



## Case report

## Case report of multiple rectal neuroendocrine tumors in a context of ulcerative colitis

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## ABSTRACT

**Introduction:** Neuroendocrine tumors (NETs) of the rectum are rare, with an estimated incidence of 0.1% of all colorectal cancers. However, it is crucial to diagnose NET, particularly in patients with ulcerative colitis, who seem to have a higher risk of cancerization according to recent studies, given the aggressiveness and poor prognosis of these tumors.

**Presentation of case:** We report the case of a 54-year-old man who developed multiple rectal NETs (approximately 10), measuring 1–6 mm, only 2 years after a primary diagnosis of ulcerative colitis.

**Discussion:** In the literature, all reported cases of NETs present patients with a long history of several years of inflammatory bowel disease; however, very little literature exists on this subject. Herein, we discussed the outcomes and a literature review of the pathology, prognosis, and management of NETs.

**Conclusion:** Despite advances in research on rectal NETs, many aspects about the disease remain unclear, partly due to its rarity.

## 1. Introduction

The incidence of idiopathic chronic inflammatory disorder of the colon mucosa is increasing globally. Studies have shown an increased risk of colorectal adenocarcinoma in these patients compared with the general population. Disease duration and inflammation severity increase the abovementioned risk [1]. In contrast, colorectal neuroendocrine carcinomas (NECs) have rarely been reported in the context of inflammatory bowel disease (IBD); moreover, the relationship between the occurrences of NECs and IBD remains debatable. However, some studies have shown a relationship between the abovementioned two conditions [2].

Herein, we report the case of a 54-year-old man who was diagnosed with ulcerative colitis (UC) 2 years earlier. The patient, who was admitted to an academic hospital, developed multiple NEC at the level of his residual rectum 2 years after undergoing total colectomy for colonic perforation with peritonitis.

In this case report, we discuss patient outcomes with a literature review of the pathology, prognosis, and management of NETs.

## 2. Presentation of case

A 54-year-old man was admitted with UC diagnosed 2 years ago.

He had a medical history of hypertension and hypercholesterolemia, with no family history of malignancies or chronic inflammatory diseases.

The history of presenting complaint began in July 2019, with severe abdominal pain for which colonoscopy was performed, leading to a diagnosis of UC. Treatment with infliximab and mesalamine was initiated. Two weeks later, he was admitted for an acute abdomen that required emergency surgery, after colonic perforation was demonstrated on abdominal CT (Fig. 1).

Intraoperatively, subtotal colectomy with caecostomy was performed for multiple perforations in the right, transverse, and left colon; furthermore, the colon was highly enlarged and inflamed. Post-operatively, the patient developed an evisceration, which required surgical revision.

Once the colonic perforations were treated, a restoration of continuity with closure of the terminal colostomy after a complementary

*Abbreviations:* NEC, neuroendocrine carcinoma; NET, neuroendocrine tumors; IBD, inflammatory bowel disease; UC, ulcerative colitis.

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proctectomy for UC was discussed with the patient. However, we explained to the patient that a good functional outcome could not be assured given his history and the presence of severe anal stenosis. After careful consideration, the patient decided to maintain the stoma.

Pathological analysis of the surgical specimen revealed an erythematous mucosa with a loss of colonic folds. The serosa was discreetly covered by fibrin, which was probably due to perforation. NETs were not observed macroscopically. Notably, these tumors are often discovered incidentally. On histological examination, we found multiple NETs measuring 1–6 mm (Fig. 2). The tumor foci were completely resected at least 1 cm from the proximal and distal margins. The tumor cells were arranged in a trabecular pattern consisting of small cells with salt-and-pepper nuclear chromatin (Fig. 3). These cells were positive for chromogranin and synaptophysin (Figs. 4 and 5). Mitosis was not observed, although 3% of the cells were Ki67-positive. These findings suggested the presence of multiple grade 2 NETs. The UC was classified as chronic rectocolitis in the quiescent phase.

The NETs were non-functional. The patient was discharged after octreoscan scintigraphy was performed to exclude metastatic lesions.

### 3. Discussion

Adenocarcinoma is the most frequent colorectal malignancy associated with UC, albeit other types of malignancies exist, such as NETs; however, NETs are extremely rare and aggressive [3]. The reported incidence of NETs is between 0.1% and 3.9% of all colorectal malignancies [4]. Less than 20 cases of NET are reported in the literature [5].

NETs can affect all parts of the gastrointestinal tract. These tumors may be symptomatic or asymptomatic, and are thus of incidental discovery. Prognostic factors include poorly differentiated tumors, high histological grade (Ki67 index >20%), and metastatic tumor [6].

It is crucial to diagnose NETs, as they carry a poorer prognosis compared to colorectal adenocarcinomas. Indeed, NETs have a higher rate of liver metastasis, and the 1-year survival is approximately 40%. Patients with NETs may benefit from treatments such as the use of chemotherapeutic agents [4]. In our case, the patient was operated only 5 months before this article was written nevertheless, the postoperative outcome is hitherto favorable, with no clinical or radiological signs of recurrence.

Importantly, the possibility of a tumor predisposition syndrome should always be considered in patients with NETs, especially duodenopancreatic NETs. Furthermore, NETs can be associated with several syndromes, such as multiple endocrine neoplasia type 1, Von Hippel-Lindau disease, or other syndromes, although this was not the case with our patient.

The main factors associated with the risk of lymph node metastases

are tumor size >15 mm, atypical endoscopic appearance such as ulceration, lymph node metastasis suspicion on MRI, muscular propria invasion (T2), grade G2, and lymphovascular invasion [7]. Our patient had multiple grade 2 NETs without metastasis. Prolonged surveillance, which may be lifelong, seems justified according to the guidelines of the French National Society of Gastroenterology [7]. Thoracic, abdominal, and pelvic CT as well as abdominal MRI with diffusion sequences are the reference surveillance modalities, and can be used alternately to detect any recurrence at early stages. There is still no consensus in the literature on the time frame for surveillance; however, surveillance is usually initiated 3–6 months after treatment and the follow-up intervals are progressively lengthened if imaging findings are unremarkable [6].

It is well known that UC predisposes a patient to the development of colorectal carcinoma [8]. Long-term disease and extended colitis seem to increase the risk of malignancy [3]. Some studies have demonstrated a relationship between UC and NET occurrences. Shigaki et al. demonstrated the presence of neuroendocrine differentiation in IBD-related carcinogenesis [2]. Moreover, they showed that neuroendocrine differentiation is relatively common and represents an early event in the UC-neoplasia pathway in which p53 and chromogranin A are coordinately up-regulated. However, other authors, such as Greenstein et al. [9], suggested that the association between UC and NET occurrences is a coincidence, and especially that no significant demographic or clinicopathological differences exist between NETs that occur in patients with or without IBD.

Interestingly, our patient developed numerous rectal NETs only 2 years after the diagnosis of UC. This may be because the disease was discovered late, or because rectal NETs are not always related to UC. It may also reflect a rapid progression of malignancy or a misdiagnosis of malignancy using endoscopy.

The identification of rectal NETs at the initial endoscopy is essential in determining the most appropriate treatment. In our case, the last colonoscopy findings were normal. The management of these tumors depends on their grades. For the management of NET grade 2 without metastasis, measuring <1 cm, complete resection is necessary, and no other treatments are needed [10].

We encountered difficulties managing our patient due to the presence of multiple rectal NETs that were found on the surgical specimen; hitherto, no study has compared the prognoses of patients with multiple and single NETs. Consequently, the patient was referred to a specialist in NETs who performed octreoscan scintigraphy and found no suspicious lesions; hence, the specialist concluded that simple monitoring was sufficient.

Despite many advances in research on rectal NETs, many aspects of this disease remain unclear, partly due to the rarity of the disease.

More randomized, multicenter studies are needed to confirm or



Fig. 1. Massive pneumoperitoneum and colonic perforation.

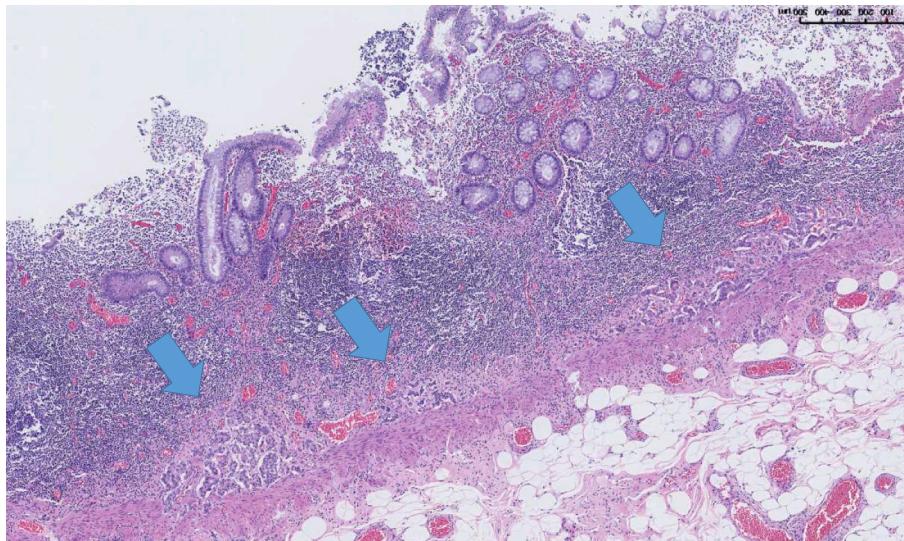


Fig. 2. Multiple neuroendocrine tumors.

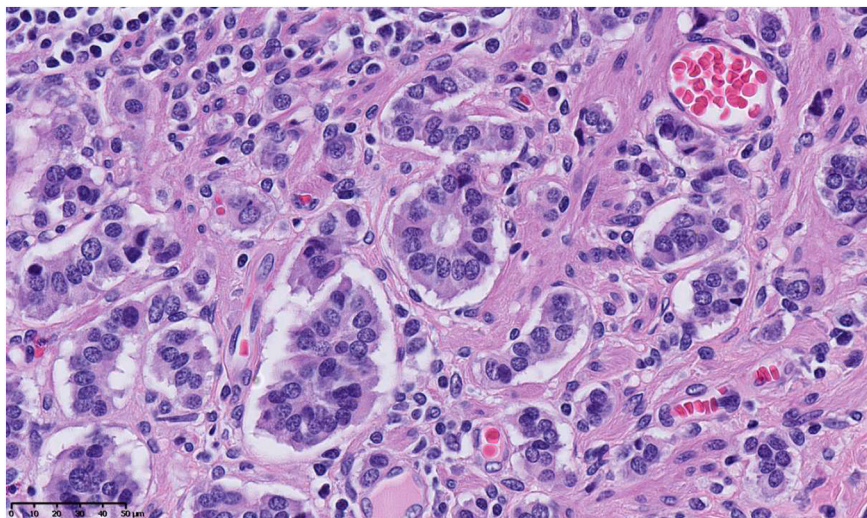


Fig. 3. Nests of tumoral cells with an eosinophilic cytoplasm and finely granular “salt and pepper” chromatin on hematoxylin and eosin staining.

refute the relationship between IBD and NET occurrences.

**4. Conclusion**

In this case report, we found that UC seems to favor the development of NETs, which is akin to some reports in the literature. However, to date, no study has described the presence of multiple rectal NETs in patients with UC. An early diagnosis of NETs is important for early management, given the poor prognosis of these tumors.

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**Ethical approval**

None declared.

**Consent**

Written informed consent was obtained from the patient for the

publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

**Author contribution**

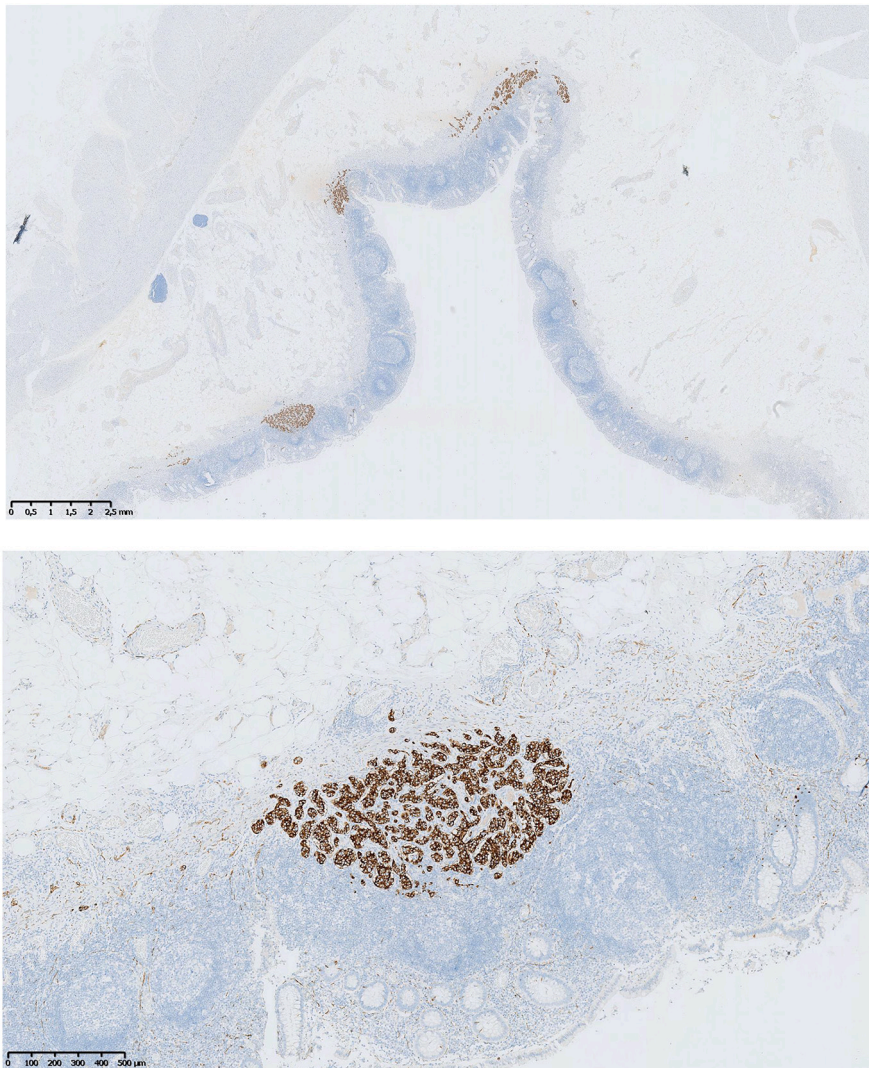
- KM: Patient care and wrote the paper.
- RC: Patient care and supervision of the paper.
- BR: Patient care.
- LD: Patient care.
- SM: Reviewed the histological section and selected the images for the paper.
- KA: Patient care and supervision of the paper.

**Registration of research studies**

Not applicable.

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**Figs. 4-5.** Neuroendocrine tumoral cells are chromogranin- and synaptophysin-positive.

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#### Provenance and peer review

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#### Declaration of competing interest

All authors disclose no financial and personal relationships with other people or organizations that could inappropriately influence (bias) this work.

The authors declare no conflict of interest.

#### References

- [1] S. Cohen-Mekelburg, Y. Schneider, S. Gold, E. Sherl, A. Steinlauf, Advances in the diagnosis and management of colonic dysplasia in patients with inflammatory bowel disease, *Gastroenterol. Hepatol.* 13 (2017) 357–362.
- [2] K. Shigaki, H. Mitomi, T. Fujimori, et al., Immunohistochemical analysis of chromogranin a and p53 expressions in ulcerative colitis-associated neoplasia: neuroendocrine differentiation as an early event in the colitis-neoplasia sequence, *Hum. Pathol.* 44 (2013) 2393–2399.
- [3] R. Ridell, Dhanpat J. Lewin, Weinstein and Riddell's *Gastrointestinal Pathology and Its Clinical Implications*, 2nd ed., Lippincott Williams & Wilkins, Philadelphia, PA, 2014.
- [4] P.E. Bernick, D.S. Klimstra, J. Shia, B. Minsky, L. Saltz, W. Shi, Thaler, J. Guillem, P. Paty, A.M. Cohen, W.D. Wong, Neuroendocrine carcinomas of the colon and rectum, *Dis. Colon Rectum* 47 (2004) 163–169.
- [5] E. Bolzacchini, C. Chini, C. Cortelezzi, I. Vallini, G. Pinotti, S. La Rosa, S. Uccella, Poorly differentiated neuroendocrine carcinoma of the sigmoid tract in long-standing colitis: report of a case and review of literature, *Int. J. Surg. Pathol.* (2018) 1–5.
- [6] L. De Mestier, C. Lepage, E. Baudin, R. Coriat, F. Courbon, A. Couvelard, C. Do Cao, E. Frampas, S. Gaujoux, R. Gincul, P. Goudet, C. Lombard-Bohas, G. Poncet, D. Smith, P. Ruzsniwski, T. Lecomte, O. Bouché, T. Walter, G. Cadiot, Thésaurus National de Cancérologie Digestive (TNCD), Digestive Neuroendocrine Neoplasms (NEN): French Intergroup clinical practice guidelines for diagnosis, treatment and follow-up (SNFGE, GTE, RENATEN, TENPATH, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, SFR), *Dig. Liver Dis.* 52 (5) (2020) 473–492. Epub 2020 Mar 28.
- [7] G. Cadiot, E. Baudin, A. Couvelard, C. Dromain, C. Lepage, C. Lombard-Bohas, G. Poncet, P. Ruzsniwski, D. Smith, Tumeurs neuro-endocrines, in: Thésaurus National de Cancérologie Digestive, 03-2016.
- [8] J.A. Eaden, K.R. Abrams, J.F. Mayberry, The risk of colorectal cancer in ulcerative colitis: a meta-analysis, *Gut* 48 (2001) 526–535.
- [9] A.J. Greenstein, S. Balasubramanian, N. Harpaz, M. Rizwan, D.B. Sachar, Carcinoid tumor and inflammatory bowel disease: a study of eleven cases and review of the literature, *Ann. J. Gastroenterol.* 92 (1997) 682–685.
- [10] J.K. Ramage, W.W.D. Herder, G.D. Fave, P. Ferolla, D. Ferone, T. Ito, P. Ruzsniwski, A. Sundin, W. Weber, Z. Zheng-Pei, et al., ENETS consensus guidelines update for colorectal neuroendocrine neoplasms, *Neuroendocrinology* 103 (2016) 139–143.