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Ductal breast carcinoma metastasized to the rectum: A case report and review of the literature

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Abstract

BACKGROUND

Gastrointestinal (GI) metastasis from breast cancer (BC) is rarely encountered in clinical practice. Nonspecific symptoms and long intervals make early diagnosis difficult. Therefore, increased awareness of GI metastasis secondary to BC and a deep understanding of the clinical and pathological features, and intervention for GI metastasis are fundamental to avoid delay in correct diagnosis and management.

CASE SUMMARY

The present report discusses the case of a Chinese female patient aged 36 years. The patient presented with difficult defecation along with bloody stools and hypogastralgia. In 2015, she had undergone right modified radical mastectomy and axillary lymph node dissection in another hospital to treat the infiltrating ductal breast carcinoma pT1N1M0. The presenting symptoms were investigated by colonoscopy, which indicated a circumferential stricture in the lower rectum at 3 cm from the anal edge. Further investigation with positron emission tomography-computed tomography revealed an uptake of fluorodeoxyglucose within the distal rectum as well as in the left acetabulum. The samples from laparoscopic exploration were biopsied, which revealed metastases of BC. Immunohistochemical analysis of the tumor confirmed that the patient had rectal metastasis of infiltrating ductal BC.

CONCLUSION

Rectal metastasis should be considered when patients with a history of BC present with changed bowel habits.

Key Words: Breast cancer; Ductal carcinoma; Rectal metastases; Case report

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Core Tip: Rectal metastasis of infiltrating ductal breast cancer has a low incidence. For patients with a history of breast cancer with digestive complaints, bowel metastasis must be considered.

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INTRODUCTION

Breast cancer (BC) is the most frequent malignant tumor among women and is associated with significant morbidity and mortality rates[1]. Metastatic tumors account for 30% of BC cases with a 5-year survival rate of 22%, and those metastatic cases are responsible for 90% of BC deaths[2]. BC metastasis includes contiguous, lymphatic and hematogenous forms of spread. While hematogenous spread of BC can target any site, the most common sites are bone, lung, liver and brain[3]. Metastasis to the gastrointestinal (GI) tract, and retroperitoneal organs is rare, and to the distal rectum is remarkably rare[4,5]. The differentiation of bowel metastasis from BC and primary intestinal tumor is difficult since there are nontypical, diverse symptoms and long disease-free duration of BC. The present report discusses the case of a Chinese woman aged 36 years who presented with bloody stools and hypogastralgia 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

Chief complaints

A 36-year-old Chinese woman presented with a complaint of difficult defecation, along with bloody stools and hypogastralgia. The symptoms had appeared 2 mo earlier and had progressively worsened within 2 wk, which led to hospitalization for a complete medical examination.

History of present illness

A patient with no history of colorectal surgery or irradiation presented with clinical symptomatology characterized by difficult defecation, bloody stools, and hypogastralgia.

History of past illness

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

Personal and family history

The patient denied any family history of BC or rectal cancer.

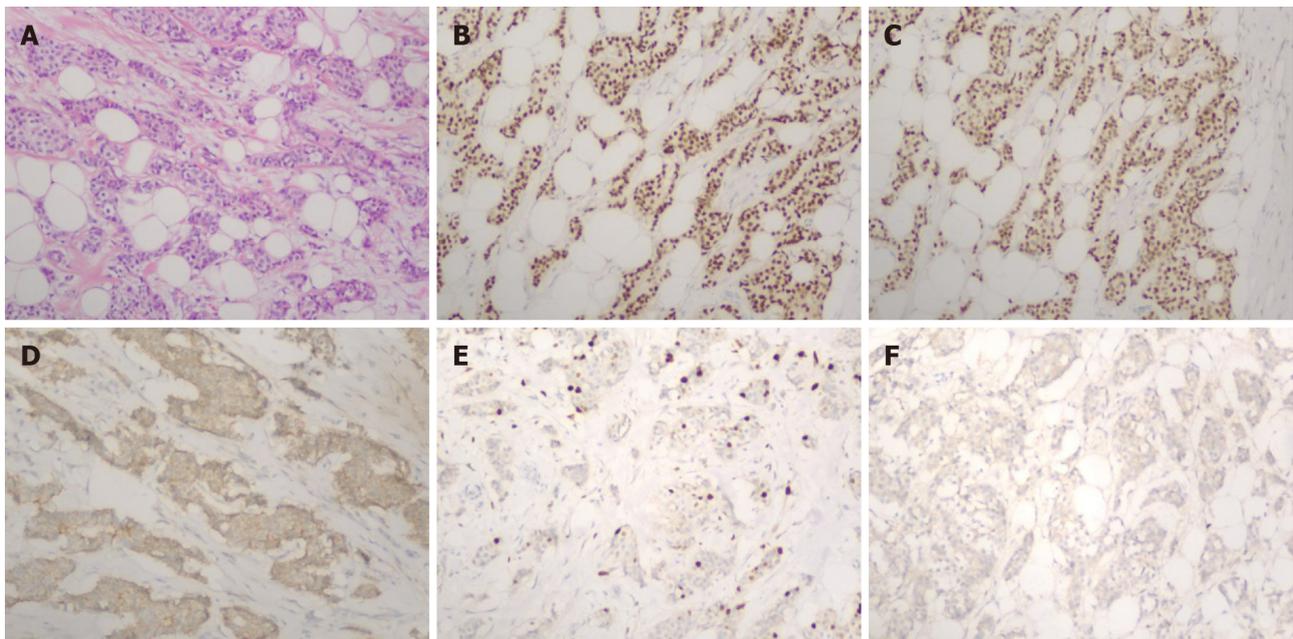


Figure 1 Histopathology and immunohistochemical findings of cancer in the right breast (100 ×). A: Hematoxylin and eosin (HE) staining. HE staining for the resected tumor samples suggested invasive ductal breast cancer; B: Estrogen-receptor-positive rate was 70% in all cancer cells; C: Progesterone-receptor-positive rate was 70% in all cancer cells; D: E-cadherin positivity; E: Ki67 positive rate was 15% in all cancer cells; F: Her2 negativity.

Physical examination

The patient’s vital signs were as follows: Body temperature, 36.3 °C; heart rate, 74 beats/min; blood pressure, 116/76 mmHg; respiratory rate, 15 breaths/min; and in-room oxygen saturation, 100%. Abdominal examination revealed no obvious abnormality. However, digital rectal examination revealed a tumor with a smooth surface 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 rectal examination.

Laboratory examinations

Results of routine laboratory tests were normal. Blood analysis revealed no abnormality in any of the blood counts. White blood cell count was 5.9×10^9 cells/L (normal limit: 3.5×10^{12} - 9.5×10^{12} cells/L), red blood cell count was 4.27×10^{12} cells/L (normal limit: 3.80×10^{12} - 5.10×10^{12} cells/L), and platelet count was 313×10^9 cells/L (normal limit: 125×10^9 - 350×10^9 cells/L). However, both carbohydrate antigen (CA)-125 and CA-153 were 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 circumferential stricture in the lower rectum at a distance of 3 cm from the anal edge. Its surface was smooth and red, which was suggestive of a submucosal tumor (Figure 2A). 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 within the left acetabulum and distal rectum, with the maximal standardized uptake values of 5.5 and 11.2, respectively, suggesting suspicious metastasis at these positions (Figure 2B and 2C).

FINAL DIAGNOSIS

In the laparoscopic exploration, a circumferential tumor was detected in the distal rectum, following which a biopsy of the tumor was performed. 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 PR and ER positive, with a positivity rate of 90% for both

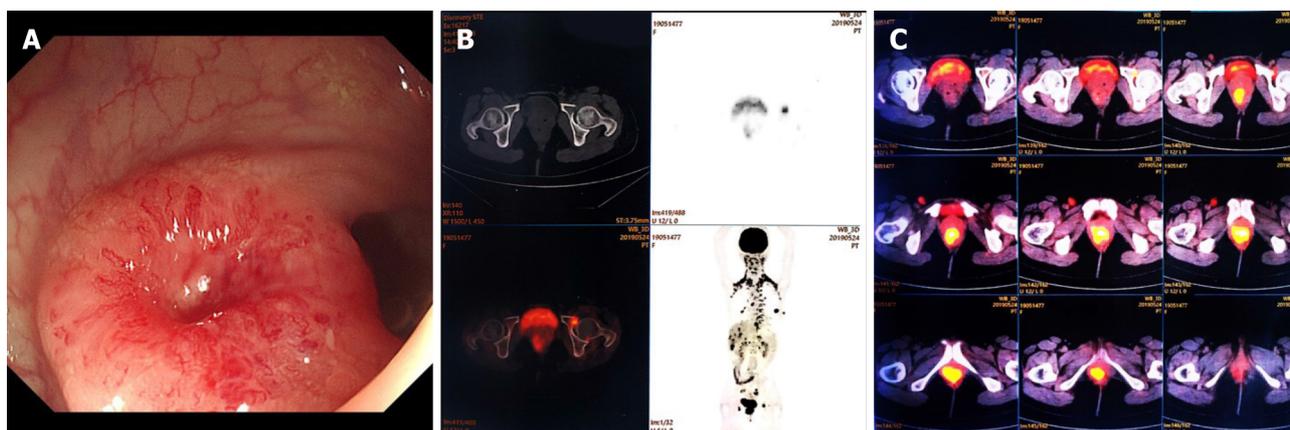


Figure 2 Results of positron emission tomography-computed tomography (PET-CT) and colonoscopy. A: Colonoscopy results indicated a lower rectal swelling, with a red and smooth surface located at 3 cm on the top of the anal verge, which suggested a submucosal tumor; B: Upper left part: local destruction of the bone cortex; lower left part: PET-CT images depicting uptake of fluorodeoxyglucose (FDG) within the left acetabulum, with the maximal standardized value of uptake (SUVmax) equal to 5.5; C: PET-CT image depicting FDG uptake in the distal rectum, with SUVmax 11.2.

(Figure 3). In contrast, the background rectal epithelial cells tested PR and ER negative. Since the patient had a history of ductal BC, she was intraoperatively diagnosed with BC rectal metastasis. Given that the tumor had caused bleeding and incomplete intestinal obstruction, which were surgical indications, a colostomy was performed laparoscopically. The surgical dissected biopsy revealed a neoplasm in the submucosal layer, while no abnormality was observed in the mucosal layer. 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 cytokeratin (CK)7, GATA3, P120 and E-cadherin and negative for CK20, caudal type homeobox (CDX)2 and stabilin (STAB)2 (Figure 4).

TREATMENT

No special event was noted after surgery. At 12 d after surgery, the patient was discharged from hospital. Afterwards, local radiotherapy was given to a total dose of 39 Gy in 13 sessions of 3 Gy, and a chemotherapy plan of gemcitabine combined with cisplatin was also applied.

OUTCOME AND FOLLOW-UP

The patient was followed-up for 10 mo after discharge from hospital. Tamoxifen administration was continued, and she remained in a stable condition.

DISCUSSION

GI metastasis from breast carcinoma is rare and has been reported to occur in 6%-18% of disseminated BC patients[6]. Metastasis may occur in all the regions of the GI tract, with the rectum being an infrequently affected site[7]. Infiltrating ductal cancer is the most frequently occurring subtype of BC, and accounts for 75% of all primary BC[1]. However, it metastasizes to the GI tract at a rate of only 0.2%, in contrast to the 4.5% metastatic rate of invasive lobular carcinoma[8,9]. Infiltrating lobular carcinoma, which accounts for only 12% of all primary BC cases, contributes 64% of the GI metastases from primary BC[10]. The different clinical metastatic patterns between infiltrating ductal carcinoma and infiltrating lobular carcinoma may be interpreted based on unique biological and histological characteristics. E-cadherin, the molecule responsible for intercellular adhesion, is present in ductal carcinoma but absent in lobular carcinoma, which possibly explains the different metastatic patterns[11]. Typically, the venous vertebral plexus (Batson's plexus) is the probable route for BC metastasis through the veins. This plexus extends from the skull to the scrum without

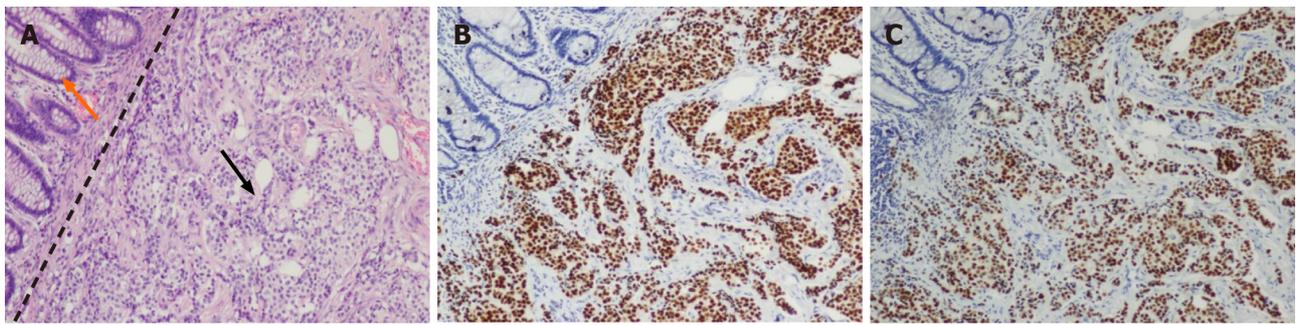


Figure 3 Fast-frozen pathology of the specimen (100 ×). A-C: Top left corner: Normal rectal mucosal layer; bottom right corner: Tumor infiltrating layer. A: Sections under hematoxylin and eosin (staining suggested that cancer cells had invaded the submucosal layer; B: Estrogen-receptor-positive rate was 90% in all cancer cells; C: Progesterone-receptor-positive rate was 90% in all cancer cells.

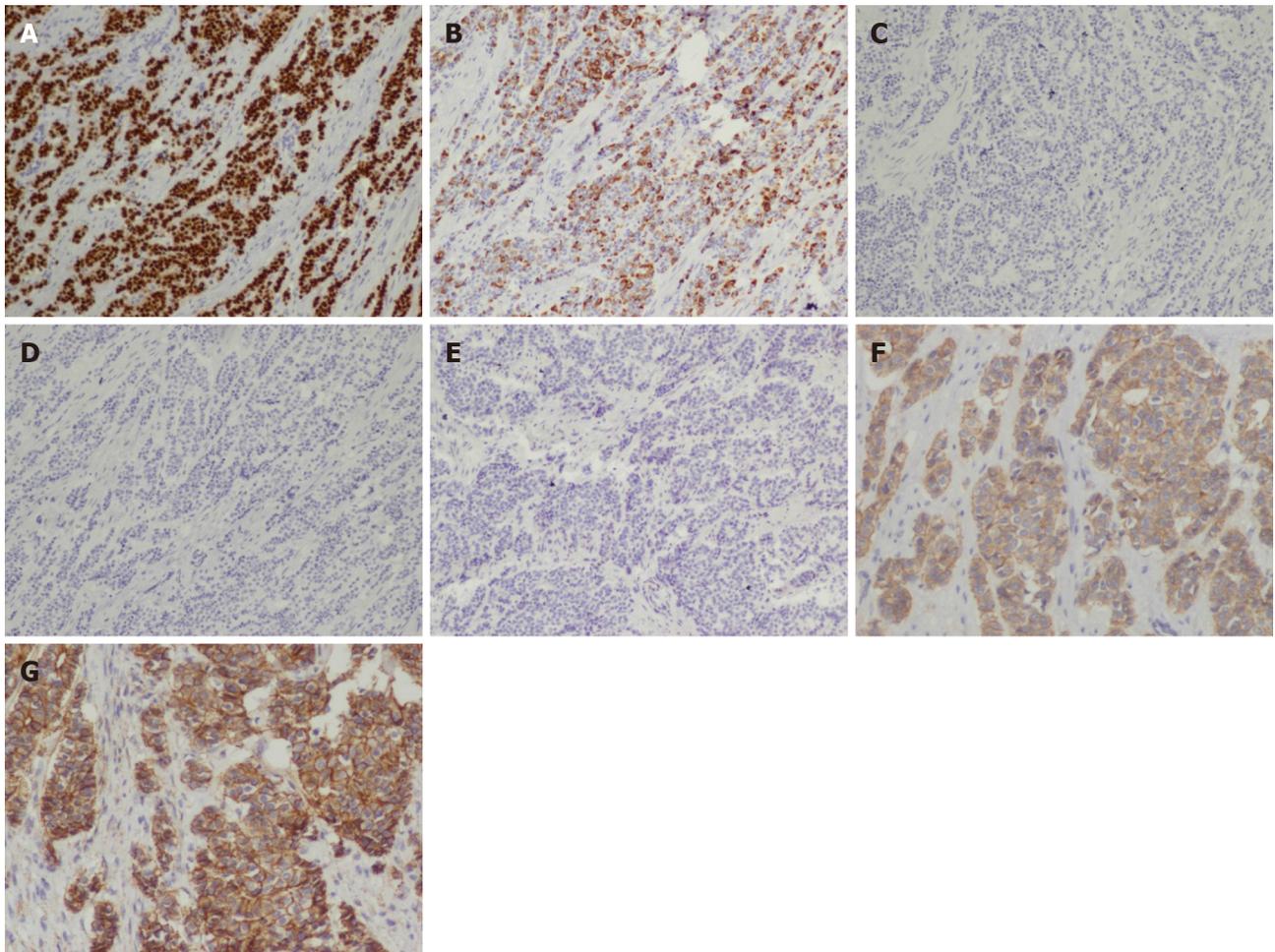


Figure 4 Further immunohistochemical analysis of tumor-infiltrating region (A-E: 100 ×; F, G: 200 ×). A: GATA3 was positive; B: Cytokeratin (CK)7 was positive; C: CK20 was negative; D: Caudal type homeobox 2 was negative; E: Stabilin 2 was negative; F: E-cadherin was positive; G: P120 exhibited membrane staining.

any valves, thereby providing an unrestricted channel for the transport of the metastatic emboli into the ribs, the distant organs, and the vertebral bones[12].

Early diagnosis is challenging for several reasons. First, the tumors metastasizing from primary BC to the GI tract manifest no specific symptoms. Montagna *et al*[8] reviewed 40 patients, among whom, 80% complained of vomiting, nausea, stomach ache, 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*[10] studied 12001 patients with BC, and metastasis detected in 11 patients remained undiagnosed until an exploratory laparotomy was conducted. Second, the long disease-free interval of BC renders the early diagnosis of metastasis

difficult. Therefore, exploring the history of BC is crucial for establishing the diagnosis of bowel metastasis. As suggested by Schwarz *et al*[13], the median interval from BC to GI metastasis was between 0.25 and 12.5 years (median: 6 years). McLemore *et al*[10] reported an average interval of 7 years. López Deogracias *et al*[14] presented a case with invasive lobular carcinoma developing a metastatic rectal lesion, which caused urethral dilation 15 years later. Mistrangelo *et al*[15] presented a patient who developed sigmoid colon metastasis from primary lobular BC after an interval of 25 years; the longest so far among the reported cases. In our case, the disease-free interval was 4 years and the time for the occurrence of metastasis was inside the highest risk window. Therefore, it is critical to include the possibility of intestinal metastasis in the early diagnosis of 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, superficial biopsy seems to have a limited role. Szabó *et al*[16] 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. Carcoforo *et al*[17] reported the case of a female patient aged 73 years with no history of cancer, who presented with vomiting, nausea and abdominal pain. 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 BC. Deep biopsy or endoscopic ultrasound-guided fine-needle aspiration may be conducive to prompt an accurate diagnosis of GI tract metastasis. Matsumoto *et al*[18] 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, esophageal metastasis from BC was confirmed through fine-needle biopsy cytology conducted endoscopically under the guidance of ultrasound. Late metastasis may affect all the intestinal layers and manifest in linitis plastica lesions, ulcers, and bleeding, thus mimicking primary intestinal tumor or inflammatory bowel disease[16, 19].

The radiologist plays a crucial role in examining the patients with BC for detecting metastasis. In abdominal CT, the common identifications are mural thickening, bowel dilation, rigidity of the colorectum, and linitis-plastica-type lesion of the stomach[20]. These macroscopic characteristics are nonspecific and indistinguishable from lowly differentiated cancer that is observed frequently in the stomach. Magnetic resonance imaging (MRI), in comparison, provides better soft-tissue contrast and a high-level description of the various histological layers of the GI wall. In a study by Lau *et al*[21], concentric mural thickening was concluded as the MRI feature of breast metastases to the rectum, while eccentric wall thickening and an obvious invasive margin were reported as the more frequently observed features in primary rectal carcinoma. PET-CT could be used 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[22]. 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[23].

Immunohistochemistry plays a decisive role in the establishment of a diagnosis. CK7 and CK20 are two effective cytokeratins among the 20 intermediate filament subtypes. CK7 expression is observed in glandular and ductal epithelial tissues in breast and lung cancers. CK20 positivity is observed in the GI epithelium[24]. CK7 positivity and CK20 negativity favor metastasis, as in our case, while a CK7-/CK20+ pattern is suggestive of a large bowel primary tumor[14,25]. *CDX2* is the caudal homeobox gene that encodes the transcription factor (TF), which plays a vital role in intestinal epithelial differentiation and proliferation. *CDX2* may be expressed in gastric cancer, primary urinary bladder adenocarcinoma, and mucinous ovarian adenocarcinoma[26]. Bayrak *et al*[24] analyzed 118 colorectal, 59 gastric and 32 pancreatic adenocarcinoma resection specimens and concluded that in colorectal adenocarcinoma, *CDX2* expression and the CK7-/CK20+ pattern were highly sensitive and specific. *SATB2*, a recently described transcriptional regulator, is reported as a highly specific and sensitive marker of colorectal cancer (CRC)[27]. Magnusson *et al*[28] reported that *SATB2* plus *CD20*+ could detect > 95% of the CRC cases. E-cadherin, the transmembrane glycoprotein, regulates intercellular adhesion in a calcium-dependent manner and participates in the adhesion of epithelial cells[29]. 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[30]. P120 catenin is stained intensely in the membrane of ductal carcinomas and strongly and diffusely stained in the cytoplasm of lobular carcinomas. Furthermore, 10%-16% of ductal carcinomas test negative for E-cadherin, and in these cases, P120 catenin maintains its membrane localization[30,31]. 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 BC, with an estimated expression rate of > 90%. When confronting a neoplasm with unclear origin, particularly in the case of BC, routine assessment of GATA3 is recommended[32]. In the present report, negativity for both CDX2 and STAB2, along with a CK7⁺/CK20⁻ profile assisted in excluding the diagnosis of primary tumor of the rectum. Positivity for E-cadherin, P120 and GATA3 indicates metastasis of infiltrating ductal BC. In addition, for the original breast carcinoma treated 3 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 has also been reported by other reviewers, which suggests that BC presents with different biological features in the primary tumors compared to metastases[33,34].

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[35]. However, the unique role of surgical intervention cannot be ignored. Surgical intervention includes GI resection, diverting ostomy, and GI bypass. In patients with GI metastasis alone, radical surgical resection along with systemic treatment is reported to have a better prognosis[10]. In the patients presenting disseminated disease, surgery has no prolonging effect on the overall survival, although these patients do benefit from palliative surgery, as reported previously, for relief from the symptoms[10]. 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, the metastatic tumor had caused bleeding and incomplete intestinal obstruction which were surgical indications. Therefore, colostomy was performed along with chemotherapy, endocrine treatment, and radiotherapy. This therapeutic strategy was expected to achieve long-term survival.

CONCLUSION

BC has been shown to metastasize to the GI tract, although it may have a long interval. We should also be aware that the presenting symptoms can be nonspecific and it may be difficult to diagnose metastasis on biopsy or endoscopy. Comprehensive analysis of imaging manifestations is helpful in correct diagnosis. Histopathology and immunohistochemistry play important roles in the verification of metastasis while excluding primary rectal cancer. Surgery also plays a unique and important role in its diagnosis and treatment.

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