The primary goblet cell adenocarcinoma of the rectum: A Case Report

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Case Report

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Abstract

Goblet cell adenocarcinoma (GCA) is a rare tumor, and it is characterized by its unique combination of neuroendocrine and adenocarcinoma. GCA occurs mainly in the appendix. Currently, there is no primary GCA of the rectum in the 2019 World Health Organization classification of colorectal tumors. Here, we report a case of the primary GCA of the rectum that combined examinations via histological morphology, immunohistochemistry, transmission electron microscopy (TEM), and molecular detection. We demonstrate that this tumor is the primary rectum GCA for the first time worldwide. Our work will help to improve the diagnosis of the primary GCA of the rectum and avoid misdiagnosis and mistreatment.

1. Introduction

Goblet cell adenocarcinoma (GCA) was first reported in 1969, and it had unique mixed endocrine-exocrine features [1]. GCA occurs mainly in the appendix. GCA is derived from undifferentiated stem cells and it is different from typical carcinoids [2]. GCA is more aggressive than typical carcinoid. The median age of onset of GCA is 59 years and there is no significant gender disparity [3]. It is mainly composed of goblet-like cells, neuroendocrine cells, and Paneth-like cells [4]. GCA is positive immunoreactivity for the CK20, CDX2, Syn, SSTR2, and CD56 in the same cell [5, 6]. However, recent molecular studies have proved that their biology is quite different from classic neuroendocrine tumors and adenocarcinoma [7, 8]. The most commonly mutated genes include ERBB2, ARID, as well as in Wnt pathway genes in GCA [8]. However, no colorectal adenocarcinoma-associated gene mutations were discovered in the primary GCA, such as BRAF, KRAS, NRAS, APC [8].

Currently, there is no primary GCA of the rectum in the 2019 World Health Organization classification of colorectal tumors. In our case, we describe the histopathology of an unusual primary GCA of the rectum. We demonstrate that this tumor is the primary GCA of the rectum via histological morphology, immunohistochemical, transmission electron microscopy, and gene analysis for the first time.

2. Case Report

A 73-year-old Chinese woman presented with hematochezia without obvious inducement, accompanied by mucus, about twice a day, for 24 days, and she denied the family genetic history. Pelvic magnetic resonance imaging (MRI) scan showed a tumor in the lower rectum. Abdominoperineal combined rectum resection was carried out. The size of the tumor was 3.2cm×6.5cm×1.8cm, and the section was grey-white occupying the entire circumference of the rectum (Fig. 1-A). No other organs were involved by the tumor. Histopathologic evaluation showed a malignant neoplasm is mainly composed of goblet-like cells with rich mucus in the cytoplasm, neuroendocrine cells, and Paneth-like cells. The tumor cells arranged as the nest and sieve shapes (Fig. 1-B). The tumor was located in the lower segment of the rectum and infiltrated into presentational adipose tissue. Histological grade: G3, poorly differentiated. Tumor

budding: a high score. Lymph node metastasis: 2/20. These tumor cells showed venous invasion and perineural invasion.

Immunohistochemical staining was performed with the MXB biotechnology kit. The tumor cells were positive for CK20, CDX2, SSTR2, Syn, CD56, E-cad, Ki-67 (60%+), P53(80%+, mutant), and negative for MMR by immunohistochemistry. D-AB/PAS staining showed that PAS was positive for mucus in tumor cells, occasional AB was positive for mucus (Fig. 2). Transmission electron microscopy **(TEM)** was performed in our work. The neuroendocrine granules and mucous vesicles were observed in the same goblet-like cell of the tumor tissue under TEM. The results confirmed that this tumor is the GCA**(**Fig. 2**).**

Paraffin-embedded sections were subjected to comprehensive next-generation sequencing (**NGS**) analysis with 437 predefined cancer-related genes. Enriched libraries were sequenced on the HiSeq4000 platform (Illumina). Data were analyzed by an effective bioinformatics process. Germline mutations were filtered out by comparing to patient's whole blood controls. The detection results included point mutation, small fragment insertion-deletion mutation, gene fusion, copy number variation, MSI, and tumor mutational burden. In our case, NGS detected an ERBB2 missense mutation, c.929C > T (p.S310F). The mutation was involved in tumorigenesis, increased susceptibility to ERBB inhibitors, and was likely pathogenic. A TP53 missense mutation, c.581T > G (p.L194R) was detected and it was pathogenic. A CTCF Shearing mutation, c.1999 + 1G > A was detected and it was likely pathogenic. A PBRM1 missense mutation, c.1449G > C (p.K483N), was detected, but the significance was unclear. The significance of BCR missense mutation, c.3361G > A (p.V1121M) was unclear. These results were supportive of the GCA. Our NGS test included the whole transcriptome sequencing, but no mutations were detected in *MSI, KRAS, NRAS, BRAFV600E, PDGFRA, KIT, and NTRK*. No germline mutation was detected in her family.

The above test results showed that this primary tumor of the rectum was different from the adenocarcinoma and neuroendocrine tumor. The treatment of advanced primary GCA of the rectum is also different from adenocarcinoma and neuroendocrine tumors and affects the prognosis and survival of patients. In our case, the primary GCA of the rectum infiltrated perirectal tissue but did not involve other organs. The tumor stage was pT4bN1bMx in our case. Abdominoperineal combined rectum resection was performed. The patient received radiotherapy and chemotherapy, and her condition was stable in the 6-month follow-up. Therefore, an accurate and standardized pathological diagnosis of the primary GCA of the rectum is very important for the treatment. Our work will help to improve the diagnosis of the primary GCA of the rectum and avoid misdiagnosis and mistreatment.

3. Discussion

GCA mainly involves the appendix, but rarely occurs in the rectum, ileum, and colon [9]. The staging of GCA is similar to adenocarcinomas because it is more aggressive than NET [10]. Most of the patients at the time of diagnosis already have advanced-stage disease. The most common metastatic regions are the peritoneal surfaces of the pelvis, abdominal cavity, and ovaries [11]. Patients with GCA of the rectum

have a prognosis intermediate between carcinoid and adenocarcinoma [11]. Therefore, early and accurate diagnosis has a great significance for the prognosis of patients.

Pathologists particularly need to distinguish the primary GCA of the rectum from the following similar tumors. We know that adenocarcinoma in the stomach also can have a mutation in ERBB2. When distinguishing the GCA from signet-ring cell carcinomas in the stomach, the following aspects must be considered. Histologically, signet-ring cell carcinomas usually originate from rectal mucosa and do not have any neuroendocrine granules in the cytoplasm. Immunohistochemically, signet-ring cell carcinomas do not express neuroendocrine markers (Syn, CgA, CD56). At the molecular level, the GCA is usually free of KRAS, NRAS, BRAF(V600E) mutations [12]. Adenocarcinoma in the rectum usually has a TP53 mutation but does not express neuroendocrine markers. Carcinoid usually doesn't have goblet-like cells and there is no mutation in ERBB2. Clear cell carcinoid with clear cytoplasm has a foamy cytoplasmic appearance, but intracytoplasmic mucin usually is absent. This tumor does not express CK20, CDX2 and the D-AB/PAS staining is negative [11]. Classic carcinoid (lipid-rich variant) usually has a classic nested or trabecular neuroendocrine pattern. The tumor cells express Syn and SSTR2 but do not express CDX2 and CK20 [13]. Our work has two limitations. Firstly, no germline mutation was detected in her family in our case. Second, we report one case of GCA, which cannot cover all situations. However, we demonstrate that this tumor is the GCA via the histological morphology, immunohistochemistry, transmission electron microscopic, and gene analysis for the first time. Identification of more cases of the primary GCA of the rectum will help to improve the diagnosis of rectal tumors and avoid mistreatment. Our work plays an important role in guiding the treatment and it is important for the prognosis of patients.

4. Conclusion

We have confirmed that this tumor is the primary GCA of the rectum for the first time, which will help to improve the diagnosis and avoid mistreatment. Early and accurate pathological reports and adequate treatment are key for the achievement of longer overall survival.

Declarations

Ethics Statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author Contributions

The first author (RR, F) wrote and edited the final manuscript and performed the lab work. The co-first author (J, G) performed the lab work. The second author (DH, Z) and the third author (XY, F) provided the case clinical information. The corresponding author (MZ, L) guides the manuscript writing.

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Conflicts of interest

The authors declare that they have no conflict of interest in this case report.

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Figures

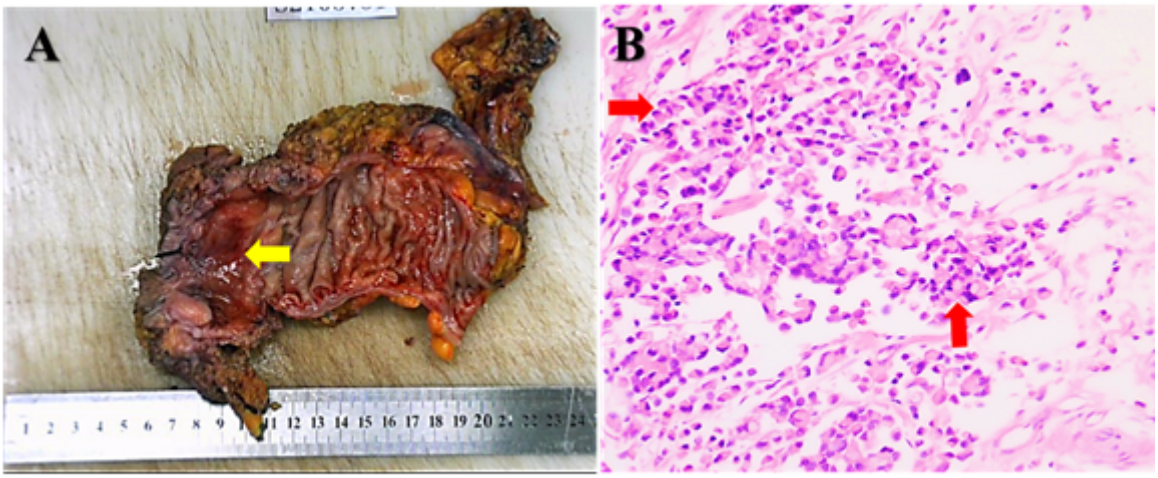

Figure 1

(A) Gross specimens of the rectum and tumor (**yellow arrow**). **(B)** HE pictures of the tumor. The tumor is mainly composed of goblet-like cells with abundant mucus in the cytoplasm (**red arrow**), neuroendocrine cells, and Paneth-like cells. These tumor cells arranged as nest and sieve shapes.

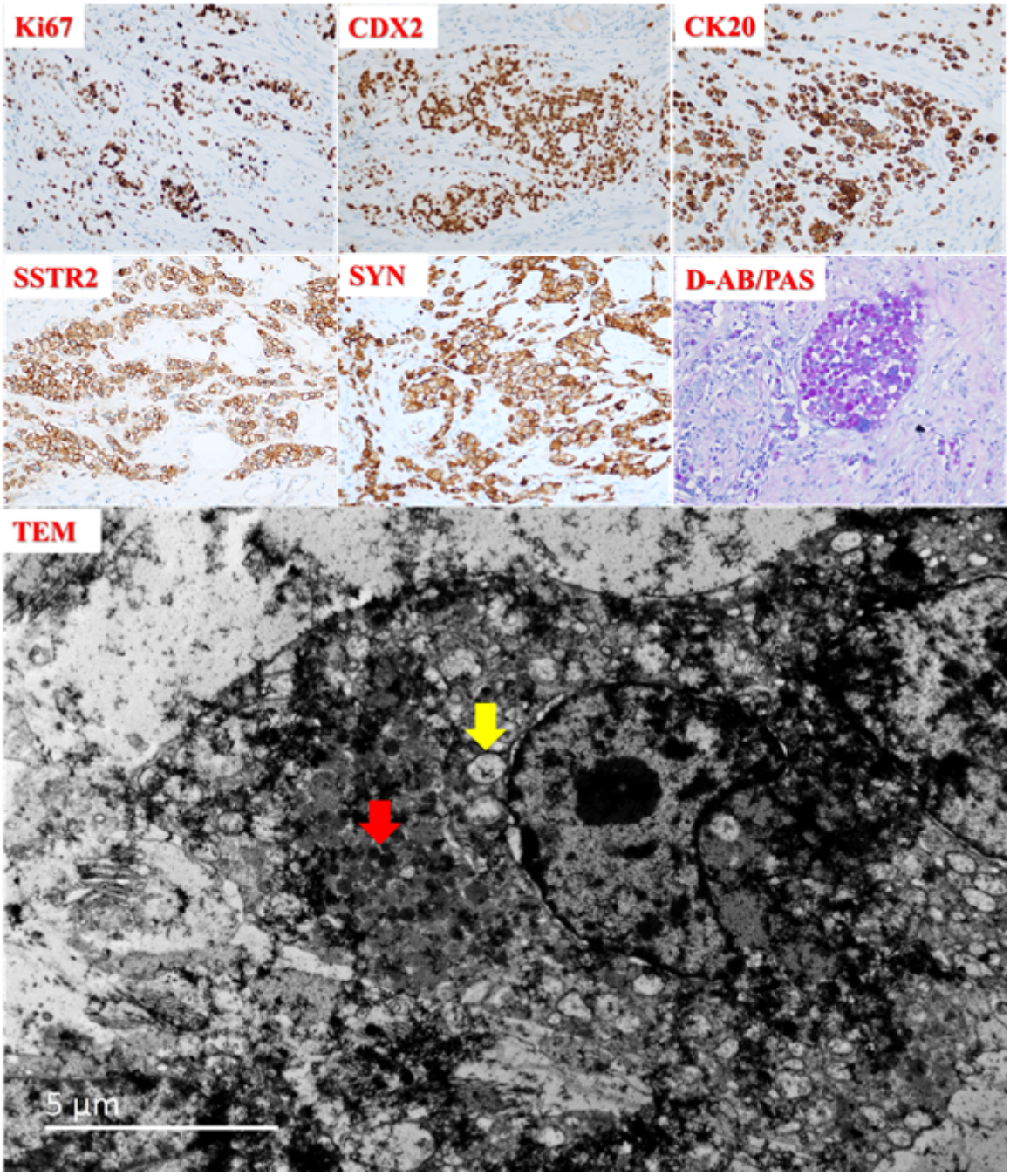

Figure 2

Immunohistochemical staining results showed that the Ki-67 proliferation marker had a high percentage (60%) of cell staining, CK20, CDX2, SSTR2, and SYN were expressed, and D-AB/PAS staining showed that PAS was positive for mucus in tumor cells, occasional AB was positive for mucus. The neuroendocrine granules (**red arrow**) and mucous vesicles (**yellow arrow**) were observed in the same tumor cell under **TEM** (**Below**).