CASE REPORT

Primary high-grade neuroendocrine carcinoma emerging from an adenomatous polyp in the setting of familial adenomatous polyposis

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SUMMARY

Familial adenomatous polyposis (FAP) is a rare inherited syndrome that is characterised by innumerable adenomas of the colon and rectum, a high risk of colorectal cancer and a variety of extracolonic manifestations. FAP presents as hundreds to thousands of colonic adenomas beginning in adolescence. The syndrome is associated with less than 1% of all colorectal cancer cases, but there is a nearly 100% lifetime risk of colorectal cancer in individuals with FAP. This case demonstrates a 60-year-old man with FAP who developed high-grade neuroendocrine carcinoma with glandular and squamous differentiation, and regional lymph node and liver metastases. Early diagnosis of FAP is of the utmost importance to start screening colonoscopies to assess disease burden, perform polypectomies and to make management decisions. Neuroendocrine carcinomas rarely occur in patients with FAP, and awareness of this association among general medical physicians and pathologists is essential for the diagnosis and care of these patients.

BACKGROUND

Familial adenomatous polyposis (FAP) is a rare inherited syndrome that is characterised by innumerable adenomas of the colon and rectum, a high risk of colorectal cancer and a variety of extracolonic manifestations.¹ Individuals with FAP may remain asymptomatic for years until polyps or cancer cause non-specific gastrointestinal symptoms such as rectal bleeding or change in bowel habits.¹ The lifetime risk of colorectal cancer in untreated individuals nears 100%, and early screening implementation is vital to the management of colon cancer risk in these patients.^{2,3} Typically, FAP colorectal cancer is of the adenocarcinoma type. We present a novel case of high-grade neuroendocrine carcinoma of the colon in the setting of FAP. Neuroendocrine carcinomas of the colon are highly aggressive tumours with a worse prognosis stage-for-stage than colonic adenocarcinomas.⁴ Patients and physicians need to be aware that this aggressive tumour can arise in patients with FAP.

CASE PRESENTATION

A 60-year-old man with a history of gastro-oesophageal reflux disease presented with epigastric pain to his primary care physician. Subsequent upper and lower endoscopies demonstrated thousands of polyps in the stomach, duodenum and colon. A CT scan of the abdomen showed a mass at

the base of the caecum, with pericaecal lymphadenopathy and two small lesions within the liver. Biopsy of the caecal mass revealed moderately differentiated invasive adenocarcinoma. Other polyps were negative for invasive malignancy.

The patient then sought further work up and treatment at Duke University Hospital. He was referred to the Hereditary Cancer Clinic for genetic testing. The patient's family history included stomach, prostate, throat, lung, breast and ovarian cancers. Testing identified a pathogenic mutation in the *APC* gene, confirming the diagnosis of FAP. Tests for microsatellite instability were negative.

A total proctocolectomy, ileal pouch with anal anastomosis and diverting loop ileostomy were performed. A small lesion on the left lobe of the liver was seen during surgery and thought to be suspicious for a metastatic deposit. The patient tolerated the procedure well and was discharged 6 days later.

INVESTIGATIONS

Gross examination of the total colectomy specimen showed innumerable sessile and pedunculated polyps carpeting the mucosa; these ranged from 0.2 cm up to 6.5 cm in greatest dimension (figure 1). The polyps were more concentrated in the caecum, ascending colon and transverse colon. There was a 6.3×5.5×1.5 cm sessile and fungating mass in the caecum, which grossly invaded into the surrounding fat.

Histology demonstrated high-grade neuroendocrine carcinoma arising out of a tubulovillous adenoma with high-grade dysplasia (figure 2A). The tumour was heterogeneous, with focal areas representing adenocarcinoma (figure 2B) and

Figure 1 Gross specimen of total colectomy with innumerable mucosal polyps and a large caecal mass.

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Figure 2 Photomicrograph showing colectomy specimen with high-grade neuroendocrine carcinoma arising in a background of tubular adenoma (A, H&E, 2×) with areas of adenocarcinoma (B, H&E, 10×) and squamous cell carcinoma (C, H&E, 10×).

squamous cell carcinoma (figure 2C). The tumour invaded through the muscularis propria into subserosal adipose tissue. Immunohistochemical staining of the neuroendocrine carcinoma revealed positive staining for synaptophysin, CD56, CK5/6 and CDX2, with a Ki-67 of >90%. Staining for chromogranin was negative. The areas with traditional adenocarcinoma were positive for CK20 and CDX2, while the areas with squamous cell carcinoma showed positive staining for p40, p63 and CK5/6.

The diagnosis of mixed adenoneuroendocrine carcinoma (MANEC) of the colon was considered. However, per WHO guidelines, a diagnosis of high-grade neuroendocrine carcinoma

Figure 3 Photomicrograph showing lymph node metastasis with neuroendocrine carcinoma, adenocarcinoma (A, H&E, 2×) and squamous cell carcinoma (B, H&E, 4×).

was rendered because traditional adenocarcinoma comprised less than 30% of the total tumour.⁵

Four of twelve regional lymph nodes were positive for metastatic carcinoma and the foci were composed of neuroendocrine carcinoma, adenocarcinoma and squamous cell carcinoma (figure 3). The remaining colon showed innumerable tubular adenomas with no high-grade dysplasia and no invasive carcinoma.

Figure 4 Photomicrograph showing liver biopsy specimen with metastatic neuroendocrine carcinoma and adenocarcinoma (H&E, 20×).

Subsequent MRI of the abdomen identified multiple liver metastases up to 3.1 cm, and fine-needle core biopsy showed metastatic high-grade neuroendocrine carcinoma with focal traditional adenocarcinoma (figure 4).

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of a colonic mass against a background of gastrointestinal polyposis includes:

- ▶ FAP
 - Attenuated FAP
 - Gardner syndrome
 - Turcot syndrome
- ▶ Lynch syndrome/hereditary non-polyposis colon cancer
- ▶ Muir-Torre syndrome
- ▶ PTEN hamartomatous tumour syndrome
- ▶ Cronkhite-Canada syndrome
- ▶ Hyperplastic polyposis syndrome
- ▶ Juvenile polyposis syndrome
- ▶ MutYH-associated colorectal cancer
- ▶ Peutz-Jeghers syndrome)

TREATMENT

Well-differentiated neuroendocrine tumours (WHO grades I and II) that tend to be indolent are typically treated with octreotide.⁶ When these tumours become more functional, with evidence of progression of disease, patients are treated with more aggressive therapy such as everolimus, sunitinib or a combination of capecitabine and temozolomide.^{7–9} In contrast, patients with poorly differentiated neuroendocrine tumours are typically treated with a combination of cisplatin and etoposide, a regimen used for the treatment of small cell lung cancer as the genetic pathological and clinical features of these diseases are similar.^{10 11} Unfortunately, this patient presented with adenocarcinoma and poorly differentiated neuroendocrine carcinoma, and there is minimal benefit of treating patients with colorectal adenocarcinoma with cisplatin and etoposide. However, there are small studies suggesting a benefit of an oxaliplatin-based regimen, a standard of care treatment of adenocarcinoma of the colon, for the treatment of poorly differentiated neuroendocrine tumour.^{12–14} Therefore, 7 weeks after his colectomy, the patient was started on capecitabine and oxaliplatin. The patient's treatment was complicated by carcinoid syndrome, which presented with nausea and high-output liquid stool from his ostomy (4–6 L/day). He was initially treated with antidiarrheal medications (imodium and lomotil), but 6 weeks after starting chemotherapy, he was briefly hospitalised for high-ostomy output. He was started on octreotide and tincture of opium, and also continued his lomotil and imodium. Follow-up 3 weeks later revealed persistent liquid stools. Capecitabine and oxaliplatin were discontinued, and the patient was switched to folinic acid, fluorouracil and oxaliplatin chemotherapy, as there was concern for capecitabine-induced diarrhoea.

OUTCOME AND FOLLOW-UP

The patient's ostomy output improved, and his first staging CT scan 3 months after initiation of therapy revealed significant decrease in size of his liver lesions.

DISCUSSION

FAP is a rare inherited disorder characterised by hundreds to thousands of adenomas of the colon and rectum, a high risk of colorectal cancer, and a variety of extracolonic manifestations.¹ Although only 1% of colorectal cancers are associated with FAP, there is a nearly 100% lifetime risk of colorectal cancer in

untreated individuals, and the average age of cancer diagnosis is 39 years.^{2 3} Attenuated FAP is a less severe form of FAP, characterised by few polyps, later onset and a lower overall risk of colorectal cancer.^{2 15}

FAP can present as non-specific gastrointestinal symptoms such as rectal bleeding, change in bowel habits and abdominal pain or non-gastrointestinal symptoms such as anaemia or weight loss.¹ While FAP is better known for its colonic polyps, other gastrointestinal lesions can develop including fundic gland polyps of the stomach, adenomatous polyps of the duodenum, small bowel adenomas, and an increased risk of cancer in the stomach and small bowel.^{1 16–21} FAP also has extragastrointestinal manifestations including osteomas, dental abnormalities, congenital hypertrophy of the retinal pigment epithelium, desmoid tumours, and cancers of the thyroid, liver, bile ducts and central nervous system.^{1 22–25} Some extragastrointestinal manifestations of FAP have been organised into syndromes: Turcot syndrome refers to FAP in association with a medulloblastoma brain tumour, and Gardner syndrome refers to FAP in association with osteomas, dental abnormalities and fibromas.^{1 22 24}

FAP is diagnosed by the correlation of clinical findings, family history and endoscopy, with confirmation by genetic testing. It is an autosomal dominant inherited disease caused by mutations in the *adenomatous polyposis coli* (APC) gene.^{26 27} Most patients with FAP will have a family history of colorectal cancer, but 25–30% may be new mutations.²⁸

Early diagnosis of FAP is essential for the timely start of proper screening and management of colorectal cancer risk. Most important is the initiation of colonoscopy at age 10–12 years for classical or age 20–25 years for attenuated FAP.²⁹ Colonoscopies should be performed annually or less often depending on the polyp burden at the last colonoscopy.¹ Upper endoscopy is also essential for screening and should be performed every 1–5 years depending on polyp burden.^{1 19} Adenomatous lesions are removed endoscopically and surgical management is reserved for large lesions or cancer, usually by the late teens or early 20s.³⁰

The typical histological type of colorectal cancer in patients with FAP is adenocarcinoma. Neuroendocrine carcinomas arising in the context of FAP have only rarely been reported in the literature.^{31–34} Mutations in the APC gene have been shown to be associated with neuroendocrine carcinomas of the small and large intestines in patients without FAP.^{35–39} Additional driver mutations besides APC for our patient's tumour, including TP53, KRAS and FBXW7, are unknown. Microsatellite instability testing performed in our patient's tumour was negative, as would be expected if this were a colorectal adenocarcinoma arising from the APC/chromosomal instability pathway.

Gastrointestinal neuroendocrine neoplasms range from well-differentiated neuroendocrine tumours to poorly differentiated neuroendocrine carcinomas, and are classified according to WHO 2010 criteria on morphology and proliferation rate.^{5 40 41} Gastrointestinal neuroendocrine carcinoma can also rarely occur in the setting of MANEC, in which at least 30% of the tumour is composed of neuroendocrine carcinoma and at least 30% of the tumour is composed of traditional adenocarcinoma.⁵ MANECs can occur as a collision tumour or as a composite lesion.^{5 40 42} When two separate tumours collide and have two different histological patterns, endocrine and exocrine, it results in what is called a collision tumour.⁴² When one tumour has two different histological patterns, endocrine and exocrine, then it is called a composite tumour.⁴² The glandular components of MANECs range from well to poorly

differentiated adenocarcinoma, and the neuroendocrine components must meet diagnostic criteria for WHO Grade III neuroendocrine carcinoma.⁵ Squamous cell carcinoma components have also been reported.^{5–43} Metastases to lymph nodes or distant sites have been reported to contain only neuroendocrine carcinoma components or a mixture of adenocarcinoma and neuroendocrine carcinoma components.⁴³ The diagnosis of MANEC of the colon was considered in our case. However, per WHO guidelines, a diagnosis of high-grade neuroendocrine carcinoma was rendered because less than 30% of traditional adenocarcinoma was present.⁵

The association between FAP and neuroendocrine carcinoma is not well-documented. With evidence demonstrating APC gene mutations in neuroendocrine carcinoma, and rare reports in the literature of FAP and neuroendocrine carcinoma coexisting, we suspect that patients with FAP are also at an increased risk for neuroendocrine carcinomas and MANECs of the large intestine, and possibly of the small intestine. Additional research on the shared molecular pathways of these two intestinal malignancies may be helpful to support or refute this possibility.

Learning points

- Familial adenomatous polyposis (FAP) is a rare inherited syndrome that is characterised by innumerable adenomas of the colon and rectum, a high risk of colorectal cancer and a variety of extracolonic manifestations.
- FAP presents with non-specific gastrointestinal symptoms.
- Early diagnosis is vital to allow screening and management of colon cancer risk.
- Patients with FAP have a nearly 100% lifetime risk of adenocarcinoma of the colon and may be at increased risk for colonic neuroendocrine carcinomas or mixed adenoneuroendocrine carcinomas arising in this context.
- Metastases from mixed lineage colon cancer in the setting of FAP may be of adenocarcinoma, neuroendocrine carcinoma, or mixed origin.

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REFERENCES

- Half E, Bercovich D, Rozen P. Familial adenomatous polyposis. *Orphanet J Rare Dis* 2009;4:22.
- Patel SG, Ahnen DJ. Familial colon cancer syndromes: an update of a rapidly evolving field. *Curr Gastroenterol Rep* 2012;14:429–38.
- Galiasatos P, Foulkes WD. Familial adenomatous polyposis. *Am J Gastroenterol* 2006;101:385–98.
- Brenner B, Tang LH, Shia J, et al. Small cell carcinomas of the gastrointestinal tract: clinicopathologic features and treatment approach. *Semin Oncol* 2007;34:43–50.
- Bosman FT, Carneiro F, Hruban RH, et al. *WHO classification of tumours of the digestive system*. 4th edn. Sterling: Stylus Publishing LLC, 2010. 13–14, 174–177. Print.
- Rinke A, Müller H, Schade-Brittinger C, et al, PROMID Study Group. Placebo-controlled, double blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID study group. *J Clin Oncol* 2009;27:4656–63.
- Pavel ME, Hainsworth JD, Baudin E, et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. *Lancet* 2011;378:2005–12.
- Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med* 2011;364:514–23.
- Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med* 2011;364:501–13.
- Mitry E, Baudin E, Ducreux M, et al. Treatment of poorly differentiated neuroendocrine tumours with etoposide and cisplatin. *Br J Cancer* 1999;81:1351–5.
- Fjallskog ML, Granberg DP, Welin SL, et al. Treatment with cisplatin and etoposide in patients with neuroendocrine tumors. *Cancer* 2001;92:1101–7.
- Fine RL, Gulati AP, Tushima D, et al. Prospective phase II study of capecitabine and temozolomide (CAPTEM) for progressive, moderately, and well-differentiated metastatic neuroendocrine tumor (abstract 179). *J Clin Oncol* 2014;32(Suppl 3). <http://meetinglibrary.asco.org/content/122616-143> (accessed 02 Mar 2014).
- Bergsland EK, Ko AH, Tempero M, et al. Phase II trial of FOLFOX plus bevacizumab in advanced, progressive neuroendocrine tumors (abstract 216). Data presented at the 2008 ASCO Gastrointestinal Cancers Symposium, Orlando, FL, January 25–27, 2008. http://www.asco.org/ASCOV2/Meetings/Abstracts?&view=abst_detail_view&confID=53&abstractID=10380 (accessed 10 Feb 2011).
- Hadoux J, Malka D, Planchard D, et al. Post first line FOLFOX chemotherapy for grade 3 neuroendocrine carcinoma. *Endocr Relat Cancer* 2015;22:289–99.
- Knudsen AL, Bisgaard ML, Bülow S. Attenuated familial adenomatous polyposis (AFAP). A review of the literature. *Fam Cancer* 2003;2:43–55.
- Bianchi KL, Buerke CA, Bennett AE, et al. Fundic gland polyp dysplasia is common in familial adenomatous polyposis. *Clin Gastroenterol Hepatol* 2008;6:180–5.
- Abraham SC, Nobukawa B, Giardiello FM, et al. Fundic gland polyps in familial adenomatous polyposis: neoplasms with frequent somatic adenomatous polyposis coli gene alterations. *Am J Pathol* 2000;157:747–54.
- Spigelman AD, Williams CB, Talbot IC, et al. Upper gastrointestinal cancer in patients with familial adenomatous polyposis. *Lancet* 1989;2:783–5.
- Bulow S, Bjork J, Christensen IJ, et al. Duodenal adenomatosis in familial adenomatous polyposis. *Gut* 2004;53:381–6.
- Bertoni G, Sassatelli R, Tansini P, et al. Jejunal polyps in familial adenomatous polyposis assessed by push-type endoscopy. *J Clin Gastroenterol* 1993;17:343–7.
- Matsumoto T, Esaki M, Yanaru-Fujisawa R, et al. Small-intestinal involvement in familial adenomatous polyposis: evaluation by double-balloon endoscopy and intraoperative enteroscopy. *Gastrointest Endosc* 2008;68:911–19.
- Lyons LA, Lewis RA, Strong LC. A genetic study of Gardner syndrome and congenital hypertrophy of the retinal pigment epithelium. *Am J Hum Genet* 1988;42:290–6.
- Nieuwenhuis MH, Lefevre JH, Bülow S, et al. Family history, surgery, and APC mutation are risk factors for desmoid tumors in familial adenomatous polyposis: an international cohort study. *Dis Colon Rectum* 2011;54:1229–34.
- Turcot J, Despres JP, St Pierre F. Malignant tumors of the central nervous system associated with familial polyposis of the colon: report of two cases. *Dis Colon Rectum* 1959;2:465–8.
- Groen EJ, Roos A, Muntinghe FL, et al. Extra-intestinal manifestations of familial adenomatous polyposis. *Ann Surg Oncol* 2008;15:2439–50.
- Groden J, Thliveris A, Samowitz W, et al. Identification and characterization of the familial adenomatous polyposis coli gene. *Cell* 1991;66:589–600.
- Leoz ML, Carballal S, Moreira L, et al. The genetic basis of familial adenomatous polyposis and its implications for clinical practice and risk management. *Appl Clin Genet* 2015;8:95–107.
- Bisgaard ML, Fenger K, Bülow S, et al. Familial adenomatous polyposis (FAP): frequency, penetrance, and mutation rate. *Hum Mutat* 1994;3:121–5.
- Levin B, Lieberman DA, McFarland B, et al, American Cancer Society Colorectal Cancer Advisory Group; US Multi-Society Task Force; American College of Radiology Colon Cancer Committee. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *Gastroenterol* 2008;134:1570–95.
- Philips RK, Spigelman AD. Can we safely delay or avoid prophylactic colectomy in familial adenomatous polyposis? *Br J Surg* 1996;83:769–70.
- July LV, Northcott KA, Yoshida EM, et al. Coexisting carcinoid tumors in familial adenomatous polyposis-associated upperintestinal adenomas. *Am J Gastroenterol* 1999;94:1091.
- Rybalov S, Kotler DP. Gastric carcinoids in a patient with pernicious anemia and familial adenomatous polyposis. *J Clin Gastroenterol* 2002;35:249.
- Camp ER, Hochwald SN, Liu C. FAP with concurrent duodenal adenomatous polyposis and carcinoid tumor. *J Surg Oncol* 2004;87:187.

- 34 Grau García C, Soto Gutierrez A, Andrada Becerra E, *et al.* [Familial adenomatous polyposis and liver metastases from a neuroendocrine tumor]. *Gastroenterol Hepatol* 2011;34:329–32.
- 35 Vortmeyer AO, Lubensky IA, Merino MJ, *et al.* Concordance of genetic alterations in poorly differentiated colorectal neuroendocrine carcinomas and associated adenocarcinomas. *J Natl Cancer Inst* 1997;89:1448–53.
- 36 Arnold CN, Sosnowski A, Blum HE. Analysis of molecular pathways in neuroendocrine cancers of the gastroenteropancreatic system. *Ann N Y Acad Sci* 2004;1014:218–19.
- 37 Vanacker L, Smeets D, Hoorens A, *et al.* Mixed adenoneuroendocrine carcinoma of the colon: molecular pathogenesis and treatment. *Anticancer Res* 2014;34:5517–21.
- 38 Bottarelli L, Azzoni C, Pizzi S, *et al.* Adenomatous polyposis coli gene involvement in ileal enterochromaffin cell neuroendocrine neoplasms. *Hum Pathol* 2013;44:2736–42.
- 39 Furlan D, Cerutti R, Genasetti A, *et al.* Microallelotyping defines the monoclonal or the polyclonal origin of miollision endocrine-exocrine tumors of the gut. *Lab Invest* 2003;83:963–71.
- 40 Scoazec JY, Couvelard A., pour le réseau TENpath (réseau national d'expertise pour le diagnostic anatomopathologique des tumeurs neuroendocrines malignes de l'adulte, sporadiques et familiales). [The new WHO classification of digestive neuroendocrine tumors]. *Ann Pathol* 2011;31:88–92.
- 41 Sorbye H, Strosberg J, Baudin E, *et al.* Gastroenteropancreatic high-grade neuroendocrine carcinoma. *Cancer* 2014;120:2814–23.
- 42 Jain A, Singla S, Jagdeesh KS, *et al.* Mixed adenoneuroendocrine carcinoma of cecum: a rare entity. *J Clin Imaging Sci* 2013;3:10.
- 43 Li Y, Yau A, Schaeffer D, *et al.* Colorectal glandular-neuroendocrine mixed tumor: pathologic spectrum and clinical implications. *Am J Surg Pathol* 2011;35:413–25.

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