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Rectal Mixed Adenocarcinoma-Neuroendocrine Carcinoma with Exclusive Neuroendocrine Liver Metastasis: A Diagnostic Dilemma

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Abstract

Mixed neuroendocrine–non-neuroendocrine neoplasms (MiNENs) are uncommon tumours with both adenocarcinoma and neuroendocrine carcinoma constituents. Their treatment is fraught with diagnostic difficulty and aggressive behaviour largely determined by the neuroendocrine component. Here, we report the case of a 44-year-old male patient diagnosed with a rectal MiNEN that consisted of moderately differentiated adenocarcinoma and high-grade neuroendocrine carcinoma. Regardless of neoadjuvant chemoradiotherapy, surgical resection revealed a mixed tumor. Follow-up liver metastases were proven to be purely high-grade neuroendocrine carcinoma by histopathology and immunohistochemistry. The present case highlights the rare phenomenon of selective neuroendocrine metastasis from a MiNEN primary tumor, underscoring the need for thorough histopathological assessment of metastatic sites and individualized management strategies targeting the most aggressive tumor component.

Keywords: ***Mixed neuroendocrine-non-neuroendocrine neoplasm; MiNEN; Rectal cancer; Neuroendocrine carcinoma; Liver metastasis***

1. Introduction

MiNENs are uncommon, aggressive neoplasms characterized by the presence of neuroendocrine (NE) and non-neuroendocrine (non-NE) components each constituting at least 30% of the tumor mass, based on the WHO criteria [1-3]. Historically, they were referred to as MANECs; however, with the recognition of their varied histological patterns such as squamous or mucinous components, they were reclassified as MiNENs [4,5].

MiNENs occur throughout the gastrointestinal tract but most commonly in the colon and rectum [6,7]. The non-NE component is more commonly adenocarcinoma and the NE component may be a high-grade neuroendocrine carcinoma (NEC) with a high Ki-67 proliferation index [8;9]. Significantly, prognosis is dominated by the NEC component [10,11].

The 30% criterion in each component has been controversial because even small amounts of NE elements can have a substantial effect on the prognosis and treatment [12,13]. Molecular analysis demonstrates common mutations like TP53 and KRAS in the two components, favoring a monoclonal origin with divergent differentiation [14,15].

Correct diagnosis necessitates extensive histopathological and immunohistochemical analysis, which may be difficult, especially in small biopsies or after treatment [16,17]. Treatment typically aims the more aggressive part, with frequent use of platinum-based chemotherapy for NEC [18,19].

An uncommon but clinically relevant occurrence is isolated metastasis of the NEC component alone from a composite primary tumor [15]. We report a case of rectal MiNEN with liver metastasis having a purely high-grade NEC component, emphasizing the significance of identification of such a pattern for proper diagnosis and management.

2. Case

A 44-year-old male with no previous comorbidities initially presented elsewhere with a history of bleeding per rectum. Colonoscopy detected an ulcerative, annular lesion 5 cm from the anal verge, biopsy of which showed moderately differentiated adenocarcinoma.

Abdominal MRI done revealed circumferential wall thickening of the middle and lower rectum, about 4 cm from the anal verge, with mesorectal deposits and internal iliac lymphadenopathy. He received six cycles of neoadjuvant chemotherapy. Follow-up PET-CT revealed residual hypermetabolic thickening with perirectal soft tissue infiltration in view of which chemoradiotherapy was administered. Reassessment with 18F-FDG PET-CT showed partial metabolic response.

He then presented to our institution where a digital rectal examination revealed an ulcero proliferative lesion 3 cm above the anorectal junction. Colonoscopy revealed a friable, ulceroproliferative mass around 5 cm in size, extending up to 9 cm from the anal verge and involving approximately 50% of the luminal circumference. Biopsy revealed residual adenocarcinoma.

Subsequently he underwent laparoscopic intersphincteric resection with transverse colostomy. During surgery, there was a posterior and right lateral growth of the rectum along with associated mesorectal deposits. The liver was grossly normal. Gross inspection of the specimen removed showed an ulceroinfiltrative mass of 4.5 cm × 4 cm × 2.5 cm occupying about 80% of the lumen, 0.2 cm short of the distal margin and 0.7 cm short of the circumferential margin.

Histopathologic examination revealed two components: (1) moderately differentiated adenocarcinoma in cribriform and glandular patterns with necrosis; and (2) solid nests of small- to medium-sized cells with minimal cytoplasm, stippled chromatin, brisk mitoses (45-48 per 2 mm^2), and widespread necrosis typical of high-grade NEC (FIG. 1a, b). There was lymphovascular and perineural invasion. Treatment effect was graded as partial response (score 2).

Margins were free (nearest was the 2 mm clearance of the distal resected margin). There was necrotic metastatic carcinoma in one of the 16 lymph nodes isolated. Diffuse staining for synaptophysin, chromogranin, and INSM1 was noted in the NEC component, and Ki-67 index was 80% (FIG. 1c,d,e,f). The adenocarcinoma component stained positive for CK20 (FIG. 1g).

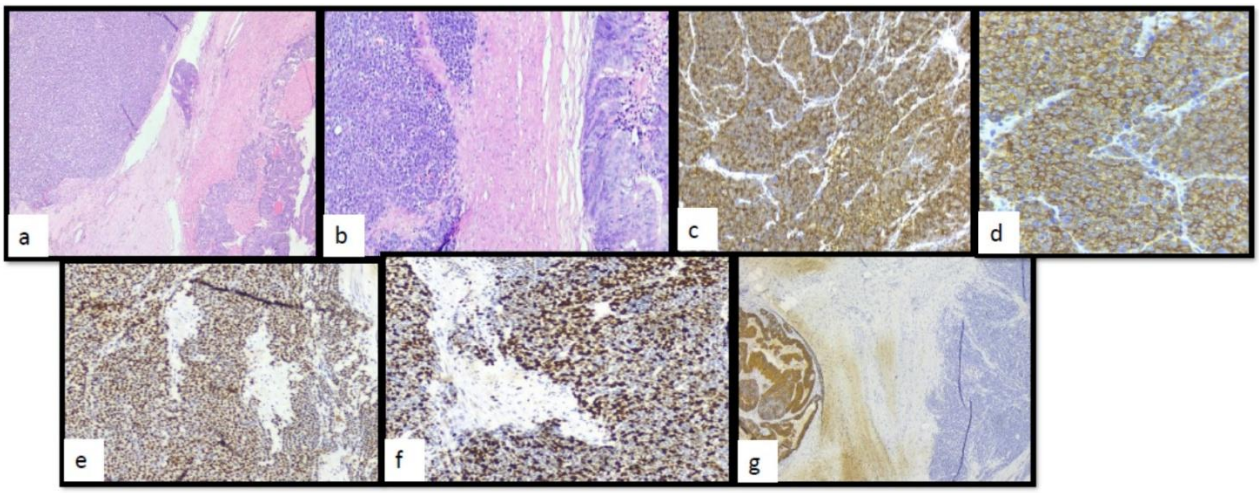

FIG. 1. **(a) Shows tumor cells arranged in glandular pattern exhibiting necrosis, as well as in solid nests (H&E,100x), (b) Shows high power view of the tumor cells (H&E,400x), (c) IHC- Chromogranin – Diffuse Positivity (400x), (d) IHC- Synaptophysin –Diffuse positivity (400x), (e) IHC- INSM1 -Diffuse Positivity (400x), (f) Ki-67- Proliferation index of 80% In the hot spots (400x), (g) IHC- CK 20 -Negative in solid areas of the tumor and positive in the glandular areas (400x).**

The diagnosis was rectal MiNEN comprising moderately differentiated adenocarcinoma and high-grade NEC. He was initiated on cisplatin-etoposide chemotherapy against the NEC component. At one of the follow-up consultations 5 months later, he was noted to have multiple new liver lesions on ultrasound scan, which were biopsied. We received two cores of hepatic tissue which was entirely demonstrating infiltration by a poorly differentiated carcinoma, the morphology of which was suggestive of an origin from the solid neuroendocrine component of the rectal neoplasm (FIG. 2a, b). Immunohistochemistry was done which showed a similar profile to that seen in the neuroendocrine carcinoma component of the original tumour with diffuse positivity for INSM1, Chromogranin and Synaptophysin with a Ki-67 index of over 80%. This further proved a metastatic neuroendocrine carcinoma component of the earlier MiNEN.

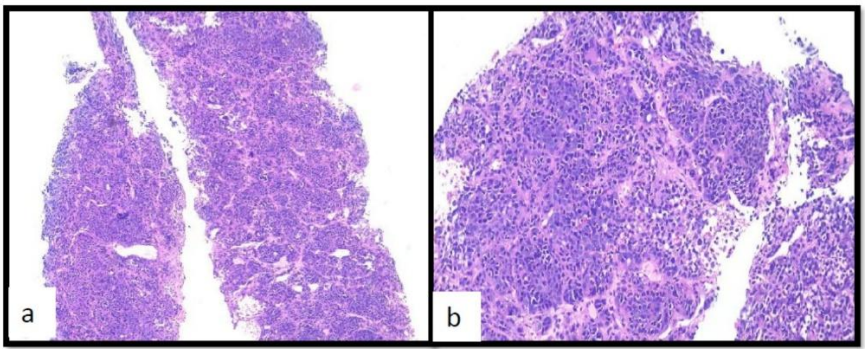

FIG. 2. **(a) Liver biopsy showing infiltrating neoplasm in solid nests (100x), (b) High power view of the tumor cells (400x).**

3. Discussion

Mixed neuroendocrine–non-neuroendocrine neoplasms (MiNENs) of the colorectum are uncommon, very aggressive tumors with biphasic differentiation into glandular (adenocarcinoma) and neuroendocrine carcinoma (NEC) components [1-3]. The WHO classification describes MiNENs as tumors in which both components are ≥ 30% of the neoplasm, although this cut-off is arbitrary and controversial [4-6].

Histologically, MiNENs can be composite (mixed components), collision (next to but distinct), or amphicrine varieties (double differentiation in single cells) [5-7]. Prognosis is largely dependent on the NEC component, which is generally characterized by high-grade morphology with brisk mitoses, necrosis, and high Ki-67 proliferation indices commonly above 50%-80% [8-10].

Current molecular pathology developments have changed our comprehension of MiNEN histogenesis. Next-generation sequencing investigations firmly advocate a monoclonal derivation, with the adenocarcinoma and NEC components sharing a mutual progenitor clone [11-13]. Concomitant driver mutations in TP53, KRAS, RB1, and PIK3CA have been repeatedly found in both components, suggesting divergent differentiation post-early oncogenic transformation [11-14].

Intra-tumor heterogeneity analyses by multi-region sequencing have shown that although early driver events are common, subsequent subclonal evolution results in genetic divergence of the two components [13,14]. This explains morphologic, immunophenotypic and clinical behaviour differences, including differential response to treatment. Importantly, the NEC component tends to accumulate further alterations of cell-cycle dysregulation and genomic instability that underlie its highly proliferative, therapy-resistant phenotype [11-14].

These molecular findings have important therapeutic implications. Modern treatment modalities are still empiric, with platinum-based chemotherapy (for example, cisplatin–etoposide) preferred for the high-grade NEC component. Molecular profiling, however, can recognize actionable mutations, such as PIK3CA or BRAF alterations, allowing for targeted therapy in certain patients [13-16]. Whole-genome sequencing may further enable stratification for immunotherapy or entry into clinical trials assessing new agents.

A particularly important and challenging phenomenon, as demonstrated in our case, is selective metastasis of pure NEC only. There have been multiple case reports of liver or distant metastasis made up entirely of NEC from mixed primaries [17-19] This selective spread points to the inherent higher metastatic potential of the NEC component, fueled by its molecular signature, proliferative rate and resistance to therapy.

Thus, biopsy and immunohistochemical analysis of metastases are necessary. Without histologic confirmation, metastatic disease can be inappropriately classified as adenocarcinoma and treated with less than optimal therapy. NEC generally demands platinum-containing regimens that are very different from usual protocols for colorectal adenocarcinoma [9,10,19].

Ultimately managing MiNENs will need a multidisciplinary framework involving pathology, molecular diagnostics, surgery, oncology, and radiation therapy. A better understanding of their molecular diversity may help refine classification and guide

treatment decisions. Further research involving large-scale molecular analyses to establish actionable targets and clinical trials of targeted therapies is needed to create evidence-based diagnostic and therapeutic guidelines for these uncommon yet aggressive tumors.

4. Conclusion

The case describes the diagnostic and therapeutic intricacy of colorectal MiNENs, especially the so-called selective NEC metastasis. The presence of liver metastasis consisting only of NEC from an otherwise mixed primary rectal tumor emphasizes the neuroendocrine component's aggressive potential and the importance of extensive histopathological and immunohistochemical assessment of metastatic lesions. Because of the rarity of MiNENs and lack of standardized guidelines for treatment, multidisciplinary input and meticulous pathologic evaluation are crucial. Enhanced knowledge of MiNEN biology, molecular characterization, and future clinical trials is required to better standardize classification criteria, best strategy of treatment and patient outcomes with these rare but extremely aggressive tumors.

5. Declaration of Patient Consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his/ her consent for his/her images and other clinical information to be reported in the journal. All identifiable information has been removed to protect patient confidentiality.

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Nil.

7. Conflicts of Interest

There are no conflicts of interest.

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