

Infiltrating Ductal Breast Carcinoma Metastasized to the Rectum: A Case Report and a Review of the Literature

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Case report

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Abstract

BACKGROUND:

Gastrointestinal (GI) metastasis in breast cancer (BC) is uncommon, although in the rare cases when it occurs, infiltrating lobular carcinoma is the most commonly reported pathological subtype. Nonetheless, gastrointestinal metastasis from infiltrating ductal breast carcinoma is extremely rare and usually occurs several years after the appearance of the primary tumor. The present study was, to the best of our knowledge, the first one to present a case of distal rectum metastasis originating from infiltrating ductal breast carcinoma.

CASE PRESENTATION:

The present report discusses the case of a Chinese female patient aged 37 years. The patient presented with diarrhea along with bloody stools and anal bearing-down pain. Earlier in 2015, she had undergone axillary lymph node dissection (LND) and right modified radical mastectomy in another hospital to treat the infiltrating ductal breast carcinoma pT1N1M0. The presented symptoms were investigated by performing colonoscopy, which indicated lower rectal swelling at 3 cm on the top of the anal verge. Further investigation with positron emission tomography-computed tomography (PET-CT) revealed an uptake of fluorodeoxyglucose (FDG) within the distal rectum as well as in the left acetabulum. The samples from laparoscopic exploration were biopsied, which revealed metastases of breast cancer. Therefore, the patient was intraoperatively diagnosed with the rectal metastasis of BC and was treated with laparoscopic radical abdominoperineal resection. Furthermore, the immunohistochemical analysis of the tumor confirmed that the patient had the rectal metastasis of infiltrating ductal BC.

CONCLUSION:

Rectal metastasis should be considered when breast cancer patients present with a complaint of changed bowel habits, even for those with a history of ductal breast cancer.

Background:

Breast cancer (BC) is a frequently occurring cancer among women, which also leads to morbidity and mortality^[1]. Approximately 60% of the BC cases have distant metastasis (DM) or lymph metastasis at the time of diagnosis, while 30–80% of the BC cases are diagnosed with metastases after chemotherapy and/or surgery, endocrine therapy, or radiotherapy^[2]. BC generally metastasizes in the brain, liver, lung, and skeleton. Ductal BC usually spreads to the bone, lung, and liver, while lobular cancer has a distinct metastatic pattern with a frequent occurrence in the gastrointestinal (GI) tract^[3–6]. The GI metastasis of BC is uncommon, and in the rare cases reported, the most common pathological subtype is the infiltrating lobular carcinoma. GI metastasis of infiltrating ductal BC presents further lower morbidity, which generally occurs several years after the appearance of the primary tumor. The present report discusses the case of a Chinese woman aged 37 years who presented with bloody stools and diarrhea and was

diagnosed with rectal metastases of infiltrating ductal BC. In addition, a review of the literature published in the English language is also presented.

Case Presentation:

A 37-year-old Chinese woman presented with a complaint of frequent diarrhea, over 6 times a day, along with bloody stools and anal bearing-down pain. The symptoms had appeared two months earlier and had progressively worsened within two weeks, which had led to hospitalization for a complete medical examination.

History of past illnesses:

In 2015, the patient had undergone axillary lymph node dissection (LND) and right modified radical mastectomy in another hospital for the treatment of infiltrating ductal breast carcinoma pT1N1M0. Her histopathological examination had revealed an infiltrating ductal BC that was 1.5 cm in size and at the histological grade 2. Moreover, among the 20 lymph nodes resected, 4 nodes were infiltrated with cancer cells. The immunohistochemistry staining had revealed a positive estrogen receptor (ER) rate of 70%, a positive progesterone receptor (PR) rate of 70%, and a positive Ki-67 rate of 15–30%. Furthermore, the human epidermal growth factor receptor 2 (Her-2) was negative and the E-cadherin positive (Fig. 1). DM was not detected at the time of diagnosis. Postoperatively, the patient underwent 6 cycles of adjuvant chemotherapy (TAC protocol), followed by an endocrine therapy with tamoxifen (a daily dose of 20 mg). The patient had deliberately discontinued the endocrine therapy one year after.

Physical examination:

The patient's vital signs were as follows: body temperature, 36.3°C; heart rate (HR), 74 beats/min; blood pressure (BP), 116/76 mm Hg; respiratory rate (RR), 15 breaths/min; and in-room oxygen saturation, 100%. Abdominal examinations revealed no obvious abnormality. However, in the digital rectal examination, a tumor with a smooth surface was detected at the knee-chest position, which was located 3 cm above the anal edge. It was a circumferential tumor with swelling. The tumor root could not be moved with palpation. No pus or dark-red blood residue was observed on the glove after the rectal examination.

Laboratory examinations:

Results of routine laboratory tests were relatively normal. Blood analysis revealed no abnormality in any of the blood counts. The white blood cell (WBC) count was 5.9×10^9 cells/L (normal limit: $3.5\text{--}9.5 \times 10^{12}$ cells/L), the red blood cell (RBC) count was 4.27×10^{12} cells/L (normal limit: $3.80\text{--}5.10 \times 10^{12}$ cells/L), and the platelet (PLT) count was 313×10^9 cells/L (normal limit: $125\text{--}350 \times 10^9$ cells/L). However, both carbohydrate antigen 125 and carbohydrate antigen 153 were slightly elevated, with values of 41.10 U/mL (normal range: 0–35 U/mL) and 36.80 U/mL (normal range: 0–31.3 U/mL), respectively.

Imaging examinations:

Colonoscopic examination revealed a lower rectal swelling with a smooth and red surface, located at 3 cm on the top of the anal verge, which was suggestive of a submucosal tumor (Fig. 2C). Therefore, multiple biopsies of the tumor were performed, which detected no malignancy. The patient was recommended to undergo positron emission tomography-computed tomography (PET-CT) for further investigation, which revealed an uptake of fluorodeoxyglucose (FDG) within the left acetabulum and distal rectum, with the maximal standardized uptake (SUVmax) values of 5.5 and 11.2, respectively, suggesting suspicious metastasis at these positions (Fig. 2A and 2B).

Final Diagnosis:

In the laparoscopic exploration, a circumferential tumor was detected in the distal rectum, following which a biopsy of the tumor was performed, which revealed no peritoneal dissemination. Fast frozen pathology of the specimen revealed that the tumor was morphologically consistent with ductal breast carcinoma and that nests of tumor cells extensively infiltrated the muscular layer. Tumor cells were detected progesterone receptor-(PR) and estrogen receptor-(ER) positive, with a positivity rate of 90% for both (Fig. 3B-3D). In contrast, the background rectum epithelial cells tested PR-and ER-negative. Since the concerned case had ductal BC, she was intraoperatively diagnosed with BC rectal metastasis. Therefore, a radical abdominoperineal resection was performed laparoscopically. The surgically dissected rectal lesion revealed a neoplasm in the submucosal layer, while no abnormality was observed in the mucosal layer. The size of the neoplasm was 3 cm in the lengthwise direction (Fig. 3A). Further immunohistochemical analysis of the tumor-infiltrating part was performed, and the results confirmed this rare metastasis. In addition, the tumor cells tested positive for CK7, GATA3, P120, and E-cadherin and negative for CK20, CDX2, and STAB2 (Fig. 4).

Treatment:

No special event was noted after the surgery. At 12 days post-surgery, the patient was discharged from the hospital, following which she commenced with the radiotherapy for bone metastases.

Outcome And Follow-up:

The patient was followed-up for six months after discharge from the hospital. Letrozole administration was continued, and she remained in a stable condition.

Discussion:

BC accounts for 15% of all cancer cases among female patients^[7] and ranks second among the most common primaries metastasizing to the gastrointestinal tract, next to malignant melanoma^[8]. GI tract metastases are uncommon and are, therefore, detected more frequently through autopsies rather than through clinical suspicion^[9]. Metastasis may occur in all the regions of the GI tract, with the rectum being an infrequently affected site^[2]. However, rare presentations and DM would be encountered more frequently in the future due to an increase in the number of aging people and cancer survivors^[10–12].

Infiltrating ductal cancer is a frequently occurring subtype of BC. However, it metastasizes to the gastrointestinal tract at a rate of only 0.2%, in contrast to the 4.5% metastatic rate of invasive lobular carcinoma^[13, 14]. Infiltrating lobular carcinoma, which accounts for only [approximately] 12% of all primary breast cancer cases, contributes 64% of the gastrointestinal tract metastases^[15]. The predilection of the invasive lobular carcinoma for spreading to the gastrointestinal tract may be interpreted based on unique biological and histological characteristics. E-cadherin, the molecule responsible for intercellular adhesion, is absent in the infiltrating lobular carcinoma, which possibly facilitates the GI propensity^[3, 16]. Typically, the venous vertebral plexus (Batson's plexus) is the probable route for BC metastasis through the veins^[17]. This plexus extends from the skull to the sacrum without any valves, thereby providing an unrestricted channel for the transport of the metastatic emboli into the ribs, the distant organs, and the vertebral bones^[18].

The early diagnosis is challenging due to several reasons. First, the tumors metastasizing from primary BC to the GI tract manifest no specific symptoms. Montagna et al.^[13] reviewed 40 patients, among which 80% of the patients complained of vomiting, nausea, bellyache, altered bowel habits, fatigue, and unsuspected weight loss, all of which are commonly observed symptoms in primary as well as secondary intestinal tumors. McLemore et al.^[19] studied 12,001 patients with breast cancer and BC metastasis detected in 11 patients remained undiagnosed until an exploratory laparotomy was conducted. Second, the concerned patient in the present study had a 3-year disease-free interval after BC, which renders the early diagnosis of metastasis difficult. Therefore, exploring the history of breast cancer is crucial for establishing the diagnosis of bowel metastasis. As suggested by Schwarz and colleagues, the median interval from BC to GI was between 0.25 and 12.5 years (median: six years)^[20]. McLemore and coworkers reported an average interval of seven years^[15]. López Deogracias and coworkers presented a case with invasive lobular carcinoma developing metastatic rectal lesion, which caused urethral dilation 15 years later^[21]. Mistrangelo and colleagues presented the case of a patient who developed sigmoid colon metastasis of primary lobular BC after an interval of 25 years, the longest so far among the reported cases^[22]. Therefore, it is critical to include the possibility of intestinal metastasis in the early diagnosis of the cases presenting with digestive complaints along with a history of BC.

At the early stage of metastasis, the general endoscopic appearance is normal mucosa, as the lesions often involve the submucosal layer rather than the mucosal layer. Therefore, biopsy plays a crucial role. Szabó et al. reported a case of infiltrating lobular carcinoma mimicking Crohn's disease, for which biopsy suggested necrosis and not cancer. However, the histopathological examinations conducted after surgery

indicated terminal ileal metastasis of invasive lobular carcinoma^[23]. Carcoforo et al. reported the case of a female patient aged 73 years and no previous history of cancer, who presented with a complaint of vomiting, nausea, and abdominal pain. Her colonoscopy revealed a stricture at 15 cm on the top of the anal verge. Moreover, negative results were obtained in repeated biopsies, while biopsies combined with exploratory laparotomy revealed intestinal metastases of invasive lobular carcinoma.^[24] Endoscopic ultrasound-guided fine-needle aspiration may be conducive to prompt an accurate diagnosis of the alimentary tract metastasis. Matsumoto et al. reported the case of an 84-year-old woman with progressive dysphagia. Her endoscopy revealed esophageal stenosis located 30 cm away from the incisors, although no abnormality was observed in the overlying mucosa. In addition, no abnormality was detected in the biopsies. Finally, esophagus metastasis from breast cancer was confirmed through fine-needle biopsy cytology conducted endoscopically under the guidance of ultrasound^[25]. Late metastasis may affect all the intestinal layers and manifest in linitis plastica lesions, ulcers, and bleeding, thus mimicking primary intestinal tumor or the inflammatory bowel disease^[23, 26].

The radiologist plays a crucial role in examining the patients with breast cancer for detecting metastasis. In abdominal CT, the common identifications are mural thickening, bowel dilation, the rigidity of the colorectum, and linitis plastica-type lesion of the stomach^[27]. These macroscopic characteristics are nonspecific and indistinguishable from lowly-differentiated cancer that is observed frequently in the stomach. MRI, in comparison, provides better soft-tissue contrast and a high-level description of the various histological layers of the gastrointestinal wall. In a study by Lau, LC et al., concentric mural thickening was concluded as the MRI feature of breast metastases to rectum, while eccentric wall thickening and an obvious invasive margin were reported as the more frequently observed features in primary rectal carcinoma^[28]. PET-CT could be employed to detect DM, such as in the case analyzed in the present study, as PET-CT presents high specificity and sensitivity in the detection of DM compared to conventional imaging^[29]. However, PET-CT is not the preferred diagnostic tool in BC due to its low sensitivity and specificity, which are in the range of 48–96% and 73–100%, respectively^[30].

Immunohistochemistry plays a decisive role in the establishment of a diagnosis. CK7 and CK20 are two effective cytokeratins among the 20 intermediate filament subtypes of cytokeratins. CK7 expression is observed in glandular and ductal epithelial tissues in breast and lung cancers. CK20 positivity is observed in the gastrointestinal epithelium^[31]. CK7 positivity and CK20 negativity favor metastasis, as in our case, while a CK7-/CK20+ pattern is suggestive of a large bowel primary tumor^[21, 32]. Tot T reported that the conventional use of CK20 in addition to ER staining is useful in distinguishing primary gastrointestinal carcinomas from metastatic breast carcinomas. The CK20+/ER- phenotype may identify most of the gastrointestinal tumors^[33]. CDX2 is the caudal homeobox gene that encodes the transcription factor (TF), which plays a vital role in intestinal epithelial differentiation and proliferation. The expression of CDX2 is mainly, although not absolutely, limited to the adenocarcinomas located between the proximal duodenal tissue and the distal rectal tissue. CDX2 may be expressed in gastric cancer (GC), primary urinary bladder adenocarcinomas, and mucinous ovarian adenocarcinomas^[31, 34, 35]. Bayrak R et al. analyzed 118 colorectal, 59 gastric, and 32 pancreatic adenocarcinoma resection specimens and concluded that in

colorectal adenocarcinomas, CDX2 expression and the CK7-/CK20+ pattern were highly sensitive and specific^[31]. SATB2, a recently described transcriptional regulator, is reported as a highly specific and sensitive marker of colorectal cancer (CRC)^[36, 37]. Magnusson K et al. reported that SATB2 plus CD20+ could detect over 95% of the CRC cases^[37]. E-cadherin, the transmembrane glycoprotein, regulates intercellular adhesion in a calcium-dependent manner and participates in the adhesion of epithelial cells^[38]. E-cadherin has also been frequently used as a marker to distinguish ductal carcinoma from the lobular one. E-cadherin is expressed within the cell membrane in most ductal carcinomas. On the contrary, E-cadherin is absent in several lobular carcinomas^[39, 40]. P120 catenin is stained intensely in the membrane of ductal carcinomas and strongly and diffusely stained in the cytoplasm of lobular carcinomas. Furthermore, approximately 10–16% of ductal carcinomas test E-cadherin-negative, and in these cases, P120 catenin maintains its membrane localization^[39, 41–43]. GATA3, one of the TF proteins, plays a vital role in enhancing the differentiation and proliferation of mammary ductal epithelial cells. GATA3 is regarded as the most sensitive single marker of invasive breast cancer, with an estimated expression rate of over 90%. When confronting a neoplasm with unclear origin, particularly in the case of BC, routine assessment of GATA3 is recommended^[44, 45]. In the present report, negativity for both CDX2 and STAB2, along with a CK7+/CK20- profile assisted in excluding the diagnosis of the primary tumor of the rectum. Positivity for E-cadherin, P120, and GATA3 indicates that the metastasis of infiltrating ductal BC. In addition, for the original breast carcinoma treated three years ago in our case, 70% ER and PR positive rates were observed, while for the rectal metastatic lesion, the rates were 90%. This difference is also reported by other reviewers, which suggests that BC presents different biological features in the primary tumors compared to metastases^[46, 47].

The cases with GI tract metastases are frequently treated with systemic treatment (endocrine therapy and/or chemotherapy), as the GI metastasis is generally associated with extensive metastases^[10]. However, the unique role of surgical intervention cannot be ignored. Surgical intervention includes gastrointestinal resection, diverting ostomy, and gastrointestinal bypass. In patients with gastrointestinal metastasis alone, radical surgical resection along with systemic treatment is reported to have a better prognosis^[1, 15]. In the patients presenting disseminated disease, surgery has no prolonging effect on the overall survival (OS), although these patients do benefit from palliative surgery, as reported previously, for relief from the symptoms^[15]. Typically, perforation, bleeding, and intestinal obstruction are the surgical indications for such cases, and surgery should, therefore, be performed to avoid severe complications and improve supportive care. Moreover, surgery plays a crucial role in obtaining a timely and accurate diagnosis of bowel metastasis, as stated earlier. In summary, for such cases, the decision for surgery should be undertaken on the basis of the general condition, symptoms, clinical presentations, and a quality-of-life assessment. In our case, since the patient was experiencing long-enduring rectal bleeding and was relatively young and in good general condition, a radical local resection and radiotherapy were performed along with an endocrine treatment, and this therapeutic strategy was expected to provide her a relatively long-term survival.

Conclusion:

Rectal metastasis should be considered when patients present with a complaint of changed bowel habits, particularly if they have a history of breast cancer. Although rectal metastasis from ductal breast cancer is extremely rare compared to its lobular counterpart, it nonetheless requires attention. Endoscopic fine-needle aspiration under the guidance of ultrasound and a PET-CT may be useful in obtaining a prompt and accurate diagnosis. Histopathology and immunohistochemistry play important roles in the verification of metastasis while excluding the primary rectal cancer. Surgery also plays a unique and important role in its diagnosis and treatment.

Abbreviations

GI

gastrointestinal

BC

breast cancer

LND

lymph node dissection

DM

distant metastasis

PET-CT

positron emission tomography-computed tomography

FDG

fluorodeoxyglucose

Declarations

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Author contributions:

Bo Ban was the patient's surgeon, reviewed the literature and contributed to manuscript drafting; Yong-Ping Yang, Jian-Nan Li, Kai Zhang, Tong-Jun Liu and Jian Shi were responsible for the revision of the manuscript for important intellectual content; all authors issued final approval for the version to be submitted.

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All data generated during this study are included in this published article.

Ethics approval and consent to participate:

This study was performed in accordance with the principles of the Declaration of Helsinki. The requirement for ethical approval was waived by the Jilin University Second Hospital Review Board.

Consent for publication:

Written informed consent was obtained from the patient for the publication of this case report and the accompanying images.

Competing interests:

The authors declare that they have no competing interests.

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Figures

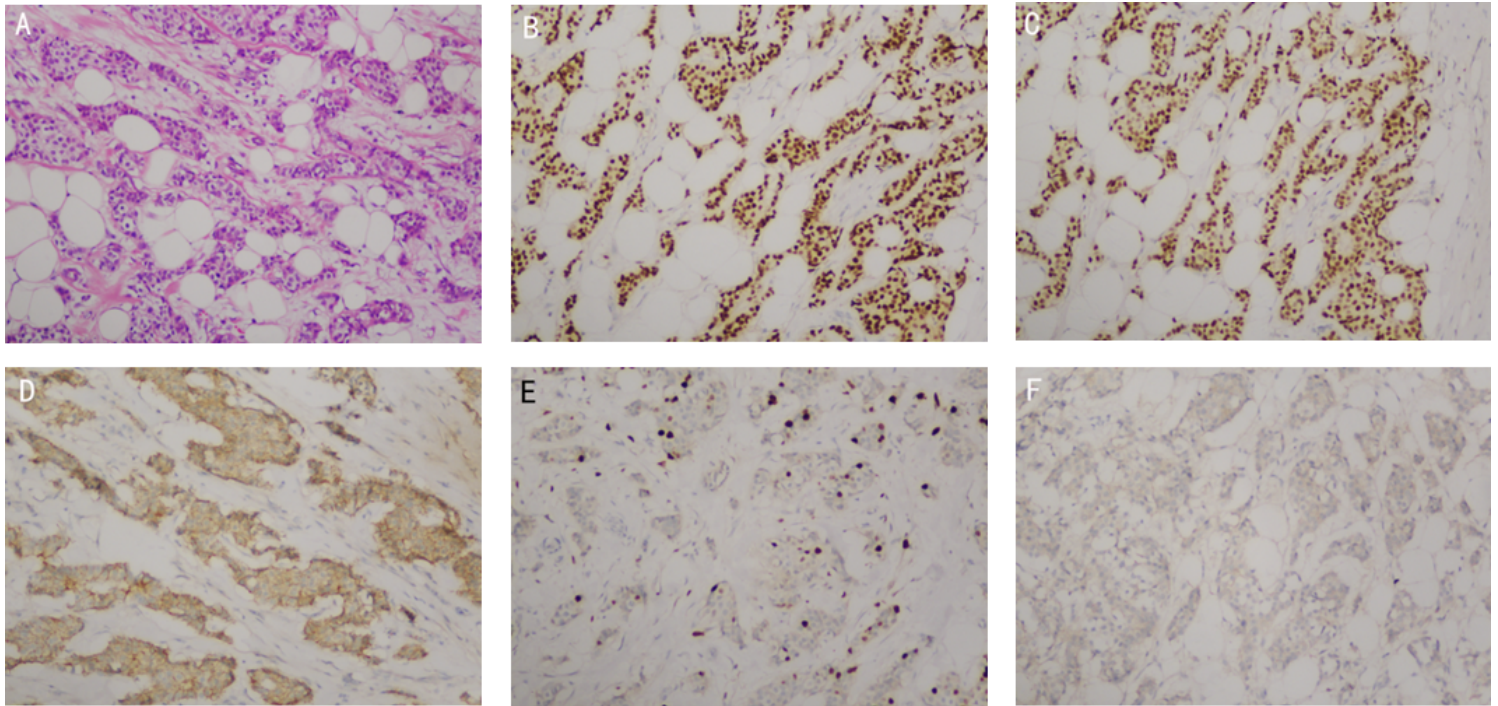


Figure 1

Histopathology and immunohistochemical findings of cancer in the right breast (original magnification: 100x). A: Hematoxylin and eosin (HE) staining. HE staining for the resected tumor samples suggested invasive ductal BC. B: The ER-positive rate was 70% in all cancer cells. C: The PR positive rate was 70% in all cancer cells. D: E-cadherin positivity. E: The Ki67 positive rate was 15% in all cancer cells. F: Her2 negativity.

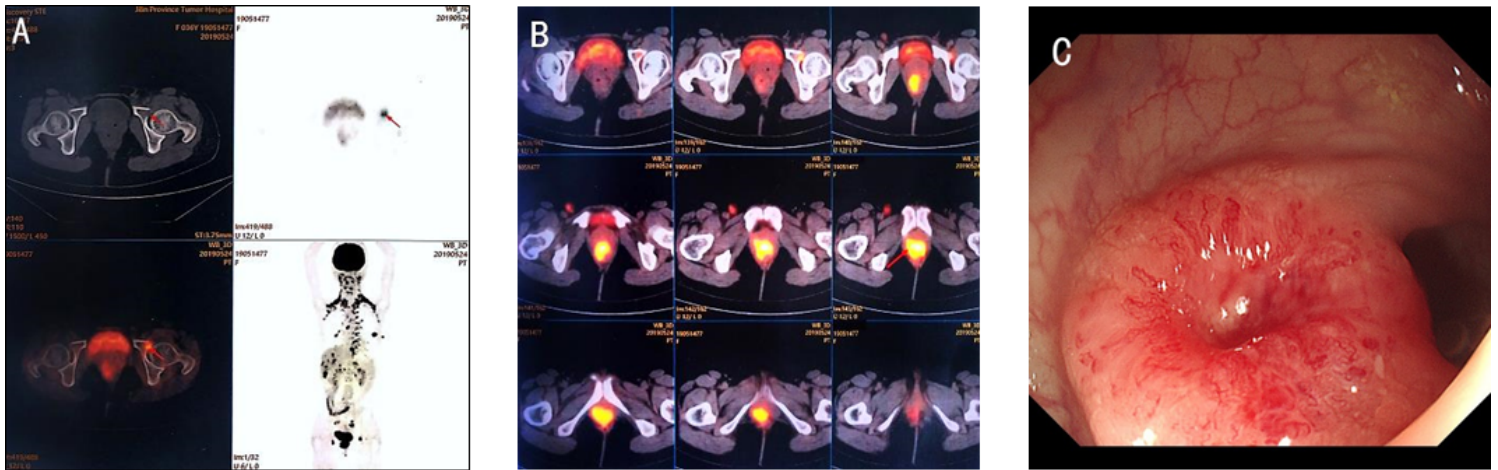


Figure 2

Results of PET-CT and colonoscopy. A: Upper left part: local destruction of the bone cortex; lower left part: PET-CT images depicting the uptake of fluorodeoxyglucose (FDG) within the left acetabulum, with the maximal standardized value of uptake (SUVmax) equal to 5.5. B: PET-CT image depicting the fluorodeoxyglucose (FDG) uptake in the distal rectum, with the maximum standardized uptake value

(SUVmax) of 11.2. C: Colonoscopy results indicated a lower rectal swelling, with a red and smooth surface located at 3 cm on the top of the anal verge, which suggested a submucosal tumor.

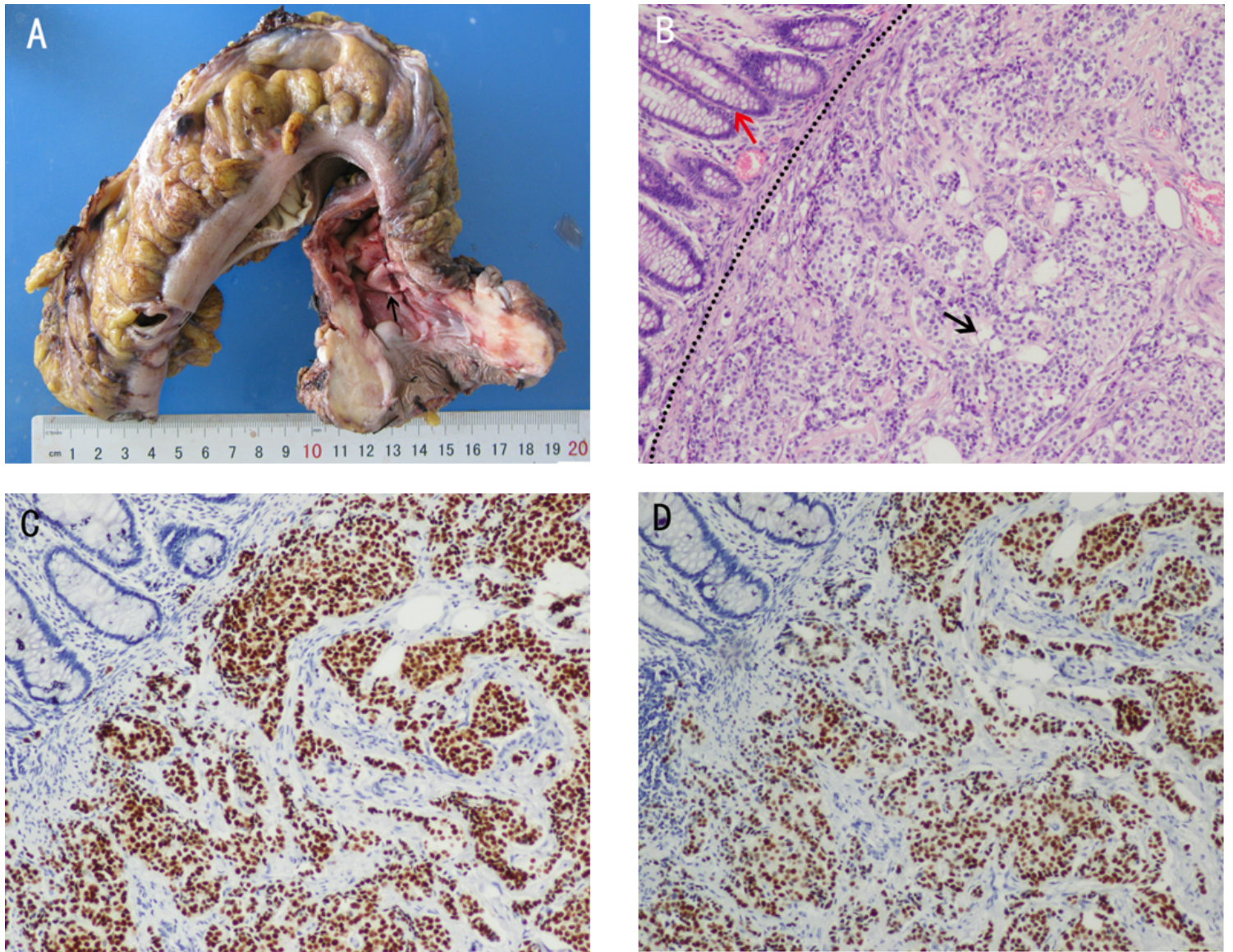


Figure 3

Surgical specimen and the fast-frozen pathology of the specimen (B–C: original magnification: 100x). A: A surgical specimen of the rectal lesion depicting a neoplasm (3 cm in longitudinal diameter) in the submucosal layer and no abnormality in the mucosal layer. The swelling marked by the black arrow was also indicated in colonoscopy (Figure 2C). B–D (top left corner: normal rectal mucosal layer; bottom right corner: tumor infiltrating layer.) B: the sections under hematoxylin and eosin (HE) staining suggested that cancer cells had invaded the submucous layer. C: The ER-positive rate was 90% in all cancer cells. D: The PR positive rate was 90% in all cancer cells.

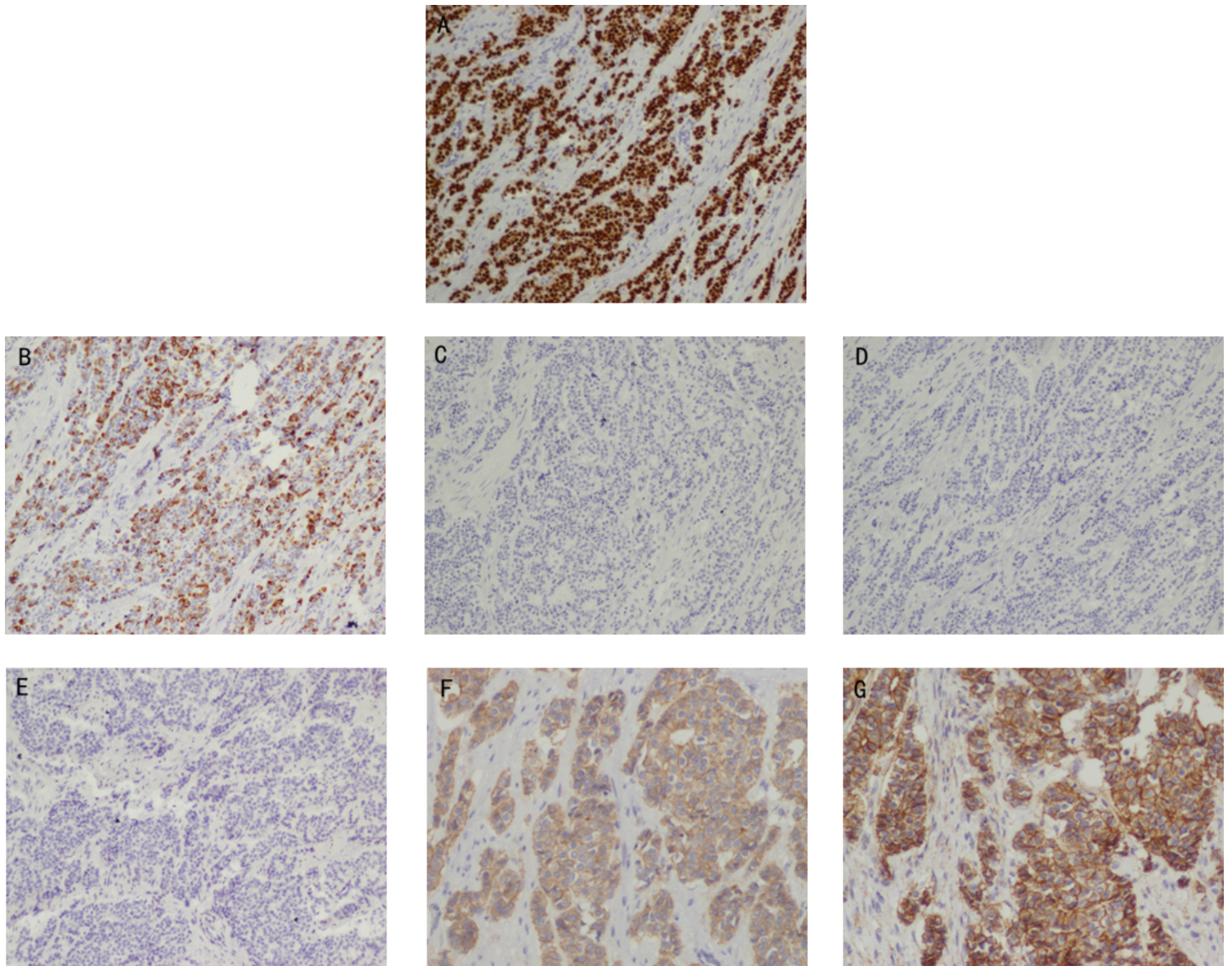


Figure 4

Further immunohistochemical analysis of the tumor infiltrating region (A–E: the original magnification: 100x; F and G: the original magnification: 200x). A: GATA3 was positive. B: CK 7 was positive. C: CK 20 was negative. D: CDX 2 was negative. E: STAB 2 was negative. F: E-cadherin was positive. G: P120 exhibited membrane staining.