



Case Report

An Unexpected Finding: High Grade Neuroendocrine Tumor in a Patient with Known Familial Adenomatous Polyposis (FAP)

Timothy R Johnson^{1*}, Jeffrey Wright³, Jillian Grau², Maged Khalil¹

¹Department of Medical Oncology/Lehigh Valley Health Network, Allentown, PA, USA

²Pathology Department/ HNL Lab, Allentown, PA, USA

³Department of Internal Medicine/Lehigh Valley Health Network, Allentown, PA, USA

***Corresponding author:** Timothy R Johnson, Department of Medical Oncology/Lehigh Valley Health Network, Allentown, PA, USA

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Abstract

Familial Adenomatous Polyposis (FAP) is an inherited, autosomal dominant condition with a well-known predisposition for causing colorectal carcinoma. Notably, this predisposition often afflicts people at a significantly earlier age than de novo colorectal cancer. Thus, screening practices for patients with FAP are more rigorous and begin at an earlier age. Importantly, in FAP, morbidity may arise from less ubiquitously recognized conditions, such as gastric polyps, osteomas, or thyroid carcinomas, to name a few. In this setting, we describe the case of a 27-year-old gentleman, with known FAP, found to have a grade 3, metastatic neuroendocrine tumor (NET) with additional discussion regarding the evaluation and treatment of NETs.

Keywords: Familial Adenomatous Polyposis; FAP; Neuroendocrine Tumor; NET; Colorectal Cancer.

Introduction

Familial Adenomatous Polyposis (FAP) is an inherited, autosomal dominant condition, in which the APC (adenomatous polyposis coli) gene on chromosome 5q21 is mutated, resulting in the development of an expansive number of polyps in the colon and rectum [1]. While the prevalence of FAP has been projected to be as little as 1:37,600 cases, the implications of disease are quite significant with the need for annual screening endoscopies starting as early as age 16. Despite annual screening protocols, FAP often portends to significant mortality (reported to be of 100%) related to adenomatous transformation into colorectal cancer, if not treated with surgical prophylaxis. Thus, to decrease the risk of malignant transformation, patients are often recommended to undergo procedures such as subtotal colectomy with ileorectal anastomosis [2]. In addition to colorectal adenocarcinoma, patients with FAP have increased risk of extra-colonic disease which can

present as gastric polyps, duodenal polyps, osteomas, congenital hypertrophy of retinal pigment epithelium (CHRPE), or thyroid carcinomas, among others [3]. An important, but lesser-known manifestation of FAP is an association with neuroendocrine tumor (NET) development. In this case, we present a 27-year-old man with abdominal pain and abnormal CT imaging, who presented 10 months after a screening colonoscopy and was found to have an aggressive neuroendocrine tumor.

Case Report

A 27-year-old man with a family history of FAP in his father, brother and uncle had recent genetic testing, which confirmed he had a personal mutation consistent with FAP. As a result, he underwent surveillance colonoscopy and upper endoscopy in early 2022, which showed multiple colonic tubular adenomas and a single fundic gland polyp with low-grade dysplasia. There was no abnormality up to the second portion of the duodenum, or on visual inspection of the periampullary region. Following this evaluation, he was recommended to undergo total colectomy, but had opted

not to undergo surgical prophylaxis. 10 months later, he presented to the emergency room with four days of abdominal pain with nausea, vomiting, and significant weight loss. A CT scan revealed irregular cecal wall thickening with multiple enlarged mesenteric lymph nodes and hypo dense liver lesions, concerning for metastatic disease. There was concern for colonic obstruction, and the patient was taken for loop ileostomy, with liver and peritoneal biopsies/washings. Biopsies confirmed synaptophysin positive, chromogranin focal positive, Ki-67 of 35%, AE 1/3 positive, and CDX2 positive consistent with well differentiated, grade 3 neuroendocrine tumor involving both the peritoneum and liver. A gallium-68 dotatate PET-CT scan showed avidity within the cecum and liver, with similar uptake in the lymphadenopathy noted on CT-Scan. He was started on Temozolamide and Capecitabine, with Octreotide added during cycle 2. Approximately 3 months into treatment, he presented to the emergency department with intractable pain and question progressive disease involving the pancreas and liver. Given this progression, he was switched to Carboplatin + Etoposide for second line treatment and is currently following with medical oncology.

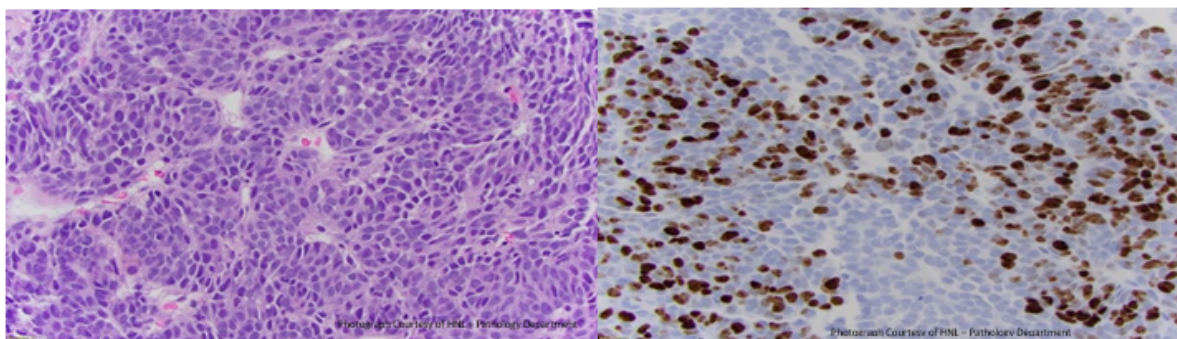


Figure 1: H&E-stained liver biopsy specimen, revealing a well differentiated neuroendocrine tumor (left) with corresponding Ki-67 (MIB-1) immunohistochemical stained section (right).

Discussion

NETs that demonstrate well differentiated histology are graded based on the proliferative rate (i.e., mitoses and Ki-67 (MIB-1) index). This schema is 3-tiered, with most tumors falling into the low or intermediate grade category (G1-G2). If the mitotic rate is greater than 20/ 2 mm² or the Ki-67 (MIB-1) index greater than 20%, these tumors are classified as high grade (G3). Whereas, according to the WHO 2022 classification, high grade tumors with poorly differentiated morphology are termed neuroendocrine carcinoma (NEC), fall into the categories of small cell or large cell types, and, by definition, are grade 3 [4]. As described in a review of neuroendocrine tumors from 2019, gastrointestinal primary sites of disease are principally found in the small intestines (38% of cases), followed by the rectum and appendix accounting for 19% and 15% of cases, respectively [5]. Our patient had screening endoscopies with both esophagoduodenoscopy (EGD) and colonoscopy ten months prior to his presentation with metastatic disease. There was no evidence of similar grade 3 NET on biopsies taken during his screening exams. Thus, given the localized extent of disease noted in the cecum, it is likely that the primary tumor site was within either the appendix or the distal ileum. Further suggestive of this is the presence of CDX2 positivity, which has shown to have 94-100% specificity for ileal NETs [6]. Familial Adenomatous Polyposis (FAP) is a

known cause of both colonic and extra-colonic manifestations of disease with ailments including colorectal adenoma, fundic gland polyp, duodenal polyp, desmoids tumor(s), hepatoblastoma and thyroid malignancy [2]. Despite the familiarity of physicians with these associated conditions, less frequent conditions such as the development of NETs have been described. In a case series by Kidambi et al, the presence of lower gastrointestinal NETs, in patients without a known hereditary predisposition, are described to be considered a syndromic-associated malignancy for patients that have indication for genetic testing [7]. It should be noted that other hereditary conditions including MEN1 & 2, VHL, and Neurofibromatosis Type 1 are syndromes with well-established potential for neuroendocrine tumor development [8]. A sparse number of case reports describing NETs in the setting of FAP have been noted including those by Detweiler et al, Camp et al, and Venu et al [9-11]. In addition, Weidner et al reported a case of NET in the setting of MUTYH Adenomatous Polyposis, an autosomal recessive disorder with a similar predisposition to adenomatous development within the gastrointestinal tract [12]. Important in the work-up of NET, is the use of a functional imaging modality. For our case, a gallium-68 (GA-68) dotatate PET scan was performed to identify the presence of neuroendocrine disease involvement. This scan utilizes a radioactive tracer, which is bound to a somatostatin analog allowing for identification of cells abundant

with somatostatin receptors. It has been reported that GA-68 PET scans have sensitivity and specificity for neuroendocrine disease in 93% and 91%, respectively [13]. Our patient had a GA-68 scan detailing disease within the cecum, mesenteric and right pelvic lymph nodes, and innumerable lesions within the liver. Treatment for NETs can vary based on grade or extent of disease. Options can include surgical resection, chemotherapy, and somatostatin analogue therapy. In patients with metastatic disease that is amenable, local directed therapy with chemoembolization or resection may be offered [14]. Our patient was diagnosed with metastatic, well differentiated, grade 3 NET with extensive burden of disease involving the cecum, abdominal lymph nodes and bilateral liver lobes. He was determined to have favorable biology based on a $ki-67 < 55\%$, however given the extensive metastatic burden would be considered high risk. Thus, systemic, first-line treatment with capecitabine and temozolomide (CAPTEM) was offered, with the addition of octreotide following cycle 1 of chemotherapy given the avidity on GA-68 PET Scan. In this clinical scenario, systemic therapy options included CAPTEM or platinum-based doublet with etoposide, as seen in the American Society of Clinical Oncology's (ASCO) 2021 review on management of NETs [15]. Unfortunately, our patient had a rapid progression of disease 3 months following treatment and was switched to second line therapy with Carboplatin-Etoposide, in hopes of slowing his aggressive disease state.

Conclusion

We present a case of a patient with known familial adenomatous polyposis that had recently undergone screening endoscopic evaluation and presented with symptoms and imaging consistent with metastatic disease. Upon further work-up, he was found to have a metastatic NET, most likely originating from the distal ileum. We discuss this case given the paucity of case reports in this setting, and to highlight the association of FAP with malignancy potential apart from the well-known colorectal adenocarcinoma.

Conflict of Interest: NTD.

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