Mixed laterally spreading tumour and neuroendocrine tumour in the rectum: a case report

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Case presentation

A 58-year-old female presented to our hospital with a 1-year history of recurrent mucous stools. She had no significant medical or family history of cancer. Laboratory tests for intestinal pathogens, rheumatological markers, and tumour markers were all within normal limits. Abdominal imaging did not reveal any abnormalities. Colonoscopy showed a laterally spreading tumour measuring approximately 25 × 40 mm located about 5 cm from the anal verge. The tumour exhibited granular, nodular, and lobulated features with abundant mucus adhering to the surface (Fig 1a). Despite repeated washing, mucus remained attached to the tumour surface. Subsequently, we performed indigo carmine staining, which revealed well-delineated tumour margins (Fig 1b). Endoscopic ultrasound showed the lesion originated from the mucosal layer. A local biopsy revealed a tubulovillous adenoma with high-grade dysplasia. The patient was deemed suitable for endoscopic submucosal dissection (Fig 1c to e).

Whole tumour pathology was highly unusual, a combination of tubulovillous adenoma with high-grade dysplasia and a neuroendocrine neoplasm (NEN) component. Interestingly, the neuroendocrine tumour had a maximum diameter of approximately 0.3 cm, representing around 3% of the lesion. Immunohistochemistry staining revealed positive expression of CK, Syn, CD56, CgA, Ki-67 (<1%) and CD34 (Fig 2). This pathological manifestation did not align with the current classification of NENs.

About one and a half years postoperatively, colonoscopy showed a scar at the site of the previous rectal procedure (Fig 1f). Enhanced

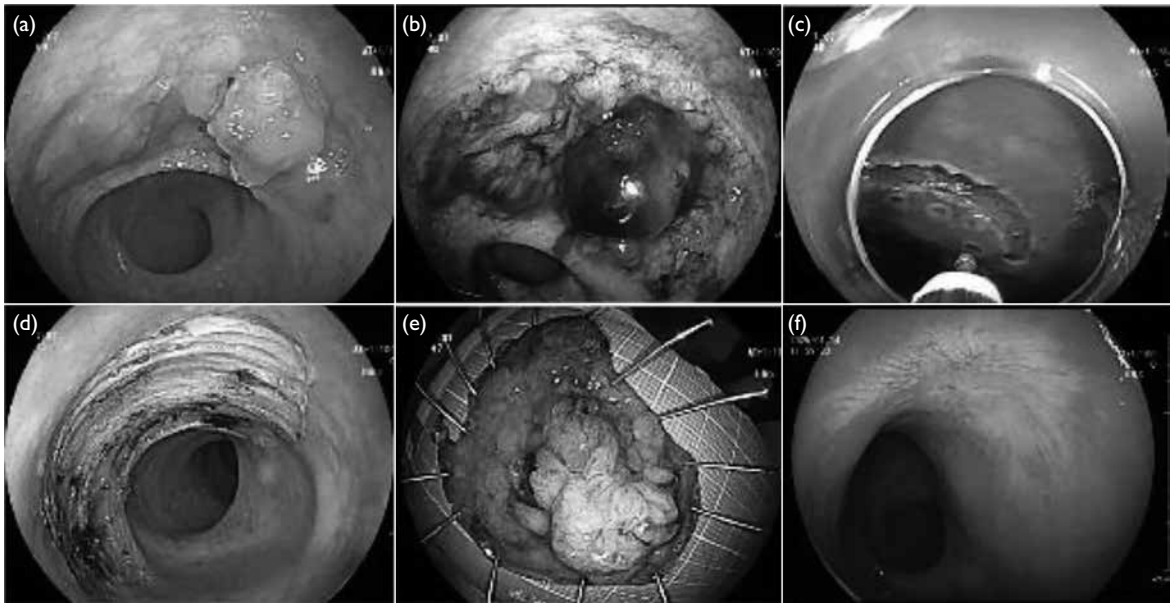

FIG 1. Tumour morphology and process of endoscopic submucosal dissection (ESD). (a) Endoscopic features; (b) indigo carmine staining; (c-e) ESD procedure; (f) follow-up endoscopy approximately 1.5 years after ESD

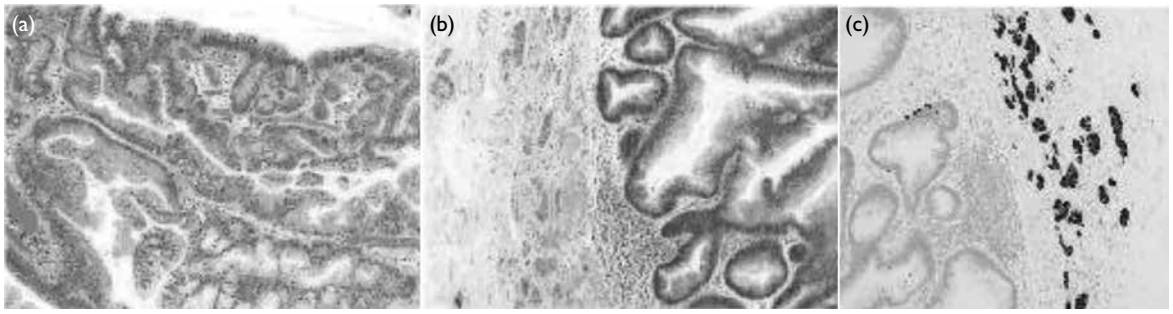

FIG 2. Pathology and immunohistochemistry staining of the tumour. (a, b) Haematoxylin-eosin staining (a: ×100; b: ×200); (c) chromogranin A staining (×200)

chest and abdominal computed tomography scans showed slight thickening of the rectal mucosa without evidence of regional or distant lymph node enlargement.

Discussion

Neuroendocrine neoplasms are a rare type of tumour and encompass three major subtypes: neuroendocrine tumours, neuroendocrine carcinomas and mixed neuroendocrine–non-neuroendocrine neoplasms (MiNENs). Among these, MiNENs are a special type with high invasiveness. Our case resembled a MiNENs but exhibited some distinct differences.

In this case, the pathology was special. It did not align with the current World Health Organization classification of NENs.[1] These neoplasms, known as MiNENs, are characterised by a combination of neuroendocrine and non-neuroendocrine components, both of which comprise at least 30% of the neoplasm.[1] Although our case shared similarities with MiNENs in terms of mixed histology, it differed significantly in the proportion of components, with the neuroendocrine tumour component constituting less than 30%. Evidently, this case did not meet the current definition of MiNENs. In fact, the definition of MiNENs remains controversial.

These mixed tumours (neuroendocrine–non-neuroendocrine neoplasms) were first described in 1924.[2] In 2000, a classification system for endocrine tumours was implemented and defined mixed exocrine–endocrine carcinomas as tumours in which each component constitutes at least 30% of the neoplasm.[2] In 2010, the World Health Organization classified mixed neuroendocrine and exocrine tumours as mixed adenoneuroendocrine carcinomas.[2] Subsequently, in 2017, mixed adenoneuroendocrine carcinomas were reclassified as MiNENs. The term "exocrine" was replaced with "non-neuroendocrine" to encompass a broader range of possible histological variants, including glandular, squamous, mucinous, and sarcomatoid phenotypes.[3] As for the threshold of at least 30% for each component, it is highly unusual for a component with a lower representation to affect the biological behaviour of a cancer.[2] Nonetheless, the threshold was arbitrarily set without clinical or scientific evidence.[4] Given the emergence of our case, we believe that this threshold requires further optimisation.

Regarding the pathology in our patient, we proposed the following explanations. First, there are two widely accepted hypotheses for the origin of MiNENs.[5-8] The first posits that both tumour components originate from a single precursor cell but proliferate and differentiate along distinct pathways. The second hypothesis also suggests a common cellular origin. Nonetheless, it proposes that during tumour progression, a subset of the non-neuroendocrine component accumulates sufficient genetic mutations to transform into neuroendocrine cells. These theories suggest that the composition of MiNENs is dynamic, with potentially varying proportions of components at different stages of tumour development. Second, with growing health awareness and the widespread adoption of endoscopic screening, early-stage tumours are more readily identified. These early-stage neoplasms are typically smaller in size and exhibit a lower degree of malignancy. These factors collectively contribute to the evolving landscape of MiNENs diagnosis and classification, necessitating ongoing refinement of diagnostic criteria and classification systems.

In terms of endoscopic manifestation, there was something worth considering. In this case, the surface of the tumour was repeatedly washed, but mucus adhesion persisted, more similar to the manifestation of mucinous adenocarcinoma or serrated adenocarcinoma.[9] Notably, the absence of classic carcinoid syndrome symptoms and negative tumour markers further set this case apart. Although villous tubular adenomas can secrete mucus, the tumour in this case exhibited unusually copious and rapid mucus production. We suspected the neuroendocrine tumour may possess paracrine functions that further stimulated

secretion from the adenoma. Nonetheless, there have been no experiments supporting this viewpoint. Experimental validation in the future is needed to elucidate the potential interplay between these neoplastic entities and their secretory mechanisms.

In terms of treatment, although a definitive classification of this tumour type has not been established, the existing treatment principles for NENs remain applicable. For this patient, the neuroendocrine tumour lesion was less than 10 mm in size, with a Ki-67 index of less than 3%, classifying it as a G1 stage tumour, and there was no evidence of metastasis to other organs or tissues. We performed endoscopic submucosal dissection to remove the tumour. Nonetheless, it was important to consider the depth of resection. Resection above the muscularis mucosae may result in incomplete tumour removal, while excision below this layer risks vascular injury. We recommended resection close to the muscularis mucosa to minimise bleeding and to prevent tumour seeding into blood vessels. Another critical consideration was the extent of resection. It was imperative to ensure negative tumour margins to guarantee complete excision of the neoplasm.

Our case indicates that the current classification system for NENs remains inadequate. Specifically, there is no clear classification for tumours that contain a minor component of neuroendocrine cells, highlighting an urgent need for further refinement of MiNENs.

Author contributions

Concept or design: W Zhou and X Ke.
Acquisition of data: W Zhou and X Ke.
Analysis or interpretation of data: W Zhou and X Ke.
Drafting of the article: All authors.
Critical revision for important intellectual content: L Liu.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Ethics approval

The patient was treated in accordance with the Declaration of Helsinki. The patient provided informed consent for all procedures agreement for publication of this article.

References

1. Washington MK, Goldberg RM, Chang GJ, et al. Diagnosis of digestive system tumours. Int J Cancer 2021;148:1040-50.
2. Díaz-López S, Jiménez-Castro J, Robles-Barraza CE, Ayala-de Miguel C, Chaves-Conde M. Mixed neuroendocrine non-neuroendocrine neoplasms in gastroenteropancreatic tract. World J Gastrointest Oncol 2024;16:1166-79.
3. Kanthan R, Tharmaradinam S, Asif T, Ahmed S, Kanthan SC. Mixed epithelial endocrine neoplasms of the colon and rectum—an evolution over time: a systematic review. World J Gastroenterol 2020;26:5181-206.
4. Toor D, Loree JM, Gao ZH, Wang G, Zhou C. Mixed neuroendocrine-non-neuroendocrine neoplasms of the digestive system: a mini-review. World J Gastroenterol 2022;28:2076-87.
5. Frizziero M, Chakrabarty B, Nagy B, et al. Mixed neuroendocrine non-neuroendocrine neoplasms: a systematic review of a controversial and underestimated diagnosis. J Clin Med 2020;9:273.
6. Bazerbachi F, Kermanshahi TR, Monteiro C. Early precursor of mixed endocrine-exocrine tumors of the gastrointestinal tract: histologic and molecular correlations. Ochsner J 2015;15:97-101.
7. Scardoni M, Vittoria E, Volante M, et al. Mixed adenoneuroendocrine carcinomas of the gastrointestinal tract: targeted next-generation sequencing suggests a monoclonal origin of the two components. Neuroendocrinology 2014;100:310-6.
8. Yuan W, Liu Z, Lei W, et al. Mutation landscape and intra-tumor heterogeneity of two MANECs of the esophagus revealed by multi-region sequencing. Oncotarget 2017;8:69610-21.
9. Lee CT, Huang YC, Hung LY, et al. Serrated adenocarcinoma morphology in colorectal mucinous adenocarcinoma is associated with improved patient survival. Oncotarget 2017;8:35165-75.

