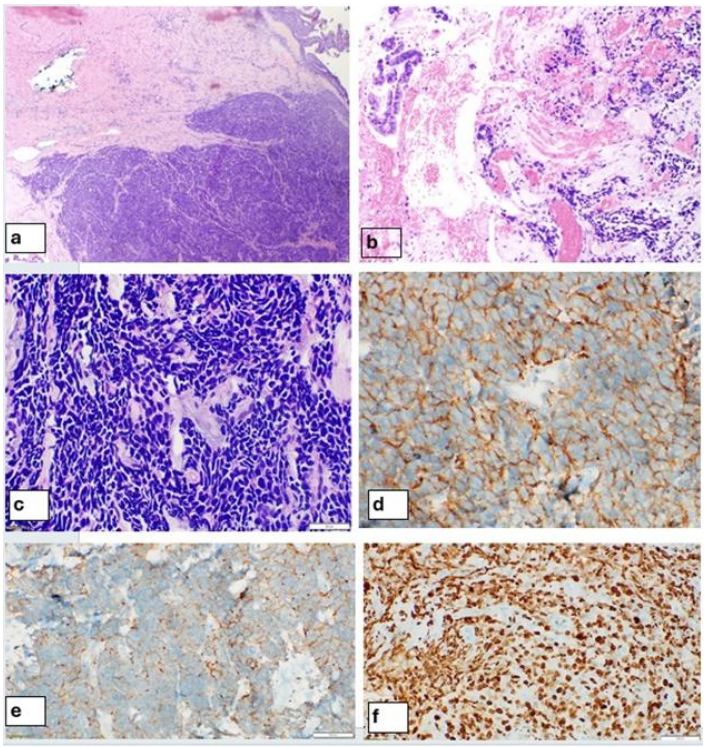


***Figure 1: (a,b) Microscopic examination showing two components- malignant cells in glandular pattern and sheets of cells with ovoid hyperchromatic nuclei ( H&E, X100), (H&E, X200), (c) Higher magnification showing the second component with ovoid hyperchromatic nuclei, nuclear moulding and increased mitotic activity ( H&E, X400), (d)Tumour cells showing positivity for synaptophysin (IHC, X400), (e) Tumour cells showing patchy positivity for chromogranin ( IHC, X400), (f) High MIB 1 labelling index( IHC, X400).***

## Discussion

Mixed neuroendocrine non-neuroendocrine neoplasms (MiNEN) are hybrid tumors comprising neuroendocrine and non-neuroendocrine components, with each component accounting for at least 30% of the tumor [1].

Neuroendocrine and non-neuroendocrine neoplasms can coexist with variable proportions of the two components, each representing from 1% to 99% of the tumor mass. The two components of these mixed neoplasms can exhibit variable morphological features and degrees of differentiation. The two components can be combined in different patterns. They can be intimately intermingled (composite tumors) or they can exist as separate, juxtaposed areas (collision tumors). This has to be differentiated from amphicrine tumors where neuroendocrine and non-neuroendocrine features coexist at a cellular level, with the same cells showing both neuroendocrine and non-neuroendocrine features [2, 3, 4].

By definition, MiNEN should contain both a neuroendocrine and a non-neuroendocrine component, with each component accounting for at least 30% of the tumor. The rationale behind the 30% threshold is that a lesser represented component is unlikely to influence the biological behavior of the whole neoplasm [1].

Different and inconsistent terminologies have been used in the diagnosis of tumors showing both neuroendocrine and non-neuroendocrine features, including goblet cell carcinoid (GCC), collision tumors, adenocarcinoid, composite tumors, and mixed endocrine-exocrine tumors. In 2010, the mixed neoplasms were named "mixed adeno-neuroendocrine carcinoma (MANEC)" by the World Health Organization [5]. As the spectrum of mixed neoplasms also included well-differentiated neuroendocrine tumors, precursor lesions, and squamous cell carcinoma, usage of the term "MANEC" led to confusion.

To better cover the heterogeneous spectrum of different components, the term "mixed neuroendocrine non-neuroendocrine neoplasms (MiNEN)" was recommended [1]. The term "non-neuroendocrine" was introduced to include histological variants other than adenocarcinoma (e.g., squamous or sarcomatoid phenotypes), and the term "carcinoma" was substituted by "neoplasm" to include components that exhibit low-grade malignant behavior, such as adenoma and well-differentiated neuroendocrine tumor. Compared to "MANECs," the term "MiNENs" better addresses the heterogeneous spectrum of possible combinations between neuroendocrine and non-neuroendocrine elements [1, 4].

Mixed tumors consisting of endocrine and exocrine components have been well-documented throughout the gastrointestinal tract, but they mainly occur in the large bowel. More than 70% of large bowel small cell carcinomas reported by Burke et al. were associated with overlying adenomas or adenocarcinoma. By contrast, this kind of lesion is very rare in the appendix [2, 3, 6].

It is well known that goblet cell carcinoma of the appendix frequently exhibits both glandular and endocrine differentiation in the same tumor cells. By contrast, mixed tumors with separate epithelial and neuroendocrine components are quite rare in the appendix compared with those occurring elsewhere in the intestine. Though neuroendocrine tumors grade 1 and 2 are common in the appendix, the occurrence of neuroendocrine carcinoma is extremely rare in this site. The vast majority of small cell carcinomas occur in the lung. Extrapulmonary small cell carcinomas are rare and have been described in the kidney, bladder, prostate, endometrium, salivary glands, nasal sinuses, and intestinal tract [2, 6, 7]. The occurrence of small cell carcinoma of the appendix is uncommon, with isolated case reports [2, 3, 7].

The pathogenesis of MiNENs remains unclear. The occurrence of two closely juxtaposed, distinct lesions showing different phenotypes raises the question of whether the different components are genetically related. Three main theories have been proposed. According to the first theory, the neuroendocrine and non-neuroendocrine components arise independently from

different precursor cells and merge. The second theory postulates the origin of two components from a common pluripotent stem cell progenitor, which acquires biphenotypic differentiation during carcinogenesis. The third theory hypothesizes that the neuroendocrine differentiation develops from an initially non-neuroendocrine cell phenotype through the progressive accumulation of molecular/genetic aberrations [2, 4].

Molecular studies suggest the great majority of combined adenocarcinoma and endocrine tumors in the gastrointestinal tract originate from a single multipotential epithelial stem cell following a glandular-to-endocrine sequence, supporting a monoclonal origin rather than the hypothesis of a "collision" tumor derived from two separate progenitor cells [8].

Vortmeyer et al., in their study on four cases of combined poorly differentiated neuroendocrine carcinoma-adenocarcinoma, demonstrated LOH of the APC, DCC, and p53 genes involving the same allele in both components [9].

Kim et al. and Furlan et al. also found concurrent LOH of the same allele in endocrine and adenocarcinoma components of the great majority of intestinal combined tumors. However, these same researchers noted the existence of mixed tumors showing clonal divergence and a different oncogenetic pathway in the different components [10, 11].

The optimal strategy of management is unclear due to the rarity of these neoplasms. However, there is general agreement that the management should be focused on the more aggressive tumor component as defined by histopathological criteria. MiNEN containing a well-differentiated NET component and an adenocarcinoma component should be treated as adenocarcinoma, whereas MiNEN containing a poorly differentiated NEC component should be treated like NECs [4, 12].

## Conclusion

It is well known that goblet cell adenocarcinoma of the appendix frequently exhibits both glandular and endocrine differentiation in the same tumor cells. By contrast, mixed tumors with separate epithelial and neuroendocrine components are quite rare in the appendix compared with those occurring elsewhere in the intestine. Due to the rarity of this diagnosis and the use of inconsistent terminologies, the incidence, prognosis, and best therapeutic management of patients with MiNEN remain unclear.

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## References

1. Klimstra D, Klöppel G, La Rosa S, Rindi G. Classification of neuroendocrine neoplasms of the digestive system. In: WHO Classification of Tumours, 5th Edition, Digestive System Tumours. 2019. p. 16-9.
2. Rossi G, Bertolini F, Sartori G, Bigiani N, Cavazza A, Foroni M, et al. Primary mixed adenocarcinoma and small cell carcinoma of the appendix: a clinicopathologic, immunohistochemical, and molecular study of a hitherto unreported tumor. Am J Surg Pathol. 2004;28:1233-9.
3. Kim WS, Lee DG. Primary mixed adenocarcinoma and small-cell carcinoma of appendix: A case report (CARE-compliant). Medicine (Baltimore). 2019;98(19)
4. Frizziero M, Chakrabarty B, Nagy B, Lamarca A, Hubner RA, Valle JW, et al. Mixed Neuroendocrine Non-Neuroendocrine Neoplasms: A Systematic Review of a Controversial and Underestimated Diagnosis. J Clin Med. 2020;9(1):273.
5. Rindi G, Arnold R, Bosman FT. World Health Organization classification of tumours of the digestive system. 4th ed. Lyon: IARC Press; 2010. p. 13-4.
6. Chen ZZ, Huang W, Wei ZQ. Small-cell neuroendocrine carcinoma of the rectum - a rare tumor type with poor prognosis:

A case report and review of literature. World J Clin Cases. 2020;8(23):6095-102.

7. O'Kane AM, O'Donnell ME, Shah R, Carey DP, Lee J. Small cell carcinoma of the appendix. World J Surg Oncol. 2008;6:4.
8. Capella C, La Rosa S, Uccella S, Billo P, Cornaggia M. Mixed endocrine-exocrine tumors of the gastrointestinal tract. Semin Diagn Pathol. 2000;17:91-103.
9. Vortmeyer AO, Lubensky IA, Merino MJ, Wang CY, Pham T, Furth EE, et al. Concordance of genetic alterations in poorly differentiated colorectal neuroendocrine carcinomas and associated adenocarcinomas. J Natl Cancer Inst. 1997;89(19):1448-53.
10. Furlan D, Cerutti R, Genasetti A, et al. Microallelotyping defines the monoclonal or the polyclonal origin of mixed and collision endocrine exocrine tumors of the gut. Lab Invest. 2003;83:963-71.
11. Kim KM, Kim MJ, Cho BK, Choi SW, Rhyu MG. Genetic evidence for the multi-step progression of mixed glandular-neuroendocrine gastric carcinomas. Virchows Arch. 2002;440:85-93.
12. La Rosa S, Marando A, Sessa F, Capella C. Mixed Adenoneuroendocrine Carcinomas (MANECs) of the Gastrointestinal Tract: An Update. Cancers (Basel). 2012;4(1):11-30.