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Mixed Neuroendocrine-Non-Neuroendocrine Neoplasm (MiNEN) of the Colon: A Case Report

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Abstract

Here we report a rare case of mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs). A 51-year-old lady with no known family history of malignancies developed this rare type of malignancy without any active gastrointestinal symptoms. However, during a routine health check, physicians noticed a raised Carcinoembryonic Antigen (CEA) level and the patient subsequently was referred to the surgical department for further management. A colonoscopy and CECT abdomen were done and she was electively admitted for a left hemicolectomy operation for a splenic flexure tumour. The histopathological report revealed the tumour is a case of mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs) [moderately differentiated adenocarcinoma and neuroendocrine tumour grade 3]. TNM (8th edition, 2016): pT3, pN2 (20/21), pMX. Both resection margins were clear from malignant cells. Colorectal MiNENs, constitute a rare group of gastrointestinal tumours composed of both neuroendocrine and non-neuroendocrine components. Given their non-diagnostic macroscopic features, specific histological features and lack of disease awareness which are responsible for the underestimated incidence and conflicting data. In this case, a multidisciplinary team approach is important in managing patients with this malignancy to achieve the best outcome.

Keywords

Mixed Neuroendocrine-Non-Neuroendocrine Neoplasms (MiNENs), Contrast-Enhanced Computed Tomography (CECT), Carcinoembryonic Antigen (CEA)

1. Introduction

In 2019, malignant epithelial tumours of the colon and rectum were broadly

classified by the World Health Organisation (WHO) into Adenocarcinoma, Neuroendocrine tumours, Neuroendocrine carcinoma and MiNEN. Epithelial neoplasms are composed of two different cellular components; neuroendocrine and non-neuroendocrine which are rare entities and may occur in different anatomic sites. In 2010, the World Health Organization (WHO) classification of Digestive System tumours established that mixed neuroendocrine-non-neuroendocrine neoplasms were composed of at least 30% of each component and identified as "Mixed Adenoneuroendocrine Carcinomas (MANEC) [1]. MANEC is defined as a tumour with both morphologically recognizable glandular epithelial and neuroendocrine phenotypes and is also considered a cancer because both elements are malignant. A mixture of squamous cell carcinoma and neuroendocrine elements has also been identified in some oesophagal and anal tumours [2]. Besides gastrointestinal segments, cases of MANEC were also reported to occur in the pancreas, gallbladder, and uterine cervix [3]. In comparison to "MANECs", the term "MiNENs" is believed to better address the heterogeneous spectrum of possible combinations between neuroendocrine and non-neuroendocrine elements and the variability of morphologies, which are largely determined by the site of origin [4]. The new 5th edition WHO classification provided a new framework based on the degree of cellular differentiation creating a group of mixed neuroendocrine-non-neuroendocrine neoplasms (MiNEN) [5]. For a neoplasm to qualify as MiNEN, both elements of neuroendocrine and non-neuroendocrine should be morphologically and immunohistochemically recognized [6]. The neuroendocrine element should be confirmed by immunohistochemical staining for synaptophysin and/or chromogranin. Ideally and by arbitrary convention, each element should constitute > 30% of neoplasm for the neoplasm to be included within the MiNEN category. To our knowledge, there was only one case of MiNEN reported in Malaysia and it was reported that the said case was a patient who had triple primary malignancy in which one of the malignancies was MiNEN of the colon [7]. Furthermore, evidence from the literature on MiNEN was almost exclusively derived from case reports and retrospective studies. Due to the rarity of this diagnosis, the limited quality of published data, and the use of inconsistent terminology, the epidemiology, prognosis, and best therapeutic management of patients with MiNEN remains unknown. Hence, this case report aims to accumulate the existing evidence on colorectal MiNEN in Malaysia with special attention towards understanding the morphology and clinicopathological features of MiNENs, as definitive diagnosis of MiNEN usually only follows after surgical resection.

2. Case Presentation

A 51-year-old lady, with underlying dyslipidemia and hypertension was referred to the surgical team to investigate her raised Carcinoembryonic Antigen (CEA). Her CEA level increased to 10 nanograms per millilitre of blood (ng/mL). She was soon investigated for this increased CEA level and subjected to colonoscopy

and a few radiological tests. She denies any active gastrointestinal symptoms or any constitutional symptoms. She also denied any family history of cancer. The patient was electively admitted to the surgical ward with no active complaints. She was stable and able to tolerate foods and drinks without any symptoms of intestinal obstruction. A colonoscopy was also done during her admission, which revealed a fungating tumour located 60 cm from the anal verge. She also went for a CECT abdomen (Figure 1) that revealed a descending colon tumour with few enlarged mesenteric nodes and two hypodense liver lesions. The patient did not experience any surgical complications post-surgery and was discharged home 5 days later. Approximately two weeks post-operation, the patient had her follow-up at our surgical clinic. On examination, the patient's abdominal wound healed well and she had no active complaints. They had a further discussion with a visiting clinical oncologist regarding the need for any adjuvant chemotherapy. The patient was counselled for adjuvant chemotherapy: 8 cycles of Oxyplatin and Capecitabine (XELOX) for 3 weeks. The adjuvant chemotherapy is planned after two months of operation.

3. Histopathology

Macroscopic examination of the resected specimen (Figure 2) revealed a nearly circumscribed, firm and greyish fungating splenic flexure tumour measuring 42 × 25 × 10 mm. Further cross-section of the tumour showed that the tumour has a cream-tan cut surface (Figure 3) and it is also grossly seen invading beyond

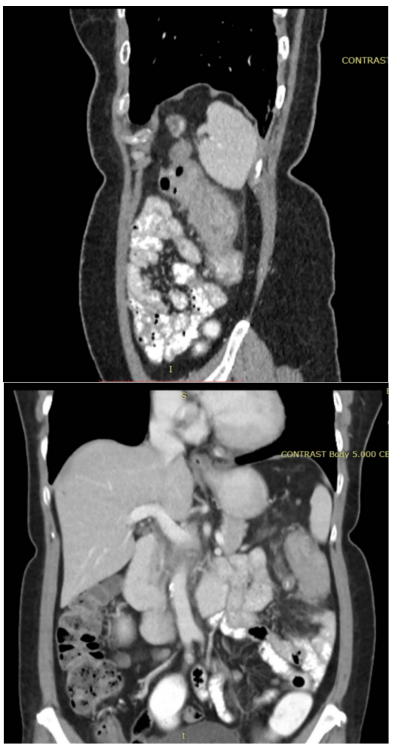


Figure 1. CECT Abdomen which shows a descending colon tumour.

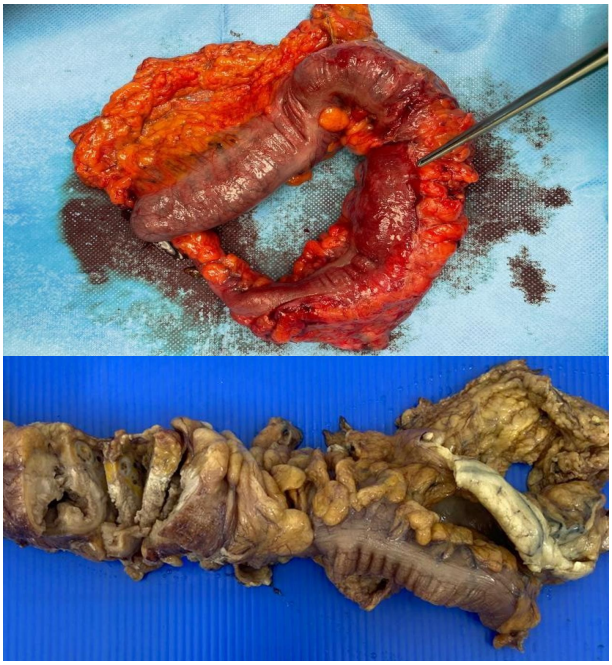


Figure 2. Fresh hemicolectomy specimen (above) and formalin fixed sample (below).

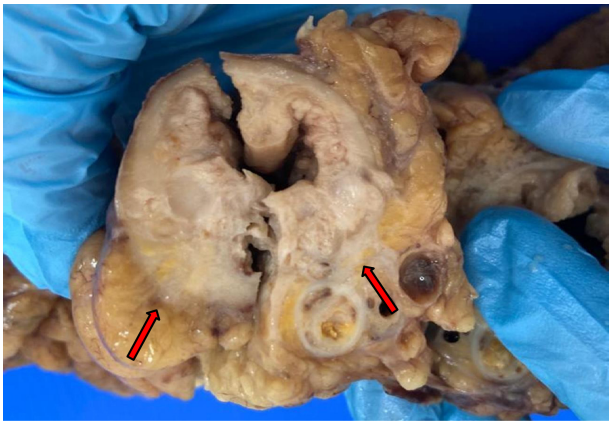


Figure 3. Cross-section of the splenic flexure revealed a cream-tan tumour that breaches beyond the Muscularis Propria (marked with red arrow) into the surrounding fat.

the Muscularis Propria into the surrounding fat. Both resected margins were far away from the main tumour. No other precursor lesions were seen. A total of 21 lymph nodes were harvested. Hematoxylin and eosin (H&E) stainings of the tumour showed a mixed component of malignant cells composed of 40% carcinomatous (non-neuroendocrine element) and 60% neuroendocrine element (**Figure 4**). The non-neuroendocrine element (**Figure 5**) is composed of malignant cells arranged in villiform and irregular glandular patterns and they display hyperchromatic nuclei with moderate nuclear pleomorphism and prominent nucleoli (**Figure 6**). Mitosis is frequently observed. The neuroendocrine element is composed of malignant cells arranged in clusters and sheets, displaying large

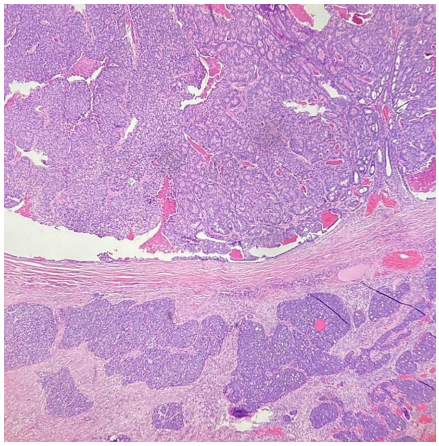


Figure 4. (H&E staining): Low power showing mixed components of carcinomatous (non-neuroendocrine) and neuroendocrine elements.

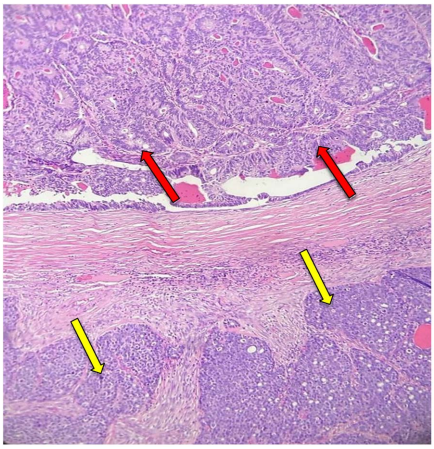


Figure 5. (H&E staining): Higher power shows the carcinomatous (non-neuroendocrine element) [red arrows] is composed of malignant cells arranged in villiform and irregular glandular patterns. The neuroendocrine element [yellow arrows] is composed of malignant cells arranged in clusters and sheets.

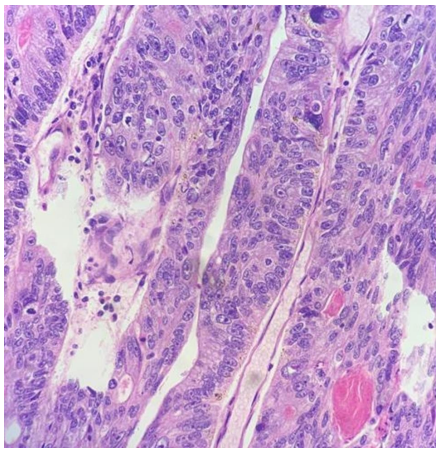


Figure 6. Higher power shows the carcinomatous element of the tumour showing tumour cells which are rounded to oval with moderate pleomorphism, hyperchromatic, prominent nucleoli and scanty cytoplasm.

cells with vesicular nuclei and prominent nucleoli (Figure 7). Mitosis is frequently observed (19/10 hpf). Extensive lympho-vascular invasion was also identified (Figure 8). The malignant cells infiltrate beyond the Muscularis Propria into surrounding pericolic fat. Multiple lymph nodes were harvested and 20 lymph nodes out of a total of 21 lymph nodes showed evidence of metastasis (Figure 9). Immunohistochemical stains showed that the tumour cells of the

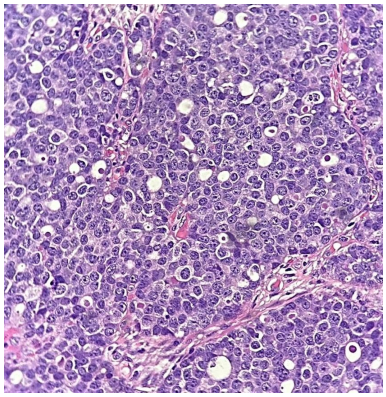


Figure 7. Higher power shows the neuroendocrine part of the tumour displaying uniform, large cells with vesicular nuclei and prominent nucleoli.

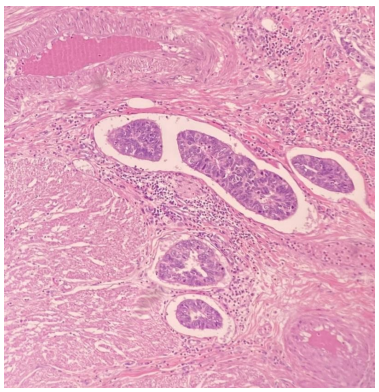


Figure 8. Evidence of lymphovascular tumour invasion.

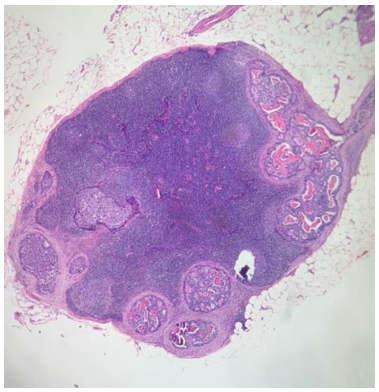
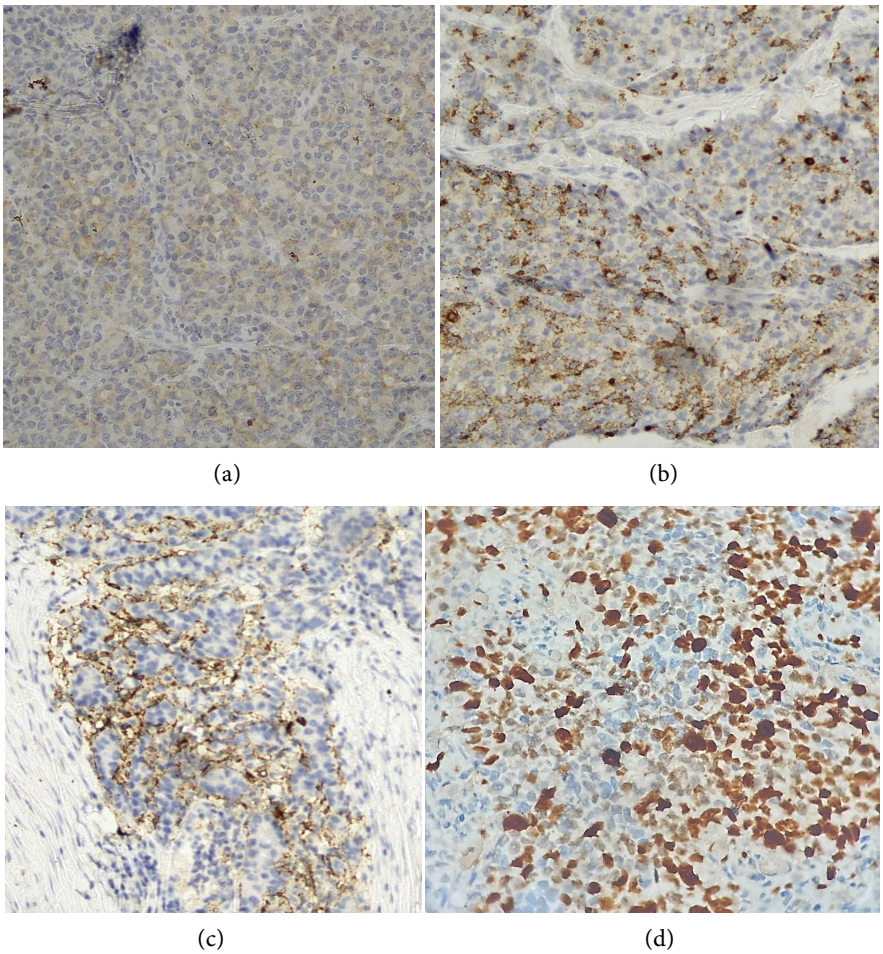


Figure 9. One of the lymph nodes that showed evidence of metastasis.

neuroendocrine element were positive for Synaptophysin (Figure 10(a)), Chromogranin A (Figure 10(b)) and CD56 (Figure 10(c)). The Ki 67 proliferative index is about 30 to 40% (Figure 10(d)).

4. Discussion

Colorectal MiNEN is an uncommon tumour to be encountered. The true prevalence of MiNEN is unknown, especially in Malaysia. Overall, the only available evidence is from case reports and retrospective studies. Regarding the best choice of treatment in cases of MiNEN, with the absence of good data from clinical trials, the management depends on which of the two components shows the most aggressive histological morphology. If the neuroendocrine part appears more aggressive, MiNENs are generally treated according to the standard management used for neuroendocrine carcinoma counterpart. If the non-neuroendocrine counterpart appears more aggressive, some clinicians might be treating



(a) (b)

(c) (d)

Figure 10. (a): The neuroendocrine element showed positivity towards Synaptophysin; (b): The neuroendocrine element of the tumour showed positive staining of Chromogranin A; (c) The neuroendocrine element of the tumour showed positive staining of CD 56; (d) Ki 67 of the neuroendocrine part of the tumour. The proliferative index is about 30 to 40%.

these patients according to the standard epithelial tumours of the colon. However, both approaches are not supported by any evidence from prospective randomised trials [8]. In this patient's case, the clinician opted for adjuvant chemotherapy given the tumour's neuroendocrine carcinoma counterpart appeared more aggressive.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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