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CASE REPORT

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Case report: Coexistence of rectal signet ring cell carcinoma with neuroendocrine components

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Abstract

Background Signet ring cell carcinoma is a rare histological type among the various forms of colorectal cancers. Even rare is when it coexisted with neuroendocrine components in one tumor. To date, there is little literature reported case of colorectal cancer diagnosed as signet ring cell carcinoma with neuroendocrine components.

Case presentation This report presents a unique case manifested as obstructed defecation for more than one month but with negative endoscopic biopsies. Laparoscopic abdominoperineal resection was performed. Based on the postoperative pathology, the patient was finally diagnosed as signet ring cell carcinoma with neuroendocrine differentiation among poorly differentiated adenocarcinoma.

Discussion and conclusions We highlight the rare coexistence of signet ring cell carcinoma and neuroendocrine differentiation in this case. We also emphasize the special characteristic of intramural growth without penetrating the mucosa in signet ring cell carcinoma, further to pose the pitfalls and share lessons during our diagnosis and treatment process.

Keywords Signet ring cell carcinoma, Neuroendocrine differentiation, Low rectal cancer, Biopsy, Laparoscopic abdominoperineal resection

Introduction

Colorectal cancer (CRC) is the third most prevalent cancer and ranks as the second common cause of cancer-related death in the world [1]. Adenocarcinoma represents the most common histologic subtype of CRC [2]. The presence of adenocarcinoma mixed with other types of CRC in one tumor is rare.

Primary signet ring cell carcinoma (SRCC) is more likely to be seen in the stomach, with the typical characteristic of "signet rings" as the nucleus are pushed to the cell periphery by a large amount of intracytoplasmic mucin. Colorectal SRCC is a very rare type accounting for less than 1% of all CRC types and about 1.39% of rectal cancers [3, 4]. It is almost always diagnosed at an advanced stage and correlated with poor prognosis, as compared with conventional adenocarcinoma [5, 6]. According to the World Health Organization (WHO) classification, SRCC are defined as having more than 50% signet ring cells [7]. However, tumors with less than 50% signet ring cells are classified as having signet ring cell components (SRCc). Both SRCC and SRCc are correlated

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with aggressive features, advanced stages and peritoneal metastases [8].

Neuroendocrine differentiation (NED) has been observed in several cancers of non-neuroendocrine organs, including gastrointestinal cancers [9]. Studies have suggested that the CRC containing more than 2% but less than 25% neuroendocrine components should be defined as CRC with NED [10]. NED has been regarded as an independent prognostic marker in CRC of stage III and IV, and was often found in poorly differentiated colorectal cancer [11]. However, some other studies suggested that NED had little influence on patients' survival [12–14]. The ability of NED to predict long term outcomes in CRC is still controversial and needs to be further discussed.

SRCC with NED has been reported in several malignant tumors of the ampulla of Vater [15], stomach [16], endocervix [17] and ovary [18]. To our knowledge, there is little literature reported case of CRC diagnosed as SRCC with NED. We aim to unmask the pitfalls and provide a reference in diagnosis and treatment of such case, and further improve our understanding of biological behaviors and clinicopathological features of these mixed tumors.

Case presentation

A 69-year-old female patient presented to our hospital in July 2023, complaining of having difficulty in defecation for more than one month. She had presented with the sensation of rectal obstruction, passage of hard stools and reduced stool frequency. She denied any history of drinking, smoking or other concomitant diseases. There is no history of cancer or other related diseases.

Before her admission at our hospital, she was admitted to local hospital and took a series of examinations. The colonoscopy suggested a rectal stricture and obstruction in the lower rectum (Fig. 1A, B). An endoscopic biopsy was performed for the rectal mass, and the pathological histology revealed intestinal mucosal atrophy with interstitial hemorrhage. The second endoscopic biopsy again revealed negative histopathology. In the enhanced CT and MRI examination, the tumor presented as a circular wall thickening that located in the lower rectum below the level of the anterior peritoneal reflection (Fig. 2A, B). There were no suspicious regional lymph nodes and involved vessels in vicinity of tumor on the MRI report.

At our hospital, we did a digital rectal examination and found that the tumor was about 2 cm distance from the anal edge, with no blood found on the finger pad. Routine blood tests showed that the patient had leukopenia (white blood cell count 2.93×10^9 cells/L). The test of tumor markers revealed increase in carcinoembryonic antigen (CEA, 24.81ng/ml; normal value (n.v.), <5.00ng/ml), squamous cell carcinoma (SCC, 2.51ng/ml; n.v., <1.50 ng/ml), carbohydrate antigen (CA)-242 (17 IU/ml; n.v., <10.0 IU/ml), and CA-724 (30.6 IU/ml; n.v., <6.00 IU/ml). Other laboratory examinations showed no significant abnormalities. Thus, based on the patient's chief complaint, the physical examination, the results of laboratory examinations, and the imaging reports, a clinical diagnosis of rectal carcinoma was made. However, it still remains challenging to make subsequent therapeutic strategy in the absence of the histopathological diagnosis.

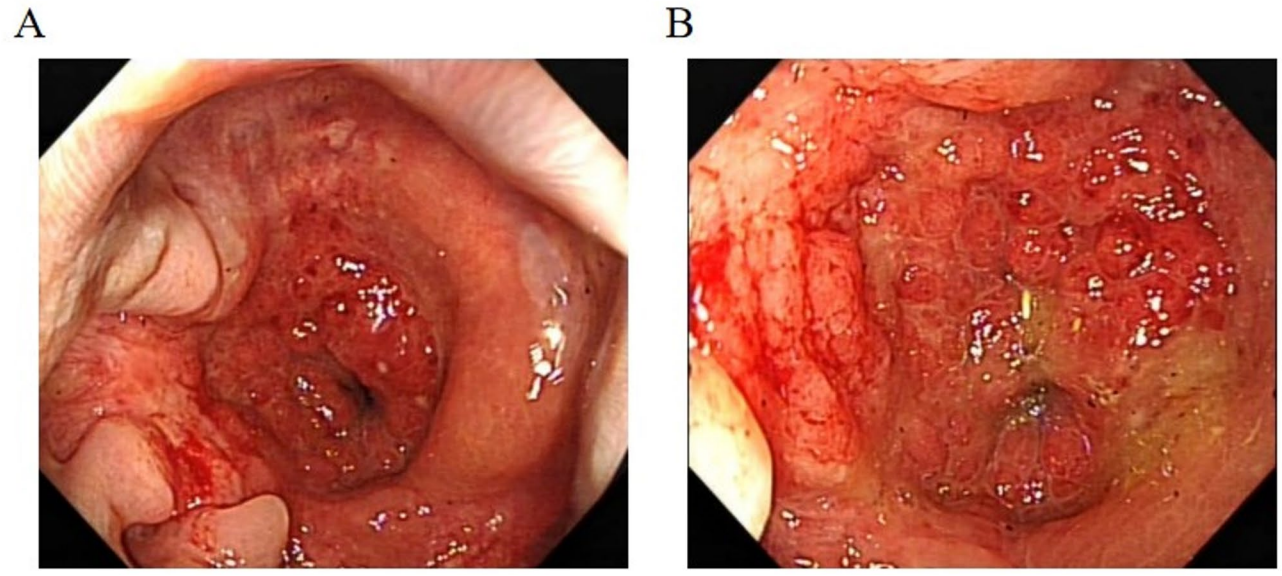

Fig. 1 **A**, **B**. Endoscopic appearance of the patient before surgery. Colonoscopy showed that the intestinal lumen was apparently narrowed in the lower rectum

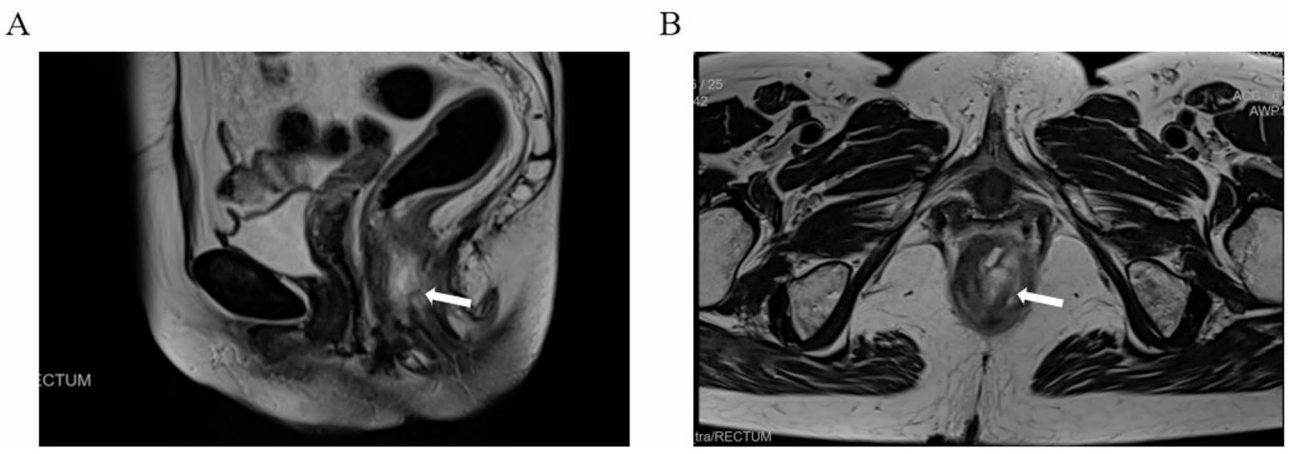

Fig. 2 **A**, **B**. MRI examination of the patient. The tumor (arrow) presented as a circular wall thickening that is located in the lower rectum below the level of the anterior peritoneal reflection

Considering that no tumor cells were found in the two previous endoscopic biopsies, ultrasound-guided biopsy of the mass was finally performed on the patient. The pathological report concluded poorly differentiated AC with partial cells signet ring changes.

We didn't apply neoadjuvant therapy to treat the patient, given that her symptoms of intestinal obstruction showed no significant improvement following conservative treatment, with pronounced abdominal pain and distention, and lack of flatus. The patient then underwent laparoscopic abdominoperineal resection. Macroscopically, the tumor was 4.6*4.0*1.5 cm in size, and was about 2 cm distance from the anal edge. Histopathological examination confirmed that it was a signet ring cell carcinoma with neuroendocrine differentiation among poorly differentiated adenocarcinoma. Signet ring cells occupies>60% of the whole tumor (Fig. 3A). The tumor invaded subserosa, with a depth <5 mm to the serosa. Signet ring cell components were identified in the metastatic lymph nodes (10/14) around the intestinal segment. No cancer cells were found in the cutting edge of the specimen. The followed immunohistochemical staining showed MLH (+), MSH2 (+), MSH6 (+) and PMS2 (+), suggesting mismatch repair proficient (pMMR). Ki-67 proliferation index was 80%. In addition, about 20% cells were positive for Syn and CgA, which indicated that it owned a neuroendocrine component (Fig. 3B, C). Both preoperative chest and abdominal CT scans, combined with intraoperative laparoscopic exploration findings, revealed no evidence of distant tumor metastasis. Consequently, the patient was pathologically staged as $pT_3N_2M_0$ according to the AJCC/UICC TNM classification system. The patient was discharged 10 days after surgery, and received the first XELOX chemotherapy one month later. Unfortunately, the patient was lost to follow-up due to self-reported intolerance to chemotherapy, resulting in discontinuation of further therapeutic interventions at our center.

Discussion and conclusion

The presence of signet ring cells in CRC has been reported to associate with aggressive behavior [8]. A number of studies have shown that colorectal patients with any components signet ring cells, regardless of the extent (<50% or>50%), shared similar clinicopathological features, had poor prognosis, and should be given significant attention [8, 19–21]. It was reported in a retrospective study ($N=170$) that 91.2% of patients with colorectal SRCC were already in stage III and IV at diagnosis [22]. In a population-based study ($N=1972$), SRCC had a worse 5-year survival of 19.5% in the rectum compared with 58.5% for conventional AC [23].

Unlike the intraluminal mass in traditional AC, the patient with SRCC in this case manifests as having a prominent rectal wall thickening and an obvious lumen stenosis. Unexpectedly, two endoscopic biopsies revealed negative results, making it difficult to diagnose. Similarly, in a case control study reported by Wen et al.., most colorectal cancer cases (93.1%) in control group (non-SRCC) were diagnosed through endoscopic biopsy, whereas 4 of SRCC patients (22.2%) ever received endoscopic biopsy failed to identify malignant cells [24]. Likewise, in a recently published case of colorectal SRCC, a patient manifested as recurrent intestinal obstruction underwent a colonoscopy during his first hospitalization, the endoscopic images suggested ileocecal intraluminal stricture while the endoscopic biopsies revealed negative histopathology [25]. He was readmitted a month later with worsening symptoms of intestinal obstruction, and finally diagnosed with SRCC of the colon by postoperative pathology. Also difficult in diagnosis and differential diagnosis is colorectal lymphoma, which is an extremely

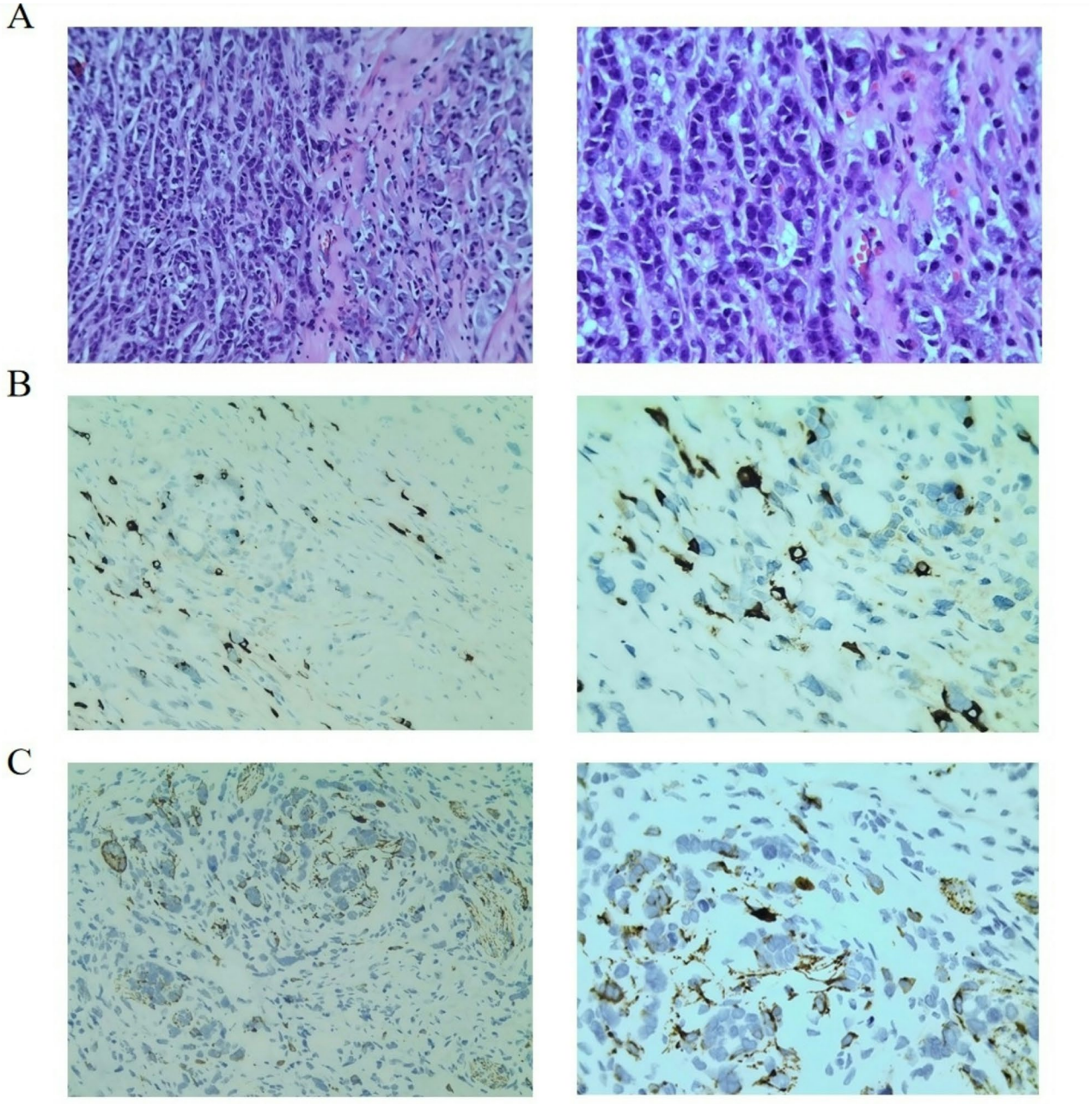

Fig. 3 **A**, **B**, **C**. Histopathology of surgical specimens. Postoperative histopathology showed SRCC with NED among poorly differentiated AC in the rectum. HE staining showed SRCC (**A**). Immunohistochemistry staining showed CgA (**B**) and Syn (**C**) positive in partial (about 20%) tumor cells. Pictures were magnified ×200 on the left, and ×400 on the right

rare disease. Most patients with colorectal lymphoma have non-typical symptoms or negative biopsies [26]. Thus, as such tumor has a special feature of intramural growth and is often difficult to differentiate from inflammatory processes [25, 27], comprehensive assessment of diagnostic methods and timely surgical intervention are necessary to avoid misdiagnosis or delaying treatment.

Some studies have shown that patients of CRC with NED tended to have higher incidence of metastasis and worse prognosis [28–31]. Though the biological mechanisms remain unclarified. Song et al. compared the difference among colorectal adenocarcinoma, neuroendocrine carcinoma (NEC), mixed adenoendocrine carcinoma (MANEC), and adenocarcinoma with NED (ANED) [32]. He found that MANEC and ANED could be grouped together by reason of their similar clinicopathological characteristics and survival. The prognosis of ANED/MANEC was the poorest, compared to AC and NEC. In

terms of therapy, surgery was conducive to improve the prognosis of the ANED/MANEC patients with stage IV, while chemotherapy was advantageous for the prognosis of the patients with stage III/IV [32]. Another previous study had suggested that the neuroendocrine phenotype was correlated with increased chemosensitivity in colorectal cell lines [33]. However, an effective and normative therapeutic strategy has not been established so far to treat colorectal ANED [34]. Further explorations are required in this area.

NED is not a rare event in poorly differentiated CRC [9]. However, it is rare when it co-existed with signet ring cell components. Previously, signet ring cells in gastric carcinomas have been suggested to be of neuroendocrine origin, as a high proportion of these cells express specific neuroendocrine markers, such as synaptophysin and CgA [16, 35]. However, there is scant literature that reported an association between NED and SRC in CRC, which need further investigation. SRCC with NED has been classified as goblet cell carcinoid (GCC) in some case reports [36–38], which is a rare mixed endocrine-exocrine neoplasm that usually arises in the appendix [39]. GCC is categorized as a neuroendocrine tumor in the WHO classification. However, compared to typical neuroendocrine tumors, GCC exhibits more aggressive biological behavior, and is more similar to adenocarcinomas [40].

In this case, we have reported a rare composite tumor in CRC that combine signet ring cell and neuroendocrine components. It presented the special characteristic of intramural tumor growth of SRCC. It gives us a lesson that we need to adjust our diagnostic strategy timely to avoid missed diagnosis and misdiagnosis when we meet patients who present with obstructed defecation but with negative endoscopy biopsy. Several limitations should be acknowledged in this case report. Firstly, due to the patient's financial situation and personal preferences, we were unable to utilize emerging immunohistochemical markers for further analysis of the tumor or to perform additional testing on the metastatic tissue at the time. Secondly, the follow-up period for this case was short, without capturing long-term outcomes, recurrence, or late complications. Lastly, as a result of the rarity of this type of tumor, there are no established evidence-based guidelines for its management. Further investigations are required to treat this type of tumor.

Abbreviations

CRC	Colorectal cancer
SRCC	Signet ring cell carcinoma
WHO	World health organization
SRCc	Signet ring cell components
NED	Neuroendocrine differentiation
CEA	Carcinoembryonic antigen
SCC	Squamous cell carcinoma
CA	Carbohydrate antigen
pMMR	Mismatch repair proficient
NEC	Neuroendocrine carcinoma
MANEC	Mixed adenoendocrine carcinoma
ANED	Adenocarcinoma with neuroendocrine differentiation
GCC	Goblet cell carcinoid

Supplementary Information

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Supplementary Material 1

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Author contributions
QW had the original idea for the article and guided treatment for the patient. XBL reevaluated the pathological results and provided figures for this case. QW guided the writing ideas and reviewed the manuscript. LX researched the data and wrote the article. ZH, CF, YW, AW, GT, JH edited the manuscript. All authors contributed to the article and approved the final version.

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Data availability
Data is provided within the manuscript.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Written informed consent was obtained from the patient for publication of this manuscript and images.

Competing interests
The authors declare no competing interests.

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References

1. Siegel RL, Miller KD, Wagle NS, et al. Cancer statistics, 2023 [J]. CA Cancer J Clin. 2023;73(1):17–48.
2. Luo C, Cen S, Ding G, et al. Mucinous colorectal adenocarcinoma: clinical pathology and treatment options [J]. Cancer Commun (Lond). 2019;39(1):13.
3. Nitsche U, Friess H, Agha A, et al. Prognosis of mucinous and signet-ring cell colorectal cancer in a population-based cohort [J]. J Cancer Res Clin Oncol. 2016;142(11):2357–66.
4. Chen J-S, Hsieh P-S, Hung S-Y, et al. Clinical significance of signet ring cell rectal carcinoma [J]. Int J Colorectal Dis. 2004;19(2):102–7.
5. Inamura K, Yamauchi M, Nishihara R, et al. Prognostic significance and molecular features of signet-ring cell and mucinous components in colorectal carcinoma [J]. Ann Surg Oncol. 2015;22(4):1226–35.
6. Psathakis D, Schiedeck TH, Krug F, et al. Ordinary colorectal adenocarcinoma vs. primary colorectal signet-ring cell carcinoma: study matched for age, gender, grade, and stage [J]. Dis Colon Rectum. 1999;42(12):1618–25.
7. Barresi V, Pedrazzani C. Colorectal signet ring cell carcinoma: advancing research in a rare cancer [J]. Future Oncol. 2020;16(17):1161–3.
8. Enblad M, Egerszegi PP, Birgisson H et al. Signet ring cell colorectal and appendiceal cancer: A small signet ring cell component is also associated with poor outcome [J]. Cancers (Basel), 2023;15(9).

9. Chen Y, Liu F, Meng Q, et al. Is neuroendocrine differentiation a prognostic factor in poorly differentiated colorectal cancer? [J]. World J Surg Oncol. 2017;15(1):71.
10. Suresh PK, Sahu KK, Pai RR, et al. The prognostic significance of neuroendocrine differentiation in colorectal carcinomas: our experience [J]. J Clin Diagn Res. 2015;9(12):EC01–4.
11. Shinji S, Naito Z, Ishiwata T, et al. Neuroendocrine cell differentiation of poorly differentiated colorectal adenocarcinoma correlates with liver metastasis [J]. Int J Oncol. 2006;29(2):357–64.
12. Lloyd RV, Schroeder G, Bauman MD, et al. Prevalence and prognostic significance of neuroendocrine differentiation in colorectal carcinomas [J]. Endocr Pathol. 1998;9(1):35–42.
13. Cho YB, Yang SS, Lee WY, et al. The clinical significance of neuroendocrine differentiation in T3-T4 node-negative colorectal cancer [J]. Int J Surg Pathol. 2010;18(3):201–6.
14. Mori M, Mimori K, Kamakura T, et al. Chromogranin positive cells in colorectal carcinoma and transitional mucosa [J]. J Clin Pathol. 1995;48(8):754–8.
15. Fornelli A, Zanini N, De Biase D, et al. Signet ring cell carcinoma of the ampulla of vater with focal neuroendocrine differentiation of the amphicrine type: report of a case with Long-Term survival [J]. Int J Surg Pathol. 2019;27(1):89–93.
16. Bartley AN, Rashid A, Fournier KF, et al. Neuroendocrine and mucinous differentiation in signet ring cell carcinoma of the stomach: evidence for a common cell of origin in composite tumors [J]. Hum Pathol. 2011;42(10):1420–9.
17. Cardosi RJ, Reedy MB, Van Nagell JR, et al. Neuroendocrine signet ring cell adenocarcinoma of the endocervix [J]. Int J Gynecol Cancer. 1999;9(5):433–7.
18. Pongsuvareeyakul T, Charoenkwan K, Suprasert P, et al. Primary signet ring cell carcinoma with neuroendocrine differentiation arising in mucinous borderline tumor of the ovary [J]. Gynecol Oncol Rep. 2020;31:100522.
19. Wei Q, Wang X, Gao J, et al. Clinicopathologic and molecular features of colorectal adenocarcinoma with Signet-Ring cell component [J]. PLoS ONE. 2016;11(6):e0156659.
20. Tan Y, Fu J, Li X, et al. A minor (< 50%) signet-ring cell component associated with poor prognosis in colorectal cancer patients: a 26-year retrospective study in China [J]. PLoS ONE. 2015;10(3):e0121944.
21. Song IH, Hong S-M, Yu E, et al. Signet ring cell component predicts aggressive behaviour in colorectal mucinous adenocarcinoma [J]. Pathology. 2019;51(4):384–91.
22. Tamhankar AS, Ingle P, Engineer R, et al. Signet ring colorectal carcinoma: do we need to improve the treatment algorithm? [J]. World J Gastrointest Oncol. 2016;8(12):819–25.
23. Hugen N, Verhoeven RH, Lemmens VE, et al. Colorectal signet-ring cell carcinoma: benefit from adjuvant chemotherapy but a poor prognostic factor [J]. Int J Cancer. 2015;136(2):333–9.
24. Weng M-T, Chao K-H, Tung C-C, et al. Characteristics of primary signet ring cell carcinoma of colon and rectum: a case control study [J]. BMC Gastroenterol. 2022;22(1):173.
25. Li Y, He G, Zhong R, et al. Case report: intramural colonic signet ring cell carcinoma presenting as intestinal pseudo-obstruction: A case presentation and review of the literature [J]. Front Oncol. 2023;13:1059368.
26. Pyeon SI, Song GA, Baek DH, et al. Primary follicular lymphoma in the rectum incidentally found on screening colonoscopy [J]. Korean J Gastroenterol. 2017;69(2):139–42.
27. Mizushima T, Nomura M, Fujii M, et al. Primary colorectal signet-ring cell carcinoma: clinicopathological features and postoperative survival [J]. Surg Today. 2010;40(3):234–8.
28. Grabowski P, Schindler I, Anagnostopoulos I, et al. Neuroendocrine differentiation is a relevant prognostic factor in stage III-IV colorectal cancer [J]. Eur J Gastroenterol Hepatol. 2001;13(4):405–11.
29. Zeng Y-J, Lai W, Liu L, et al. Prognostic significance of neuroendocrine differentiation in colorectal adenocarcinoma after radical operation: a meta-analysis [J]. J Gastrointest Surg. 2014;18(5):968–76.
30. Liu Y, He J, Xu J, et al. Neuroendocrine differentiation is predictive of poor survival in patients with stage II colorectal cancer [J]. Oncol Lett. 2017;13(4):2230–6.
31. Guo J, Zheng P, Wang R, et al. Prognostic relevance of neuroendocrine differentiation in colorectal cancer: a population-based, propensity score matching study [J]. Int J Colorectal Dis. 2020;35(12):2185–95.
32. Song L-J, Yuan L. Comparative analysis of colorectal mixed adenoneuroendocrine carcinoma and adenocarcinoma with neuroendocrine differentiation: a population-based study [J]. Int J Clin Exp Pathol. 2019;12(3):922–32.
33. Park JG, Oie HK, Sugarbaker PH, et al. Characteristics of cell lines established from human colorectal carcinoma [J]. Cancer Res. 1987;47(24 Pt 1):6710–8.
34. Kakuta S, Takayama W, Kou T, et al. A case of descending Colon adenocarcinoma with neuroendocrine differentiation successfully treated with FOLFIRI plus bevacizumab [J]. Gan Kagaku Ryoho. 2016;43(1):129–32.
35. Bakkelund K, Fossmark R, Nordrum I, et al. Signet ring cells in gastric carcinomas are derived from neuroendocrine cells [J]. J Histochem Cytochem. 2006;54(6):615–21.
36. Yamabuki T, Omi M, Yonemori A, et al. Goblet cell carcinoid of the rectum with lymph node metastasis: report of a case [J]. Surg Today. 2011;41(9):1284–9.
37. Inoue Y, Horie H, Homma Y, et al. Goblet cell carcinoid of the rectum: a case report [J]. Surg Case Rep. 2020;6(1):174.
38. Wakahara T, Yamamoto S, Fujita S, et al. A case of advanced rectal adenocarcinoid tumor with long-term survival [J]. Jpn J Clin Oncol. 2010;40(7):690–3.
39. Roy P, Chetty R. Goblet cell carcinoid tumors of the appendix: an overview [J]. World J Gastrointest Oncol. 2010;2(6):251–8.
40. Jiang Y, Long H, Wang W, et al. Clinicopathological features and Immunoexpression profiles of goblet cell carcinoid and typical carcinoid of the appendix [J]. Pathol Oncol Res. 2011;17(1):127–32.

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