Well-differentiated neuroendocrine tumor of the ileal pouch in a patient with ulcerative colitis and primary sclerosing cholangitis: report of a case and review of the literature

Ondřej Fabián[1,2], Andrea Heribanová[1], Pavel Drastich[3], Luděk Voska[1]

[1]Clinical and Transplant Pathology Centre, Institute for Clinical and Experimental Medicine, Prague, Czech Republic
[2]Department of Pathology and Molecular Medicine, 3rd Faculty of Medicine, Charles University and Thomayer Hospital, Prague, Czech Republic
[3]Department of Gastroenterology and Hepatology, Institute for Clinical and Experimental Medicine, Prague, Czech Republic

SUMMARY
Gastrointestinal tract is the most common locality for well-differentiated neuroendocrine tumors (NET). While their occurrence in patients with ulcerative colitis (UC) is uncommon, it has been well documented. However, the causal relationship between development of NET and chronic intestinal inflammation or dysplasia remains controversial. The presence of NET in the ileal pouch in UC patients has been described only in a few reports to date. In this article, we present a case of such a tumor arising in the pouch in a patient with primary sclerosing cholangitis-associated UC, who underwent a restorative proctocolectomy with ileal pouch anal anastomosis and liver transplantation. The case is supported by a review of a relevant literature.

Keywords: carcinoid – neuroendocrine tumor – pouch – ulcerative colitis

Dobře diferencovaný neuroendokrinní tumor ileálního pouche u pacienta s ulcerózní kolitidou a primární sklerozující cholangoitidou: popis případu a přehled literatury

SOUHRN
Gastrointestinální trakt představuje častou lokalitu pro dobře diferencované neuroendokrinní tumory (NET). Jejich výskyt u pacientů s ulcerózní kolitidou (UC) není častý, je však dobře dokumentovaný. Případný kauzální vztah mezi rozvojem NET a chronickým zánětem střevní sliznice či dysplázií epitelu nicméně zůstává nejasný. Výskyt NET v ileálním pouchi u pacientů s UC byl dosud popsán jen v několika kazuistických sděleních. Prezentujeme zde případ takovéhoto nádoru vznikajícího ve sliznici pouche u pacienta s UC asociovanou s primární sklerozující cholangoitidou, který podstoupil transplantaci jater a restorativní kolektomii s následnou ileální pouch-anální anastomózou. Popis případu je doplněn o přehled dostupné literatury.

Klíčová slova: karcinoid – neuroendokrinní tumor – pouch – ulcerózní kolitida

Cesk Patol 2024; 60(3): 155–158

Up to one-third of the patients with ulcerative colitis (UC) will require surgical intervention during their life due to refractory inflammatory activity or the development of dysplasia or cancer (1,2). Restorative proctocolectomy with ileal pouch anal anastomosis (IPAA) is still considered a gold standard for the surgical treatment of those patients (3). This continence-preserving procedure represents a more feasible option compared to total abdominal colectomy with ileorectal anastomosis (IRA) or total proctocolectomy with permanent ileostomy, since IRA is suitable only for patients with minimal inflammatory activity and no dysplasia in the rectum (4) and a permanent ileostomy precludes a subsequent reconstruction of the bowel continuity (5). Patients with IPAA can subsequently develop neoplastic changes in the pouch mucosa. These cases are uncommon and occur years or even decades after the onset of UC (6). They are usually represented by intraepithelial neoplasia (dysplasia) or invasive adenocarcinoma. The presence of neuroendocrine neoplasm in the pouch is an exceedingly rare phenomenon that has been described only in a few reports in English literature so far (7-9). The proper management of these patients is unclear, and the necessity of surgical intervention remains controversial. In this work, we report a case of a well-differentiated neuroendocrine tumor (NET) in the ileal pouch of a patient with UC associated with primary sclerosing cholangitis (PSC).

✉ ***Correspondence address:***
Ondrej Fabian
Clinical and Transplant Pathology Centre
Institute for Clinical and Experimental Medicine
Videnska 1958/9
Prague, 14021
Czech Republic
ondrej.fabian@ikem.cz; ondrejfabian5@gmail.com

CASE REPORT

A 35-year-old man was diagnosed with PSC-UC in 2004. In August 2009, he underwent a proctocolectomy with ileostomy for refractory disease followed by an IPAA in January 2010. Since that time, he has not shown any clinical or endoscopic signs of intestinal inflammation, except for a short episode of acute pouchitis in June 2016. He also underwent liver transplantation for PSC-associated cirrhosis in June 2014 and a re-transplantation in December 2021 for the disease recurrence. In June 2021, he was

admitted to the hospital for a routine endoscopic examination. The endoscopy showed normal-looking mucosa, but a biopsy from the pouch revealed an incidental grade 1 well-differentiated NET, situated in deeper levels of lamina propria (Figure 1A-D). The tumor measured 2 mm in the largest diameter and consisted of medium-sized polygonal epithelial cells with eosinophilic cytoplasm and oval nuclei with a salt-and-pepper character of the chromatin. The neoplastic cells grew predominantly in a solid-islet pattern and were strongly diffusely immunopositive for chromogranin and synaptophysin. No mitotic figures were seen within the tumor and Ki67 proliferative index was less than 1 %. No vascular or perineural invasion was found either. The tumor was reaching margins of the bioptic sample, and thus the completeness of the removal could not be guaranteed. The surrounding ileal mucosa showed signs of mild chronic pouchitis with flattened villi and a lymphoplasmatic infiltration of the lamina propria accompanied by scattered neutrophils. The patient underwent a thorough clinical examination with a staging abdominal and pelvic computer tomography scan (CT) and scintigraphy, finding no evidence of mass in the pouch wall, no pelvic lymphadenopathy and no distant metastases. Due to negative staging and normal endoscopic appearance, the surgical removal of the pouch was omitted, and the patient was put on active endoscopic surveillance. The same tumor was found also in the next endoscopic biopsy in March 2022 and showed no increased mitotic activity. Subsequent biopsies in August 2022 and January 2023 were negative. At the time of publication, the patient was in endoscopic remission with no signs of tumor progression.

DISCUSSION

Gastrointestinal (GI) tract represents the most common locality for well-differentiated NETs. In the small and large bowel, the tumors constitute 35-42 % and 0,1-3,9 % of all malignancies, respectively (10,11). They are commonly encountered in duodenum due to regularly performed endoscopic examinations, but the real incidence seems to be higher for jejunal and ileal cases, representing approximately three-quarters of all cases (12). The risk of metastatic spread largely depends on the size of the tumor. NETs smaller than 1 cm harbor a 2 % risk of metastases, while tumors of size 1-2 cm have 50 %, and tumors larger than 2 cm have an 80 % risk of dissemination (13). An overall five-year survival rate for the metastatic small bowel NET is 75 % though (14). On the other hand, poorly differentiated neuroendocrine carcinomas are a rare finding in the GI tract, with a reported incidence of 0,1 - 3,9 % of all large bowel cancers (15).

Neuroendocrine neoplasms may also occur in patients with UC. The development of dysplasia or cancer is the most severe complication of a longstanding disease. The risk of malignancy in patients with UC is 2 % within ten years, 8 % at twenty years, and 18 % at thirty years of duration of the disease (16). The most common type is adenocarcinoma, but other malignancies were also reported, including squamous cell carcinoma, hepatoid carcinoma, or various sarcomas or lymphomas (17). Neuroendocrine neoplasms in the UC are rare findings. Most of the reported cases fall into the category of well-differentiated NETs. They are usually incidental findings in resection specimens and are often found in regions not affected by chronic

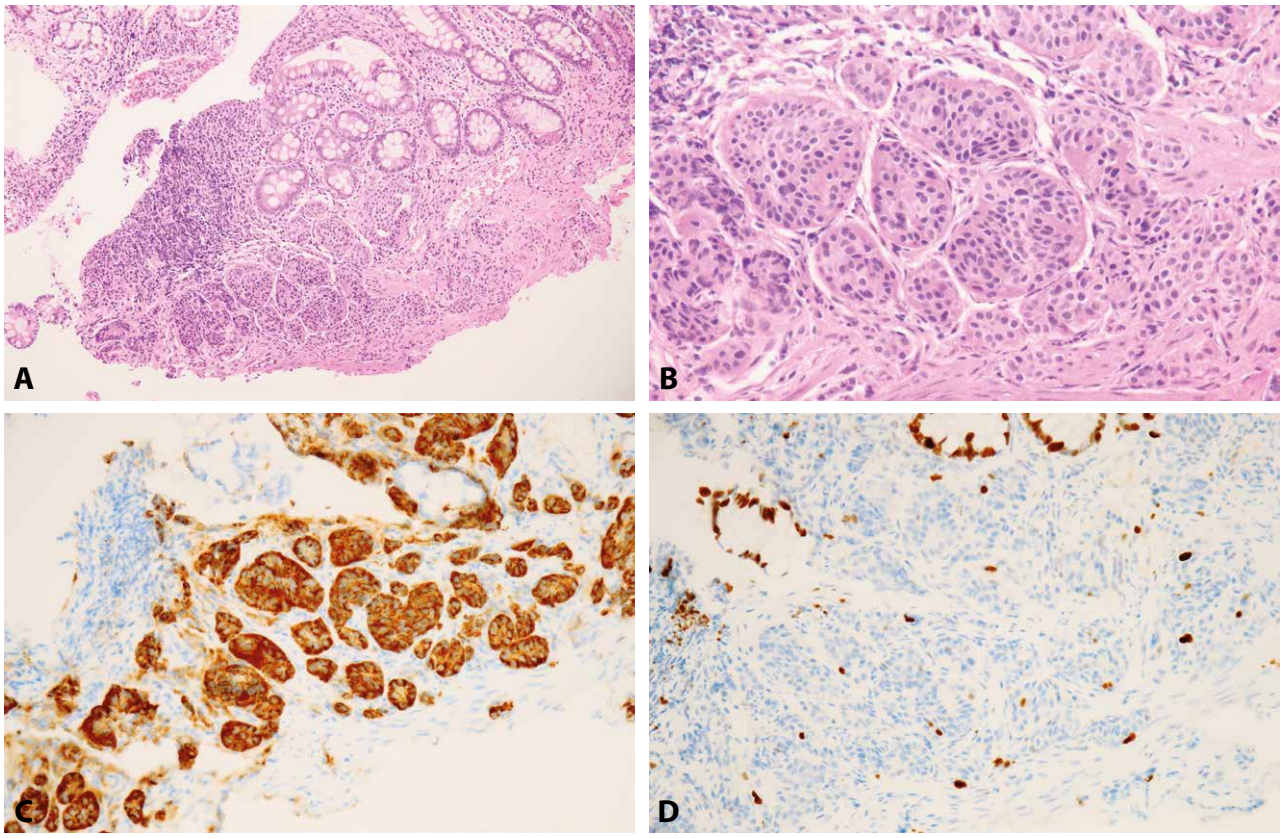

Figure 1. Microphotographs demonstrating grade 1 well-differentiated neuroendocrine tumor of the ileo-anal pouch.
A: The tumor consisted of solid nests of neoplastic cells embedded in the ileal mucosa (hematoxylin and eosin; original magnification 200x).
B: On higher magnification, the neoplastic cells were medium-sized, polygonal, with eosinophilic cytoplasm and slightly atypical nuclei, often showing salt-and-pepper chromatin pattern. No mitotic figures are seen (hematoxylin and eosin; original magnification 600x).
C: Strong diffuse cytoplasmic positivity of chromogranin in neoplastic cells (anti-chromogranin; original magnification 200x).
D: Ki67 highlighted less than 1 % of positive neoplastic cells (anti-Ki67; original magnification 200x).

inflammation (18). Despite the well-documented phenomenon of enteroendocrine cell hyperplasia in the terrain of longstanding UC (19), an exact mechanism of the tumor development has still not been fully elucidated and the causal relationship with chronic inflammation or dysplasia has not been confirmed. In the study of Greenstein AJ et al. (18), the authors reported 11 cases of NETs in the group of 5 UC patients and 6 patients with Crohn's disease (CD). Nine cases were appendiceal tumors and two were located in the ileum. All tumors were incidental findings and no patient presented with distant metastases. On the other hand, Sigel EJ et al. (20) described a cohort of 6 UC and 8 CD patients with neuroendocrine neoplasms, of which 11 cases were well-differentiated NETs and 3 were represented by mixed small cell neuroendocrine carcinomas/adenocarcinomas. Interestingly, all tumors were found in the inflamed regions of the bowel, and one-third of the tumors showed dysplastic changes in the surrounding epithelium. Similarly, Grassia R et al. (10) reported two cases of rectal large-cell and small-cell neuroendocrine carcinomas arising in the terrain of longstanding left-sided UC. Both groups of authors speculate that the tumors may develop as a consequence of neuroendocrine differentiation from immature multipotent cells within the dysplastic epithelium. They also propose a hypothesis of pancellular dysplasia in chronically inflamed mucosa involving all cell types including enterocytes, goblet cells, Paneth cells, and neuroendocrine cells.

Neoplastic lesions may also develop in the ileal pouch. They represent rare findings and usually take the form of epithelial dysplasia. Review from Um JW et al. (6) describes 28 patients with pouch dysplasia and 43 patients with invasive cancer. From the cohort of cancer patients, only 11 of them had a tumor in the pouch body, while 32 cases were actually situated in the anal transition zone (ATZ). For all cases, the time period from the onset of the UC to the development of the neoplasia exceeded 10 years. In 2007, Scarpa M et al. (21) published a systematic review aiming at pouch dysplasia and found 23 observational studies and case series with a total sum of 2040 patients. According to their analysis, a pooled prevalence of dysplasia in the ileal pouch was 1,13 %, of which 0,98 % was represented by low-grade dysplasia and 0,15 % by high-grade dysplasia. Dysplastic changes were equally distributed among a pouch body, rectal cuff, and ATZ. To this day, there is no clear consensus on the risk factors of pouch dysplasia development. The only confirmed risk factor seems to be the presence of dysplasia or cancer in the previous resection specimen, showing a cumulative incidence of 4.2 % at 20 years after restorative proctocolectomy (21,22). Other risk factors, particularly a longstanding pouchitis and the presence of PSC, have also been speculated (23-25), but they have not been confirmed by larger cohort studies or systematic reviews.

To the best of our knowledge, only a few cases of neuroendocrine neoplasms in the ileal pouch have been reported so far. Resnick M et al. (7) described a case of an 81-year-old woman who underwent a proctocolectomy with a subsequent IPAA 23 years ago. She was referred to the hospital due to a monthly history of crampy lower abdominal pain. A CT scan was performed and revealed a 1,5 cm sized mass in the wall of the ileal pouch with no signs of regional lymphadenopathy or distant metastases. In endoscopy, a submucosal bulk was noted, and subsequent biopsy revealed a focus of carcinoid tumor (a term used by the authors). The patient underwent a pouch excision with a permanent ileostomy and the presence of the tumor was confirmed also in the resection specimen. Al-Khyatt W et al. (8) published a case of a 46-year-old man, who underwent a proctocolectomy 8 years ago. At that time, he was admitted to the hospital due to abdominal pain and rectal bleeding. During the flexible endoscopy, a 3 cm large, ulcerated polyp was found in the pouch body. The biopsy samples showed only an inflamed ileal mucosa, and since the patient's symptoms subsequently ceased, he was treated conservatively, and the control endoscopy was repeated 4 months later. During the second endoscopy, the polyp was still present and multiple biopsies were taken, finally revealing the presence of a carcinoid tumor. Staging CT and octreotide scans found no signs of tumor dissemination and the patient underwent a pouch excision. Three years after the resection, the patient was free of local or systemic recurrence. The last publication comes from Parpounas C et al. (9) who described a case of 34-years-old male with an incidental finding of 2 cm ulceration in the pouch mucosa during a routine endoscopy performed 16 years after the initial proctocolectomy. The endoscopy was repeated three months later and at that time, a larger tumor with a central necrotic core was revealed. The tumor was confirmed also by pelvic magnetic resonance imaging. The patient underwent a complete removal of the pouch, and the subsequent histopathological examination described presence of a carcinoid tumor. The authors do not specify the exact type of the tumor, but according to the attached microphotographs, it consisted of small to moderate cells, and plentiful mitotic figures were seen. Fifteen months after the resection, the patient showed no signs of local or systemic recurrence. A presence of neuroendocrine neoplasia in the ileal pouch in a patient with PSC-UC is an exceedingly rare phenomenon. In our case, the conservative approach was preferred, since the patient was asymptomatic and had normal endoscopic findings in the pouch mucosa. After the systemic disease was excluded, the patient was put on active surveillance, and at the time of this publication, he showed no signs of disease progression.

In conclusion, patients with UC may infrequently develop dysplastic changes or invasive malignancy in the ileal pouch. Therefore, a possibility of a neoplastic complication should be kept in mind and these patients should undergo routine endoscopic surveillance. In rare instances, a tumor can show neuroendocrine differentiation. Since these tumors have been published only in a few reports, the outcome of the patients remains uncertain and there is still no clear consensus on the management of these patients or the necessity of eventual surgical intervention.

ACKNOWLEDGEMENTS

We would like to thank Dalibor Drab for reviewing the manuscript.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

REFERENCES

1. **Langholz E, Munkholm P, Davidsen M, Binder V.** Colorectal cancer risk and mortality in patients with ulcerative colitis. *Gastroenterology* 1992; 103(5): 1444-1451.
2. **Bach SP, Mortensen NJ.** Ileal pouch surgery for ulcerative colitis. *World J Gastroenterol* 2007; 13(24): 3288-3300.
3. **Grieco MJ, Remzi FH.** Surgical Management of Ulcerative Colitis. *Gastroenterol Clin North Am* 2020; 49(4): 753-768.
4. **Bulow S, Bulow C, Vasen H, Jarvinen H, Bjork J, Christensen IJ.** Colectomy and ileorectal anastomosis is still an option for selected patients with familial adenomatous polyposis. *Dis Colon Rectum* 2008; 51(9): 1318-1323.
5. **Das P, Smith JJ, Tekkis PP, Heriot AG, Antropoli M, John Nicholls R.** Quality of life after indefinite diversion/pouch excision in ileal pouch failure patients. *Colorectal Dis* 2007; 9(8): 718-724.

6. **Um JW, M'Koma AE.** Pouch-related dysplasia and adenocarcinoma following restorative proctocolectomy for ulcerative colitis. *Tech Coloproctol* 2011; 15(1): 7-16.
7. **Resnick M, Pricolo V, Chen S.** Carcinoid tumor of the ileoanal pouch in a patient with ulcerative colitis. *R I Med J* 2013; 96(1): 30-31.
8. **Al-Khyatt W, Abercrombie JF.** Carcinoid tumour complicating a restorative ileo-anal pouch for ulcerative colitis. *Colorectal Dis* 2013; 15(1): e62-63.
9. **Parpounas C, Richards B, Kourounis G, Poullou C, Tekkis P, Georgiou C.** Carcinoid tumor on ileo-anal pouch. *Ann Surg Case Rep* 2018; 1(1): 1002.
10. **Grassia R, Bodini P, Dizioli P, et al.** Neuroendocrine carcinomas arising in ulcerative colitis: coincidences or possible correlations? *World J Gastroenterol* 2009; 15(33): 4193-4195.
11. **Barsouk A, Rawla P, Barsouk A, Thandra KC.** Epidemiology of cancers of the small intestine: trends, risk factors, and prevention. *Med Sci (Basel)* 2019; 7(3): 46.
12. **Scherubl H, Schwertner C, Steinberg J, et al.** Neuroendocrine tumors of the small bowels are on the rise: early tumors and their management. *Z Gastroenterol* 2010; 48(3): 406-413.
13. **Modlin IM, Kidd M, Latich I, Zikusoka MN, Shapiro MD.** Current status of gastrointestinal carcinoids. *Gastroenterology* 2005; 128(6): 1717-1751.
14. **Strosberg J, Gardner N, Kvols L.** Survival and prognostic factor analysis of 146 metastatic neuroendocrine tumors of the mid-gut. *Neuroendocrinology* 2009; 89(4): 471-476.
15. **Bernick PE, Klimstra DS, Shia J, et al.** Neuroendocrine carcinomas of the colon and rectum. *Dis Colon Rectum* 2004; 47(2): 163-169.
16. **Eaden JA, Abrams KR, Mayberry JF.** The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut* 2001; 48(4): 526-535.
17. **Wong NA, Harrison DJ.** Colorectal neoplasia in ulcerative colitis-recent advances. *Histopathology* 2001; 39(3): 221-234.
18. **Greenstein AJ, Balasubramanian S, Harpaz N, Rizwan M, Sachar DB.** Carcinoid tumor and inflammatory bowel disease: a study of eleven cases and review of the literature. *Am J Gastroenterol* 1997; 92(4): 682-685.
19. **Le Marc'hadour F, Bost F, Peoc'h M, Roux JJ, Pasquier D, Pasquier B.** Carcinoid tumour complicating inflammatory bowel disease, A study of two cases with review of the literature. *Pathol Res Pract* 1994; 190(12): 1185-1192; discussion 1193-1200.
20. **Sigel JE, Goldblum JR.** Neuroendocrine neoplasms arising in inflammatory bowel disease: a report of 14 cases. *Mod Pathol* 1998; 11(6): 537-542.
21. **Scarpa M, van Koperen PJ, Ubbink DT, Hommes DW, Ten Kate FJ, Bemelman WA.** Systematic review of dysplasia after restorative proctocolectomy for ulcerative colitis. *Br J Surg* 2007; 94(5): 534-545.
22. **Kariv R, Remzi FH, Lian L, et al.** Preoperative colorectal neoplasia increases risk for pouch neoplasia in patients with restorative proctocolectomy. *Gastroenterology* 2010; 139(3): 806-812, 812.e801-802.
23. **Remzi FH, Fazio VW, Delaney CP, et al.** Dysplasia of the anal transitional zone after ileal pouch-anal anastomosis: results of prospective evaluation after a minimum of ten years. *Dis Colon Rectum* 2003; 46(1): 6-13.
24. **Veress B, Reinholt FP, Lindquist K, Lofberg R, Liljeqvist L.** Long-term histomorphological surveillance of the pelvic ileal pouch: dysplasia develops in a subgroup of patients. *Gastroenterology* 1995; 109(4): 1090-1097.
25. **Shen B, Fazio VW, Remzi FH, et al.** Risk factors for diseases of ileal pouch-anal anastomosis after restorative proctocolectomy for ulcerative colitis. *Clin Gastroenterol Hepatol* 2006; 4(1): 81-89; quiz 82-83.