



Management Challenges of Colorectal Mixed Adeno-Neuroendocrine Carcinoma (MANEC): Case Report and Literature Review

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Case Blog

We report a case of a 49-year-old man who presented acutely with abdominal pain due to caecal MANEC with liver metastasis. His father died aged 52 from metastatic colon cancer. On examination he had right lower abdominal tenderness and guarding. CT showed a fluid filled appendix with surrounding fat stranding, an irregular hyperdense mass in the caecal pole and localized lymphadenopathy (Figure 1). Laparotomy revealed a bulky caecal tumor adhered to the peritoneum and terminal ileum, an inflamed, enlarged retrocaecal appendix and bilobed liver metastases. A right hemi colectomy was performed with En bloc resection of the involved terminal ileum.

Histological sections from the caecal tumor confirmed malignant epithelial cells diffusely permeating ileocaecal and appendiceal submucosae and muscularis propriae, with tumor extension through pericolic soft tissues onto serosal surface. The neoplasm predominately revealed small cell morphology (A), with high grade pleomorphic cells possessing minimal cytoplasm and displaying abundant mitotic and apoptotic figures (Figure 2) with frequent tumor cell necrosis. The tumor also had areas of glandular differentiation (B) and unusual foci of squamous differentiation (C). Widespread lymphovascular invasion was evident, with 6/10 lymph nodes involved by metastatic disease.

Postoperative recovery was complicated by ileus and persistent fevers and lethargy thought due to tumor burden as no septic source or carcinoid syndrome was detected. Palliative chemotherapy (oral etoposide and IV carboplatin) was commenced on D27. The patient deteriorated and treatment was withdrawn on D40, the patient died on D42. The clinical course of this patient highlights the aggressive nature of these tumors. Although rare, clinicians and pathologists should be aware of this entity so that patients can be identified and managed appropriately.

Classification: Although first described in 1924 the classification of these rare tumors has remained controversial. They have previously been named composite carcinoid, mucin producing carcinoid, small cell undifferentiated and mixed exocrine-neuroendocrine tumor. In 2010 they were renamed MANEC and defined by the WHO as gland forming epithelial and neuroendocrine neoplasms, where each component represents 30% of the tumor, and both components are malignant.

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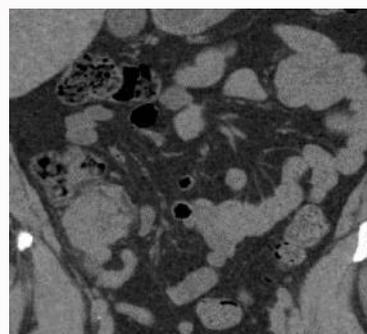


Figure 1: Non contrast CT Abdomen.

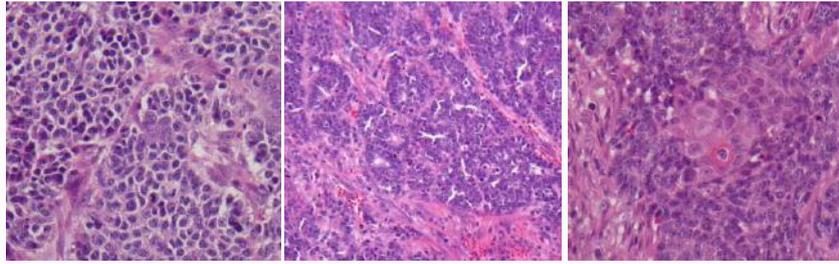


Figure 2: Microphotographs of MANEC A. H &E x 200, B. H&E x 200, C H&E x.

Characteristics: Colonic neuroendocrine tumor is known to be a high grade, poor prognosis tumor. La Rosa et al. [1] found a mean survival of 16.6 months for MANEC, with no difference in prognosis compared to colonic NEC.

The clinicopathological behavior of these tumors remains uncertain. Yunru et al. [4] reported a mean age at diagnosis of 61.9 years. In this series 78% of patients presented with metastases to lymph nodes and 38% to the liver. The authors concluded the poorly differentiated component was more likely to metastasize.

Aetiology: The aetiology of divergent differentiation remains elusive. Vortmeyer et al. [3] performed genetic analysis on 6 cases, and found that when heterozygosity was lost in the adenocarcinoma component it was also lost in the NEC component, suggesting a common progenitor cell. Kawaski et al. [1] reported a similar case to ours, where an adeno-neuroendocrine tumor also contained foci of squamous cell carcinoma. The authors concluded this occurrence supports the theory that neoplastic cells are capable of multidirectional differentiation regardless of their cell or origin. La Rosa et al. found greater than 90% of MANEC tumors exhibited hypermethylation of GATA5, a gene that displays hypermethylation in exocrine colorectal carcinomas.

Management: A multidisciplinary consensus regarding diagnosis and selection of appropriate systemic therapy is essential to the

management of these patients. Choice of adjuvant therapies should target the poorly differentiated component of the tumor. Sadly in this case and in many others reported in the literature the prognosis remained unaltered. Further studies into the molecular, epigenetic and the immunohistochemical profiles of these rare tumors are required and will require collaboration between specialist centres.

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