Case Report

rare tumors

Rare Tumors
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Amphicrine carcinoma of the right colon, a report of a case and review of literature

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Abstract

Mixed neuroendocrine and non-neuroendocrine neoplasms, recently recognized in the WHO classification as (MiNEN), are rare tumors of the gastrointestinal tract. These tumors are composed of two distinct cellular components; a well- or poorly differentiated neuroendocrine tumor and a non-neuroendocrine tumor, usually in the form of an adenocarcinoma, either admixed with or adjacent to one another. A rarer phenotype is a tumor in which the endocrine and epithelial cell features occur within the same cell; i.e. amphicrine carcinoma. Herein, we report the case of an 80-year-old female patient who presented with melena, and who, on biopsy was diagnosed as amphicrine carcinoma that was mismatch repair deficient (MMRd) with loss of MLH1/PMS2 nuclear expression by immunohistochemistry. The histological and immunohistochemical findings of this rare entity are presented with review of pertinent literature.

Keywords

Amphicrine carcinoma, neuroendocrine carcinoma, colonic adenocarcinoma, synaptophysin, mismatch repair deficiency

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Introduction

Mixed neuroendocrine and non-neuroendocrine neoplasms (MiNEN), formerly known as mixed adenoneuroendocrine carcinoma (MANEC), has been described in the WHO classification as a rare tumor in various gastrointestinal sites.[1] Historically, the nomenclature of these tumors was proposed by Lewin more than 30 years ago. He divided them into three separate groups, mixed or composite tumors, collision tumors and amphicrine tumors.[2] Within the MiNEN group, both components; the neuroendocrine component, which is usually in the form of a neuroendocrine carcinoma, and the conventional carcinoma component, should be distinct morphologically and by immunoprofile, each constituting ≥30% of the neoplasm.[3] In amphicrine carcinoma, the malignant cells show hybrid differentiation. They exhibit both an adenocarcinoma and neuroendocrine carcinoma immunoprofile within the same cell.[3] To the best of our knowledge, only rare cases have been reported in the colon.[4] Furthermore, the status of mismatch repair (MMR) proteins was not described in the literature. Here we describe the rare occurrence of an MMR-deficient amphicrine carcinoma in an 80-year-old female patient in the right colon.

Case Report

An 80-year-old female patient with a past medical history of diabetes and dyslipidemia, presented with anemia and

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melena. Colonoscopy showed an ascending colon mass. Biopsy revealed an infiltrative tumor composed of sheets of two types of cells, some of which show signet ring cell morphology containing intracytoplasmic mucin, as confirmed by Diastase-PAS special stain and Alcian blue-PAS special stain with eccentric hyperchromatic nuclei. While the second component is composed of monomorphic smaller cells with indistinct cytoplasm and high nuclear-to-cytoplasmic ratio with nuclei showing homogenous fine chromatin with no evidence of prominent nucleoli (Figure 1(a)). The tumor cell demonstrated high proliferative activity with abundant mitosis exceeding 20 mitoses per high power field, in addition to high proliferative index of up to 90% by Ki-67 immunostain. There was no evidence of necrosis. Tumor cells of both morphologies were immunoreactive for CDX2 (Figure 1(b)), Synaptophysin (Figure 1(c)), INSM-1 (Figure 1(d)), and SATB2 (not shown), but were immunonegative for Chromogranin-A and CD56. In addition, MMR proteins (MLH1 and PMS2) showed loss of nuclear staining (Figure 1(e) and (f)) while MSH-2 and MSH-6 nuclear staining was intact. Accordingly, we performed immunostain for BRAF p. V600 E (Figure 1(g)) which was positive, in support of MLH-1 methylation. Based on morphologic and immunohistochemical features, we diagnosed the case as an amphicrine carcinoma, MMR-deficient. Subsequently the patient underwent a laparoscopic right hemicolectomy. Examination of the specimen revealed a 4.5 × 3.0 × 1.0 cm exophytic mass with central ulceration in the ascending colon. No adjacent polyps were seen. Microscopy showed a tumor, with similar appearance to the tumor in the biopsy, that invaded the muscularis propria. Neither a precursor lesion nor dysplasia were seen in the adjacent mucosa. In addition, twenty-six harvested lymph nodes were negative for metastatic carcinoma. The final stage of the tumor was pT2N0. The patient's post operative course was smooth and she was discharged without complications. Subsequently, no further treatment was given. The patient is alive with no evidence of disease 6 months following surgery.

Discussion

Mixed neuroendocrine and non-neuroendocrine tumors (MiNEN) has been proposed by La Rosa et al. and recently adopted by the WHO to describe a heterogeneous group of rare tumors that constitutes a neuroendocrine population and a non-neuroendocrine population, both accounting for at least 30% of the whole tumor area.[5] Very rarely, the same tumor cells may exhibit both endocrine and exocrine features, which is referred to amphicrine (in Greek, amphi- means "both" or "double"). Gastrointestinal tract amphicrine carcinomas are very rare, with only a few case reports in the literature, mostly in the stomach.[6,7] Occasionally, amphicrine carcinoma has been described in the lower gastrointestinal tract. Li Zhiwen et al described the clinicopathological features of eight colorectal amphicrine carcinoma, including four cases in the sigmoid, which was

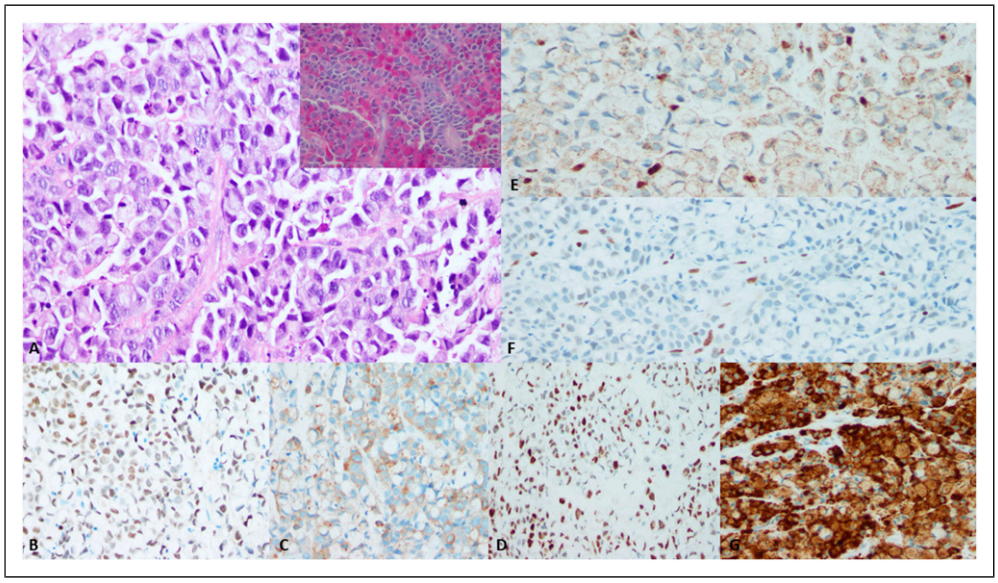

Figure 1. The morphology and immunoprofile of the original colonic biopsy. (a) There is proliferation of sheets of cells with signet-ring like appearance that contain intracytoplasmic mucin, highlighted by Diastase PAS (Inset). (b) CDX-2 immunostain is positive in the tumor cell nuclei. (c) Synaptophysin is positive in the tumor cell cytoplasm. (d) INSM-1 is positive in tumor cell nuclei. (e) and (f) Loss of PMS2 and MLH1 nuclear staining in the tumor cells, in the presence of internal positive control, consistent with MMR-deficient tumor. (g) BRAF p. V600 E shows strong diffuse cytoplasmic staining.

the most common site, three cases in the rectum and a single case in the transverse colon.[4]

In addition, amphicrine carcinoma have been reported in other gastrointestinal sites. One case was reported in the gallbladder in a 57-year-old female.[8] Another case was reported at the duodenojejunal junction in a 72-year-old female.[9] Occasionally, amphicrine carcinoma has been described at extra-gastrointestinal locations including a series of five cases reported in the prostate.[10]

Interestingly, amphicrine carcinoma has been described in the stomach in a 64-year-old female during immunotherapy for melanoma. Morphologically the tumor showed double expression of neuroendocrine markers and the exocrine pancreatic acinar cell markers.[11]

The status of MMR proteins immunostain has not been reported previously. For conventional adenocarcinoma of the gastrointestinal tract, including colonic adenocarcinoma, determining the status of the MMR proteins, through the use of MMR immunostains, is of paramount importance for screening of patient with Lynch syndrome, and more importantly for management and prognostic value.[12] Literature is limited, though, on the status of MMR proteins in neuroendocrine tumors, MiNEN, and amphicrine carcinomas.[13,14] Sahnane et al described 11 unstable neuroendocrine carcinoma, four of which were of MANEC type, and seven were neuroendocrine carcinomas.[15] Of these, only six cases were of colorectal origin.

Molecular alteration appears to support that amphicrine carcinoma is separate from MiNEN. Huang et al reported on a pan-cancer transcriptome analysis of four gastric amphicrine carcinoma, all of which exhibited transcriptional homogeneity with conventional adenocarcinoma and genetic diversity from neuroendocrine tumors.[7] Another study that described genetic alteration of this tumor in the stomach, reported no copy number variant genes shared between amphicrine carcinoma and components of MiNEN, thus supporting their distinct nature.[16] Given their aggressive behavior and similarity to conventional adenocarcinoma, these rare tumors should be distinguished from MiNEN, and should be treated as conventional adenocarcinoma.

An important differential diagnosis that should be considered is goblet cell adenocarcinoma. These tumors are described in the WHO as amphicrine tumors with predilection to the appendix with only rare case reported in the colon.[17,18] Histologically, these tumors are composed of a variable amount of goblet -like mucinous cells mixed with neuroendocrine cells.[17] Although defined in the WHO as amphicrine, their amphicrine nature is controversial as the goblet-like mucinous cells in goblet cell adenocarcinoma do not show aberrant expression of the neuroendocrine markers.[18] in contrast, our case showed diffuse expression of neuroendocrine markers within the mucin secreting signet-ring like cells.

Survival outcomes of gastrointestinal amphicrine carcinoma were analyzed by Dan Huang.[7] There was no evidence of disease several months after diagnosis in six cases with follow up periods ranging from 6 to 63 months, while three cases died of disease. The treatment modality varied among these patients. Complete surgical resection was performed in seven patients followed by chemotherapy in three, with chemotherapy being given to two patients, and the third not receiving any therapy after diagnosis. Of the three reported deaths, two had surgery and one received only palliative chemo- and radiotherapy.

Conclusion

Amphicrine carcinoma is a rare tumor, which can occur in any site throughout the gastrointestinal tract. It is of paramount importance to identify these tumors, as they behave more aggressively than neuroendocrine tumors; similar to conventional adenocarcinoma. Association with MMR deficiency opens the door for the use of immunotherapy in this group of patients.

Author Contributions

All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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Ethial statement

Ethical approval

Include full name of committee approving the research and if available mention reference number of that approval: This case report was approved by KHCC IRB (ID approval: 23KHCC134).

Informed consent

Written informed consent was obtained from the patient(s) for their anonymised information to be published in this article.

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