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Case Report

Mixed adenoneuroendocrine carcinoma: report of two cases

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ABSTRACT

Mixed adenoneuroendocrine carcinoma is a rare tumor that is pathologically and clinically distinct from both its neuroendocrine and adenocarcinoma components. Confusion still exists regarding its histogenesis and therefore definite treatment protocol for its management has yet to be developed. Recent molecular characterization has been able to throw some light into the molecular profiles and mutations associated with the tumor. However, large scale studies are still to be carried out to unmask the true nature of this tumor. We report two cases of mixed adenoneuroendocrine carcinoma, one of the rectum and another of the sigmoid colon.

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INTRODUCTION

Gastrointestinal tumors with exocrine and neuroendocrine components in the same tumor was first described by Cordier in 1924.[1] Later, Lewin classified these tumors into three different groups which consisted of combined, collision and amphicrine tumors.[2] In 2010, the World Health Organization (WHO) classification defined tumors containing both exocrine and neuroendocrine malignant components, with each component comprising at least 30% of the tumor as mixed adenoneuroendocrine carcinoma (MANEC).[3] We report two cases of MANEC, one of the rectum and another of the sigmoid colon along with a review of literature.

CASE REPORT 1

A 65-year male was admitted to the hospital with complains of altered bowel habit for one year, per rectal bleeding and lower abdominal pain for four months. Digital rectal examination showed decreased anal tone with an irregular, soft, friable mass palpable around 3.5 cm from the anal verge, occupying 2/3rd of circumference posteriorly, upper border of which could not be appreciated. Lower gastrointestinal endoscopy showed cauliflower like friable mucosal growth extending 3-4 cm from anal canal towards the sigmoid colon. Computed tomography scan (CT scan) suggested a diagnosis of colorectal carcinoma T3N2M0. The CEA level was 6.37 ng/mL. He had no other comorbidities. The patient underwent lower anterior resection with colorectal anastomosis.

Gross evaluation of the specimen revealed an ulceroproliferative mass measuring 5.5x4x2.5cm extending from the rectum into the sigmoid colon. Histopathological evaluation showed a dual component of neoplastic cells infiltrating up to muscularis propria (pT2N0). The predominant component showed neuroendocrine differentiation with tumor cells having uniform round to oval nuclei, granular nuclear chromatin with a moderate amount of eosinophilic cytoplasm arranged in broad trabeculae. Many areas showed tumor cells forming rosettes (fig.1). Immunohistochemistry for Synaptophysin, and Chromogranin A were positive in these tumor cells. The adenocarcinoma component comprised of more than 30% of tumor with cells arranged in glands and cribriform pattern. Individual tumor cells had round to oval hyperchromatic nuclei with irregular nuclear membrane, conspicuous nucleoli and a moderate amount of cytoplasm.

Immunohistochemistry for CDX2 and cytokeratin were positive in these tumor cells, hence confirming the dual nature of the tumor. Mitosis was noted at 24/10 HPF in mitotically active areas. Ki-67 proliferative index was 70 to 80 % in highest proliferating areas. No lymphovascular or perineural invasion were seen. All 22 lymph nodes were negative for tumor emboli. The patient was planned for cell cycle inhibitor chemotherapy, but the patient refused further treatment.

CASE REPORT 2

A 54-year male was admitted to the hospital with complains of generalized abdominal pain and distention and inability to pass stool/ flatus for 10 days. He was hypertensive under treatment for 5 years. CT scan showed mild circumferential thickening in recto- sigmoid region causing luminal narrowing. Colonoscopic examination revealed friable mucosal growth with stricture in the sigmoid colon. The patient was planned for an exploratory laparotomy with Hartman's operation.

The gross evaluation revealed an ulceroinfiltrative mass measuring 7x0.8cm in the sigmoid colon. Histopathological evaluation showed a tumor consisting of adenocarcinomatous (60%) and neuroendocrine (40%) differentiation infiltrating up to muscularis propria (pT2N0). The adenocarcinoma component consisted of tumor cells arranged in glands, solid sheets and cribriform patterns and showed mild pleomorphism with nuclear membrane irregularities, hyperchromatic to vesicular nuclear chromatin, many with macro-nucleoli and moderate amount of eosinophilic cytoplasm. The neuroendocrine differentiation exhibited tumor cells arranged in broad trabeculae with nuclear palisading and rosettes (fig.2). The individual tumor cells were uniform, polygonal to cuboidal with granular eosinophilic cytoplasm, stippled chromatin, and inconspicuous nucleoli. Lymphovascular invasion was identified, however, perineural invasion was not seen. Immunohistochemistry was not performed. Unfortunately, the patient expired on the 14th post-operative day due to surgical complications. Molecular studies were not performed in both cases due to their unavailability in our setting.

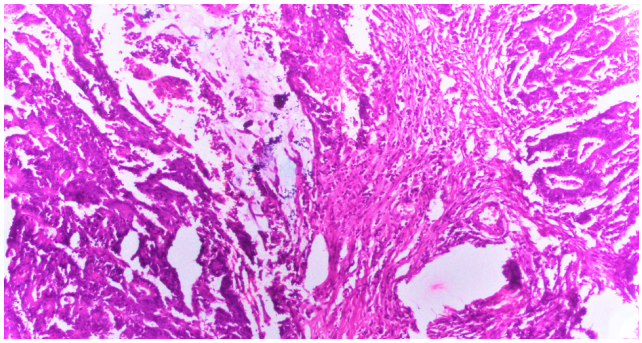

Figure 1: *Section showing neuroendocrine component (lower left) and adenocarcinoma component (upper right) (HE stain, X100).*

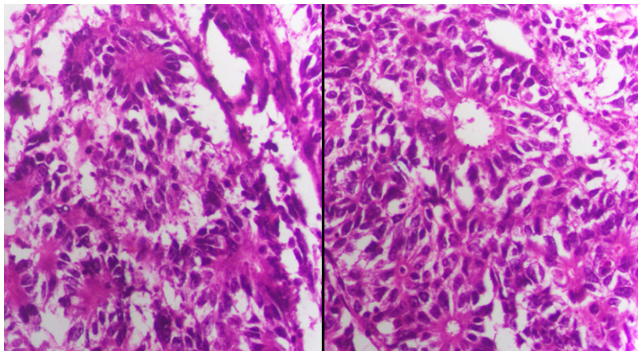

Figure 2: *Section showing Homer Wright rosettes (left) and Flexner Wintersteiner rosettes (right) in neuroendocrine component (HE stain, X400).*

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DISCUSSION

MANEC comprises of neoplasms with a dual component of adenocarcinoma and neuroendocrine carcinoma, which is responsible for its varying clinical behavior as compared to its individual components. Tumors that satisfy the criteria of MANEC defined by 2010 WHO classification of tumors of the digestive tract are rare.[3] This case report aims to highlight this rare entity and discuss the recent advances and research regarding it. We also aim to emphasize the various contradictory findings of different studies regarding its pathogenesis, prognosis, and treatment.

The common sites for MANEC are colon and stomach, but cases have been reported from the esophagus, rectum, pancreas, biliary tract and uterine cervix.[4] There is no clear gender predilection for MANEC.[4-7] Most cases are locally aggressive during the time of diagnosis (≥ pT3) however both our cases were at stage pT.[2,5,7] Colonoscopy is a relatively reliable modality for diagnosing colorectal carcinoma, however, the gross morphology of MANEC is similar to adenocarcinoma hence histopathological examination is crucial for diagnosis.[8] Extensive sampling of the tumor for histopathological examination is also vital in order to detect both of the components and avoid misdiagnosis. The differential diagnosis for MANEC includes Goblet cell carcinoid (GCC), adenocarcinoma ex GCC, and mixed endocrine-exocrine tumor. GCC was excluded from 2010 WHO classification of MANEC as it did not include the neuroendocrine carcinoma component. The undifferentiated variant of GCC has a poor prognosis similar to MANEC. The neuroendocrine component of MANEC is classified as small cell and large cell carcinoma, similar to neuroendocrine carcinoma of the lung, however, no strong data exists supporting variation in prognosis between the two subtypes.[8,9]

Recent molecular studies have shown both components of MANEC to have similar molecular profiles which suggest an origin from common progenitor tumor cells.[10] These include composite and amphicrine tumors as classified by Lewin et al[2] where the two tumor components intermingle in composite tumors, and neuroendocrine and adenocarcinomatous features appear together within the same tumor cells in amphicrine tumors. Another subset of MANEC includes a collision tumor where adenocarcinoma and neuroendocrine cells are arranged alongside, suggesting an origin from two cell types.[2,8] Scardoni et al[10] found a majority of a neoplastic component of MANEC to harbor driver mutations, with TP53 mutations being the most frequent alteration. Others have linked MANEC with BRAF mutations, followed by KRAS and APC mutations, which are all associated with conventional colorectal adenocarcinoma and therefore suggesting the potential response of MANEC to conventional colorectal adenocarcinoma chemotherapy.[7] However, Le et al[11] demonstrated microsatellite instability in colorectal MANEC suggesting a possible cell cycle checkpoint inhibitor therapy in this subpopulation. Hervieu et al[12] suggests MANECs with well-differentiated neuroendocrine carcinoma components be treated as adenocarcinomas where as MANECs containing poorly differentiated neuroendocrine carcinoma components be treated as neuroendocrine carcinoma. Zeng et al[13] stated that neuroendocrine differentiation was responsible for poor prognosis as they had increased the ability to recruit tumor-associated macrophages which enhanced proliferation and invasiveness of colon cancer cells via secretion of chemokines CXCL-10 and CXCL-11. In contrast, other studies have shown prominent mucinous component in MANEC to have a worse prognosis.[5,14] Other factors associated with a worse prognosis include advanced stage (pT4), lack of goblet cell clusters, percentage of tumor mucin and single cell infiltration.[5]

CONCLUSIONS

In conclusion, studies with large case volumes are required to fully understand this entity. However, the rarity of this tumor is an obstacle in this regard. We suggest developing a national or even multinational registry for collecting MANEC cases and thereby conducting a large multicenter based research in order to unveil the true nature of MANEC.

Conflict of Interest: None

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