Int J Clin Exp Pathol 2020;13(5):1270-1274
www.ijcep.com /ISSN:1936-2625/IJCEP0110314

Case Report

Breast metastases in advanced rectal cancer: a case report

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Received March 4, 2020; Accepted April 14, 2020; Epub May 1, 2020; Published May 15, 2020

Abstract: Breast metastasis from solid tumors rarely occurs, although primary breast cancer is one of the most common malignancies in women worldwide. Rectal cancer metastasis is rarely reported. We report a case of a 49-year-old Chinese woman with advanced rectal cancer, who presented with mass in her left breast and several irregular dusky-red nodular knurls in the skin around the left nipple. Based on percutaneous echo-guided biopsy of the breast lesion, a poorly differentiated adenocarcinoma was consistent with rectal cancer metastasis histologically and immunohistochemically. This should be considered in any patient with history of cancer and confirmed histologically and immunohistochemically.

Keywords: Breast metastasis (BM), cutaneous metastasis, rectal cancer

Introduction

Primary breast cancer is one of the most common malignancies in women around the world, whereas metastasis to the breast from solid tumors is rare. Breast metastases mostly developed from contralateral primary breast cancer, but only about 0.3-2% developed from extramammary solid organs, such as lung, nasopharynx, ovary, stomach, thyroid and cervix [1]. Metastasis from rectal cancer is rarely reported. Here we present a case of breast tumor and subcutaneous spreading, and multiple axillary lymph node metastases simultaneously from advanced rectal adenocarcinoma.

Case report

In December 2017, a 49-year-old Chinese woman with history of metastatic rectal carcinoma presented to our hospital with a painful mass in her left breast. In 1999, she had undergone radical resection of rectal carcinoma, which was proven to be a moderately differentiated adenocarcinoma pathologically, followed by six cycles of chemotherapy consisting of oxaliplatin and 5-fluorouracil and folinic acid (FOLFOX) and pelvic three dimensional-conformal radiotherapy (3D-CRT) with 50 Gy/25 fractions/5 weeks. The patient was treated with clinical and radiological evaluation on follow-up. Since May 2007, bilateral pulmonary, liver, and multiple bone metastases were found, including to L1-3. PD-1 inhibitor therapy using Opdivo was initiated 3 months prior to this presentation. Physical examination after hospital admission showed several irregular dusky-red nodular knurls in the skin around the left nipple with slightly higher skin temperature, but without skin dimpling and nipple retraction. Upon palpation, a round, well-circumscribed, and hard mass of 2×2 cm was found in the upper outer quadrant of her left breast. In addition, multiple hard nodules were found in her bilateral axillae with maximum size of 2.5×2 cm on the right side. Breast ultrasound confirmed the presence of a hypoechogenic tumor lesion of approximately 2×2.5 cm in the upper outer quadrant associated with enlarged multiple bilateral axillary lymph nodes. The patient underwent percutaneous echo-guided biopsy of her left breast lesion, located in the nipple and upper outer quadrant (**Figure 1**). Histology revealed poorly differentiated adenocarcinoma (**Figure**

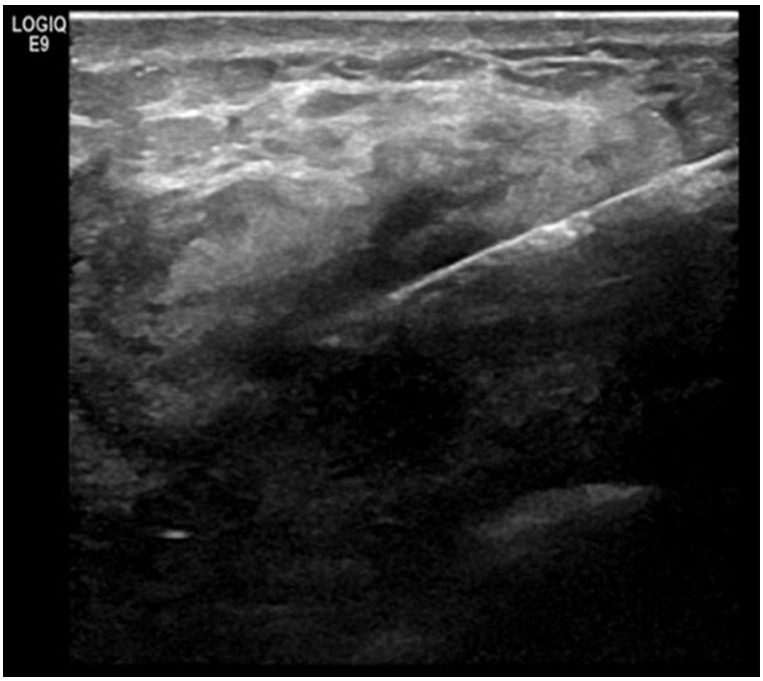

Figure 1. Percutaneous echo-guided biopsy of left breast mass.

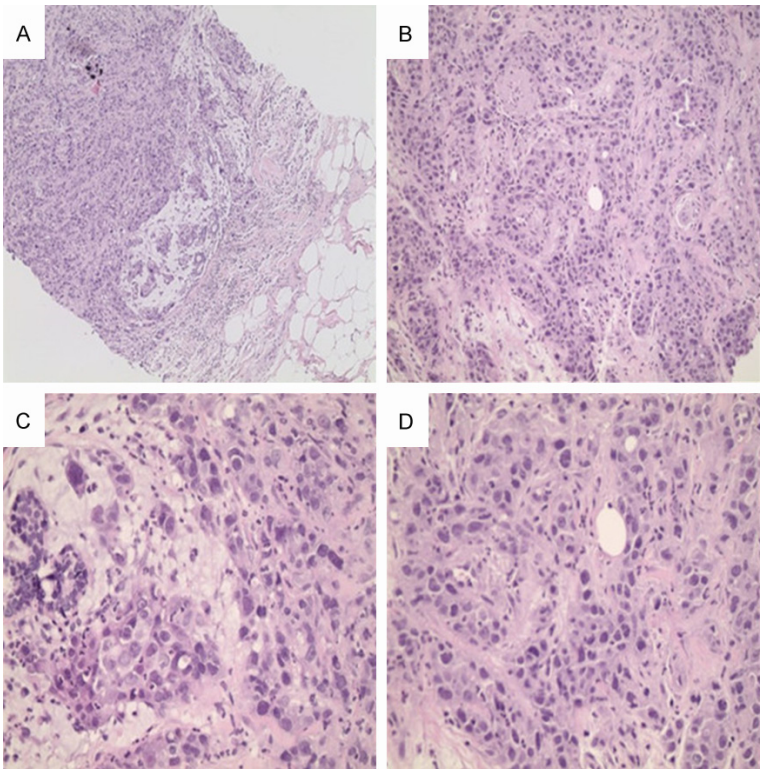

Figure 2. Histologic findings in (A and B). (A) Neoplastic tissue is in the middle and upper left region, fibroadipose tissue with infiltration of inflammatory cells in the lower right (H&E stain, ×100). (B) Tumor cells organized in small nests, strips, and glandular structures. (C and D) Tumor cells are large, dark stained, heterotypic, with high nucleo-plasm ratio and with a desmoplastic reaction, and some of them have signet ring morphology (H&E stain, ×400).

2). Immunohistochemistry showed that tumor cells were strongly positive for CA153 (+++), villin (+++), CDX2 (+++), and P53 (+++) and negative for hormone receptors (ER and PR) and human epidermal growth factor receptor 2, cytokeratins 7 and 20, mammaglobin, and GCDFP 15. The proliferation index Ki-67 was 70%, confirming the diagnosis of breastmetastasisfromrectaladenocarcinoma (**Figure 3**). During hospitalization, a cauliflower-like nodule, firm with easy bleeding, had gradually been observed in her papilla because of the rapidly growing neoplasm (**Figure 4**). The patient received palliative electron beam radiotherapy targeting the left breast metastatic lesions to prevent skin ulceration. The area of radiation was a loop that encircled the knurls and extended out for 2 cm (**Figures 4** and **5**), and the expected dose of radiotherapy was 50 Gy. Targeted treatment with multi-kinase inhibitor regorafenib was administered after the patient underwent radiotherapy. Considering the rapid deterioration of the patient's clinical condition, targeted therapy was replaced with the best supportive treatment only after 2 months since the diagnosis. At 3 months after the metastasis diagnosis, the patient died of respiratory insufficiency.

Discussion

Colorectal carcinoma is the most common gastrointestinal tumor worldwide, ranking as the 5th most prevalent male and 4th most prevalent female malignancies in China last year [2]. It often spreads to the locoregional lymph nodes, liver, lungs, bones, and some abdominal pelvic organs by

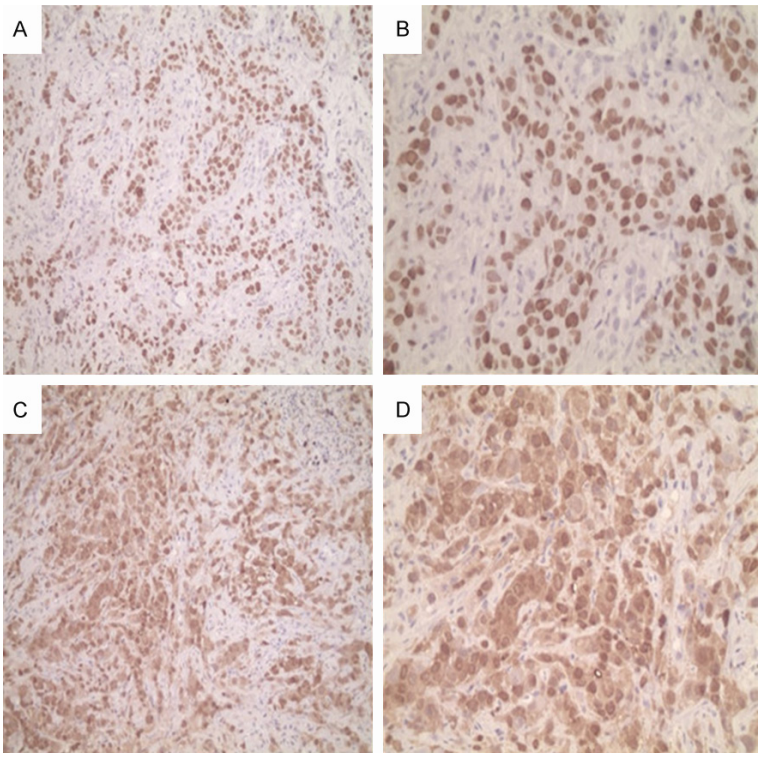

Figure 3. Immunohistochemical stainings. CDX2 stain revealed nuclear positivity in (A) (×200) & (B) (×400). Villin stain was positive in malignant cell cytoplasm in (C) (×200) & (D) (×400).

Figure 4. Physical findings of the patient's chest. The cauliflower-likegrowth of the nipple and irregular dusky-red nodular knurls in the skins around left nipple. The radiation area: the area inside the black loop.

lymph node, hematogenous, and implant metastases. Although multiple metastases are very common for patients with advanced rectal cancer, breast metastasis is an unusual event; moreover, axillary lymph node and multiple bone metastases are more likely to occur in patients with primary breast cancer.

According to the published literature, breast metastases are more common in females, occur largely at the median age of 50 (common range, 32-87) years, and are located in the left upper outer quadrant [3]. The median time is approximately 2 years from the diagnosis of primary tumor to metastatic breast malignancy, mainly at the terminal stage of cancer development with multiple metastases. Adolescence, lactation, and pregnancy have been reported as other periods associated with high incidence for breast metastasis [4]. Moreover, in some cases, the breast is found to be the only site of spread and the initial metastatic lesion.

The classic theory that metastasis that cancer cells (seed) fall from the original site and disseminate to the breast (soil) through lymphatic and hematogenous routes is widely accepted and explainable in most cases. However, why these metastases occur in women at such high frequency and are the initial and only event for some tumors is not explained by that theory. Some existing research indicated that neurohumoral factors may be involved in the event. For example, female hormones can act as a positive regulator to promote breast angiogenesis. Consistent with the hypothesis, besides female patients, breast metastasis can be found in some men with prostatic carcinomas who have been treated with estrogens.

Clinically, it is characterized by single or multiple, round or oval-shaped, painless and fast-growing masses without skin dimpling or nipple retraction and discharge [5]. Typical ultrasound (US) features include well-circumscribed, hypoechogenic masses without spiculations, cal-

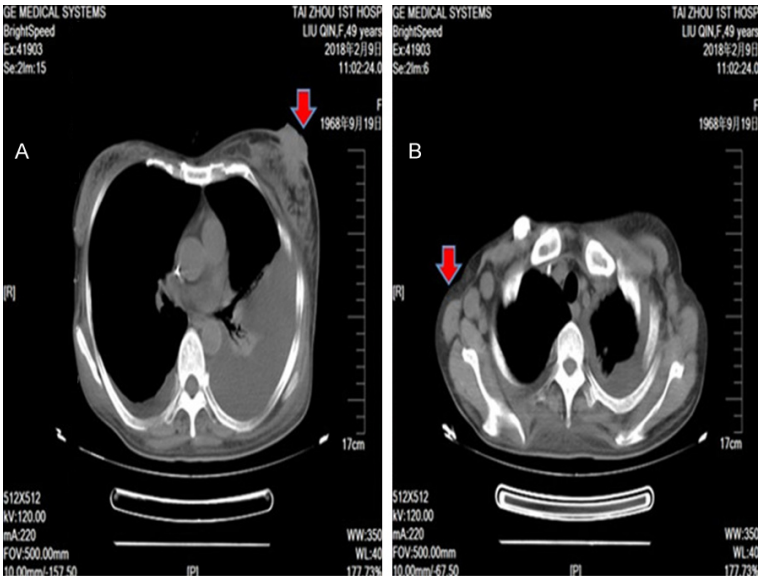

Figure 5. The chest computed tomographic scan showing before radiotherapy in (A and B). (A) An irregular tumoral lesion of the left breast (red arrow) and bilateral pleural effusion, especially in the left. (B) Multiple right lymph node enlargements (red arrows).

cifications, or architectural distortion and skin changes [6]. The appearance of penetrating vascularity is suggestive of malignancy [6]. Occasionally, US shows a diffusely and heterogeneously increased density in the subcutaneous fat and glandular tissue and a thick trabecular pattern with secondary skin thickening, lymphedema, and lymph node enlargement, a feature of lymphatic metastasis and similar to inflammatory breast cancer [7]. A mammogram shows well-circumscribed masses without spiculations or a peritumoral stromal response, which makes it difficult to differentiate from primary breast cancer or fibroadenoma [7].

Histology is crucially important to establish a correct diagnosis. Compared with fine-needle aspiration biopsy, core percutaneous biopsy is recommended. The knowledge of comprehensive history and review of previous histologic slides are important for accurate diagnosis. However, in some patients with unclear clinical history or unattainable previous slides, immunohistochemistry may be helpful for differential diagnosis. Combined application of CK7/CK20 is the first option in distinguishing between primary and metastasis of breast tumors. CK20+ is highly suggestive of non-mammary origin. In most patients, the gastrointestinal tract, pancreaticobiliary duct, and mucinous ovarian cancers express CK7-/CK20+, and this phenotype was found in 65.8% of patients with colorectal cancer, according to Bayrak's study [8]. In our patient, both CK7 and CK20 were negative. However, CDX2, intestinal-specific transcription factors, and villin, a highly specific marker for gastrointestinal and pancreatic adenocar-cinoma, were both strongly positive. In addition, negative results with ER, PR, and Her2/neu proved metastatic breast cancer. In addition, gene detection in the patient's serum or breast tumor, especially KRAS/NARS and BRAF mutation analysis, was recommended but the patient refused. The given history, histology, and immunohistochemistry confirmed that the breast mass metastasized from rectal cancer. However, the consistency of gene mutation status of the breast tumor with that of the original rectal adenocarcinoma specimen may provide more powerful evidence for the last prognosis.

The management of breast metastasis from rectal cancer depends on several factors, including patients' condition, disease stage, and metastatic sites. However, in most cases, breast metastasis, characterized by extramammary widespread dissemination, is a terminal event. Palliative treatment is most common. Surgery is not recommended unless performed to relieve symptoms [9]. A combination of local therapy with systemic chemotherapy may also be considered if the patient has breast mass ulceration or chest wall invasion, as well as disseminated metastases [10]. In our case, palliative radiotherapy was performed for rupture and effusions of the nipple. In addition, she received a multi-kinase inhibitor, regorafenib, in accordance with guidelines of Chinese colorectal cancer diagnosis and treatment in 2017. The prognosis is poor with the average time of < 1 year after the diagnosis. Our case should alert physicians to consider breast metastasis in patients with advanced rectal cancer.

Conclusion

Although breast metastasis is relatively rare, it may be considered in any patient with history of cancer for the diagnosis of a suspicious breast mass. The final diagnosis can be confirmed histologically and immunohistochemically.

Disclosure of conflict of interest

None.

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