CASE REPORT

Aggressive large-cell neuroendocrine carcinoma of the sigmoid colon in a patient with ulcerative colitis

Patrick Stoner,¹ Taban Ghaffaripour,³ David Cohen²¹Department of Medicine, University of Florida College of Medicine, Gainesville, Florida, USA²Department of Medicine, Division of Gastroenterology, Mount Sinai Medical Center, Miami Beach, Florida, USA³Department of Pathology, Mount Sinai Medical Center, Miami Beach, Florida, USA

Correspondence to

Dr Patrick Stoner, patrick.stoner@medicine.ufl.edu

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SUMMARY

Colonic inflammation seen in inflammatory bowel disease (IBD) predisposes to the development of colorectal adenocarcinoma. In contrast, colorectal neuroendocrine carcinomas (NECs) have rarely been reported in the setting of IBD, and no definitive relationship between these tumours and IBD has been established. Dysplasia from chronic inflammation leading to neuroendocrine cell differentiation may be responsible for NEC development, though this finding has not been seen consistently. We present a case of large-cell neuroendocrine carcinoma of the sigmoid colon in a 65-year-old woman with long-standing ulcerative colitis. Although she underwent regular endoscopic follow-ups and was receiving the tumour necrosis factor alpha inhibitor infliximab, her tumour was large and aggressive, with metastases to the liver discovered at time of diagnosis. This case highlights the aggressive nature and poor prognosis of NECs and stresses the need to identify patients at high risk of developing NECs and develop improved surveillance guidelines for detecting them.

BACKGROUND

It is well documented that inflammatory bowel disease (IBD), in particular long-standing, extensive ulcerative colitis (UC), predisposes to the development of colorectal cancer (CRC). A comprehensive meta-analysis by Eaden *et al*¹ in 2001 estimated the overall prevalence of CRC in any patient with UC to be 3.7%, with a CRC risk of 2% by 10 years, 8% by 20 years and 18% by 30 years of disease. Based on this increased risk, specific guidelines for the screening and surveillance of CRC in patients with UC have been established to detect neoplasia at a surgically curable stage and to reduce CRC-related mortality.^{2,3}

While adenocarcinoma is the most common colorectal cancer associated with IBD, other types of malignancies, such as squamous cell carcinoma, sarcomas, lymphomas and hepatoid adenocarcinomas, have been reported in colitic bowel. Neuroendocrine tumours (NETs) have been reported in IBD as well, but the majority of these tumours have been carcinoids, which are well differentiated and clinically indolent.^{2,4} Neuroendocrine carcinomas (NECs) of the colon and rectum are an extremely rare, malignant subtype of NET, with a reported incidence of 0.1% to 3.9% of all colorectal malignancies.^{5,6} These tumours are poorly differentiated, extremely aggressive and carry a poor prognosis, with about 70% of patients presenting with

metastatic disease and a reported median survival rate of between 5 and 11 months.^{5–7}

Studies seem to suggest that long-standing inflammation is directly responsible for the development of NETs.^{2,3} However, no causal relationship between IBD and NET development has been firmly established nor has there been any proof that these tumours occur more frequently in IBD than in healthy, non-inflamed colons. Here we present a case of metastatic high-grade large-cell NEC of the colon arising in the setting of UC.

CASE PRESENTATION

A 65-year-old woman with a several years history of UC presented to the clinic complaining of bloody diarrhoea. Her disease had previously been well controlled on infliximab for the last 30 months, with the last infusion 1 month prior. She had never received any other immunosuppressant therapy. A surveillance colonoscopy 11 months prior showed a few friable pseudopolyps but no masses or signs of active colitis. Random colon biopsies did not reveal any dysplasia.

INVESTIGATIONS

A colonoscopy performed 4 days after current presentation revealed a large, nearly obstructing, polypoid tumour in the midsigmoid colon (figure 1). Multiple biopsies were taken, which were inconclusive and only showed inflammatory debris. A repeat sigmoidoscopy was done and multiple biopsies of the mass were again performed. Initial pathology was interpreted as undifferentiated carcinoma with extensive necrosis (figure 2). However, immunohistochemical stains for CK7, CK20 and CAM5.2 were all negative, failing to support the diagnosis of carcinoma. CD3, CD20 and SOX10 stains were also negative, helping to rule out lymphoid or melanocytic differentiation. In addition, GATA3 and CD56 stains were focally positive. A subsequent CT scan of the abdomen and pelvis showed the mass to be at least 5.5 cm with prominent adjacent lymph nodes in the sigmoid mesocolon (figure 3). In addition, two hypoattenuating lesions concerning for metastasis were seen in the right lobe of the liver.

TREATMENT

Given the inconclusive diagnosis yielded by colonoscopy biopsies and ongoing refractory bleeding (made worse by the multiple biopsies taken of the mass), the patient opted for surgical resection of the mass with biopsies of the liver lesions seen on CT

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Figure 1 Large, nearly obstructing polypoid tumour in the midsigmoid colon.

scan. The patient was admitted to the hospital and underwent a laparoscopic sigmoidectomy with loop colostomy and liver biopsy.

OUTCOME AND FOLLOW-UP

Pathology of the surgical specimen (figure 4) revealed an 8.5 cm undifferentiated malignant neoplasm with ulceration and extensive necrosis. Eighteen of the 20 seven total lymph nodes present in the specimen showed metastatic disease. Immunohistochemical stains were positive for the neuroendocrine markers synaptophysin, CD56 and chromogranin (figures 5, 6 and 7, respectively) while negative for several keratin markers, melanoma markers and the lymphocytic marker CD45. The liver core biopsy displayed similar cytomorphological features to the colonic neoplasm noted above and also stained positive for synaptophysin. Overall, the immunochemical and histological findings favoured a high-grade large-cell NEC of the sigmoid colon with metastases to the liver (T3N2bM1a).

A follow-up CT scan less than 3 weeks after surgery, performed for evaluation of a wound infection and possible abscess, revealed

Figure 2 Undifferentiated malignant neoplasm.

Figure 3 CT scan showing 5.5 cm mass in sigmoid colon with prominent adjacent lymph nodes in the sigmoid mesocolon.

significant increase in the size of the hepatic metastatic lesions, with the largest lesion measuring 8.5×7.3×7.7 cm. The patient was given one cycle of chemotherapy consisting of 5 FU 740 mg, leukovorin 740 mg and irinotecan 333 mg. She was transferred to the rehabilitation floor, where her clinical status deteriorated. Nine days later, the patient went into cardiac arrest and was not able to be resuscitated. She died 2 months after the diagnosis was made.

DISCUSSION

According to the WHO classification of 2010, NETs are classified as either G1, G2 or G3 based on tumour differentiation and grade. Well-differentiated NETs are G1 and G2, whereas poorly differentiated NECs, separated into either large cell type or small cell type, are classified as G3. NET grade is determined by the mitotic count and by the Ki-67 index. Ki-67 is a marker of cellular proliferation with an established role of predicting the invasive potential of gastrointestinal NETs. NET G1 tumours (eg, carcinoid tumours) have a low mitotic rate of less than 2 per 10 high-power fields (HPF) and a Ki-67 index of <2%, G2 tumours have a mitotic rate of 2–20 per 10 HPF and a Ki-67 index of 3%–20%, and G3 tumours have a mitotic rate of >20 per 10 HPF and a Ki-67 index of >20%.^{5,8}

Gastrointestinal NECs are subdivided into small cell and large cell types based on their morphological and immunohistochemical features. These features are similar to their more frequently encountered pulmonary homonyms (small cell lung cancer (SCLC) and large cell neuroendocrine lung cancer). In addition, gastrointestinal NECs also act similarly to their pulmonary relatives with regards to biological behaviour, clinical course and chemotherapy responsiveness. Given these similarities, treatment regimens for gastrointestinal NECs largely parallel those established for SCLC, generally consisting of platinum-based chemotherapy such as cisplatin/etoposide or cisplatin/irinotecan.^{5,9}

Figure 4 Undifferentiated malignant neoplasm of 8.5 cm with ulceration and extensive necrosis.

Figure 5 Diffuse synaptophysin positivity.

There are a limited number of studies investigating risk factors for NETs in the literature and risk factors for the development of gastrointestinal NECs are particularly poorly defined. A meta-analysis by Leoncini *et al*¹⁰ showed that a family history of any cancer was the most relevant risk factor for NET development at all investigated sites (lung, stomach, pancreas, small intestine, appendix, colon and rectum), followed by diabetes and high body mass index. Heavy alcohol use was associated with an increased risk of rectal NETs, whereas cigarette smoking was not identified as a statistically significant risk factor for rectal NETs. Neither of these exposures on colon NET risk specifically has never been studied.¹⁰ In addition, well-differentiated NETs are not thought to transform into NECs, as NECs and NETs are usually not found together on pathological exam.⁹

Figure 6 CD56 positivity (patchy).

Figure 7 Chromogranin positivity (patchy).

Large-cell neuroendocrine carcinomas (LCNECs) are characterised histologically by a neuroendocrine appearance under light microscopy (including an organoid, nesting, trabecular, rosette and palisading pattern), large patches of necrosis and are composed of large cells with a polygonal shape, coarse chromatin, frequent nucleoli and ample cytoplasm.^{5 11} In addition, LCNEC usually stain positive for one or more neuroendocrine immunohistochemical markers (chromogranin, synaptophysin, CD56 and neuron-specific enolase).^{2 5 11} As mentioned previously, these tumours are especially rare: In a study of 6495 patients with colorectal cancer by Bernick *et al*,⁶ only 38 patients (0.6%) had NECs, of which only 13 were LCNEC.

There have been cases of NETs in the setting of UC reported previously, but the majority of these have been of the well differentiated, clinically indolent 'carcinoid' type (NET G1 or G2). The only reported series of neuroendocrine tumours other than carcinoids arising in the setting of IBD was by Sigel *et al*⁴ in 1998. They evaluated 14 patients with IBD (8 CD, 6 UC) who had developed NETs in IBD-involved areas. Only 3 of the 14 cases involved poorly differentiated tumours, and 2 of these patients died within 12 months of surgical excision. These authors suggested that neuroendocrine differentiation may evolve from multipotential cells in dysplastic epithelium based on their findings that dysplasia was found in adjacent mucosa in more than one-third of their cases. Shigaki *et al*³ observed similar findings in their 2013 study, with 30%–50% of UC-associated neoplasia displaying features of neuroendocrine differentiation.

In our case, dysplasia was not observed in the mucosa adjacent to the resected tumour nor in the random colon biopsies performed during the surveillance colonoscopy 11 months prior. Our patient had been compliant with all treatments and had been receiving routine surveillance colonoscopies with multiple site biopsies to rule out dysplasia for several years. This case, similarly to previous reports,^{2 7 12} highlights the aggressiveness of NECs and the profound limitations that current IBD surveillance guidelines have in detecting them. The rarity of cases of NECs arising in patients with IBD further limits the ability to identify a subgroup of patients at high risk.^{7 12} Identifying this high-risk subgroup may not

Learning points

- Neuroendocrine carcinomas (NECs) of the colon and rectum are a malignant and extremely rare subtype of neuroendocrine tumours, with a reported incidence of 0.1% to 3.9% of all colorectal malignancies. These tumours are poorly differentiated, extremely aggressive, and carry a poor prognosis, with about 70% of patients presenting with metastatic disease and a reported median survival rate of between 5 and 11 months.
- We present a case of large-cell NEC of the sigmoid colon in a 65-year-old woman with long-standing ulcerative colitis. While colonic inflammation in inflammatory bowel disease (IBD) is known to predispose to colorectal adenocarcinomas, colorectal NECs have only rarely been reported in the setting of IBD, and no definitive relationship between these tumours and IBD has been established.
- The rarity of cases of NECs arising in patients with IBD further limits the ability to identify a subgroup of patients at high risk. Identifying this high-risk subgroup may not only improve surveillance efforts but might also influence the management of these patients.

only improve surveillance efforts but might also influence the management of these patients, possibly leading to earlier elective prophylactic colectomies.

Of note, the patient in this case had been started on the tumour necrosis factor alpha (TNF- α) inhibitor infliximab (Remicade) for her UC 30 months prior to her cancer diagnosis. TNF- α is a pro-inflammatory cytokine that is likely a crucial mediator of the initiation and progression of colitis-associated colon carcinogenesis.¹³ Blocking TNF- α activity has been shown to reduce mucosal damage and thereby decrease colon cancer formation in an animal model.¹³ However, since this class of drugs suppress the immune system by inhibiting the immunological activity of TNF, the theoretical potential of these drugs actually causing malignancy has been a concern. While there have been no reported cases of NECs associated with infliximab use, postmarketing reports of Hepatosplenic T-cell lymphoma, melanomas and Merkel cell carcinomas linked to infliximab use have been described.¹⁴ However, several large cohort studies^{15–17} have shown no increased risk of malignancy associated with TNF- α inhibitor usage in the treatment of IBD. These studies were of short duration and do conclude, however, that long-term observational studies are needed to better assess this risk.

Contributors PS contributed to the conception and design of the manuscript and the acquisition and interpretation of data. He also drafted the manuscript. DC contributed to the conception and design of the manuscript and revised the article critically for intellectually important content. He also provided final approval of the submitted manuscript. TG acquired the pathology slides and gross specimen pictures and labelled them. She also reviewed and revised the portions of the manuscript relating to pathological interpretation.

Competing interests None declared.

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