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Case Report: Synchronous cervical, gastric and rectal metastases in occult breast cancer

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Occult breast cancer (OBC) is characterized as a breast carcinoma that remains undetectable through imaging modalities. OBC is a rare condition, accounting for only 0.3%-1.0% of all breast cancers, and is often clinically associated with metastases to the axillary and cervical lymph nodes. Metastasis of occult primary breast cancer to the cervix, stomach, or rectum is exceptionally rare. Here, we report the case of a 64-year-old woman presenting with clinical symptoms of urinary urgency, frequency, severe rectal discomfort, and altered stool morphology. Ga68-positron emission tomography-computed tomography (Ga68-FAPI PET/CT) identified diffuse tumor-associated fibrin expression within the gastric wall, while 18F-fluorodeoxyglucose PET/CT (18F-FDG PET/CT) revealed marked annular thickening of the rectal wall. Notably, imaging evaluations, including mammography, breast ultrasonography, and 18F-FDG PET/CT, failed to detect primary breast lesions. Histopathological examination and immunohistochemical analysis of biopsied cervical, gastric, and rectal lesions confirmed the diagnosis of OBC. Following six months of treatment with letrozole (1mg/day) in combination with dalpiciclib the patient demonstrated significant symptomatic relief, with remarkable reduction in the lesions located in the cervix, stomach, and rectum. This case represents the first documented instance of occult primary breast cancer with simultaneous metastases to the cervix, stomach, and rectum.

KEYWORDS

occult primary breast cancer, simultaneous metastases, cervical, gastric and rectal metastasis, endocrine therapy, CDK4/6 inhibitors

Introduction

Breast cancer is the most common malignancy among women and remains the leading cause of cancer-related mortality in women worldwide. In 2020, approximately 2.3 million new cases of breast cancer were reported globally, with more than half of these diagnoses occurring in low-and middle-income countries. That same year, breast cancer claimed the

lives of 685,000 women (1). China bore the highest burden of breast cancer, with 357,200 newly diagnosed cases and 75,000 deaths reported in 2020 (2).

Occult breast cancer (OBC) is a rare clinical entity, defined as metastatic cancer originating from malignant primary breast tumors that remain undetectable on clinical examination and radiological imaging. OBC accounts for 0.3%-1.0% of all breast cancers and typically presents at a median age of approximately 55 years (3, 4). The diagnosis of OBC is often challenging due to its non-specific symptoms and the absence of detectable breast lesions. Axillary lymph node metastasis is the most common clinical presentation (5), although metastases to other sites, including the bone, liver, lymphatic system, skin, orbit, bone marrow, lung, spleen, and cervix, have also been reported (6–12). OBC predominantly affects older adults and is generally diagnosed at an early stage, often associated with a favorable prognosis. However, to date, no cases of simultaneous metastases of primary OBC to the cervix, stomach, and rectum have been reported in the literature. Here, we present a unique case of concurrent cervical, gastric, and rectal metastases in a patient with occult primary breast cancer. This report aims to provide insights into the diagnostic challenges and therapeutic approaches for this rare presentation.

Case report

A 64-year-old postmenopausal Chinese woman with a 10-year history of hypertension, managed with regular oral antihypertensive medication, presented in May 2023 with complaints of urinary urgency, frequent urination, severe urgency, altered stool morphology, occasional abdominal distension, and abdominal pain. These symptoms were alleviated following initial treatment. Notably, there was no vaginal bleeding, fluid discharge, dysuria, or hematochezia. A review of her medical history revealed no significant findings, and she reported no history of smoking, alcohol consumption, illicit drug use, or a family history of cancer.

On physical examination, there was no palpable axillary, supraclavicular, or inguinal lymphadenopathy. However, a cervical mass was identified during anal examination, while endoscopy revealed an intra-anal annular mass. A gynecological examination further identified a frozen pelvis, with the cervix described as hyperplastic, firm, and morphologically fair. The vaginal vault and upper vaginal tissue on both sides were palpably firm and hardened.

Breast ultrasound and mammography did not identify any breast masses. Magnetic resonance imaging (MRI) demonstrated cervical occupation (Figures 1A, B) and thickening of the rectal wall (Figures 2A, B). Gallium-68 fibroblast activation protein inhibitor positron emission tomography-computed tomography (Ga68-FAPI PET/CT) revealed diffuse fibroblast activation in the gastric wall (Figure 3). Additionally, 18F-fluorodeoxyglucose positron emission tomography-computed tomography (18F-FDG PET/CT) identified diffuse annular thickening of the rectal wall (Figure 4). Notably, 18F-FDG PET/CT did not reveal any lesions in the breast (Figure 5).

Pathological examinations of biopsy samples from the cervix, stomach, and rectum were conducted. The cervical biopsy revealed diffuse infiltration of heterotypic cells within the cervical stroma (Figure 6A). Immunohistochemical analysis yielded the following results: AE1/AE3 (+), P63 (-), vimentin (-), CD38 (-), Ki-67 (5% positive cells), CK7 (+), CK20 (-), Synaptophysin (Syn) (-), CDX2 (-), GATA3 (+) (Figure 6B), estrogen receptor (ER) (90% strongly positive) (Figure 6C), Pax-8 (-), GATA3 (+), E-cadherin (-), HER2 (1+, 60% strongly positive), and TRPS1 (+) (Figure 6C). Based on these findings, a mammary origin was strongly suggested, consistent with the diagnosis of poorly differentiated adenocarcinoma.

Secondly, gastroscopy revealed mucosal congestion and edema in the gastric body, along with a bulging lesion approximately 1 cm in size located on the posterior wall of the anterior pyloric area. Pathological examination identified heterotypic cells within the mucosa of both the gastric antrum (Figure 7A) and the gastric body (Figure 7B). Immunohistochemical analysis yielded the following results: AE1/AE3 (+), CDX2 (-), CD68 (-), Synaptophysin (Syn) (-), CD56 (-), Ki-67 (5%-20% positive cells), CK7 (+), GATA3 (+) (Figure 7C), estrogen receptor (ER) (90% strongly positive) (Figure 7D), and Pax-8 (-) (Figure 7D). Collectively, these findings indicated a diagnosis of poorly differentiated adenocarcinoma, suggesting that the breast should be evaluated as a potential primary site.

Lastly, enteroscopy revealed rectal mucosal swelling, thickening, stiffness, and lumen stenosis approximately 8 cm from the rectum and anus, making the passage of the scope difficult. Pathological examination identified a small number of heterotypic cells (Figure 8A). Immunohistochemical analysis yielded the following results: AE1/AE3 (+), CDX2 (-), CD68 (-), Synaptophysin (Syn) (-), Ki-67 (5% positive cells), CK7 (+), GATA3 (+) (Figure 8B), estrogen receptor (ER) (70% strongly positive) (Figure 8C), progesterone receptor (PR) (0% positive), HER2 (2+), Mammaglobin (+), and HER2 fluorescence *in situ* hybridization (FISH) (-). Based on these findings, a mammary origin was strongly suggested, consistent with adenocarcinoma.

Histopathological examinations of the cervix, stomach, and rectum revealed stromal adenocarcinoma. Immunohistochemical analysis demonstrated positive staining for GATA-3, whole-cell keratin, and estrogen receptor (ER), supporting the diagnosis of breast cancer metastases to these sites. Additionally, the presence of ER and GATA-3 positivity, along with negative Caudal-type homeobox 2 (CDX2) staining in samples from the cervix, stomach, and rectum, further corroborated the diagnosis of gastrointestinal and cervical metastases originating from breast cancer. However, discrepancies were observed in the expression of hormone receptors, Ki-67, and HER2 among the cervical, gastric, and rectal samples.

No lesions were detected on breast ultrasonography, mammography, or Ga68-FAPI PET/CT. However, the combination of biopsy pathology and immunohistochemical findings confirmed simultaneous metastases to the cervix, stomach, and rectum originating from occult breast cancer. Tumor marker levels were also elevated, with carcinoembryonic antigen (CEA) at 11.88 ng/ml, cancer antigen 15-3 (CA15-3) at

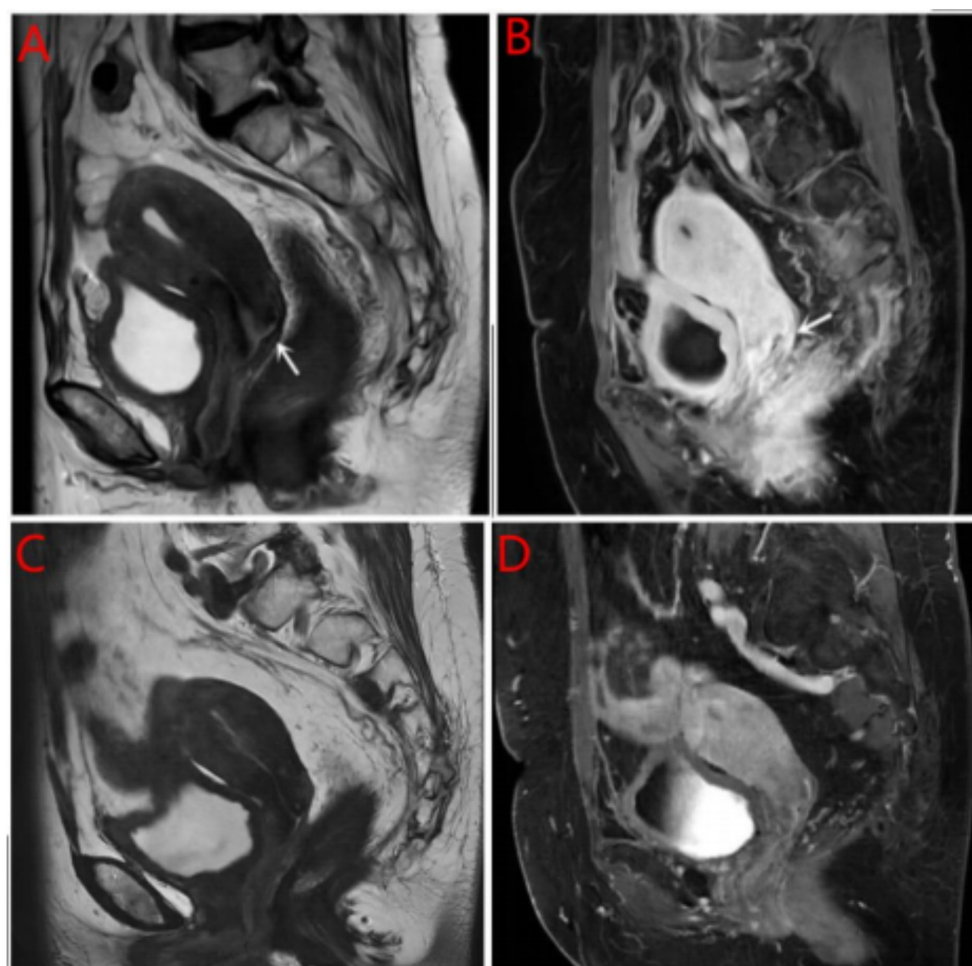


FIGURE 1

MRI cervical mass. (A) Pretreatment with MRI T2W1 imaging of the cervical mass; (B) Pretreatment with enhanced MRI imaging of the cervical mass; (C) Post treatment with MRI T2W1 imaging of the cervical mass; (D) Post treatment with enhanced MRI imaging of the cervical mass.

55.96 U/ml, and cancer antigen 125 (CA125) at 63.88 U/ml. Based on these findings, the patient was diagnosed with stage IV occult breast cancer (cTXN0M1) presenting with synchronous metastases to the rectum, stomach, and cervix.

Following the diagnosis, the case was reviewed in a multidisciplinary meeting, which recommended treatment with endocrine therapy combined with CDK4/6 inhibitors and rectal radiotherapy. The patient was prescribed letrozole and dalpiciclib for six months, resulting in a favorable clinical response. She experienced significant relief from severe symptoms, including frequency, urgency, and tenesmus, as well as improvements in stool shape. Follow-up MRI and CT evaluations revealed stable gastric wall lesions, significant reduction of rectal lesions (Figures 2C, D), and near-complete resolution of cervical lesions (Figures 1C, D) after the combined treatment. Adverse effects were tolerable and primarily included grade II myelosuppression (leukopenia and thrombocytopenia), which improved with symptomatic management. Changes in tumor marker levels during treatment are illustrated in Figure 9.

Discussion

Most patients with OBC are diagnosed at a relatively early stage, often with a favorable prognosis, and can be managed as stage II–III breast cancer (13–15). Key prognostic factors for OBC include axillary lymph node metastasis status, estrogen receptor (ER) status, and the type of local treatment administered (3, 4, 16). Among these, axillary lymph node metastasis is recognized as the most significant adverse prognostic factor (16–18).

Although the incidence of OBC is low, case reports detailing metastases to the bone, liver, lymphatic system, skin, orbit, bone marrow, lung, spleen, or cervix have been published (6–12). To the best of our knowledge, this is the first reported case of occult primary breast cancer with simultaneous metastases to the cervix, stomach, and rectum. While very few cases have documented metastasis to the stomach, rectum, or cervix individually, the rates of gastric and colon metastases in breast cancer patients are estimated as low as 3% and 5%, respectively (19). Simultaneous gastric and colon metastases are exceedingly rare, with only eight

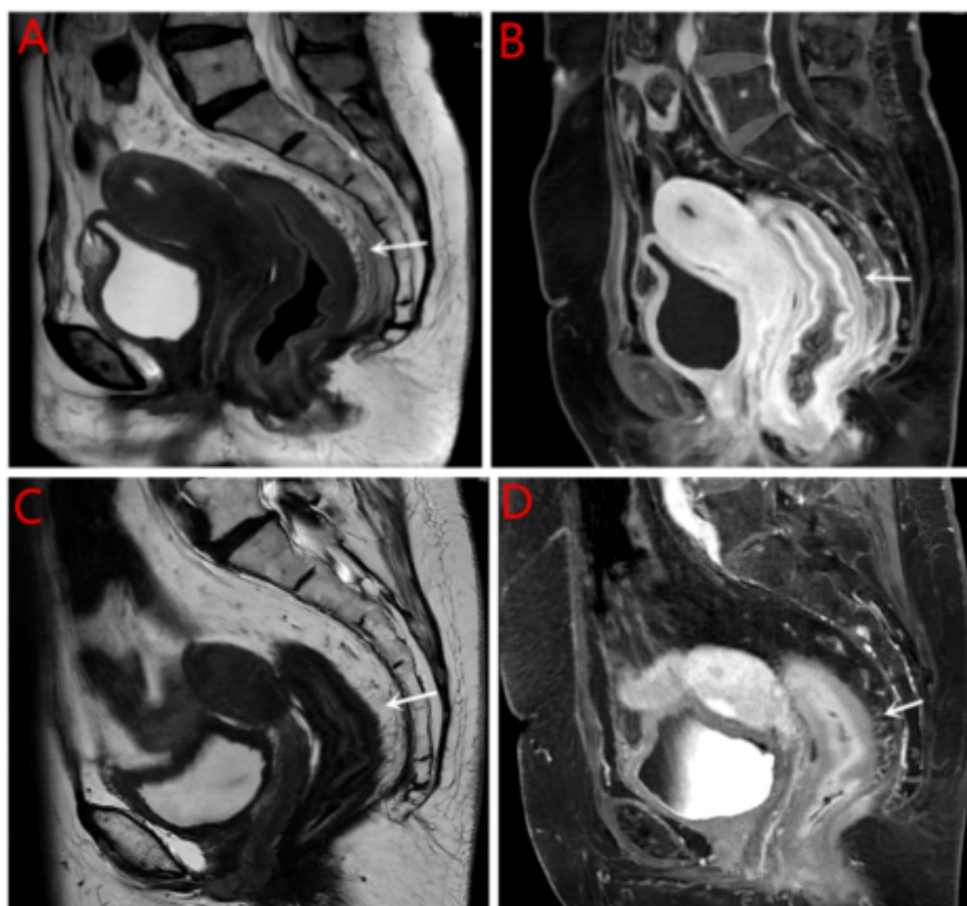


FIGURE 2

MRI rectal wall. (A) Pretreatment with MRI T2W1 imaging of the rectal wall; (B) Pretreatment with enhanced MRI imaging of the rectal wall; (C) Post treatment with MRI imaging of the rectal wall; (D) Pretreatment with enhanced MRI imaging of the rectal wall.

cases documented to date (20), and invasive lobular carcinoma is identified as the most common histological subtype associated with gastrointestinal metastasis in breast cancer (21). The likelihood of cervical metastasis in primary breast cancer is similarly rare, with reported rates ranging from 0.8% to 1.7% (22). This rarity can be attributed to the cervix's small size, dense fibromuscular structure,

and access limited to afferent lymphatic vessels, making it an uncommon target for metastatic spread (23). Over 200 cases of breast cancer metastasizing to the uterus have been documented (24). However, a review of case series highlighted that of 27 patients examined, only three presented with isolated cervical metastasis from primary breast cancer, while another 24 cases involved

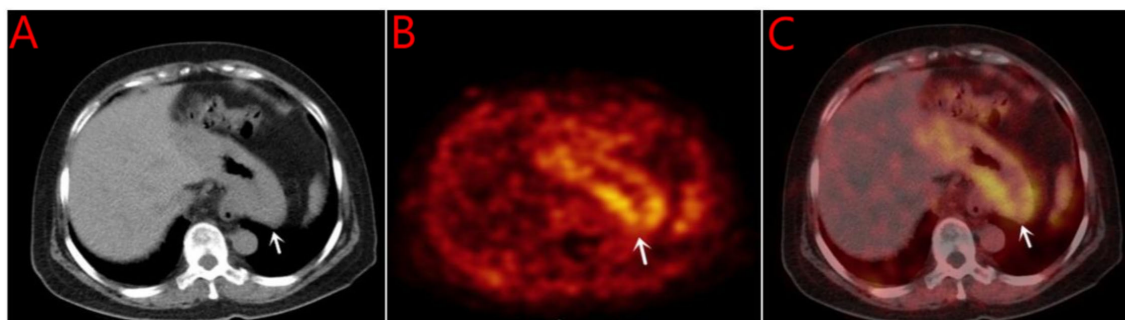


FIGURE 3

Ga68-FAPI PET/CT before gastric treatment. (A) CT shows thickening of gastric wall; (B) PET shows high metabolism; (C) MIP shows of gastric wall. Ga68-FAPI PET/CT, G68 positron emission tomography-computed tomography; MIP, Maximum Intensity Projection.

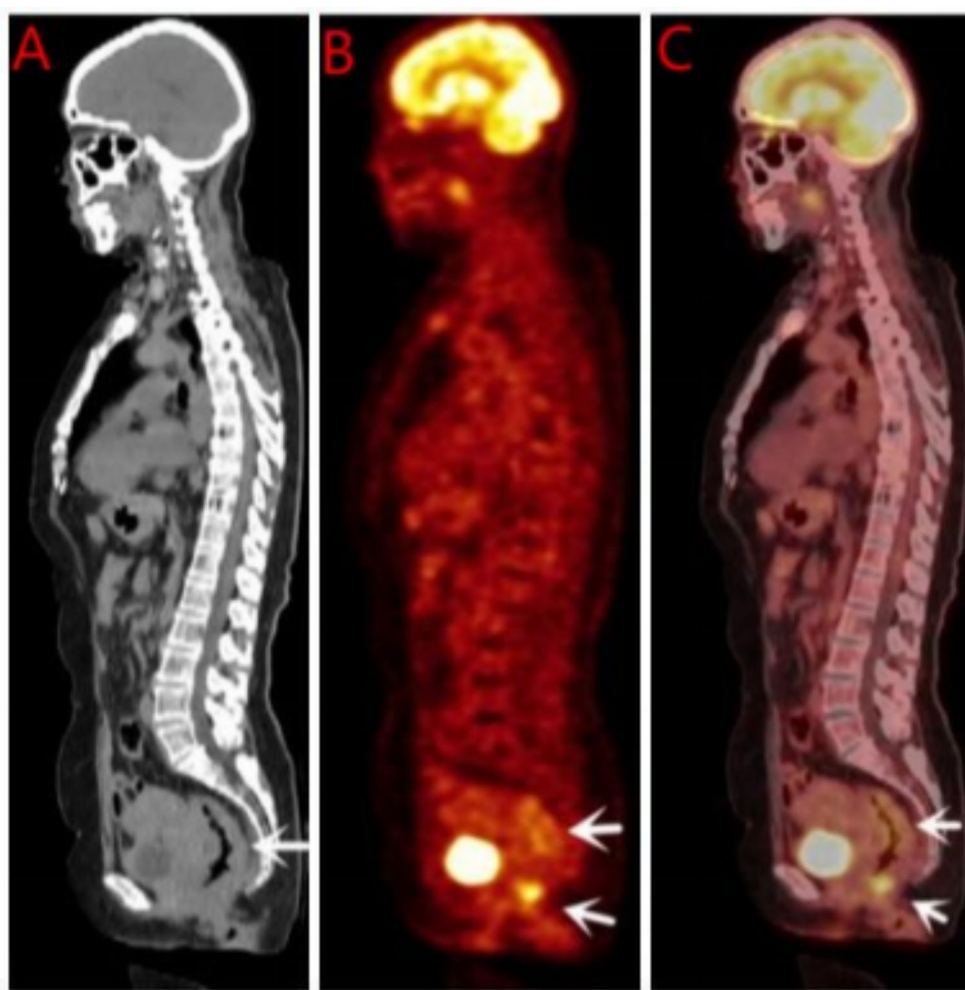


FIGURE 4

18F-FDG PET/CT before rectal treatment. (A) CT shows thickening of rectal wall; (B) PET shows high metabolism; (C) MIP shows of rectal wall. 18F-FDG PET/CT, 18F-fluorodeoxyglucose positron emission tomography-computed tomography; MIP, Maximum Intensity Projection.

cervical metastasis in conjunction with metastatic disease in other sites (20).

To achieve an accurate diagnosis of OBC, imaging studies for recessive breast cancer remain an area of ongoing investigation. According to the recommendations of the American College of Radiology, MRI, mammography, and ultrasonography should be utilized in patients with suspected OBC who lack evidence of primary breast lesions (25). The diagnostic criteria for OBC include the absence of a detectable mass on both clinical examination and breast X-ray (26). In this case, the patient did not undergo breast MRI; instead, Ga68-FAPI PET/CT was employed, inspired by findings from a relevant report (27). However, the Ga68 PET/CT scan failed to detect any breast lesions in this study.

Pelvic MRI revealed cervical involvement and rectal wall thickening in the patient. 18F-FDG PET/CT and Ga68 PET/CT demonstrated diffuse tumor-associated fibroblast activity in the gastric wall and diffuse annular thickening in the rectal wall. Despite these findings, breast ultrasonography, mammography, and 18F-FDG PET/CT did not identify any breast lesions. Pathological examinations

of the cervical, gastric, and rectal tissues were subsequently performed. Histopathological analysis revealed stromal adenocarcinoma in all three sites, and immunohistochemical testing confirmed the presence of markers consistent with breast cancer metastases to the cervix, stomach, and rectum.

For localized OBC, the current National Comprehensive Cancer Network (NCCN) guidelines recommend complete surgical resection of axillary lymph nodes, along with total breast radiotherapy or mastectomy, with or without lymph node radiotherapy (28). A meta-analysis of OBC further supports that breast surgery (BS), including modified radical mastectomy (MRM) and breast-conserving surgery (BCS), combined with radiotherapy, may represent the optimal treatment strategy for patients with localized OBC (29). With advancements in comprehensive therapy, patients with OBC who receive neoadjuvant therapy are generally associated with improved prognoses compared to those who do not undergo neoadjuvant therapy (30–33). Additionally, sentinel lymph node biopsy (SLNB), combined with radiotherapy (RT), may be considered as an alternative to axillary lymph node dissection (ALND) in select breast cancer patients.

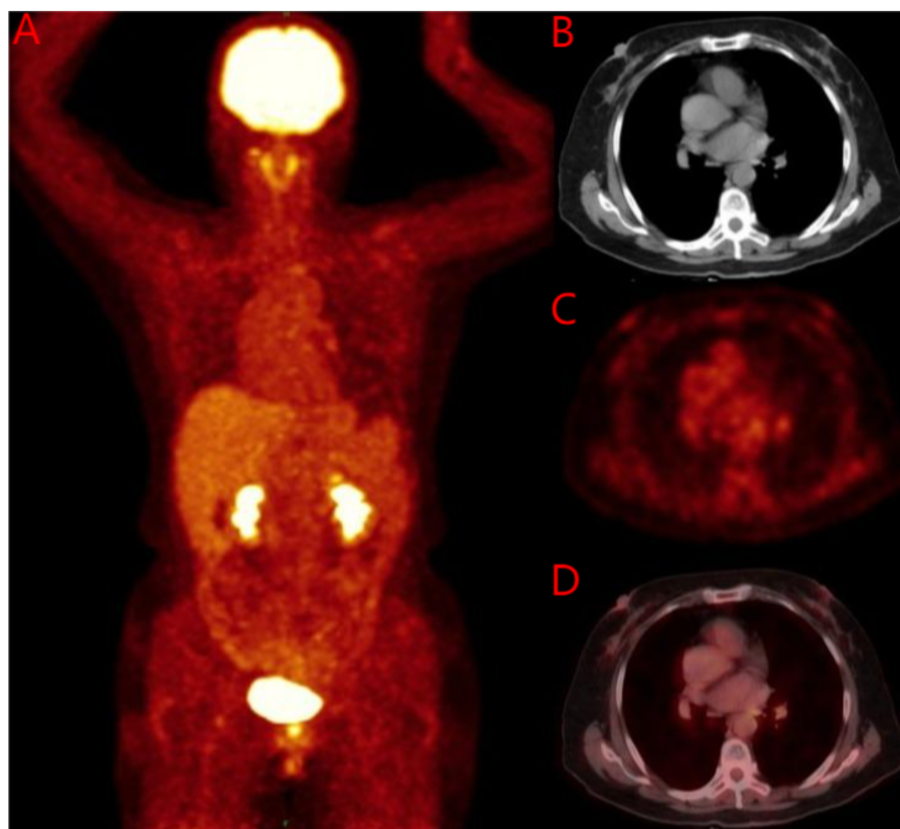


FIGURE 5

18F-FDG PET/CT before breast treatment. (A) Whole body image of 18F-FDG PET/CT; (B) No soft tissue mass was found on breast CT; (C) No soft tissue mass was found on breast PET; (D) No soft tissue mass was found on breast MIP. 18F-FDG PET/CT, 18F-fluorodeoxyglucose positron emission tomography-computed tomography; MIP, Maximum Intensity Projection.

To date, limited studies have explored the treatment of extensive metastatic OBC. Similar to the management of non-OBC, systemic therapies—including chemotherapy, radiotherapy, and hormonal therapy—are commonly employed for the treatment of extensive metastatic OBC (34, 35). According to the Guidelines for *Breast Cancer Diagnosis and Treatment* by the China Anti-Cancer Association, patients with hormone receptor-positive,

HER2-negative advanced breast cancer, and no evidence of visceral crisis can be treated with endocrine therapy combined with CDK4/6 inhibitors (36). In this case, the patient presented with advanced breast cancer, postmenopausal status, and metastases to the stomach, cervix, and rectum. She was ER-positive, PR-positive, and HER2-negative, and was treated with a regimen of letrozole and dapiiclib. Clinical trial data have demonstrated that the median

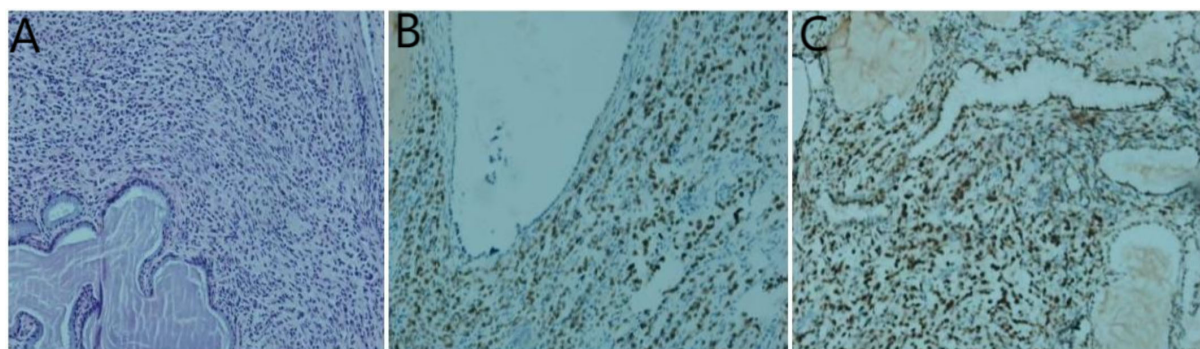


FIGURE 6

Histological examinations of the cervical specimen. (A) Hematoxylin and eosin staining demonstrates the presence of adenocarcinoma within the cervical tissue; (B) Immunohistochemistry results reveal positive staining for GATA-3; (C) estrogen receptor; (original magnification x200).

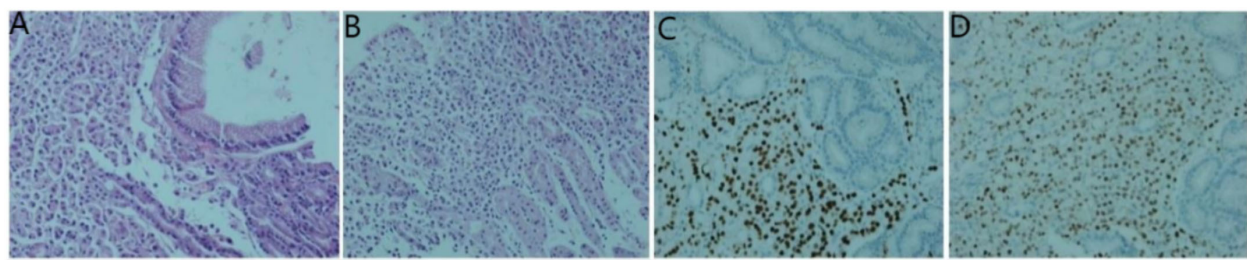


FIGURE 7
Histological examinations of the gastric specimen. (A, B) Hematoxylin and eosin staining demonstrates the presence of adenocarcinoma within the gastric antrum and body tissue; (C) Immunohistochemistry results reveal positive staining for GATA-3; (D) estrogen receptor.

progression-free survival is significantly longer in patients receiving daltapiclib compared to placebo (30.6 months [95% CI: 30.6–not reached] vs. 18.2 months; stratified hazard ratio: 0.51 [95% CI 0.38–0.69]) (37). Although the addition of daltapiclib may increase the incidence of adverse effects such as bone marrow suppression, gastrointestinal reactions, and hepatotoxicity, supportive care and dose adjustments have proven effective in mitigating these toxicities. In this case, after six months of therapy, the patient experienced significant symptom relief and marked reduction in metastatic lesions in the cervix, stomach, and rectum. The treatment regimen was well-tolerated, with manageable side effects limited to bone marrow suppression.

Conclusion

Non-specific symptoms, such as urinary frequency, urgency, and other atypical clinical manifestations, as observed in this patient, should prompt a high index of suspicion for OBC. Whole-body PET-CT plays a critical role in evaluating potential systemic involvement and identifying underlying primary tumor sites. IHC remains essential for determining the origin of metastatic tumors, even in the absence of detectable lesions in the mammary gland. Furthermore, for patients with ER-positive, HER2-negative OBC presenting at an advanced stage, endocrine therapy combined with CDK4/6 inhibitors represents a promising first-line treatment option.

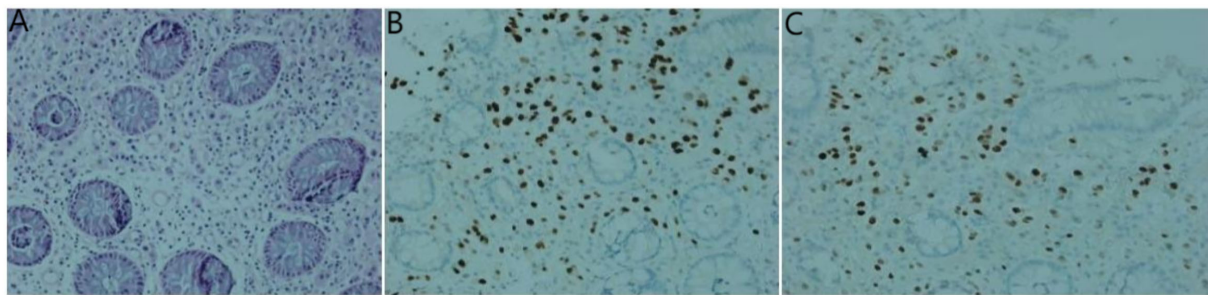


FIGURE 8
Histological examinations of the rectum specimen. (A) Hematoxylin and eosin staining demonstrates the presence of adenocarcinoma within the rectum tissue; (B) Immunohistochemistry results reveal positive staining for GATA-3; (C) estrogen receptor.

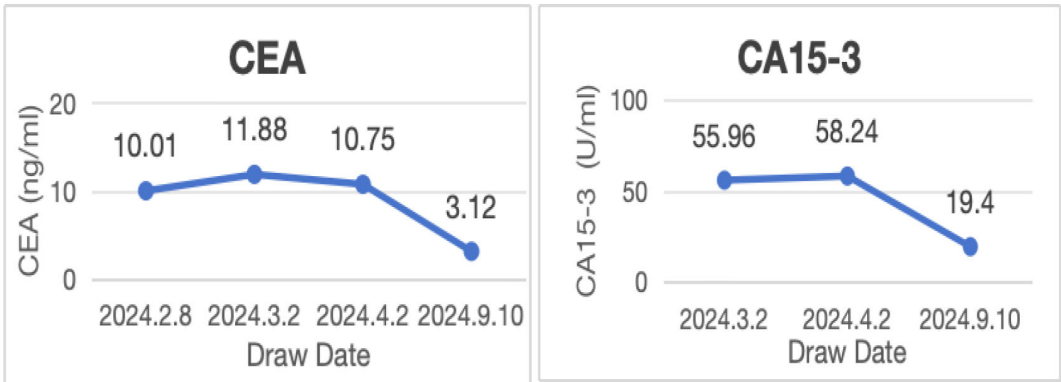


FIGURE 9
Changes in the levels of tumor markers.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Material.

Ethics statement

Ethical approval was not required for the studies involving humans because this is a patient case report that has been approved by the patient. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

RD: Investigation, Data curation, Validation, Writing – original draft. ZM: Writing – original draft, Investigation, Data curation. QL: Writing – original draft, Software. YW: Data curation, Writing – original draft, Resources. YYL: Data curation, Writing – original draft. YL: Writing – original draft, Formal Analysis, Data curation. YBL: Writing – review & editing, Resources, Funding acquisition.

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Conflict of interest

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