

# A molecularly confirmed neuroendocrine tumor resulting from Lynch Syndrome

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## Introduction

Patients with Lynch Syndrome are at a high risk of developing multiple cancers, including cancers of the colon or rectum, uterus, small bowel, stomach, renal pelvis, urether, biliary tract, ovaries, brain and pancreas (1).

The most commonly observed tumors in patients with Lynch Syndrome are colorectal and endometrial cancers. This autosomal dominantly inherited disease arises as a result of a germline mutation in one of several mismatched repair (MMR) genes. MLH-1 and MSH-2 account for 90% of all identified mutations. Herein, we report the case of a patient with a neuroendocrine tumor (NET) demonstrating lack of MLH-1 expression. Since her gastric adenocarcinoma also demonstrated lack of MLH-1 expression and the patient harbored a germline mutation in MLH-1, her NET likely developed as a consequence of the Lynch Syndrome.

## Case report

CB is a 63 year old woman with a previous history of adenocarcinoma of the colon diagnosed at age 52 and adenocarcinoma of the stomach diagnosed at age 57, each treated with surgery. Recently she presented with increasing abdominal pain and a 150 pound unintentional weight loss which developed over the preceding 5 years. An abdominal and pelvic MRI demonstrated three liver lesions suspicious for malignancy which were not seen on scanning 6 years earlier. And ultrasound-guided liver biopsy showed a "Neuroendocrine Neoplasm, High Grade" which was immunohistochemically (IHC) positive for synaptophysin, pankeratin, CD56, and chromogranin, confirming the diagnosis. Colonoscopy and upper endoscopy were performed and a mass was identified in the gastric remnant. A biopsy of the mass confirmed recurrent adenocarcinoma of the stomach.

The patient was seen by the clinical genetics service and

a germline mutation in MLH-1 [(K618del) (1852del3)] was identified. The germline mutation described was characterized as a deleterious mutation by Myriad Genetics Laboratories (Salt Lake City, UT) where the assay was done. Both the NET and the gastric cancer demonstrated lack of expression of MLH-1. The patient received carboplatin and etoposide (one cycle) followed by cisplatin and etoposide (5 cycles) chemotherapy for a total of 6 cycles. Repeat MRI showed improvement in the liver lesions after two cycles. A PET/CT scan reportedly showed no increase PET avidity in the liver. The patient underwent surgery with resection of residual adenocarcinoma of the stomach and all suspicious liver lesions. No residual malignancy was seen histologically in the liver lesions removed.

## Discussion

Inheritance of certain germline mutations in MMR genes now defines the Lynch Syndrome and results in an increased risk of a variety of malignancies. The patient described above was diagnosed with colon cancer, gastric cancer and most recently a NET. The diagnosis of the NET was confirmed histologically and with IHC.

Patients with apparent Lynch Syndrome who had an adenocarcinoma and a neuroendocrine tumor or an adenocarcinoma with neuroendocrine features have been reported. For example, a patient with a colon adenocarcinoma and an appendix carcinoid tumor was described (2). However, while the colon adenocarcinoma showed microsatellite instability (MSI), the carcinoid did not. Therefore, the authors themselves concluded that these two tumors "arose through different molecular pathways". Others have also noted a small number of cases of carcinoid tumors seen in association with Lynch Syndrome, but those tumors were not tested for lack of MMR expression or MSI, features that would more highly suggest that the carcinoids were in fact a result of a germline mutation in an MMR gene (3). In

another case report an adenocarcinoma with neuroendocrine features that lacked MSH-2 expression was described (4). However, this was not a neuroendocrine tumor, but rather an adenocarcinoma with neuroendocrine features. In still another report, a pancreatic endocrine neoplasm lacked expression of a mismatch repair gene product (MSH2/MSH6) (5). However, germline testing for this mutation was not performed in that patient. Our patient demonstrated a deleterious germline mutation in an MMR gene (MLH-1) and both her adenocarcinoma and neuroendocrine tumors showed lack of expression of MLH-1, supporting the Lynch Syndrome as predisposing to the development of each tumor.

While it is possible that the gastric adenocarcinoma differentiated into a neuroendocrine tumor and then metastasized, there were no neuroendocrine features in the gastric adenocarcinoma. Also, in the liver metastases, which were biopsied and eventually removed, the pathologist noted that the gastric and liver lesions were morphologically and histochemically distinct and there were no adenocarcinoma features in the neuroendocrine tumor. Therefore it would seem unlikely that the metastasis in the liver arose from the gastric adenocarcinoma. It is also possible that the gastric adenocarcinoma represented a new primary, rather than a recurrent adenocarcinoma. Regardless, aside from lacking MLH-1 expression, the adenocarcinoma was otherwise immunohistochemically and morphologically different from the NET. It also remains possible that our patient's neuroendocrine tumor was unrelated to her germline mutation in MLH-1, although there is little evidence that lack of expression of MLH-1 occurs in sporadic neuroendocrine tumors (6).

Lynch Syndrome due to inheritance of germline mutations in MMR genes represents the most common inherited

colorectal cancer syndrome. In our patient, a deleterious germline mutation in MLH-1 was seen with lack of MLH-1 expression in both a NET and a distinct adenocarcinoma. This case report suggests that Lynch Syndrome may predispose to NET development.

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