Case Report

The Mixed Neuroendocrine-nonneuroendocrine Neoplasm of Rectosigmoid Junction: A Rare Case Report and Literature Review

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Mixed neuroendocrine-nonneuroendocrine neoplasms (MiNENs) are a rare type of diagnosis in the gastro-entero-pancreatic system, and particularly at the rectosigmoid junction, the coexistence of mucinous adenocarcinoma and neuroendocrine tumor (NET) is even rarer.

Herein, we report an 83-year-old male patient who was brought to our hospital due to diarrhea with intermittent bloody stool for 1 year. He received colonoscopic examinations which revealed an ulcerative tumor located 12-20 cm from the anal verge. Abdominal computed tomography (CT) scans demonstrated a suspected rectosigmoid junction colon cancer with pericolic infiltration and regional metastatic lymphadenopathies, and the clinical staging demonstrated cT3N1M0 (Stage IIIB). The biopsy of this lesion showed moderately differentiated adenocarcinoma with mucinous differentiation. After shared decision-making with his family, neoadjuvant concurrent chemoradiotherapy (CCRT) was performed, with the consequent abdominal CT scans showing interval-decreased tumor size and interval shrinkage of regional lymph nodes (partial response); then, low anterior resection combined with lymph node dissection and colorectal anastomosis was carried out. The pathology of this specimen showed mixed well-differentiated neuroendocrine tumor (20%) and moderately differentiated mucinous adenocarcinoma (80%), staged as ypT3N0M0 (stage IIA).

Due to the rarity of MiNENs, precise diagnosis and pathological analysis are essential, with effective management demanding thorough postoperative monitoring and careful selection of adjuvant therapies. Investigating the mechanisms that cause coexisting NETs and adenocarcinomas is important, as this understanding could enhance treatment strategies and improve outcomes for MiNENs patients.

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Mixed neuroendocrine non-neuroendocrine neoplasms (MiNENs) are a rare type of diagnosis in the gastro-entero-pancreatic system. The variations in the proportions of each component (ranging from 1% to 99%) lead to significant morphological heterogeneity, which causes difficulties in classification and diagnosis in pathology.[1]

The two components of mixed neoplasms demonstrate variable morphological characteristics, which can vary based on the site of origin and degree of dif-

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ferentiation while presenting in distinct patterns: they may be intimately intermingled within the tumor mass, forming composite tumors; they may occupy separate, juxtaposed regions of the tumor mass, referred to as collision tumors; or, in some cases, neuroendocrine and non-neuroendocrine features may coexist within the same cell population, resulting in amphicrine tumors.[2]

These conditions present significant challenges for oncologists in determining the primary tumor component to target during therapeutic interventions. Moreover, the heterogeneity in the definitions applied to mixed epithelial tumors has led to substantial inconsistencies in the data reported in previous studies, particularly with respect to the identification of prognostic parameters that influence tumor behavior.[3] Herein, we report an 83-year-old male patient with a rectosigmoid junction MiNEN and reveal the challenges faced in managing this unique tumor.

Case Presentation

An 83-year-old male patient had a medical history of Alzheimer's disease, old brain infarction, hypertension and no surgical history. The laboratory data including complete blood cell (CBC) count, liver function and renal function showed all were within normal ranges, as was the serum level of carcinoembryonic antigen (CEA). Because he had had frequent episodes of bloody stool, a colonoscopic examination was arranged with the findings indicating an ulcerative tumor in the rectosigmoid junction with severe lumen stenosis (Fig. 1A). A biopsy was performed, subsequently demonstrating a moderately differentiated adenocarcinoma with mucinous differentiation pathologically showing clinical stage cT3N1M0, stage IIIB from the abdominal CT scans (Fig. 1B).

Due to concerns about the potential for total colonic obstruction, a diverted loop transverse colostomy with left infraclavicular venous port implantation was performed along with laparoscopic exploration, which revealed no liver or peritoneal metastases. Locally advanced rectal cancer (LARC) was finally diagnosed and neoadjuvant concurrent che-

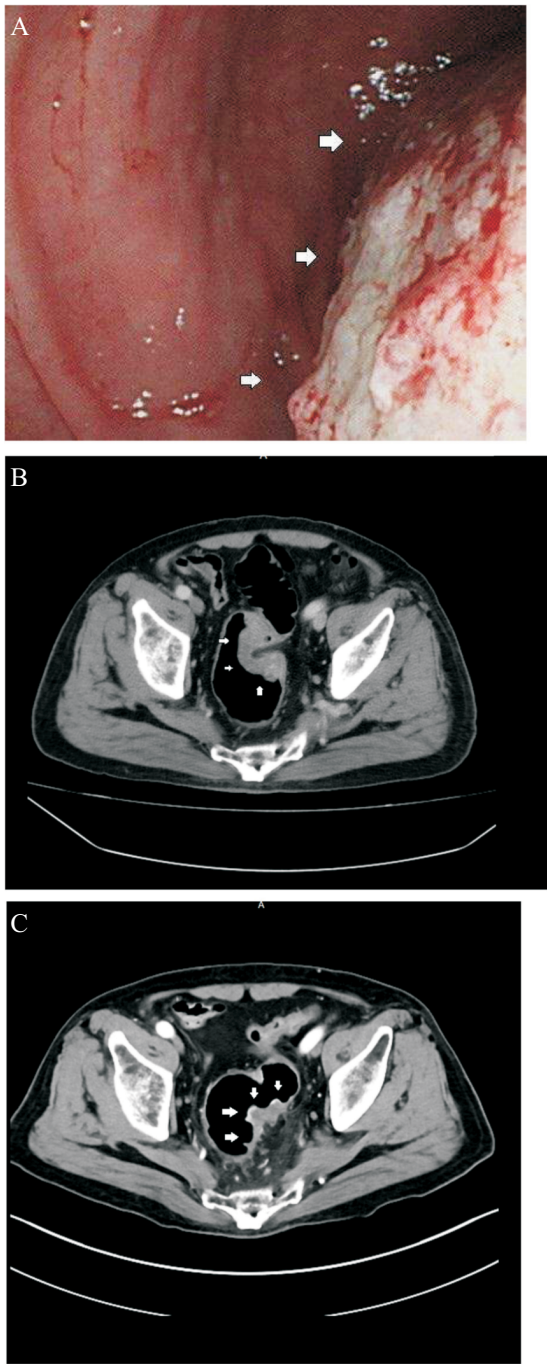

Fig. 1. (A) An ulcerative tumor in the rectosigmoid junction with severe lumen stenosis. The arrow indicates the outline of the tumor. (B) The abdominal computed tomography (CT) scans showed that a rectosigmoid junction colon tumor with pericolic infiltration, the clinical stage was cT3N1M0, stage IIIB. (C) Follow-up abdominal CT after CCRT showing interval decrease tumor size and persistently some pericolic infiltration and interval shrinkage of regional lymph nodes (Partial response, PR according to RECIST criteria).

moradiotherapy (CCRT) was arranged with the regimen being modified FOLFOX6 (mFOLFOX6). The patient underwent long-course neoadjuvant concurrent chemoradiotherapy (LCRT) with a total radiation dose of 50 Gy in 25 fractions, combined with 6 cycles of mFOLFOX6 chemotherapy. The regularly sequent abdominal CT scans showed the RECIST (Response Evaluation Criteria in Solid Tumors) was partial response (PR). Based on these findings, low anterior resection (LAR) procedure combined with lymph nodes dissection and colorectal anastomosis were then performed. The postoperative course went well, and the patient was discharged on the 12th postoperative day.

According to the pathological assessment, the tumor measured 24 × 18 mm and had invaded the subserosa (Fig. 2A), although no metastatic lesions were observed in the harvested lymph nodes. The tumor was composed of large pools of extracellular mucin containing floating malignant epithelial strips, cell clusters and single cells (Fig. 2B), so it was diagnosed as a moderately differentiated mucinous adenocarcinoma. Additionally, solid vesicles of polygonal tumor cells were noted in the submucosa (Fig. 2B); these cells exhibited poor nuclear atypia and were positive for INSM-1 (Fig. 2C), so were therefore considered as carcinoid tumors (NET G1). Based on these pathological findings,[4] the tumor was diagnosed as intermediate-grade MiNENs and classified as ypT3N0M0, Stage IIA (TNM Classification of Malignant Tumors, 8th Edition).

Discussion

This case depicted a finding of MiNENs in which rectosigmoid colon cancer and NET G1 occurred in an 83-year-old male patient. Colonic neuroendocrine tumors (Colonic-NENs) account for approximately 5-7% of all well-differentiated gastro-entero-pancreatic neuroendocrine tumors and 25% of all gastro-entero-pancreatic neuroendocrine carcinomas.[5] The average age at diagnosis for these tumors is 65 years, and their clinical presentations are similar to that of colonic adenocarcinomas. Diagnosis is typically established after biopsy of the mass or surgical resection in which most patients present with advanced disease at diagnosis; accordingly, early recognition and management of colonic neuroendocrine tumors are crucial.[5]

The prognosis of colorectal mixed neuroendocrine-nonneuroendocrine neoplasmas (MiNENs) is significantly worse than that of pure adenocarcinoma and is comparable to that of poorly differentiated neuroendocrine carcinoma (PDNEC), particularly at the metastatic stage.[6] The risk of metastasis is correlated with the grade of the neuroendocrine component.[7] In 2019, La Rosa et al. reported that MiNENs could be classi-

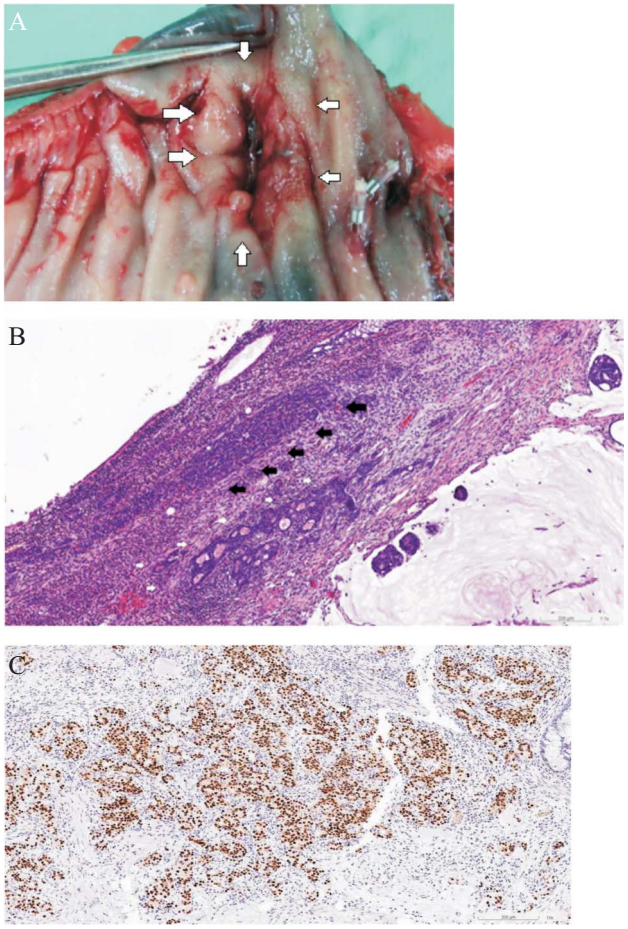

Fig. 2. (A) The tumor was 24 × 18 mm in size. The arrow indicates the outline of the tumor. (B) The tumor was mainly moderately differentiated mucinous adenocarcinoma (the black arrow), but solid vesicles of polygonal tumor cells were noted in the submucosa (the white arrow). (C) The tumor cells were positive for INSM-1.

fied into three grades (high, intermediate and low) based on prognosis, which is crucial for determining treatment strategies.[8] High-grade MiNENs, the most prevalent type, typically consist of neuroendocrine carcinoma (NEC) combined with a non-neuroendocrine tumor or adenoma, with the NEC component displaying higher aggressiveness. For localized forms, curative-intent surgery should be considered if feasible, along with adjuvant or perioperative chemotherapy.[9] Intermediate-grade MiNENs comprise a non-neuroendocrine tumor combined with a well-differentiated neuroendocrine tumor (NET), and its prognosis generally depends on the non-neuroendocrine tumor. Curative-intent surgery is recommended for resectable disease, while in metastatic disease, systemic chemotherapy should target the identified components in the metastases or be discussed based on therapies effective for both components.[8] Low-grade MiNENs, primarily found in the digestive tract, consist of an adenoma and a well-differentiated NET. These tumors, although relatively rare, should be treated as NETs due to the potential for metastasis of the NET component.[8] Response rate of neoadjuvant CCRT for rectal adenocarcinoma has been reported with a pathological complete response (pCR) rate of 14-28% and partial response (PR) rate of 48-65%.[10-13] Currently, there is no prospective randomized evidence supporting the use of chemotherapy in the adjuvant or neoadjuvant settings for patients with well-differentiated neuroendocrine tumors (NETs).[14] Moreover, many national guidelines for the management of NETs do not recommend chemotherapy in these scenarios for well-differentiated cases.[14] However, patients with grade 3 NETs have demonstrated the highest sensitivity to chemotherapy, and emerging evidence suggests that individuals with grade 2 or higher extra-pancreatic NETs may also benefit from chemotherapy.[15] Neuroendocrine tumors (NETs) typically demonstrate a reduced responsiveness to chemotherapy, presenting a marked contrast to the therapeutic outcomes seen in adenocarcinomas.[15]

In our present case, the mucinous adenocarcinoma segment represented 80% of the total tumor tissue and had invaded the subserosa, while the neuroendocrine component represented 20% of the total tumor tissue and had developed around the submucosa, so this case was diagnosed as a combined/biphasic type of MiNENs. The current tumor was histologically composed of G1 NET and mucinous adenocarcinoma, without the presence of distant metastases and classified as intermediate-grade MiNENs according to the classification of La Rosa et al. Adjuvant chemotherapy deemed appropriate followed the surgical resection of the tumor, which was performed due to the symptomatic nature of the condition.

Conclusion

In conclusion, the MiNENs of rectosigmoid junction is very rare case, and although this case was an intermediate-grade lesion combining NET with adenocarcinoma, the prognosis was not expected to be foreboding. Therapeutic management should be based on identification of the most aggressive cellular component.

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Ethical Approval

The study was approved by the Institutional Review Board of Kaohsiung Medical University Hospital (KMUHIRB-E(I)-20230267).

Declaration of Patient Consent

The authors certify that they have obtained all appropriate patient consent forms where the patient has given his consent for the images and other clinical information to be reported in the journal while understanding that his name and initials will not be published and all due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

Data Availability Statement

Data sharing is not applicable to this article because no data sets were generated or analyzed during the current study.

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Conflicts of Interest Statement

The authors declare that they have no conflict of interest with regard to the content of this article.

References

1. Elpek GO. Mixed neuroendocrine-nonneuroendocrine neoplasms of the gastrointestinal system: an update. *World J Gastroenterol* 2022;28(8):794-810. doi:10.3748/wjg.v28.i8.794
2. Volante M, Rindi G, Papotti M. The grey zone between pure (neuro)endocrine and non-(neuro)endocrine tumours: a comment on concepts and classification of mixed exocrine–endocrine neoplasms. *Virchows Arch* 2006;449(5):499-506. doi:10.1007/s00428-006-0306-2
3. La Rosa S, Sessa F, Uccella S. Mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs): unifying the concept of a heterogeneous group of neoplasms. *Endocr Pathol* 2016;27(4):284-311. doi:10.1007/s12022-016-9432-9
4. Brathwaite SA, Smith SM, Wai L, et al. Mixed adenoneuroendocrine carcinoma: a review of pathologic characteristics. *Hum Pathol* 2018;73:184-91. doi:10.1016/j.humpath.2017.12.009
5. Volante M, Grillo F, Massa F, et al. Neuroendocrine neoplasms of the appendix, colon and rectum. *Pathologica* 2021;113(1):19-27. doi:10.32074/1591-951X-230
6. Digestive System Mixed Neuroendocrine-Non-Neuroendocrine Neoplasms | Neuroendocrinology | Karger Publishers. Accessed December 10, 2024. https://karger.com/nen/article/105/4/412/220298/Digestive-System-Mixed-Neuroendocrine-Non
7. Li Y, Yau A, Schaeffer D, et al. Colorectal glandular-neuroendocrine mixed tumor: pathologic spectrum and clinical implications. *Am J Surg Pathol* 2011;35(3):413. doi:10.1097/PAS.0b013e3182093657
8. Digestive system mixed neuroendocrine-non-neuroendocrine neoplasms (MiNEN). *Ann Endocrinol* 2019;80(3):172-3. doi:10.1016/j.ando.2019.04.006
9. Smith JD, Reidy DL, Goodman KA, Shia J, Nash GM. A retrospective review of 126 high-grade neuroendocrine carcinomas of the colon and rectum. *Ann Surg Oncol* 2014;21(9):2956-62. doi:10.1245/s10434-014-3725-3
10. Aschele C, Friso ML, Pucciarelli S, et al. A phase I–II study of weekly oxaliplatin, 5-fluorouracil continuous infusion and preoperative radiotherapy in locally advanced rectal cancer. *Ann Oncol* 2005;16(7):1140-6. doi:10.1093/annonc/mdi212
11. Chang PK, Jao SW, Wu CC, Lee CC, Lee TY, Hsiao CW. Outcomes of neoadjuvant chemoradiation therapy for locally advanced rectal cancer: the effect of preoperative chemoradiotherapy followed by additional chemotherapy on advanced rectal cancer.
12. Machiels JP, Duck L, Honhon B, et al. Phase II study of preoperative oxaliplatin, capecitabine and external beam radiotherapy in patients with rectal cancer: the RadiOxCape study. *Ann Oncol* 2005;16(12):1898-905. doi:10.1093/annonc/mdi406
13. Turitto G. Phase II study of neoadjuvant concurrent chemoradiotherapy with oxaliplatin-containig regimen in locally advanced rectal cancer. *Front Biosci* 2006;11(1):1275. doi:10.2741/1880
14. Pavel M, Öberg K, Falconi M, et al. Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2020;31(7):844-60. doi:10.1016/j.annonc.2020.03.304
15. Das S, Al-Toubah T, Strosberg J. Chemotherapy in neuroendocrine tumors. *Cancers* 2021;13(19):4872. doi:10.3390/cancers13194872

病例報告

直腸乙狀結腸交界處的混合神經內分泌-非神經內分泌腫瘤：罕見病例報告與文獻回顧

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混合型神經內分泌-非神經內分泌腫瘤是消化道-胰腺系統中罕見的診斷類型，尤其是在直腸乙狀結腸交界處，同時存在黏液性腺癌與神經內分泌腫瘤的情況更為罕見。

本報告描述一名 83 歲男性患者，因腹瀉伴隨間歇性血便長達一年而至本院就診。經結腸鏡檢查發現距肛門 12-20 公分處有一潰瘍性腫瘤。腹部電腦斷層掃描顯示疑似直腸乙狀結腸交界處之結腸癌，伴有腸周侵犯及區域性轉移性淋巴結，臨床分期為 (cT3N1M0，III 期 B)。該病灶的活檢結果顯示為中分化腺癌，伴有黏液性分化。經與家屬共同決策後，進行了新輔助同步化學放射治療。隨後的腹部電腦斷層掃描顯示腫瘤大小減少，區域性淋巴結縮小 (部分緩解)。患者接受了低前位切除術，並合併淋巴結廓清術及結直腸吻合術。術後病理檢查結果顯示腫瘤為混合型良好分化神經內分泌腫瘤 (20%) 與中分化黏液性腺癌 (80%)，病理分期為 (ypT3N0M0，II 期 A)。

由於混合型神經內分泌-非神經內分泌腫瘤的罕見性，精確的診斷與病理分析至關重要。有效的治療需要徹底的術後監測以及謹慎選擇輔助治療方法。探討導致神經內分泌腫瘤與腺癌共存的機制非常重要，這種理解有助於改善治療策略並提升混合型神經內分泌-非神經內分泌腫瘤患者的預後。

關鍵詞　混合型神經內分泌-非神經內分泌腫瘤、直腸乙狀結腸交界處、罕見性、新輔助同步化學放射治療、病例報告。